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SYNTHESIS OF SULFONYL NAZAROV REAGENTS AND APPLICATION IN ORGANOCATALYSIS

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Trabajo para optar al grado de
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A mis padres.

"If you live properly, the dreams will come to you"

Randolph Frederick "Randy" Pausch (1960 - 2008)
Professor of Computer Science, Human-Computer Interaction and Design
Carnegie Mellon University (CMU), Pittsburgh, Pennsylvania

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ABBREVIATIONS AND ACRONYMS

Abbreviations and acronyms used throughout this work:

- $[\alpha]_D^{25}$: specific optical rotation
- **Ac** : acetyl
- **Ac_2O** : acetic anhydride
- **AIBN** : 2,2-azobisisobutyronitrile
- **aq** : aqueous
- **Ar** : aryl; Argon
- **atm** : atmosphere(s)
- **9-BBN** : 9-borabicyclo[3.3.1]nonyl
- **Bn** : benzyl
- **Boc** : *tert*-butoxycarbonyl
- **Boc_2O** : di-*tert*-butyl dicarbonate
- **bpy** : 2,2-bipyridyl
- ***n*-Bu** : normal (primary) butyl
- ***n*-BuLi** : butyl lithium
- ***s*-Bu** : *sec*-butyl
- ***t*-Bu** : *tert*-butyl
- **Bu_3SnH**: tributyltin hydride
- **Bz** : benzoyl
- **ºC** : degrees Celsius
- **c** : concentration
- **cat.** : catalytic
- **Calcd** : calculated
- **Cbz** : benzyloxycarbonyl
- **CH_3CN**: acetonitrile
- **cm^{-1}** : wavenumber(s)
- **conc.** : concentrated
- **COSY** : correlation spectroscopy
- **Cp** : cyclopentadienyl
- ***m*-CPBA**: *meta*-chloroperoxybenzoic acid
- **Cy** : cyclohexyl
- **δ** : chemical shift in parts per million
- **d** : doublet
- **DABCO**: 1,4-diazabicyclo[2.2.2]octane
- **DBU**: 1,8-diazabicyclo[5.4.0]undec-7-ene
- **DCC** : *N*,*N*-dicyclohexylcarbodiimide
- **DCE** : 1,2-dichloroethane
- **DCM** : dichloromethane
- **dd** : double doublet
- **ddd** : double double doublet
- **DEAD** : diethyl azodicarboxylate
- **DEPT** : distortionless enhancement by polarisation transfer
- **DHP** : 3,4-dihydro-2*H*-pyran
- **DIBAL-H**: diisobutylaluminium hydride
- **DIPEA** : *N*,*N*-diisopropylethylamine
- **DMAP** : 4-(*N*,*N*-dimethylamino)pyridine
- **DME** : 1,2-dimethoxyethane
- **DMF** : dimethylformamide
- **DMSO** : dimethyl sulfoxide
- **DNA** : deoxyribonucleic acid
- **DOS** : diversity oriented synthesis
- **d.r.** : diastereomeric ratio
- **dt** : double triplet
- **ee** : enantiomeric excess
- **equiv(s)**: equivalent(s)
- **e.r.** : enantiomeric ratio
- **Et** : ethyl
- ***et al.*** : *et alii* (and others)
- **Et_2O** : diethyl ether

Continues on next page

- **Et_3N** : triethylamine
- **EtOAc** : ethyl acetate
- **EtOH** : ethanol
- **EWG** : electron withdrawing group
- **FT** : fourier transform
- **h** : hour(s)
- ***n*-Hex** : hexane
- **HMBC** : heteronuclear multiple bond correlation
- **HMPA** : hexamethylphosphoramide
- **HMQC**: heteronuclear multiple quantum correlation
- **HOAc** : acetic acid
- **HPLC** : high-performance liquid chromatography
- **HRMS** : high-resolution mass spectrometry
- **Hz** : hertz
- **IR** : infrared
- ***J*** : coupling constant in hertzs
- **LAH** : lithium aluminum hydride
- **LDA** : lithium diisopropylamide
- **LHMDS**: lithium hexamethyldisilazide
- **µ** : micro
- **m** : multiplet (spectral); milli
- **M** : molar, mol L^{-1}
- **M^+** : parent molecular ion
- **max** : maximum
- **MBH** : Morita-Baylis-Hillman
- **MCR** : multicomponent reaction
- **Me** : methyl
- **MeOH** : methanol
- **MHz** : megahertz
- **min** : minor, minute(s); minimum
- **mg** : milligram
- **mM** : millimolar (millimoles/litre)
- **mmol** : millimole
- **mL** : millilitre
- **mol** : mole(s)
- **MOM** : methoxymethyl
- **m.p.** : melting point
- **MS** : mass spectrometry; molecular sieves
- **Ms** : methanesulfonyl
- **MW** : molecular weight
- ***ν*max** : maximum absorption in cm^{-1}
- **NaH** : sodium hydride
- **NBS** : *N*-bromosuccinimide
- **NHMDS**: sodium hexamethyldisilazide
- **NMR** : nuclear magnetic resonance
- **nm** : nanometer(s)
- **NMO** : *N*-methylmorpholine-*N*-oxide
- **nOe** : nuclear Overhauser effect
- **NOESY**: nuclear Overhauser effect spectroscopy
- **Nu** : nucleophile
- **O/N** : overnight
- **PCC** : pyridinium chlorochromate
- **PDC** : pyridinium dichromate
- **PEG** : polyethylene glycol
- **Ph** : phenyl
- **PMB** : *p*-methoxybenzyl
- **ppm** : part(s) per million
- **Pr** : propyl
- ***i*-Pr** : isopropyl
- **PTC** : phase-transfer catalysis
- **PVS** : phenyl vinyl sulfone
- **py** : pyridine
- **q** : quartet (spectral)

Continues on next page

- **quant.** : quantitative
- **redox** : reduction–oxidation
- **rel** : relative
- **ROESY**: rotating frame Overhauser effect Spectroscopy
- **rt** : room temperature
- **s** : singlet (spectral); second(s)
- **sat.** : saturated
- **t** : triplet (spectral); time
- **ta** : temperature ambiente
- **TBAB** : tetrabutylammonium bromide
- **TBAF** : tetrabutylammonium fluoride
- **TBAI** : tetrabutylammonium iodide
- **TBS** : *tert*-butyldimethylsilyl
- **TBDPS**: *tert*-butyldiphenylsilyl
- **TPAP** : tetrapropylammonium perruthenate
- **temp** : temperature
- **Tf** : trifluoromethanesulfonyl
- **TFA** : trifluoroacetic acid
- **TFAA** : trifluoroacetic anhydride
- **THF** : tetrahydrofuran
- **THP** : tetrahydropyran-2-yl
- **TLC** : thin layer chromatography
- **TMS** : trimethylsilyl
- **Tol** : tolyl, toluene
- **TOF** : time-of-flight
- **Ts** : *p*-toluene-sulfonyl (tosyl)
- **(p-)TsOH**: *p*-toluenesulfonic acid
- **TsCl** : *p*-toluene-sulfonyl chloride
- **UV** : ultraviolet

INTRODUCTION

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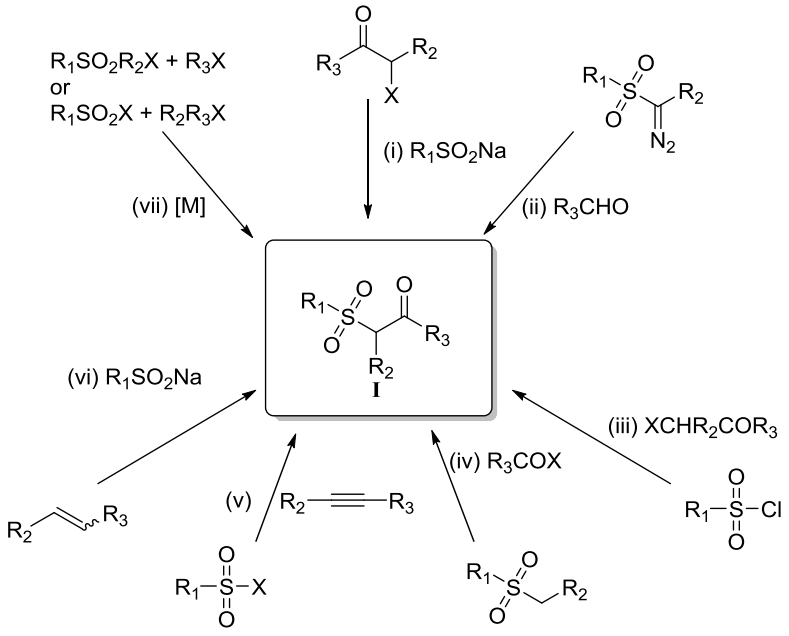
*(**NOTE**: along this Introduction and the rest of this work, only catalysts are numerated with Roman numerals (**I**, **II**, **III**…). The rest of compounds are labelled with Latin alphabet (**A**, **B**, **C**…) and these letters are independently repeated in each Scheme or Figure. In the "Results and Discussion" section, the numeration follows the same rules. Products synthesised or used in this work are named with Arabic numerals (**1**, **2**, **3**…).

This Thesis work deals with sulfonyl Nazarov reagents and their applications in organocatalysis. This type of compounds contains a β-ketosulfone unit in the structure and, for this reason, we will first review the synthesis and reactivity of such compounds.

1. Methods for the synthesis of β-ketosulfones.

β-Ketosulfones are an important class of oxygen-containing extremely versatile compounds in organic chemistry. They attract the interest of chemists due to their interesting biological properties[1] and synthetic applications on natural products[2] and organic compounds such as disubstituted acetylenes, allenes, vinylsulfones, ketones, polyfunctionalised 4*H*-pyrans, and optically active β-hydroxysulfones.[3] In light of their widespread utilities, considerable efforts have been devoted towards the synthesis of β-ketosulfones. Available routes to β-ketosulfones include **(i)** alkylation of metallic sulfur derivatives; **(ii)** reactions of diazo sulfones with aldehydes; **(iii)** arenesulfonyl chlorides and alkyl halides coupling reactions; **(iv)** acylation of alkyl sulfones; **(v)** reaction of sulfonyl derivatives with arylacetylenes; **(vi)** reaction of sodium arenesulfinates with alkenes or **(vii)** organometallic coupling chemistry (Scheme 1).



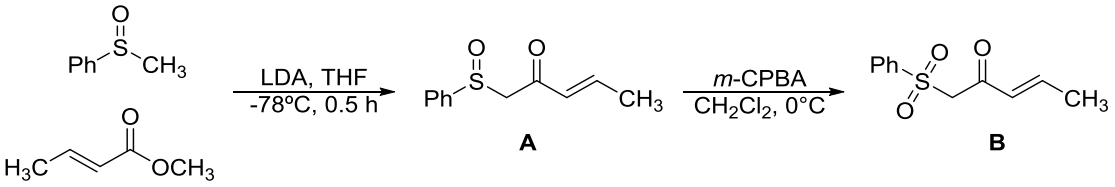
Scheme 1

Next a short revision of these synthetic methods is briefly described.

[1] Curti, C.; Laget, M.; Carle, A. O.; Gellis, A. and Vanelle, P. *Eur. J. Med. Chem.* **2007**, *42*, 880. (10.1016/j.ejmech.2006.12.015)
[2] Yang, H.; Carter, R. G. and Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238. (10.1021/ja803613w)
[3] Trost, B. M. and Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287. (10.1016/S0040-4039(01)90298-9)

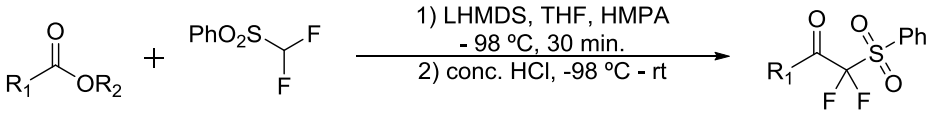
1.1. Alkylation of metallic sulfur derivatives.

β-ketosulfones were easily obtained by Deslongchamps *et al.* from methyl crotonate directly by the condensation of the anion of methylphenylsulfoxide with methyl crotonate in a 56% yield (Scheme 2). Oxidation of **A** with *m*-chloroperbenzoic acid in dichloromethane gave a 67% yield of β-ketosulfone **B**.[4]

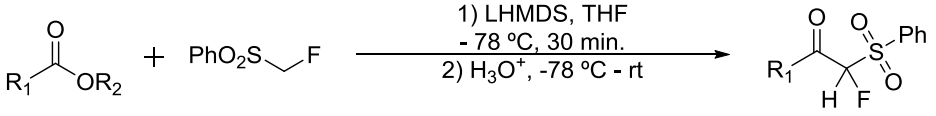


Scheme 2

The synthesis of useful building blocks fluorinated β-ketosulfones was reported by Hu *et al*. by using a nucleophilic fluoroalkylation methodology. α,α-difluoro-β-ketosulfones and α-monofluoro-β-ketosulfones were prepared in moderate to excellent yields (50 – 98%) by nucleophilic fluoroalkylation of esters and sulfinates with $PhSO_2CHF_2$ and $PhSO_2CH_2F$ in the presence of lithium hexamethyldisilazide (LHMDS) in THF (hexamethylphosphoramide, HMPA, was used as co-solvent for the synthesis of α,α-difluoro-β-ketosulfones, Scheme 3).[5]



R_1 = CH_3, C_2H_5, Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3OC_6H_4$, CH_2CH, $PhC{\equiv}C$, $COOC_2H_5$
R_2 = CH_3 or C_2H_5

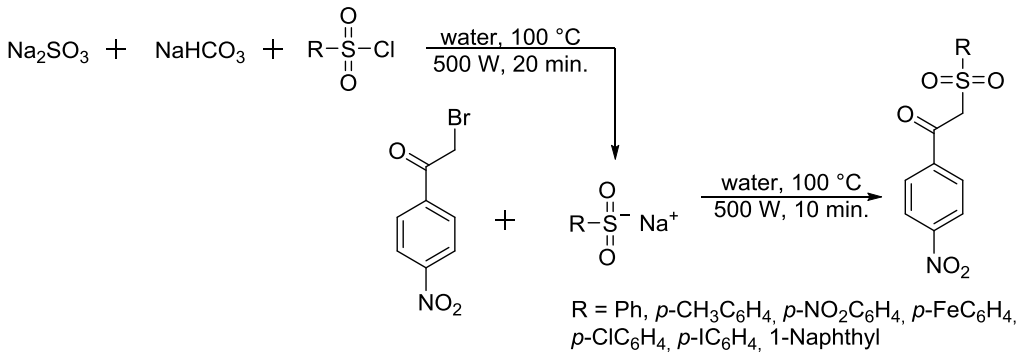


R_1 = CH_3, C_2H_5, Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3OC_6H_4$, CH_2CH, $PhC{\equiv}C$, CH_3CH_2O
R_2 = CH_3 or C_2H_5

Scheme 3

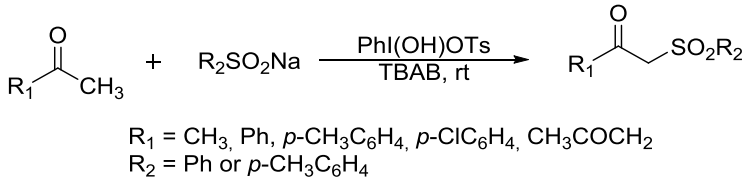
The alkylation of metallic arene sulfinates with α-halo-ketones or α-tosyloxy ketones is one of the most commonly used methods to provide β-ketosulfones. Vanelle *et al.* developed an original one-pot microwave reaction for the synthesis of sulfone derivatives used as new potent antimicrobial agents. This ecofriendly methodology conducted in 30 minutes to desired products in aqueous solutions with good yields (42 – 90%, Scheme 4).[1]

[4] Lavallée, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T. and Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406. (10.1139/v92-179)
[5] Ni, C.; Zhang, L. and Hu, J. *J. Org. Chem.* **2009**, *74*, 3767. (10.1021/jo900320b)



Scheme 4

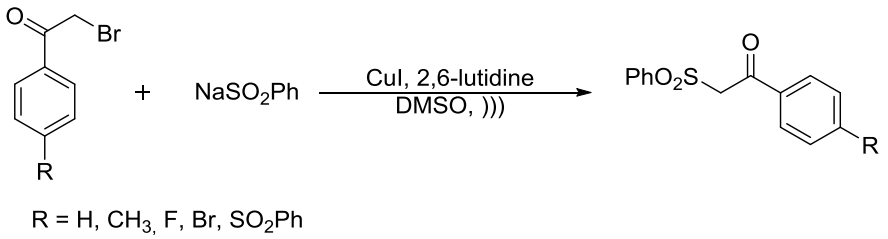
Kumar and Varma *et al.* described an easy solvent-free method for the conversion of ketones into β-ketosulfones in high yields (81 – 92%, Scheme 5) that involved the *in situ* generation of α-tosyloxyketones, followed by nucleophilic substitution with sodium arene sulfinate in the presence of tetrabutylammonium bromide and hydroxytosyliodobenzene (PhI(OH)OTs) at room temperature in short reaction times and simple work-up that precludes the use of toxic solvents.[6]



Scheme 5

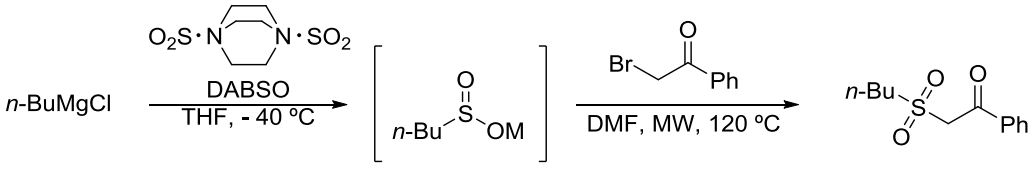
The low solubility of metal sulphinate salts in organic solvents is a common problem. The group of Venkateswarlu *et al.* has recently overcome it in two different ways. First, they reported the synthesis of β-ketosulfones by the reaction of α-haloketones with sodium alkyl/aryl sulphinates in ionic liquids possessing chiral carboxylate as reaction medium, in 5 to 10 minutes at room temperature.[7] Secondly, this group reported the same method but promoted by microwave in water in 3 to 5 minutes.[8] More recently, Jørgensen *et al.* reported the synthesis of β-ketosulfones in very good yields (90 – 95%) by reaction of α-haloketones with sodium phenylsulfinate under sonication in the presence of CuI and 2,6-lutidine in DMSO (Scheme 6).[9] These conditions were much faster and better yielding than stirring at room temperature.

[6] Kumar, D.; Sundaree, S.; Rao, V. S. and Varma, R. S. *Tetrahedron Lett.* **2006**, *47*, 4197. (10.1016/j.tetlet.2006.04.076)
[7] Suryakiran, N.; Prabhakar, P.; Rajesh, K.; Suresh, V. and Venkateswarlu, Y. *J. Mol. Catal. A: Chem.* **2007**, *270*, 201. (10.1016/j.molcata.2007.01.049)
[8] Sunitha, P.; Kumar, K. S.; Rao, B. R. and Venkateshwarlu, G. *Green Chem. Lett. Rev.* **2008**, *1*, 179. (10.1080/17518250802587873)
[9] Mady, M. F.; El-Kateb, A. A.; Zeid, I. F. and Jørgensen, K. B. *Journal of Chemistry* **2013**, 9. (10.1155/2013/364036)



Scheme 6

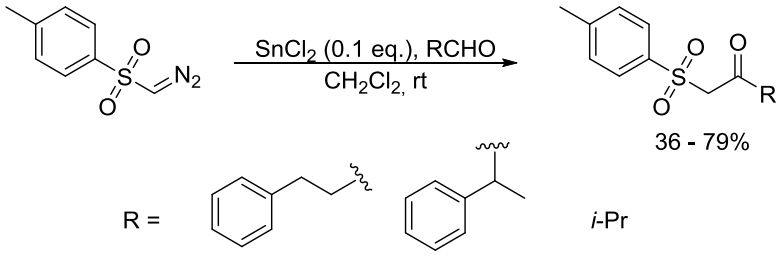
Willis *et al.* have recently developed a one-pot sulfone synthesis based on the *in situ* electrophilic trapping of metal sulfinates generated from organometallic reagents and DABSO[10] (1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct). Using this methodology, 2-*n*-butylsulfonyl-phenylethanone was synthesised in 90% yield using *n*-butyl magnesium chloride and DABSO in THF at – 40 ºC and then 2-bromo-phenylethanone as electrophile (3 equivs.) in DMF at 120 ºC using microwave heating for 3 hours (Scheme 7).[11]



Scheme 7

1.2. Reactions of diazo sulfones with aldehydes.

Roskamp *et al.* published the reaction of diazo sulfones with aldehydes in the presence of catalytic tin(II) chloride,[12] as an extension of a previous methodology which now allowed for the preparation of β-ketosulfones, β-ketophosphonates, and β-ketophosphine oxides (Scheme 8), under mild, non-basic conditions.

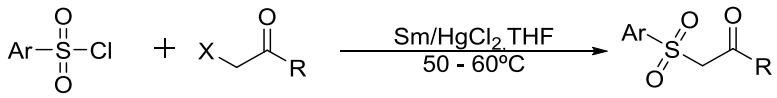


Scheme 8

[10] Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L. and Willis, M. C. *Org. Lett.* **2011**, *13*, 4876. (10.1021/ol201957n)
[11] Deeming, A. S.; Russell, C. J.; Hennessy, A. J. and Willis, M. C. *Org. Lett.* **2013**, *16*, 150. (10.1021/ol403122a)
[12] Holmquist, C. R. and Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131. (10.1016/S0040-4039(00)91877-X)

1.3. Arenesulfonyl chlorides and alkyl halides coupling reactions.

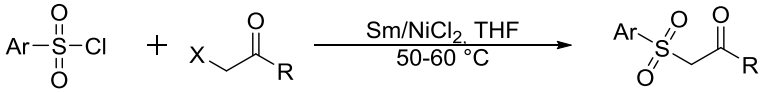
A different approach developed by Zhang *et al.* used a simple and convenient procedure with arenesulfonyl chlorides and alkyl halides in the presence of the Sm/$HgCl_2$ bimetallic system in tetrahydrofuran (Scheme 9).[13]



Ar = C_6H_5 or *p*-$CH_3C_6H_4$
XCH_2COR = $BrCH_2CO_2C_2H_5$, $BrCH_2COC_6H_5$, $BrCH_2CO$-*p*-BrC_6H_4

Scheme 9

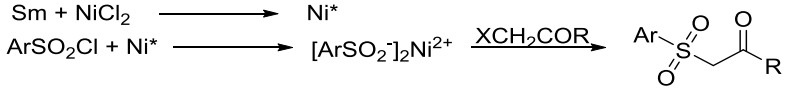
The Sm/$HgCl_2$ system mediated coupling reactions of arenesulfonyl chlorides and a number of active alkyl halides. Among them, 2-bromoacetophenone, ethyl bromoacetate and 2,4´-dibromoacetophenone proceeded smoothly to give the corresponding β-ketosulfones in good yields (57 – 73%). According to the authors, the mechanism may involve the reduction of $HgCl_2$ by metallic samarium, implicating Sm(Hg) amalgam as the promoter of the reactions. Hg and $HgCl_2$ are prohibited in industry as they are very poisonous and cause severe environmental pollution. To address this problem, Zhou and Chen *et al.* developed the Sm–$NiCl_2$ reductive system to promote the coupling reaction of aryl sulfonyl chlorides and active halides into β-ketosulfones in good yields (71 – 75%, Scheme 10).[14]



Ar = C_6H_5 or *p*-$CH_3C_6H_4$
XCH_2COR = $BrCH_2CO_2C_2H_5$ or $BrCH_2COC_6H_5$

Scheme 10

$NiCl_2$ and Ni are widely used in industry and are less poisonous. The use of Sm–$NiCl_2$ offers advantages over the Sm–$HgCl_2$ previously reported. The possible reaction mechanism of coupling of aryl sulfonyl chlorides and active halides mediated by Sm–$NiCl_2$ was explained by the authors if Sm reduces $NiCl_2$ to active Ni^*, which reacts with aryl sulfonyl chlorides to form an aryl sulfonyl anion. This anion attacks active halides to form sulfones (Scheme 11).

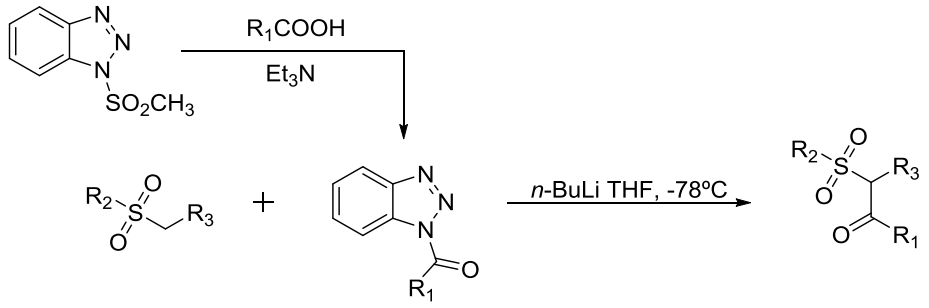


Scheme 11

[13] Zhang, J.; Zhang, J.; Zhang, Y. and Zhang, Y. *J. Chem. Res. (S)* **2001**, 516. (10.3184/030823401103168929)
[14] Ye, Y.; Zhou, Q.; Zheng, R.; Jiang, H.; Chen, R. and Zhang, Y. *Appl. Organomet. Chem.* **2011**, *25*, 331. (10.1002/aoc.1763)

1.4. Acylation of alkyl sulfones.

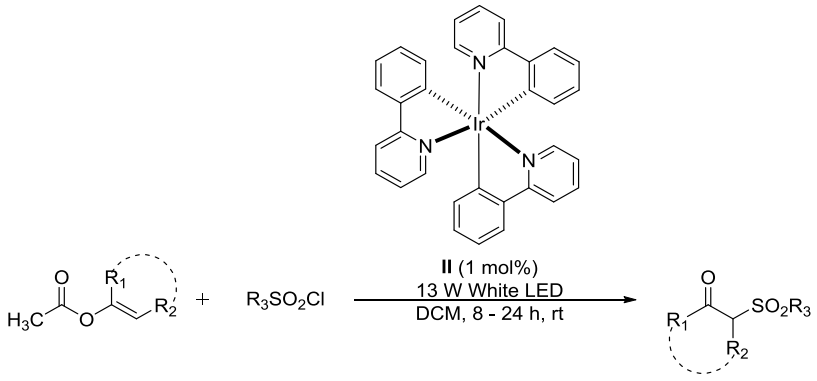
β-Ketosulfones can be prepared by the acylation of alkyl sulfones with acid chlorides, esters or *N*-acylbenzotriazoles.[15] This approach uses sulfone and *N*-acylbenzotriazole in a 1:1 ratio and affords good to excellent yields (70 – 96%, Scheme 12) thus demonstrating the potential of *N*-acylbenzotriazoles as effective C-acylation reagents, particularly when it is advantageous to use sulfone and acylating reagent in stochiometic ratio.



R_1 = Ph, *m*-ClC_6H_4, *p*-$CH_3C_6H_4$, 2-pyridinyl, 2-furyl, $(CH_3)_2CHCH_2$, 2-thienyl
R_2 = CH_3, CH_3CH_2, Ph
R_3 = H, CH_3, $CH{=}CH_2$, Ph

Scheme 12

More recently, Zhang and Yu *et al.* have reported the synthesis of β-ketosulfones by sulfonation of vinyl acetates with sulfonyl chlorides in DCM in the presence of tris[2-phenylpyridinato-C^2,*N*]iridium(III) ($Ir(ppy)_3$, **II**) using visible-light photoredox catalysis (Scheme 13).[16]



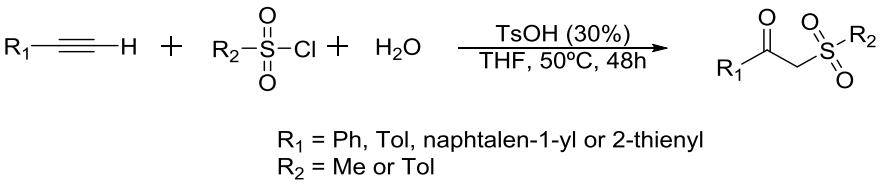
R_1 = Ph, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4
R_2 = H, CH_3 or R_1 = R_2 = -Ph-CH_2-, -Ph-$(CH_2)_3$-, -Ph-$(CH_2)_2$-
R_3 = CH_3, $(CH_2)_7CH_3$, cyclopropyl, *p*-$CH_3C_6H_4$, *o*-$CF_3C_6H_4$, *p*-$CF_3C_6H_4$, *p*-CNC_6H_4, *p*-$NO_2C_6H_4$, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-PhC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$CF_3OC_6H_4$, naphthyl, thiophen-2-yl, pyridin-3-yl

Scheme 13

[15] Katritzky, A. R.; Abdel-Fattah, A. A. A. and Wang, M. *J. Org. Chem.* **2003**, *68*, 1443. (10.1021/jo026636l)
[16] Jiang, H.; Cheng, Y.; Zhang, Y. and Yu, S. *Eur. J. Org. Chem.* **2013**, 5485. (10.1002/ejoc.201300693)

1.5. Reaction of sulfonyl derivatives with arylacetylenes.

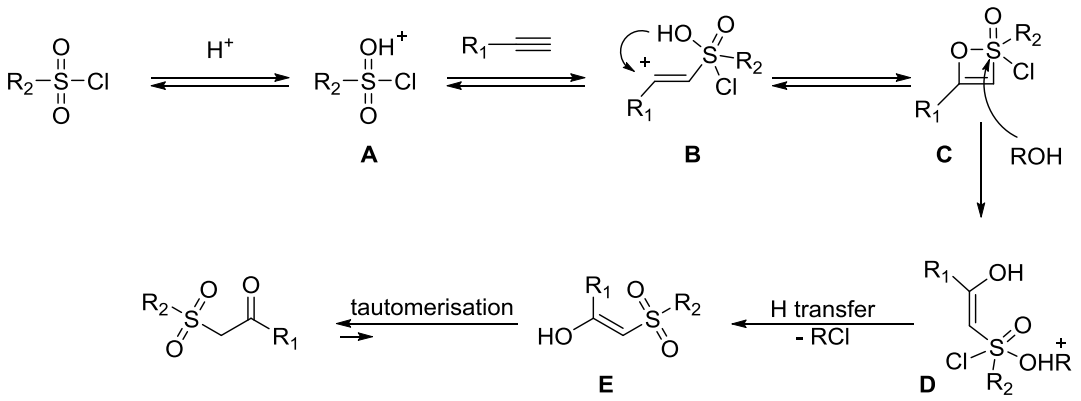
Xi *et al.* developed the reaction of sulfonyl chlorides with arylacetylenes and water in the presence of a catalytic amount of a sulfonic acid in THF to provide β-ketosulfones in good yields (49 – 55%) with excellent regioselectivity (Scheme 14).[17]



Scheme 14

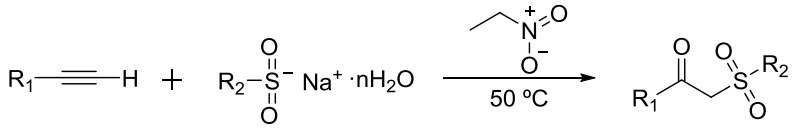
Several representative examples of sulfonic acid catalysed reactions of sulfonyl chlorides with various arylacetylenes and water afforded β-ketosulfones under these mild conditions. Using methanesulfonyl chloride (MsCl) or *p*-toluene-sulfonyl chloride (TsCl) and terminal alkynes, the regioselectivity of product was always favoring introduction of sulfone group to the terminal carbon of alkynes and the carbonyl group to the benzylic position. Besides the desired product of β-ketosulfones, corresponding vinyl sulfones were detected as side products in 10% to 20% isolated yields. When terminal aliphatic alkynes such as 1-hexyne and internal alkynes such as 1-phenyl propyne were used, only trace desired products were detected even with the increased reaction temperature and prolonged reaction time. Based on these results, the authors proposed a stepwise mechanism for the formation of β-ketosulfones (Scheme 15). The more reactive electrophile **A** is formed in the presence of a protic acid and successively attacked by arylacetylenes to produce carbocation **B**, which subsequently undergoes deprotonation to form four-membered oxathietene **C.** Then the cleavage of the O–S bond by a protic compound, such as water or alcohol, results in intermediate **D,** which undergoes *H*-transfer and elimination of HCl or RCl in sequence to give enol **E**. This produces β-ketosulfones instantly *via* tautomerism into a much stable keto form.

[17] Lai, C.; Xi, C.; Jiang, Y. and Hua, R. *Tetrahedron Lett.* **2005**, *46*, 513. (10.1016/j.tetlet.2004.10.176)



Scheme 15

A new catalyst- and additive-free protocol for the preparation of β-ketosulfones in moderate to good yields (39 – 57%, Scheme 16), using also various sodium arenesulfinates and aryl acetylenes has been recently developed by Sreedhar *et al.*[18]

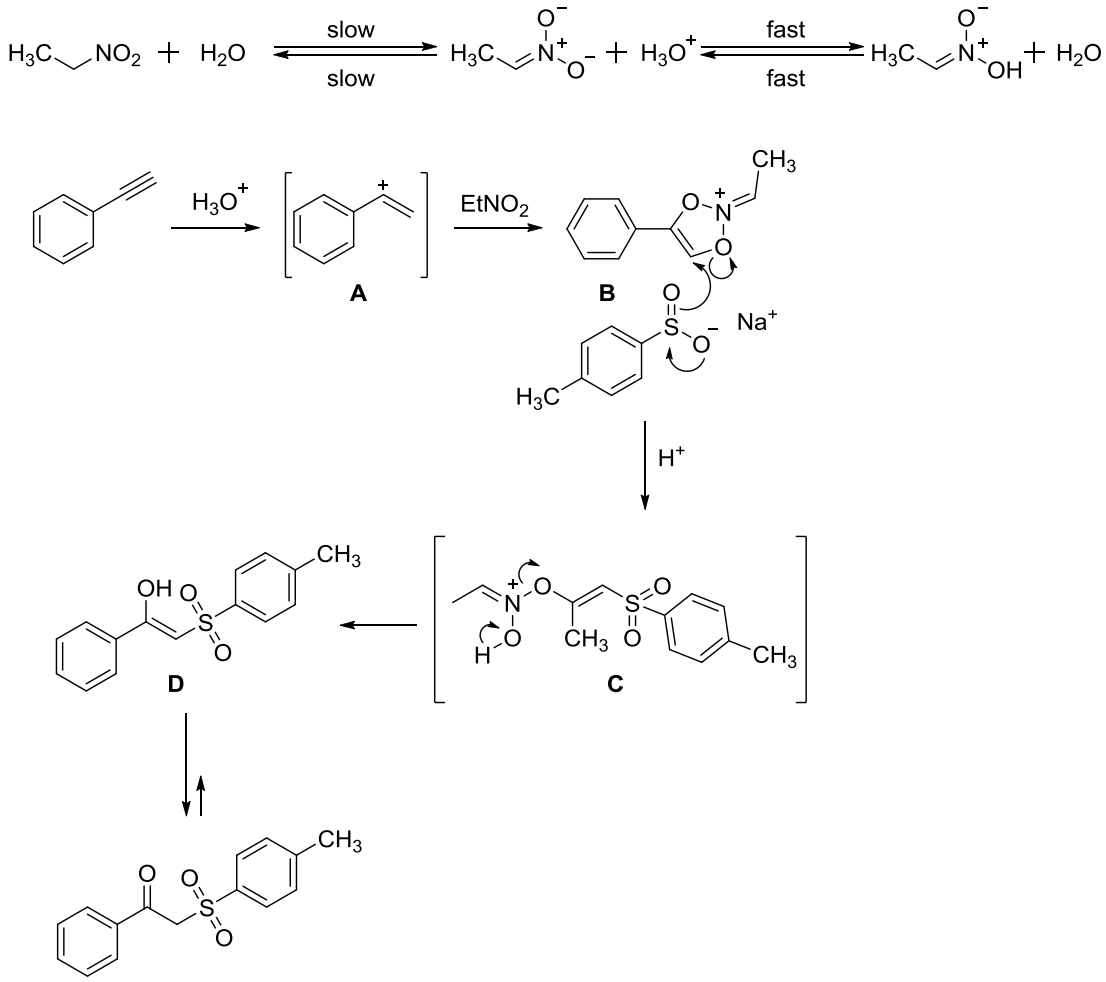


R_1 = Ph, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *m*-ClC_6H_4, *p*-$CH_3OC_6H_4$, 6-methoxynaphthalen-2-yl
R_2 = Ph or *p*-$CH_3C_6H_4$

Scheme 16

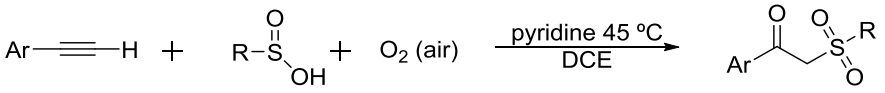
The authors proposed a plausible mechanism based on the C–H acidity of nitroalkanes and their prototropy to give nitronic acids as well as the electrophilic addition of C–H acids such as nitroalkanes to acetylenic systems and their subsequent rearrangement to α-substituted ketones (Scheme 17). Hence, protonation of the terminal carbon of the acetylene generates a vinyl cationic species **A** which reacts with nitroethane leading to the formation of vinyl nitronic ester **B**. Nucleophilic addition of sulfonyl anion on **B** generates an intermediate **C** which after nitrosoethane elimination and protonation forms enol **D** which subsequently tautomerises to the more stable keto form.

[18] Sreedhar, B. and Rawat, V. S. *Synlett* **2012**, 413. (10.1055/s-0031-1290318)



Scheme 17

Very recently, Lei *et al.* reported an aerobic oxidative difunctionalisation of alkynes towards β-ketosulfones in the presence of 4 equivalents of pyridine in dichloroethane (DCE) in moderate to good yields (34 – 88%, Scheme 18).[19] It is an environmentally oxygen-triggered oxidative radical process using oxygen as the only oxidant, and offers a sustainable radical method for highly selective synthesis of valuable β-ketosulfones, allowing a wide range of functional-groups tolerance.

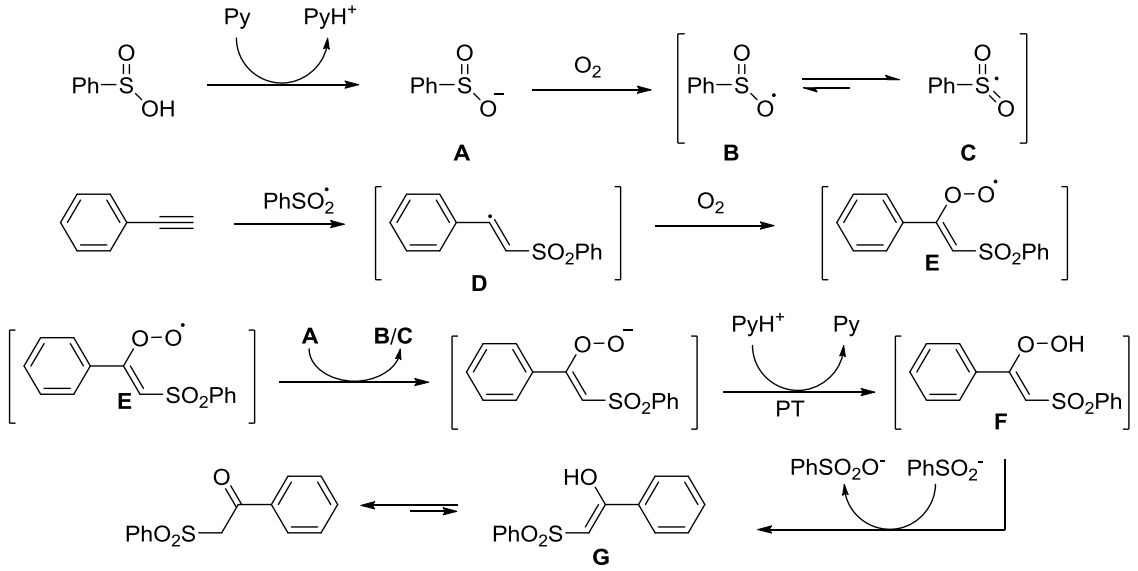


Ar = Ph, *o*-$CH_3OC_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *p*-$C_6H_4C_6H_4$, *p*-BrC_6H_4, *p*-IC_6H_4, *p*-ClC_6H_4, *o*-FC_6H_4, *p*-AcC_6H_4, *p*-$CH_3OCOC_6H_4$, 2-thienyl
R = Ph, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, 2-naphtyl, *n*-octyl

Scheme 18

[19] Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H. and Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (10.1021/ja4052685)

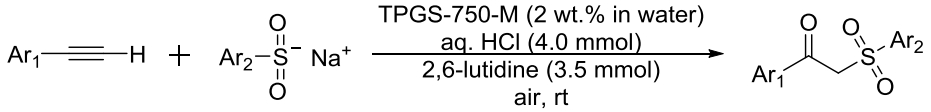
According to the authors, preliminary mechanism revealed that a radical process is involved, and pyridine not only acts as a base to successfully suppress ATRA (atom transfer radical addition) process, but also plays vital role in reducing the activity of sulfinic acids. Initially, benzenesulfinic acid is quickly transformed into sulfinyl anion **A** in the presence of pyridine (Scheme 19). Subsequently, the pathway is triggered by the autoxidation of **A** with dioxygen *via* single electron transfer (SET) process, affording an oxygencentered radical **B** which could resonate with sulfonyl radical **C**. Thereafter, sulfonyl radical addition to alkynes produces the reactive vinyl radical **D**, which could be trapped by dioxygen to form intermediate **E**. Afterward, the intermediate **E** goes through SET and proton transfer (PT) process successively with **A** and pyridinium, generating **B**/**C** and affording peroxide **F**. Finally, **F** undergoes subsequent reduction by benzenesulfinic acid, produces **G**, which isomerises and furnishes final β-ketosulfone.



Scheme 19

More recently, Lipshutz *et al*. have depeloped an environmentally friendly aerobic oxidation for converting arylalkynes and arylsulfinate salts to β-ketosulfones in good yields (62 – 84%) using a polyoxyethanyl-α-tocopheryl succinate derivative (TPGS-750-M, Scheme 20).[20] This process relies on the far greater solubility of oxygen in hydrocarbon media as found within micellar arrays than in the surrounding water. The process, enabled by a commercially available designer surfactant, is metal-free, takes place in water at room temperature using air as the oxidant, and is amenable to recycling of the aqueous reaction medium in which the amphiphile remains.

[20] Handa, S.; Fennewald, J. C. and Lipshutz, B. H. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 3432. (10.1002/anie.201310634)

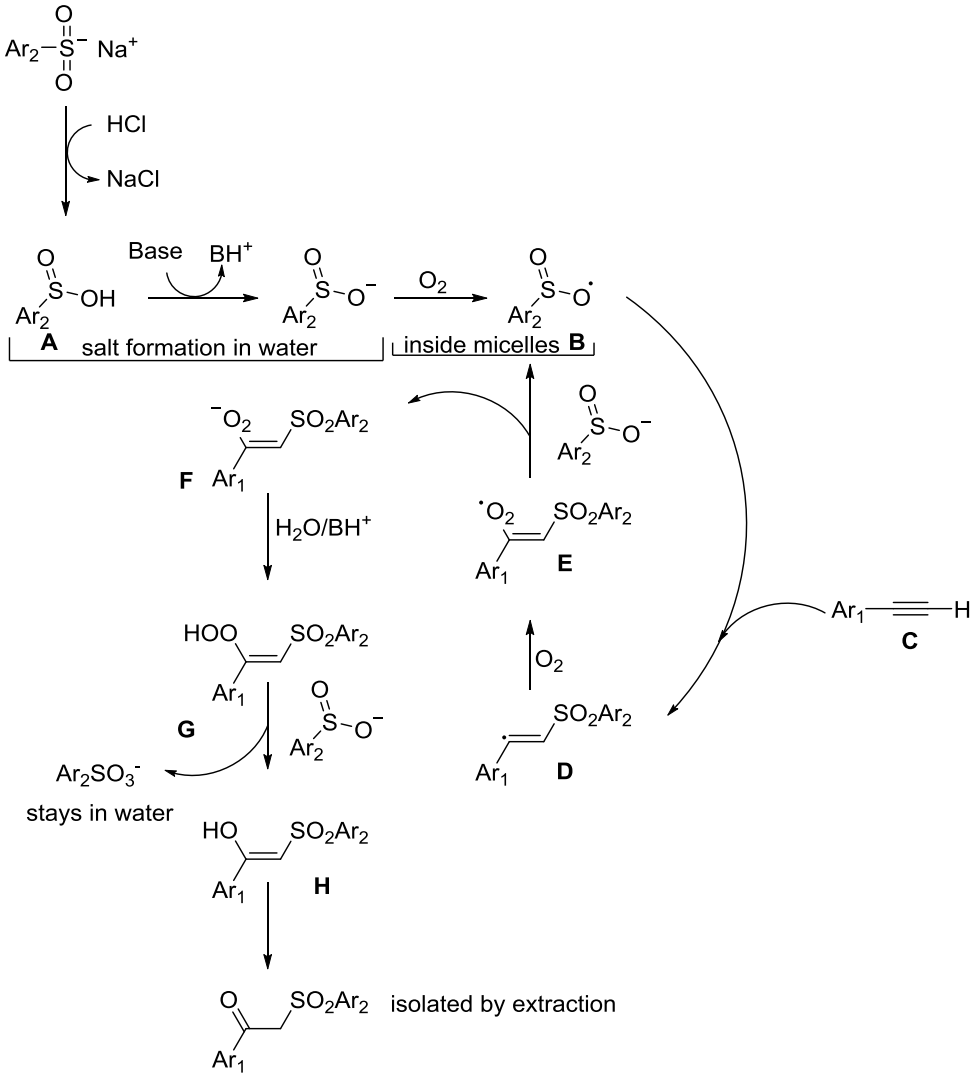


Ar_1 = Ph, *p*-$CH_3OC_6H_4$, 3,5-$(CH_3)_2C_6H_3$, benzo[*b*]thiophen-3-yl, *m*-CNC_6H_4, *p*-BrC_6H_4, *p*-$CH_3(CO)C_6H_4$, *m*-$C{\equiv}CC_6H_4$, *p*-PhC_6H_4, *o*-$CH_3C_6H_4$

Ar_2 = Ph or *p*-$CH_3C_6H_4$

Scheme 20

The mechanism proposed by the authors is depicted in Scheme 21.



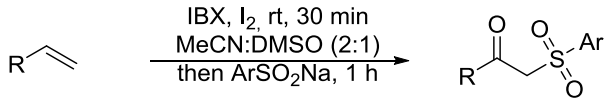
Scheme 21

The overall sequence starts from *in situ* generation of free arylsulfinic acid **A** from its sodium salt and HCl. No aerobic oxidation reaction occurs without this initial neutralisation, followed by exposure to 2,6-lutidine as base. Thus, generation of sulfonyl radical **B** requires a lutidinium salt under ambient

light, rather than the corresponding sodium salt. An aryl sulfonyl radical is then generated after single electron transfer (SET) to oxygen that is highly localised within the micelle. Radical **B** then adds to arylacetylene **C** to give vinyl radical **D** which is then trapped by oxygen to generate intermediate **E**. SET from another molecule of arylsufinate to **E** generates arylperoxide anion **F**. The newly generated arylsulfonyl radical enters the next cycle, while **F** undergoes protonation either by water or a pyridinium cation to form arylhydroperoxide species **G**. Oxidation of arylsulfinate to arylsulfonate generates enol **H** that tautomerises to final β-ketosulfone. The arylsulfonic acid generated as a byproduct remains in the aqueous phase, while the organic product can be isolated by extraction.

1.6. Reaction of sodium arenesulfinates with alkenes.

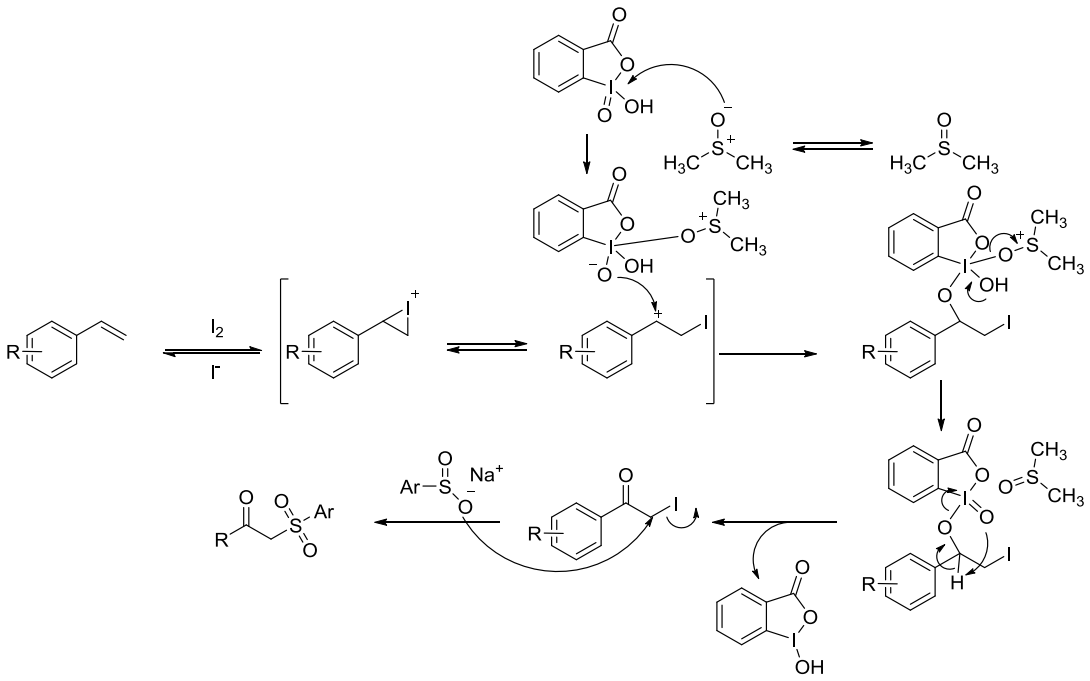
A direct synthesis of β-ketosulfones from alkenes consisting on a combination of *o*-iodoxybenzoic acid/iodine (IBX/I_2) was found by Kuhakarn *et al.* to mediate the reactions of alkenes with arenesulfinates to yield β-ketosulfones in good yields (35 – 81%) *via* a one-pot reaction (Scheme 22).[21]



R = Ph, *p*-BrC_6H_4, *o*-ClC_6H_4, *p*-ClC_6H_4, *m*-ClC_6H_4, *p*-FC_6H_4, *m*-$NO_2C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$ClCH_2C_6H_4$, *m*-$CHOC_6H_4$, *p*-$AcOC_6H_4$, *p*-$CH_3OC_6H_4$, $CH_3(CH_2)_5$, $C_6H_5O(CH_2)_3$
Ar = Ph or *p*-$CH_3C_6H_4$

Scheme 22

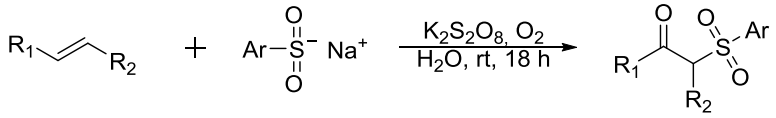
The mechanistic pathway for ketoiodination mediated by a combination of *o*-iodoxybenzoic acid/iodine was assumed by the authors based on recent work by Donohoe *et al*. proposed is depicted in Scheme 23.[22]



Scheme 23

[21] Samakkanad, N.; Katrun, P.; Techajaroonjit, T.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D. and Kuhakarn, C. *Synthesis* **2012**, 1693. (10.1055/s-0031-1290952)
[22] Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H. and Smith, I. E. D. *Org. Biomol. Chem.* **2012**, *10*, 1093. (10.1039/C1OB06587D)

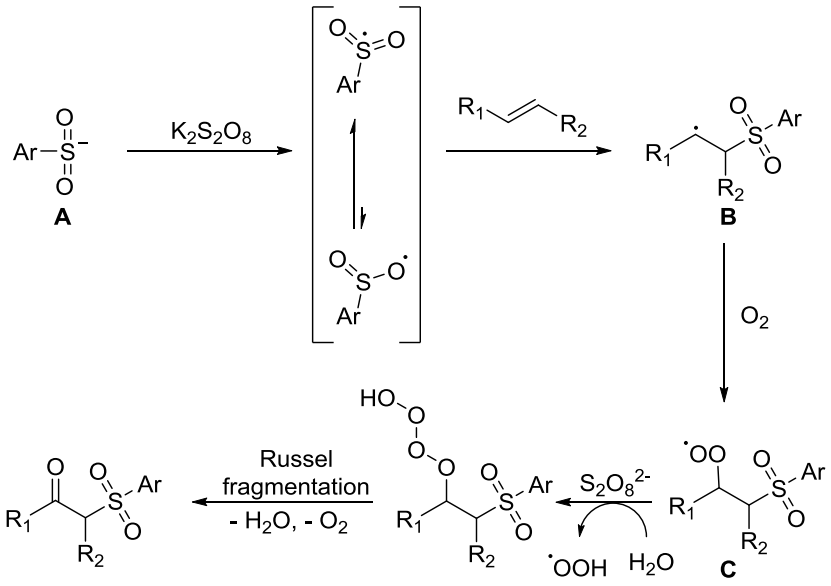
More recently Yadav *et al.* found a very mild and ecofriendly protocol for the synthesis of β-ketosulfones in good to very good yields (73 – 94%) directly from olefins by employing sodium arenesulfinates through $K_2S_2O_8$-mediated aerobic oxysulfonylation in aqueous media at room temperature (Scheme 24).[23] The formation of new C=O and C–S bonds takes place through a radical pathway in a one-pot procedure.



R_1 = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-NCC_6H_4, *p*-$CH_3OC_6H_4$, *o*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *o*-$CH_3C_6H_4$, 2-napthyl
R_2 = H, or CH_3
Ar = Ph, *p*-Tol, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$CH_3OC_6H_4$, 2-naphtyl

Scheme 24

The mechanism proposed by the authors is depicted in Scheme 25.



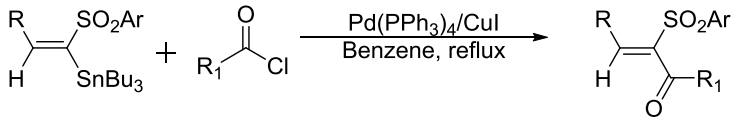
Scheme 25

The $K_2S_2O_8$-mediated formation of a sulfonyl radical takes place from the sulfinate anion **A**. This radical attacks the double bond of the olefin to furnish carbon-centred radical **B**, which is ultimately captured by oxygen to form oxygen-centred radical **C**, which in the presence of sodium sulfinate in aqueous media affords β-ketosulfone *via* Russel fragmentation.[24]

[23] Chawla, R.; Singh, A. K. and Yadav, L. D. S. *Eur. J. Org. Chem.* **2014**, 2032. (10.1002/ejoc.201301833)
[24] Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 3871. (10.1021/ja01571a068)

1.7. Organometallic coupling chemistry

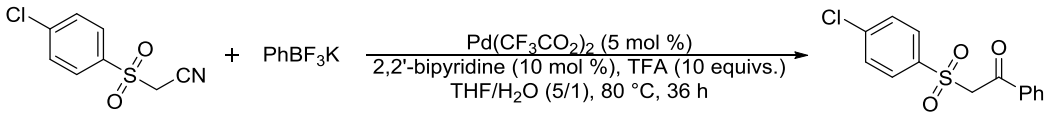
Organometallic coupling chemistry has also been used for the sytnesis of β-ketosulfones. Hence, Cai *et al.* developed stereoselective one-pot method for the synthesis of *Z*-α-arylsulfonyl-α,β-unsaturated-β´-ketones by the tandem hydrostannylation-Stille coupling reactions of acetylenic sulfones with tributyltin hydride and acyl chlorides in good yields (78 – 87%).[25]



R = *n*-Butyl or Ph
Ar = Ph or *p*-$CH_3OC_6H_4$
R_1 = Ph, *p*-$NO_2OC_6H_4$, *p*-$ClOC_6H_4$, *p*-$CH_3OC_6H_4$

Scheme 26

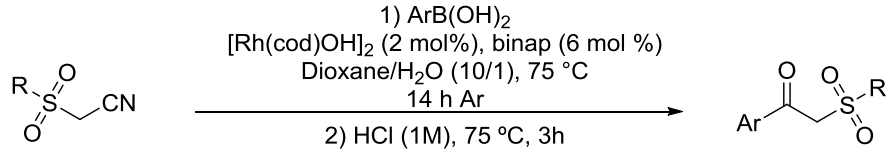
More recently, Chen and Wu *et al.* developed a palladium-catalysed addition reaction of potassium aryltrifluoroborates with aliphatic nitriles to afford a variety of alkyl aryl ketones. Among them, 2-*p*-chlorophenylsulfonyl-phenylethanone was prepared in 98% yield using 2-*p*-chlorophenylsulfonylacetonitrile and potassium phenyltrifluoroborate in the presence of $Pd(CF_3CO_2)_2$, 2,2'-bipyridine and TFA in THF/H_2O at 80 °C (Scheme 27).[26]



Scheme 27

A rhodium(I)-catalysed addition of arylboronic acids to (benzyl/arylsulfonyl) acetonitriles in a dioxane/H_2O (10/1) mixture at 75 ºC was developed by Lautens *et al.*[27] In this way novel β-sulfonylvinylamine products were synthesised in a stereoselective fashion (*Z*-alkene) which, upon hydrolysis with HCl at 75 ºC, formed β-ketosulfone products with a broad scope of aryl and sulfonyl substituent groups in very good yields (83 – 99%, Scheme 28).

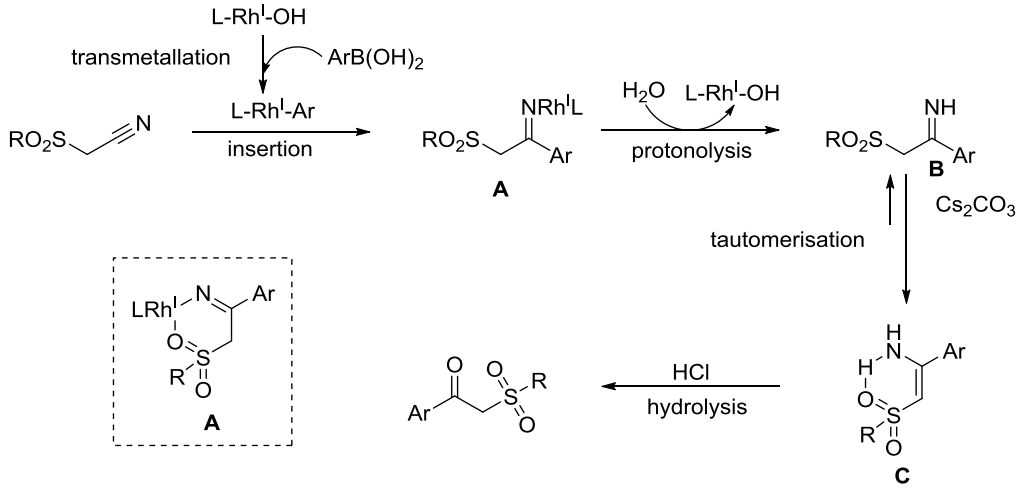
[25] You, S.; Li, J. and Cai, M. *Tetrahedron* **2009**, *65*, 6863. (10.1016/j.tet.2009.06.072)
[26] Wang, X.; Liu, M.; Xu, L.; Wang, Q.; Chen, J.; Ding, J. and Wu, H. *J. Org. Chem.* **2013**, *78*, 5273. (10.1021/jo400433m)
[27] Tsui, G. C.; Glenadel, Q.; Lau, C. and Lautens, M. *Org. Lett.* **2010**, *13*, 208. (10.1021/ol102598p)



R = Ph, *p*-$CF_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-FC_6H_4, *m*-$CH_3OC_6H_4$, *o*-$CH_3C_6H_4$, 1-naphthyl, Bn
Ar = Ph, *p*-AcC_6H_4, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *p*-$CH_3SC_6H_4$, *m*-AcC_6H_4, *m*-$CH_3OC_6H_4$, *o*-$CH_3C_6H_4$, 1-naphthyl or 3-thienyl

Scheme 28

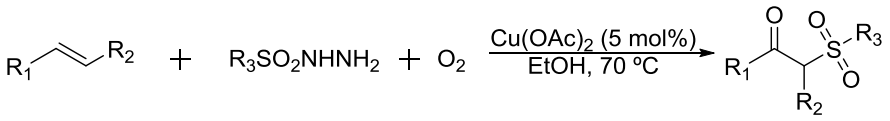
In the mechanism proposed by the authors, a rhodium-aryl species is generated from transmetalation between rhodium hydroxide and arylboronic acid. The insertion of the nitrile group into rhodium-aryl bond leads to imino-rhodium species **A**. The sulfone oxygen may coordinate to the rhodium to form a stabilised six-membered rhodacycle. Protonolysis regenerates the rhodium catalyst and forms imine product **B**. In the presence of a base, the imine product quickly tautomerises to form the more favored enamine product **C**. The driving force and *Z*-alkene selectivity are likely due to a stabilising intramolecular hydrogen bonding between the amine and sulfone groups. Sterics between the sulfonyl and aryl groups may also play a role in the *Z*-selectivity. The presence of an R-proton in **C** is necessary for the enamine formation, but an R,R-disubstituted substrate should at least lead to the imine formation, which would give the ketone product upon hydrolysis. Instead, the authors observed no reactions with these substrates. Significantly increased steric demands of the R,R-disubstituted substrates may have hindered the insertion process. Finally, product **C** was isolated or hydrolysed to afford β-ketosulfone.



Scheme 29

Despite of all these methods, most of them suffer from some limitations such as the need for multistep processes to prepare starting materials, relatively complicated or harsh reaction conditions, and undesired byproducts. Therefore, there is still a great demand for the development of more mild,

convenient and, especially, green and sustainable approaches to produce β-ketosulfones. Wang et al. recently developed an unprecedented copper-catalysed direct oxysulfonylation of alkenes with dioxygen and sulfonylhydrazides to access β-ketosulfones in moderate to good yields (50 – 72%, Scheme 30).[28]

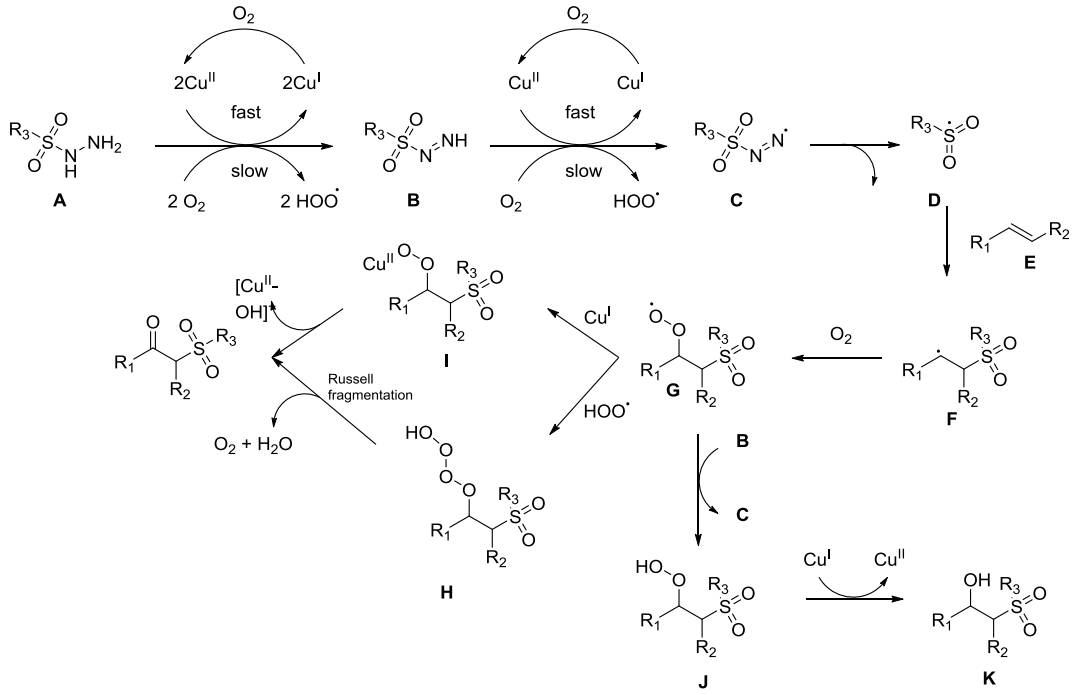


R_1 = Ph, *o*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$ClCH_2OC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-CNC_6H_4, 2-naphthyl
R_2 = H or CH_3
R_3 = Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4

Scheme 30

Isotope labeling and radical capture experiments suggested that the carbonyl oxygen atom of β-ketosulfones originated from O_2 and a radical pathway might be involved (Scheme 31). Initially, the sulfonyl radical **7** and HOO· species were generated from **2** and oxygen with the release of N_2 *via* single electron transfer and the deprotonation process. The transformations occurred faster when high oxidation-value metal salts such as Cu(II) species were employed. Then, the sulfonyl radical **B** selectively added to alkene **C** leading to alkyl radical **D**, which interacted with O_2 to afford peroxy radical **E**. Finally, **E** coupled with the HOO· species to form a monoalkyl tetroxide **F**, which decomposed to give β-ketosulfone**,** along with the generation of oxygen and water *via* Russell fragmentation. In contrast, β-ketosulfone can also formed *via* intermediate **G** followed by the elimination of $[Cu^{II}\text{-}OH]^+$ due to the low concentration of the hydroperoxide radical in the Cu-catalytic system. The side product **K** might be produced by the reduction of the hydroperoxide **J**, which was generated from **G** *via* the abstraction of an H atom from the strong H-donor.

[28] Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y. and Wang, H. *Chem. Commun.* **2013**, *49*, 10239. (10.1039/C3CC45803B)


O2
2CuII
2CuI
fast
slow
2 O2
2 HOO•
A
B
CuII
CuI
O2
HOO•
C
D
E
F
G
I
[CuII-OH]
Russell fragmentation
O2 + H2O
H
J
K
B
C
CuI
CuII

Scheme 31

2. Reactivity of β-ketosulfones.

This section will be focused on the β-ketosulfone system **I** and hence it will be classified in main chapters, namely:

(1) Reactivity of β-ketosulfones at positions 1 and 2 (Figure 1).

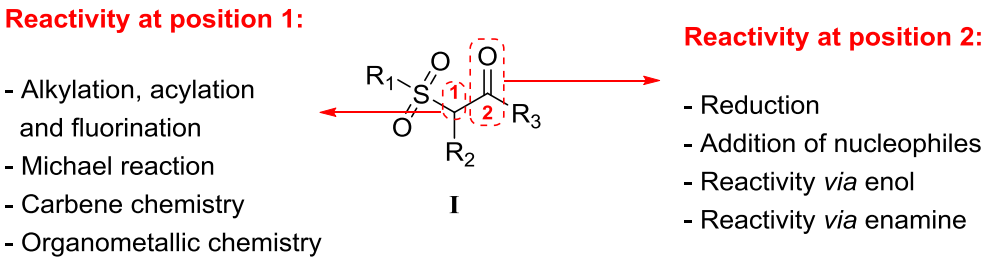


Figure 1

(2) Reactivity of α-alkyliden- and α-cyclopropyl/cyclopropenyl-β-ketosulfones (Figure 2, **A** and **B**/**C**), subdividing this chapter depending on whether these compounds are synthesised and used as starting materials or if they are generated *in situ* during the reaction.

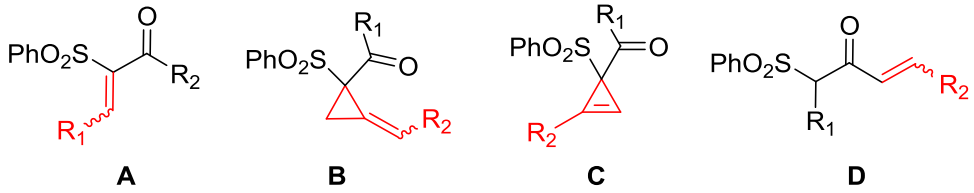


Figure 2

(3) Reactivity of γ-alkyliden-β-ketosulfones (Figure 2, **D**).

(4) Desulfonylation and other reactivity of β-ketosulfones.

2.1. Reactivity of β-ketosulfones at positions 1 and 2.

Reactivity of β-ketosulfones is mainly held at positions 1 and 2, *i.e.*, the CH_2 or CH in α to the sulfone group, and the carbonyl group. First, reactivity at position 1 will be examined and divided in the following sections: (1) alkylation, acylation and fluorination, (2) Michael reaction, (3) carbene chemistry and (4) organometallic chemistry. Reactivity of the carbonyl group at position 2 will be reviewed afterwards according to the next sections: (1) reduction (by hydrogenation, by reaction with hydrides or by biological reductions), (2) adittion of nucleophiles, (3) reactivity *via* enol (for the synthesis of furanyl derivatives) and (4) reactivity *via* enamine (for the synthesis of pyrrole and pyridine derivatives).

2.1.i Reactivity at position 1.

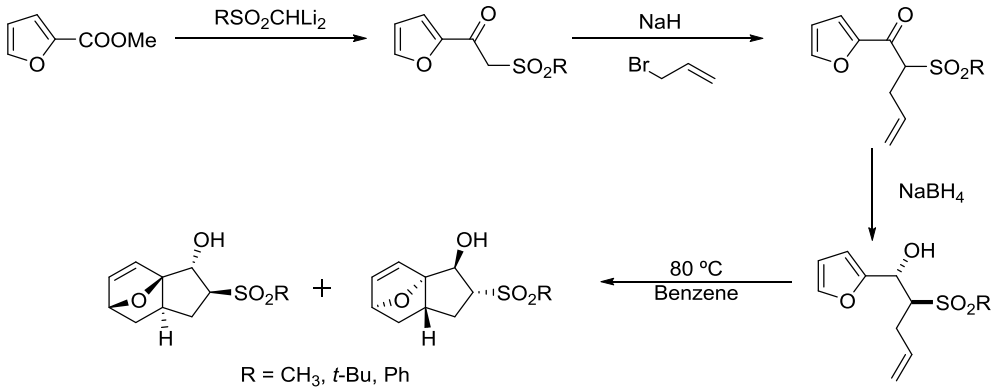
β-Ketosulfones react at position 1 mainly as nucleophile due to the acidity presented by the CH_2 or CH group between withdrawing groups, the sulfone and the carbonyl. In most cases an external base or a catalyst (either metallic or organic) is needed to promote this reactivity. This section will be divided into four main sections, namely: (i) alkylation, acylation and fluorination; (ii) Michael reaction; (iii) carbene chemistry; and (iv) organometallic chemistry.

2.1.i.1. Alkylation, acylation and fluorination.

This reactivity can be promoted just by using a simple Brönsted base as sodium hydride (NaH), triethylamine (Et_3N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Lewis bases as magnesium oxide (MgO) or aluminium oxide (Al_2O_3), however, for the synthesis of enantioenriched products, other systems are preferred, mainly using metallic or organic catalysts.

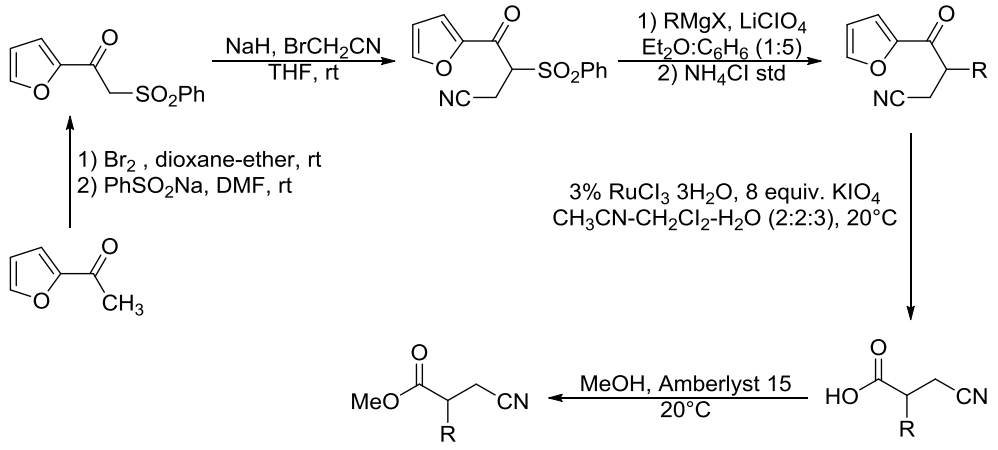
Sternbach *et al.* used the alkylation of a metallic sulfonate to prepare their β-ketosulfones which, after treatment with NaH and allyl bromide and reduction of the ketone group with sodium borohydride ($NaBH_4$) afforded the starting materials for their Diels-Alder studies (Scheme 32).[29] The nucleophilic addition did also take place with methyl *p*-bromocrotonate. Moreover, other furan derivatives with alkoxy groups were also studied in successful Diels-Alder reactions.

[29] McNelis, B. J.; Sternbach, D. D. and MacPhail, A. T. *Tetrahedron* **1994**, *50*, 6767. (10.1016/S0040-4020(01)81331-4)



Scheme 32

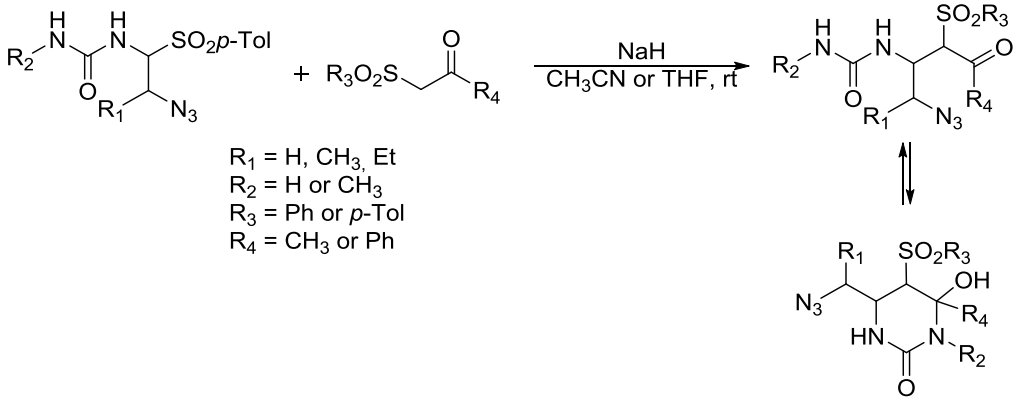
Petrini *et al.* used the same method to prepare their phenylsulfonylfurylketo-butanenitrile derivatives. In this case the β-ketosulfone was used to introduce the nitrile group. Next the sulfone group was substituted with a Grignard reagent in order to study the behaviour towards the oxidation with ruthenium tetroxide. It was observed for the first time that the carbon skeleton of the furan ring was completely removed under these oxidative conditions, affording the corresponding 2-alkyl-3-cyanopropanoic acids (Scheme 33).[30]



Scheme 33

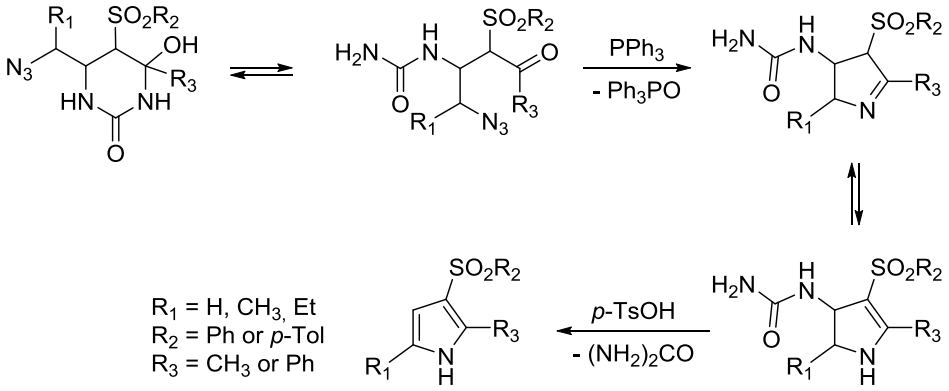
Shutalev *et al*. developed a three-step protocol for the preparation of γ-azido-β-ureido ketones bearing arylsulfonyl-substituents at the α-position to the carbonyl group and their cyclic isomers, 6-(1-azidoalkyl)-4-hydroxyhexahydropyrimidin-2-ones, in moderate to excellent yields (60 – 98%) involving amidoalkylation of β-ketosulfones with *N*-[(2-azido-1-tosyl)alkyl]ureas using NaH in CH_3CN or THF at room temperature (Scheme 34).[31]

[30] Giovannini, R. and Petrini, M. *Tetrahedron Lett.* **1997**, *38*, 3781. (10.1016/S0040-4039(97)00734-X)
[31] Fesenko, A. A. and Shutalev, A. D. *J. Org. Chem.* **2012**, *78*, 1190. (10.1021/jo302724y)



Scheme 34

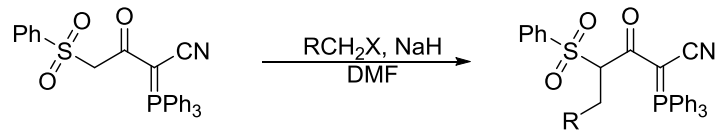
The obtained γ-azido-β-ureidoketones and their cyclic isomers were transformed into ureido-substituted Δ^1- and Δ^2-pyrrolines *via* intramolecular Staudinger/aza-Wittig reaction promoted by PPh_3.[32] The pyrrolines readily eliminated urea under acidic conditions to give 3-functionalised 1*H*-pyrroles (Scheme 35). The latter was prepared using one-pot procedures starting from *N*-[(2-azido-1-tosyl)alkyl]ureas or γ-azido-β-ureido ketones.



Scheme 35

More recently, Lee *et al.* have reported the alkylation of α-keto-β-phenylsulfonyl(cyanomethylene)triphenylphosphorane ylides (prepared, following the procedure reported by Wasserman *et al.*,[33] from phenylsulfonyl-acetic acid and cyanomethylene-triphenylphosphorane, in the presence of EDC/DMAP) in good to very good yields (79–88%) by condensation of phenylsulfonyl α-keto- (cyanomethylene)triphenylphosphorane ylide with various alkyl halides using NaH in DMF (Scheme 36).[34]

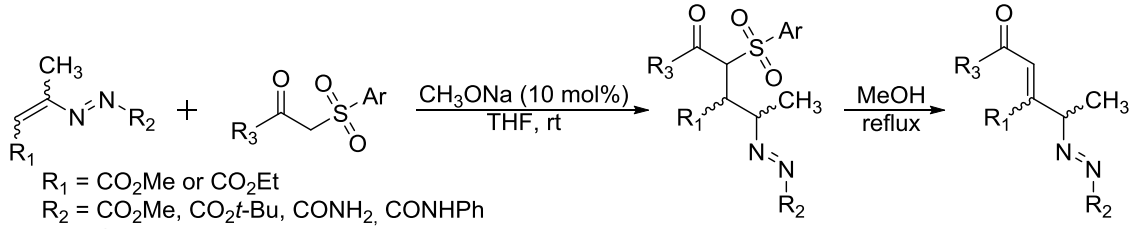
[32] van Kalkeren, H. A.; te Grotenhuis, C.; Haasjes, F. S.; Hommersom, C. A.; Rutjes, F. P. J. T. and van Delft, F. L. *Eur. J. Org. Chem.* **2013**, 7059. (10.1002/ejoc.201300585)
[33] Wasserman, H. H. and Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364. (10.1021/jo00095a005)
[34] Lee, K. and Hwang, C.-Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 2953. (10.5012/bkcs.2013.34.10.2953)



RCH_2X = $PhCH_2Br$, *o*-CH_3PhCH_2Br, $CH_3(CH_2)_6CH_2Br$, $Ph(CH_2)_2CH_2Br$, $PhCH{=}CHCH_2Br$, 2-thiophenCH_2Br, (tetrahydro-2*H*-pyran-2-yloxy)CH_2CH_2I, (1,3-dioxan-2-yl)CH_2CH_2I, (1,3-dioxan-2-yl)CH_2I

Scheme 36

Attanasi *et al.* reported the synthesis of α,β-olefinated hydrazone derivatives in moderate to very good yields (41 – 93%, although *EE*/*EZ* mixtures were observed) by addition of β-ketosulfones to conjugated azoalkenes in the presence of sodium methoxide in catalytic amount (Scheme 37).[35]

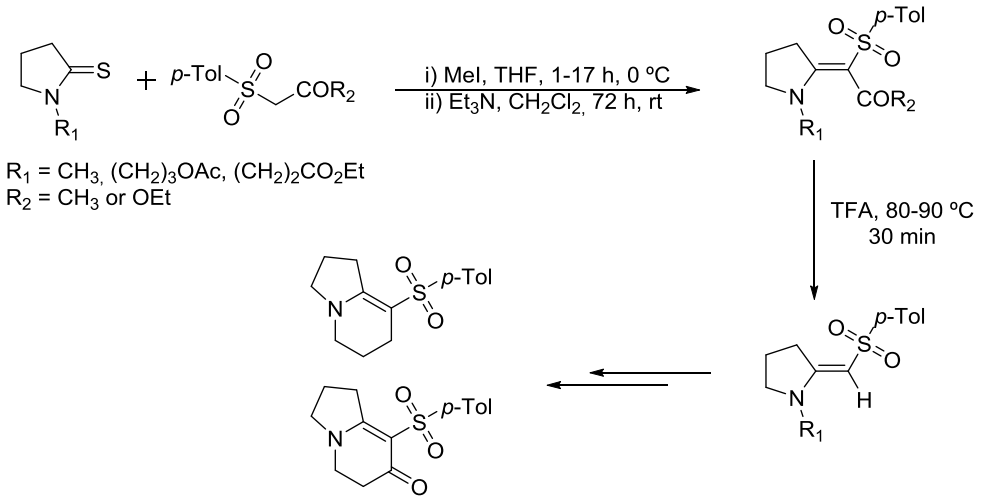


R_1 = CO_2Me or CO_2Et
R_2 = CO_2Me, CO_2t-Bu, $CONH_2$, CONHPh
R_3 = CH_3 or NH_2
Ar = Ph, *p*-CH_3Ph, *p*-ClPh

Scheme 37

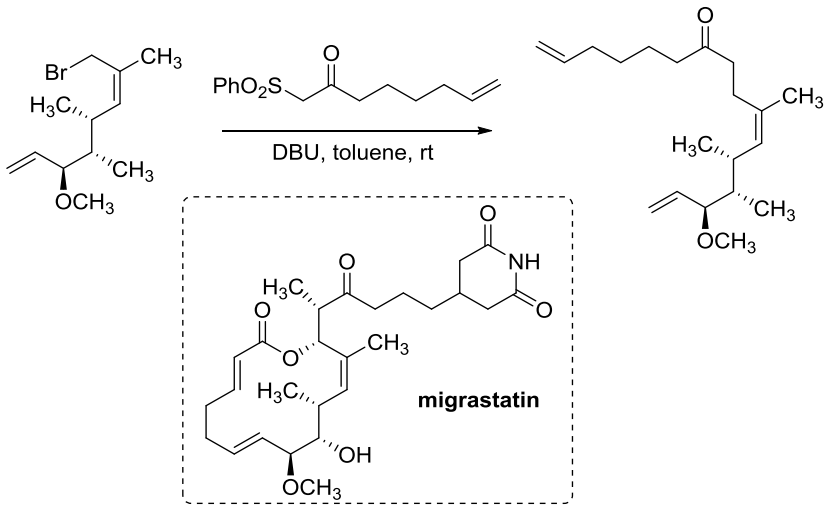
Lewis bases as Et_3N, piperidine or DBU have also been used to promote the nucleophilic addition of β-ketosulfones. For instance, Michael *et al.* demonstrated that condensation between the methiodide salts of alkylpyrrolidine-2-thiones and β-ketosulfones afforded several pyrrolidines in very good yields (85 – 95%). These β-sulfonyl enamines were sufficiently nucleophilic for cyclisation with internal electrophiles to give sulfone-substituted indolizines, potentially useful scaffolds for alkaloid synthesis (Scheme 38).[36]

[35] Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Gatti, G.; Mantellini, F. and Santeusanio, S. *Tetrahedron* **1998**, *54*, 7581. (10.1016/S0040-4020(98)00392-5)
[36] Michael, J. P.; de Koning, C. B.; Malefetse, T. J. and Yillah, I. *Org. Biomol. Chem.* **2004**, *2*, 3510. (10.1039/B413379J)



Scheme 38

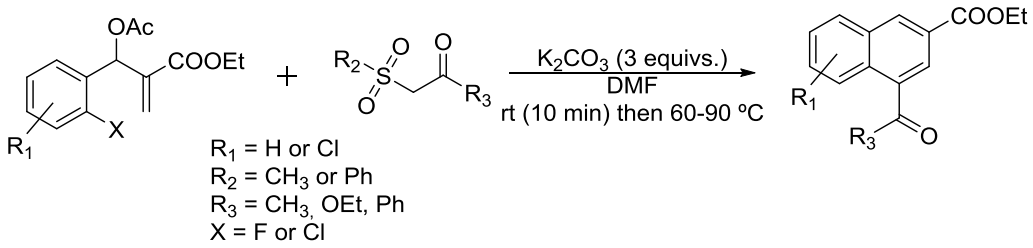
Danishefsky *et al.* used the β-ketosulfone structure to add an eight-carbon chain to an allylic bromide system, using DBU in toluene at room temperature, for the synthesis of a macroketone structurally simplified relative to migrastatin with promising anti-metastatic properties (Scheme 39).[37]



Scheme 39

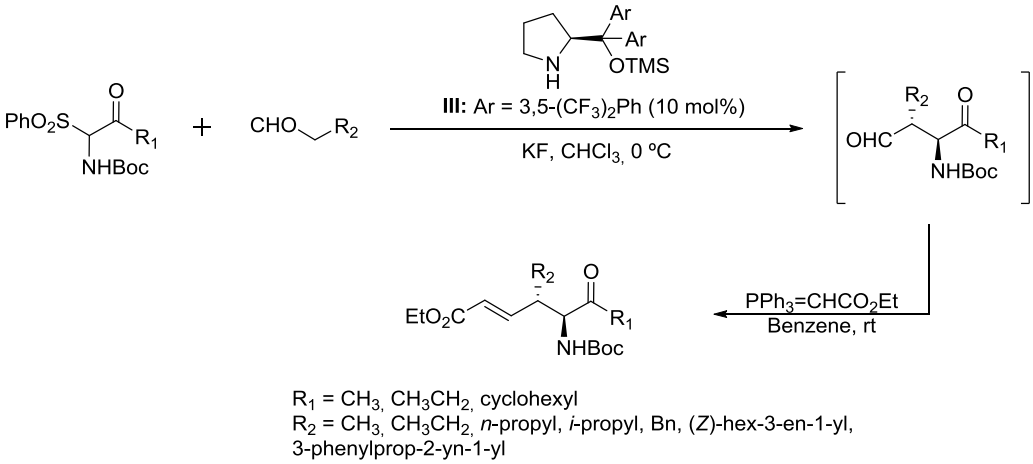
Reducing the use of hazardous solvents and reagents is always one of the most important challenges in the effort to minimise pollution and risks associated with the production of chemicals. In this way, Kim *et al.* synthetised a variety of 1,3-disubstituted naphtalenes in low to very good yields (23 – 92%) in a one-pot reaction of Baylis-Hillman acetates and β-ketosulfones using K_2CO_3 (3 equivs.) in DMF at 60-90 ºC (Scheme 40).[38]

[37] Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D.; Tong, W. P.; Huang, X.-Y.; Moore, M. A. S. and Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326. (10.1021/ja048779q)
[38] Im, Y. J.; Chung, Y. M.; Chung, Y. M. and Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 787. (10.5012/bkcs.2002.23.6.787)



Scheme 40

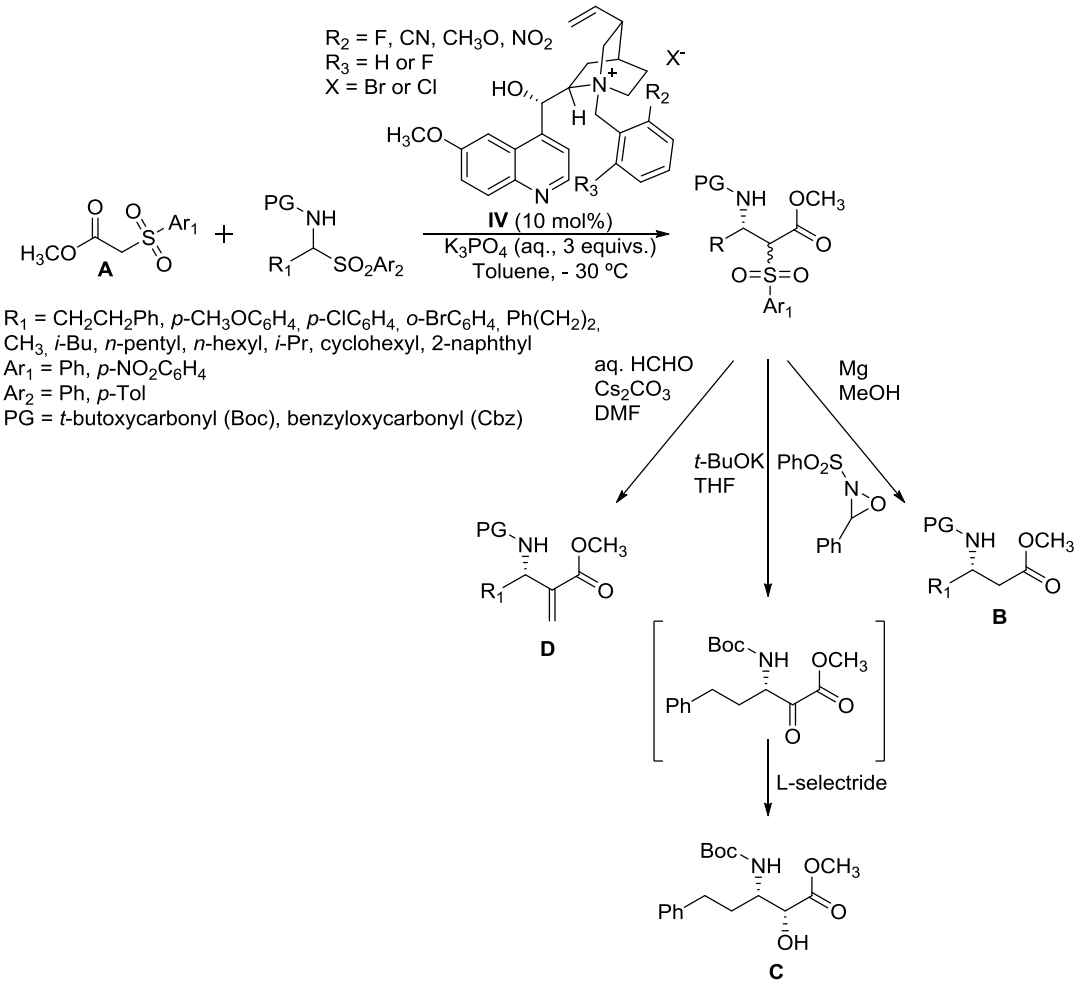
Hayashi *et al.* developed the asymmetric alkylation of α-imino-β-ketosulfones with aldehydes, in the presence of a proline derivative organocatalyst **III**, *via* Mannich reaction and consecutive sulfone elimination. Mannich products were converted to the corresponding α,β-unsaturated ester by treatment with ethoxycarbonylmethylidene triphenylphosphorane to be isolated and characterised due to partial epimerisation observed in the intermediate aldehydes obtained (Scheme 41).[39]



Scheme 41

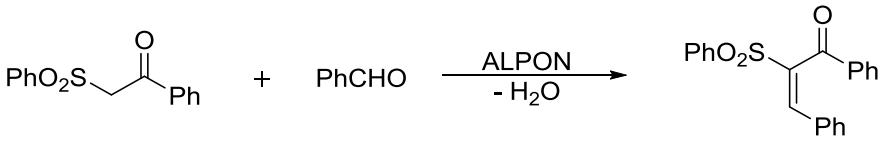
Besides proline-like organocatalysts, many others have been studied for the asymmetric alkylation of β-ketosulfones. In this manner, Bernardi and Ricci *et al*. used arylsulfonylacetates **A** in an enantioselective Mannich addition to *N*-carbamoyl imines in the presence of catalyst **IV** for the first time. Reductive removal of the sulfonyl group of the Mannich adducts gave a range of β^3-aminoester derivatives **B** through a two-step procedure. Similarly, an oxidative desulfonylation furnished a β-amino-α-hydroxyester **C**, whereas a Julia-type olefination provided access to aza-Morita-Baylis-Hillman (MBH) products **D**, enabling the use of highly unstable imines through their generation *in situ* (Scheme 42).[40]

[39] Hayashi, Y.; Sakamoto, D.; Shomura, H. and Hashizume, D. *Chem. Eur. J.* **2013**, *19*, 7678. (10.1002/chem.201300513)
[40] Cassani, C.; Bernardi, L.; Fini, F. and Ricci, A. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5694. (10.1002/anie.200900701)



Scheme 42

Corma *et al.* developed a clean process for the Knoevenagel condensation of phenylsulfonylacetophenone with benzaldehyde in low yield (20%) using aluminophosphates oxynitrides (ALPON) type materials as active and selective catalysts for this reaction (Scheme 43).[41]

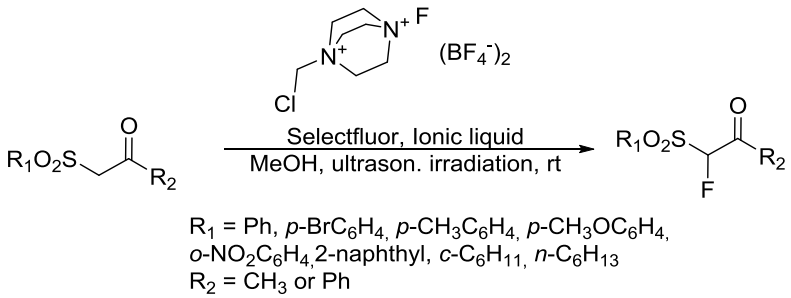


Scheme 43

Different synthetic approaches to α-fluoro-β-ketosulfones have been developed since these compounds are very useful building blocks and have been used in many synthesis steps (*vide infra*). Hence, fluorination of β-ketosulfones to produce α-fluro-β-ketosulfones was improved by Heravi *et al.* using Selectfluor™ and promoted by ionic liquids as a reaction medium with methanol as co-solvent at room temperature under ultrasonic irradiation to afford the corresponding mono and difluoro-β-ketosulfones

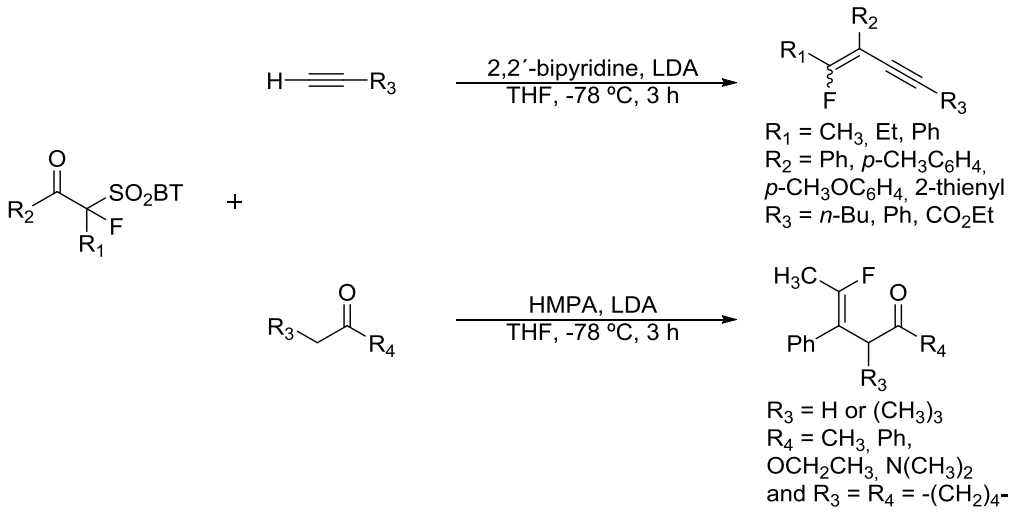
[41] Climent, M. J.; Corma, A.; Guil-Lopez, R.; Iborra, S. and Primo, J. *Catal. Lett.* **1999**, *59*, 33. (10.1023/A:1019075227734)

in moderate to excellent yields (40 – 98%). The advantages of this method include among others the use of a recyclable, non-volatile ionic liquid, which promotes this protocol without the requirement of any added catalyst (Scheme 44).[42]



Scheme 44

Liu *et al*. have also used Selectfluor™ for the preparation of α-fluoro-β-carbonyl benzothiazol-2-yl sulfones in good to very good yields (65 – 91%). These substrates were eventually used in an olefination reaction with various nucleophiles affording a series of tetrasubstituted fluoroalkenes (Scheme 45).[43]

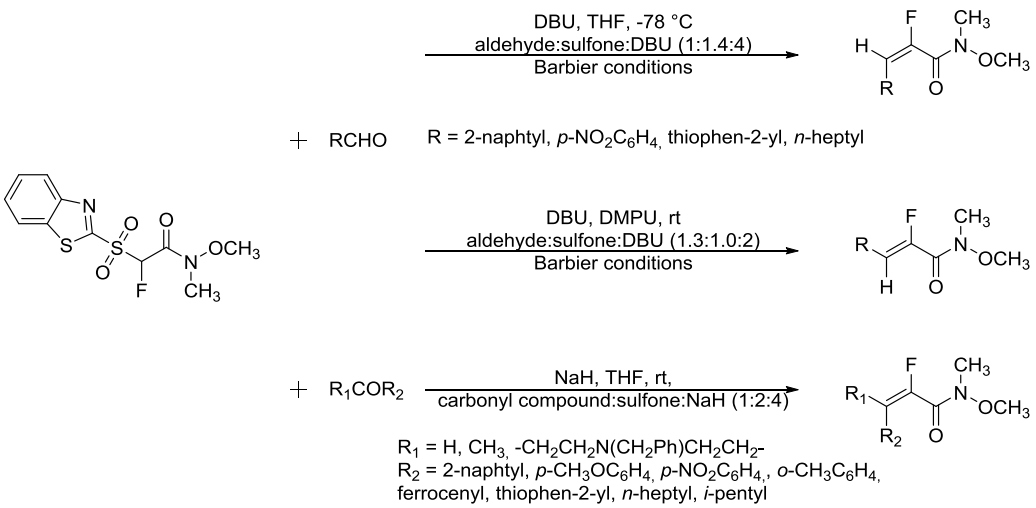


Scheme 45

The mono and difluorination of β-ketosulfones has been recently achieved by Rozen *et al.* in good to excellent yields (70 – 100%) using acetyl hypofluorite (AcOF, made from diluted fluorine and AcONa) and bases such as K_2CO_3 or *t*-BuOk in *t*-BuOH or MeOH/H_2O mixtures at room temperature. Mono or difluorination could be controlled by the number of equivalents of base and AcOF used in the reaction.[44]

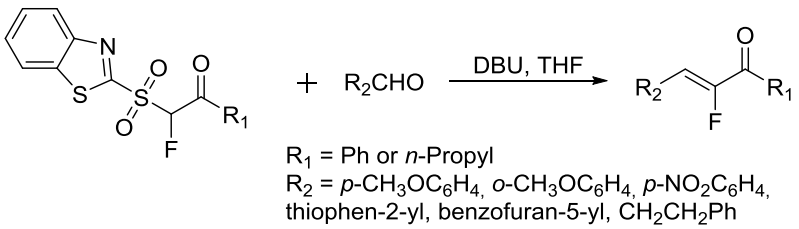
[42] Heravi, M. R. P. *Chin. Chem. Lett.* **2010**, *21*, 1399. (10.1016/j.cclet.2010.06.030)
[43] Cao, C. R.; Ou, S.; Jiang, M. and Liu, J. T. *Org. Biomol. Chem.* **2014**, *12*, 467. (10.1039/c3ob42093k)
[44] Vints, I.; Gatenyo, J. and Rozen, S. *J. Fluorine Chem.* **2013**, *146*, 66. (10.1016/j.jfluchem.2013.01.003)

Zajc *et al.* reported the synthesis of *N*-methoxy-*N*-methyl-(1,3-benzothiazol-2-ylsulfonyl)fluoroacetamide using a α-fluoro-βketosulfone in a 46% yield after 4 steps. The reactivity of this reagent was studied with aldehydes and cyclic ketones to give α-fluorovinyl Weinreb amides (Scheme 46). DBU-mediated reactions, performed under Barbier conditions,[45] proceeded with either *E*-selectivity at lower temperatures and nonpolar solvents or *Z*-selectivity with higher temperatures and polar solvents, as well as with NaH (proceeding with >98% *Z*-selectivity).[46]



Scheme 46

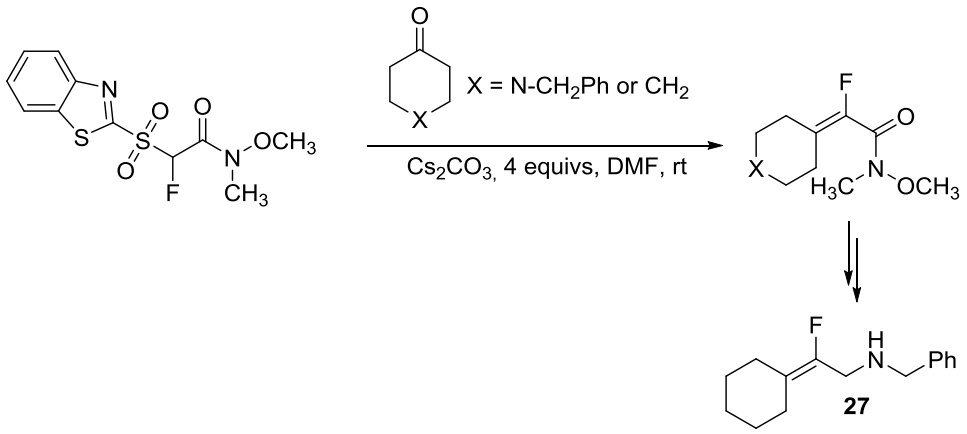
Furthermore, this group synthesised a second set of Julia reagents, namely (1,3-benzothiazol-2-ylsulfonyl)fluoromethyl phenyl and *n*-propyl ketone, which were tested for the synthesis of α-fluoro-α,β-enones by reaction with aldehydes in the presence of DBU in THF at different temperatures. Only the *Z*-isomer was observed in all cases (61 – 90% yield, Scheme 47).



Scheme 47

This group used this methodology to synthesise α-fluoro allyl amines carrying out the synthesis of α-fluoro allyl amine which presents inhibitory activity toward *dipeptidyl peptidase II* (Scheme 48).[47]

[45] Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (10.1039/B208078H)
[46] Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B. and Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689. (10.1021/jo802784w)
[47] Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A. and Augustyns, K. *J. Med. Chem.* **2004**, *48*, 1768. (10.1021/jm0495982)



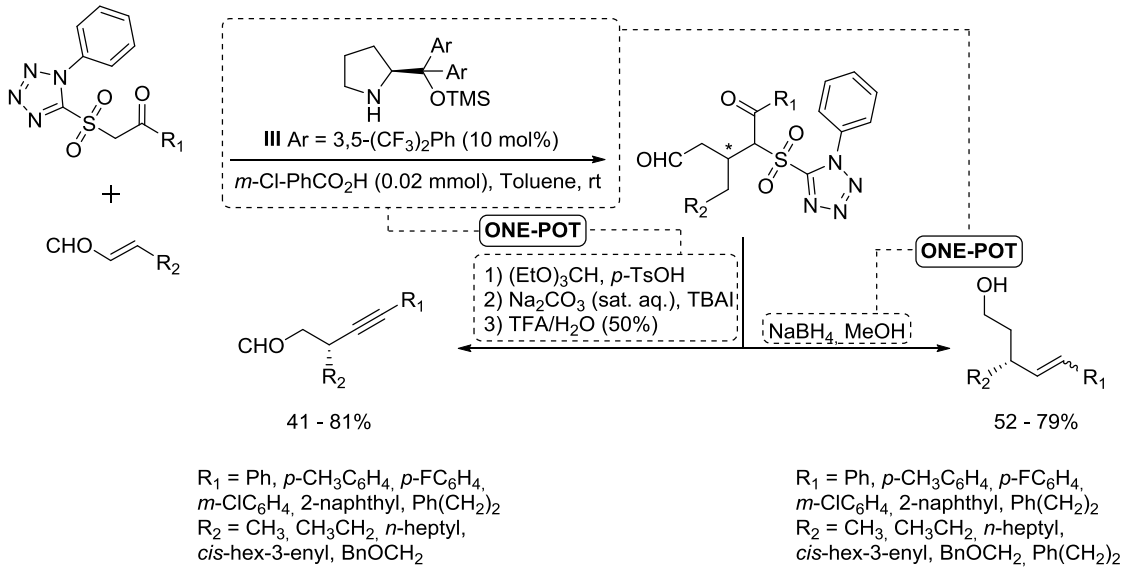
Scheme 48

For more examples regarding the use of α-fluoro-β-ketosulfones see Scheme 54, Scheme 93 or Scheme 94 (pages 61 and 83).

2.1.i.2. Michael reaction.

The development of asymmetric organocalytic approaches towards synthetically valuable target molecules has evolved into a highly credited area. Recently, the synthetic value of employing sulfones in asymmetric organocatalysis has been demonstrated, giving access to highly important enantioenriched compounds.[48,49] Jørgensen *et al.* have realised a deep work on this area, for instance, they developed a highly stereoselective organocatalytic one-pot protocol for the formal alkynylation and alkenylation of α,β-unsaturated aldehydes. Key step was a Michael addition of β-keto-heterocyclic sulfones used as donors for the alkyne and alkene functionalities in α,β-unsaturated aldehydes**,** permitting a broad range of aromatic and alkyl substituents in moderate to good yields and with enantioselectivities up to 97% ee (Scheme 49).[50]

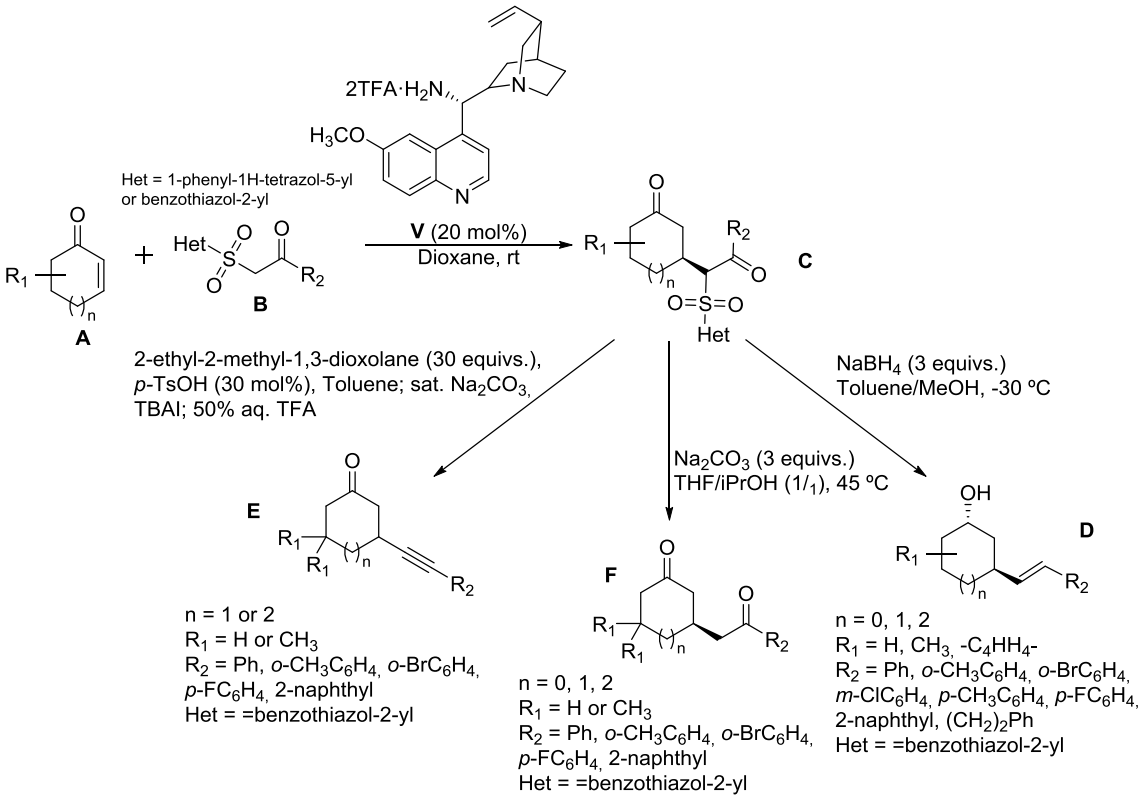
[48] Alba, A.-N. R.; Companyo, X. and Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018. (10.1039/B911852G)
[49] Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W. and Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 2668. (10.1002/anie.200906340)
[50] Nielsen, M.; Jacobsen, C. B.; Paixão, M. r. W.; Holub, N. and Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 10581. (10.1021/ja903920j)



Scheme 49

Expanding the scope of the Michael reaction with respect to the nucleophilic species, this group reported the first highly enantioselective formal alkynylation, alkenylation, and homo-ketonylation by conjugate addition of β-keto-heterocyclic sulfones **B** to cyclic α,β-unsaturated ketones **A**, catalysed by the 9-*epi*-amino cinchona alkaloid salt **V**. Applying β-ketosulfone **B** as a reaction partner lead to intermediate **C**, which could be easily transformed into the corresponding *trans*-3-alkenyl cyclohexanols **D**, β-alkynylketones **E**, or ketone products **F**, depending on the applied reaction conditions (Scheme 50).[51]

[51] Paixão, M. W.; Holub, N.; Vila, C.; Nielsen, M. and Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 7338. (10.1002/anie.200903790)

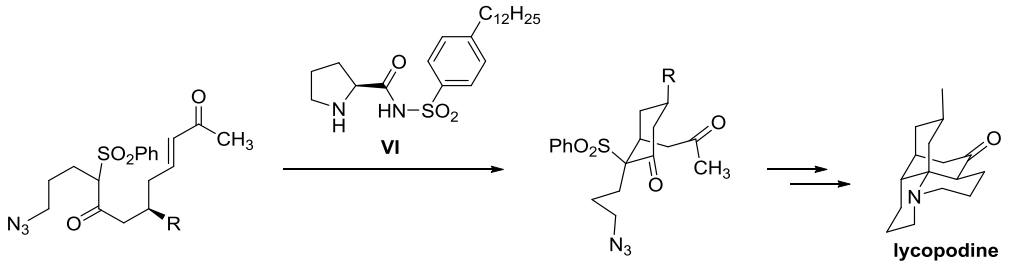


Scheme 50

Later this group optimised the synthesis of β-carbonyl phenyltetrazolesulfones up to a 99% yield. Moreover, all these β-carbonyl phenyltetrazoles were found to be reactive in the organocatalytic addition to pentenal, demonstrating again the broad applicability of this reaction.[52]

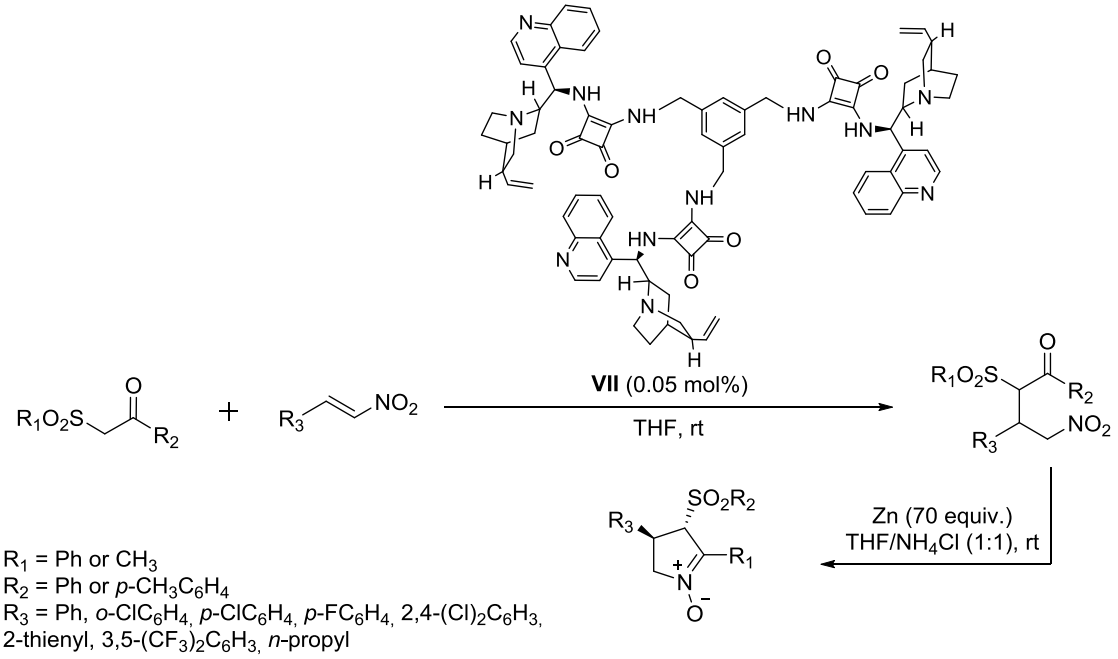
Carter *et al.* developed the first enantioselective synthesis of lycopodine (in 2008, they reported a preliminary account of this)[2] including as key steps an organocatalysed, intramolecular Michael addition of a β-ketosulfone and a tandem 1,3-sulfonyl shift/intramolecular Mannich reaction and, additionally, a novel proline-based sulfonamide organocatalyst **VI**. This study first started with diisopropylamine (*i*-Pr_2NH) as base for the non-chiral intramolecular Michael addition, which would be later optimised for the enantioselective version (Scheme 51).[53] Advancing in the use of this strategy this group accomplished the first total syntheses of three related members of the lycopodine subfamily.[54]

[52] Zweifel, T.; Nielsen, M.; Overgaard, J.; Jacobsen, C. B. and Jørgensen, K. A. *Eur. J. Org. Chem.* **2011**, 47. (10.1002/ejoc.201001426)
[53] Yang, H. and Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929. (10.1021/jo100916x)
[54] Saha, M. and Carter, R. G. *Org. Lett.* **2013**, *15*, 736. (10.1021/ol303272w)



Scheme 51

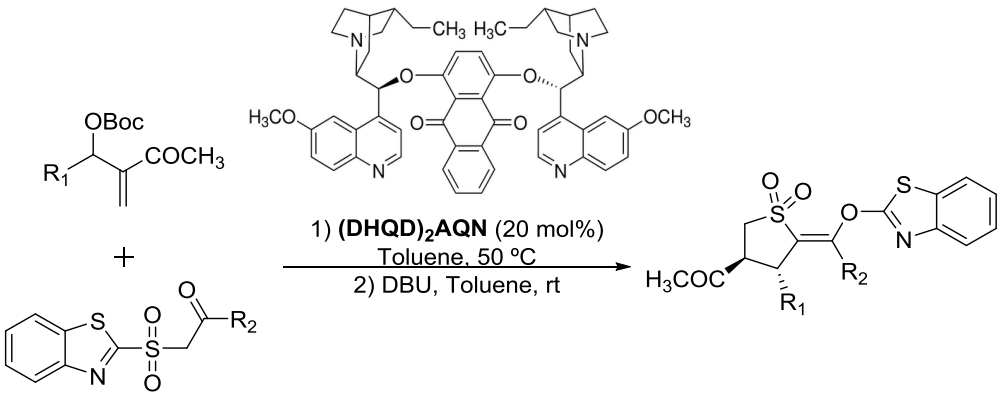
Dong *et al.* identified a cinchonine-squaramide **VII** as the best catalyst for the asymmetric Michael addition of β-ketosulfones to nitroalkenes, eventually leading to chiral cyclic nitrones in good yields (50 – 85%) and excellent enantioselectivities (Scheme 52).[55]



Scheme 52

The group of Chen *et al.* investigated the asymmetric allylic alkylation of β-keto benzothiazol-2-yl sulfones with Morita-Baylis-Hillman (MBH) carbonates catalysed by a modified cinchona alkaloid (hydroquinidine (anthraquinone-1,4-diyl) diether, (**DHQD)$_2$AQN**)). The chiral intermediates underwent intramolecular Smiles rearrangement by subsequent treatment with DBU, and an unusual intramolecular sulfinate addition was followed to give cyclic sulfone products with dense functionalities in high enantioselectivity, good diastereoselectivity and yields (45 – 83%, Scheme 53).[56]

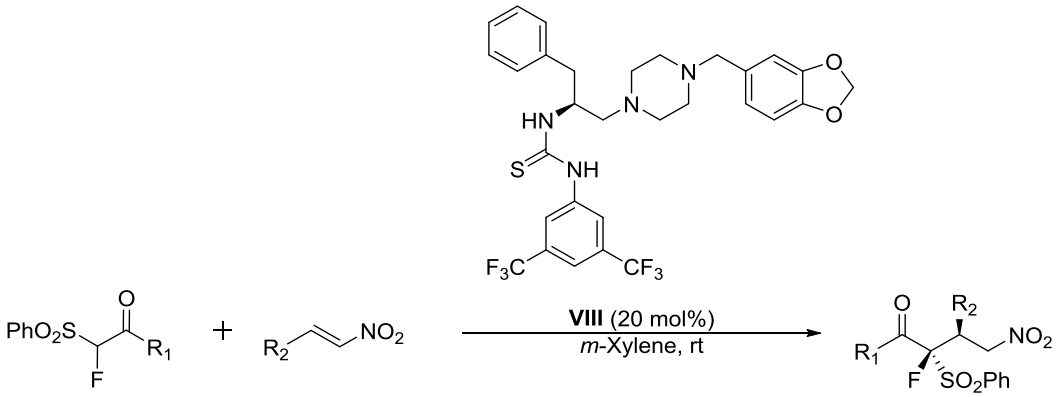
[55] Han, X.; Wu, X.; Min, C.; Zhou, H.-B. and Dong, C. *RSC Advances* **2012**, *2*, 7501. (10.1039/C2RA21162A)
[56] Wang, Q.-G.; Zhou, Q.-Q.; Deng, J.-G. and Chen, Y.-C. *Org. Lett.* **2013**, *15*, 4786. (10.1021/ol402158u)



R_1 = Ph, *o*-ClC_6H_4, *o*-BrC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, 3,4-$Cl_2C_6H_3$, *m*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, 2-naphthyl, 2-furyl, 2-thienyl, *n*-propyl
R_2 = CH_3, Ph, *p*-ClC_6H_4, *m*-BrC_6H_4, *p*-$CH_3C_6H_4$, 2-naphthyl, 2-thienyl

Scheme 53

The group of Jiang and Tan *et al.* found that α-fluoro-β-ketosulfones react with *N*-3-ethylpentan-3-yloxycarbonyl (Eoc) imine in the presence of 10 mol% of bicyclic guanidine catalyst in good yield and ee.[57] Moreover, α-fluoro-β-ketosulfones were tested in the organocatalysed asymmetric Michael addition to nitroolefins by Zhao *et al.* using phenylalanine-based bifunctional thiourea derivatives **VIII** as the catalysts, with good to very good yields (70 – 93%) and stereoselectivity (Scheme 54).[58]



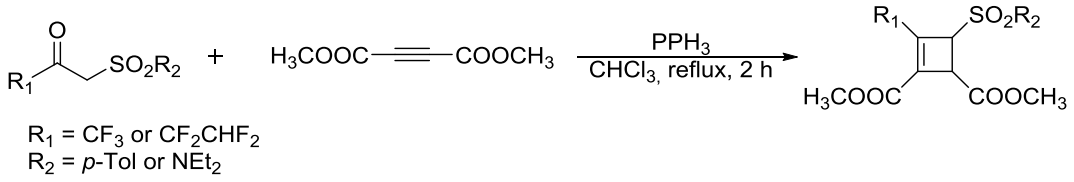
R_1 = CH_3 or Ph
R_2 = Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-PhC_6H_4, *p*-$NO_2C_6H_4$, *o*-BrC_6H_4, *m*-BrC_6H_4, 1-naphthyl, 2-furyl, 2-thienyl, *n*-Bu, *i*-Pr

Scheme 54

Michael addition of β-ketosulfones has been used as an alternative to access different cyclic structures which are difficult to obtain in other ways or that would require more steps for their syntheses.

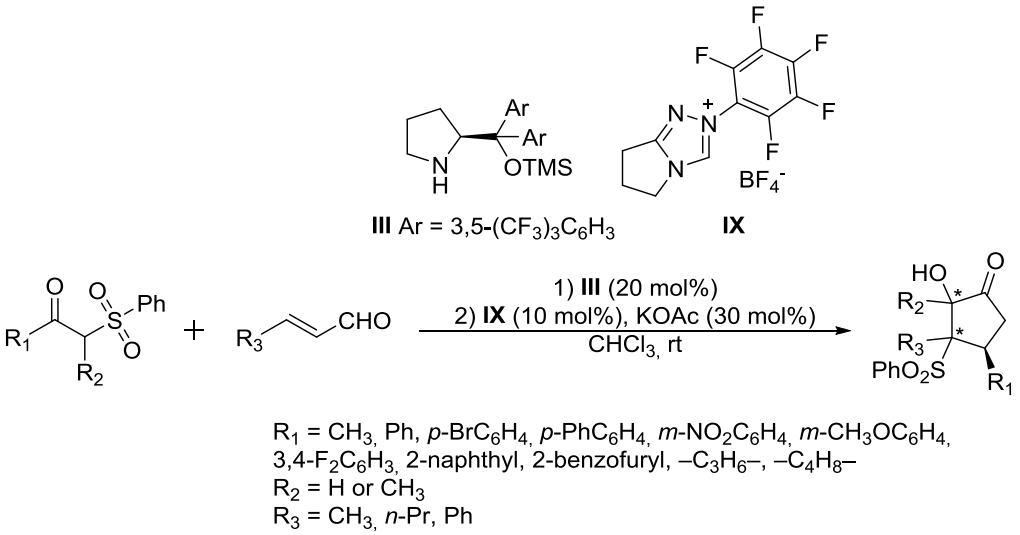
[57] Pan, Y.; Zhao, Y.; Ma, T.; Yang, Y.; Liu, H.; Jiang, Z. and Tan, C.-H. *Chem. Eur. J.* **2010**, *16*, 779. (10.1002/chem.200902830)
[58] Cui, H.-F.; Li, P.; Wang, X.-W.; Zhu, S.-Z. and Zhao, G. *J. Fluorine Chem.* **2012**, *133*, 120. (10.1016/j.jfluchem.2011.05.029)

Thus, very recently Timoshenko *et al*. have reported the stereoselective reaction of β-polyfluoroalkyl β-ketosulfones and sulfamides with dimethyl acetylenedicarboxylate and triphenyl phosphine in chloroform at reflux for the synthesis of polyfluoroalkyl cyclobut-2-ene-1,2-dicarboxylates bearing a sulfonyl or sulfamoyl functions in good yields (64 – 76%, Scheme 55).[59]



Scheme 55

Enders *et al.* developed an organocatalytic cascade reaction between β-ketosulfones and α,β-unsaturated aldehydes by utilising a dual secondary amine/*N*-heterocyclic carbene catalytic system (Scheme 56).[60] The polyfuncionalised cyclopentanones bearing a synthetically useful β-(phenylsulfonyl) group, an α-hydroxy function and three contiguous stereocenters were formed in low to excellent yields (5 – 99%), modest to excellent diastereoselectivities (58:42 – 99:1 dr) and modereate to very good enantiomeric excesses (41 – 97% ee).

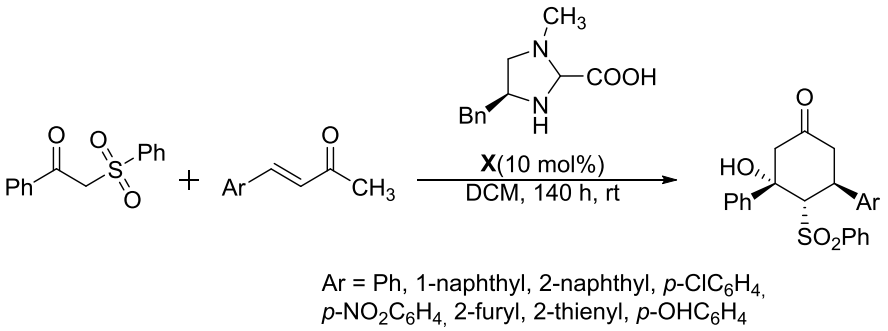


Scheme 56

Further development of the organocatalytic asymmetric reactions led the group of Jørgensen *et al.* to develop a domino Michael-aldol reaction catalysed by the chiral imidazolidine **X** to the application of β-ketosulfones with α,β-unsaturated ketones, affording optically active cyclohexanones in moderate to

[59] Timoshenko, V. M.; Markitanov, Y. M. and Shermolovich, Y. G. *Heteroat. Chem.* **2013**, *24*, 437. (10.1002/hc.21101)
[60] Enders, D.; Grossmann, A.; Huang, H. and Raabe, G. *Eur. J. Org. Chem.* **2011**, 4298. (10.1002/ejoc.201100690)

very good yields (31 – 95%), excellent diastereoselectivities (>95 dr) and good to excellent enantiomeric excesses (86 – 99% ee, Scheme 57).[61]

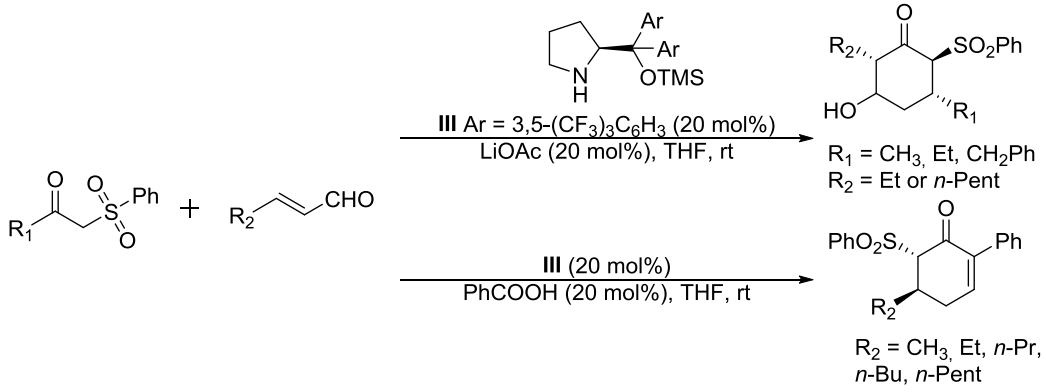


Scheme 57

Catalyst **X** is believed to have three roles during the reaction: (1) activation of the Michael acceptor by iminium ion formation, (2) deprotonation of the Michael donor, and (3) acting as a base catalyst for the intramolecular aldol step. The relative stereochemistry was determined on the basis of ^{1}H-NMR studies and by comparison with NMR spectra of similar cyclohexanones formed using acyclic β-ketoesters as Michael-aldol donors.

From the studies carried out by Alemán and Ruano *et al.* on the conjugated addition of β-ketosulfones to α,β-unsaturated aldehydes catalysed by silyl prolinol ethers,[73] this group found the reaction conditions (

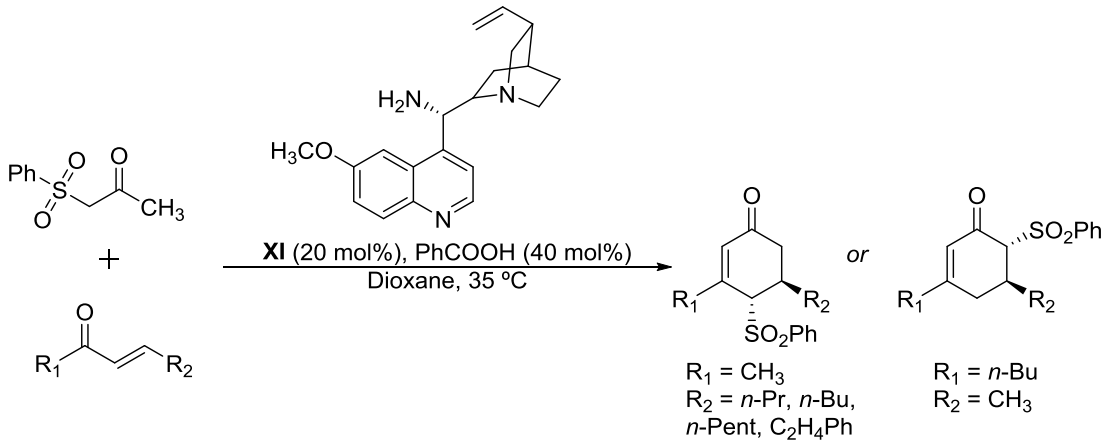
Scheme **58**) to synthesise cyclohexanones (63 – 72%, 1:1 up to 3:1 dr and 90 – 92 % ee) and cyclohexenones (60 – 68%, 90:10 – 92:8 dr and 80 – 94% ee).



Scheme 58

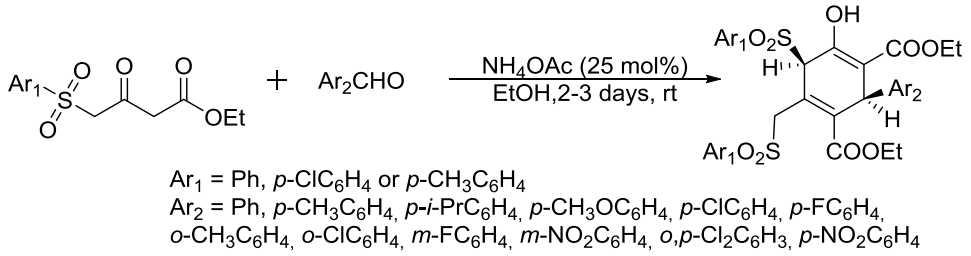
[61] Pulkkinen, J.; Aburel, P. S.; Halland, N. and Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077. (10.1002/adsc.200404115)

Ye *et al.* developed the synthesis of cyclohex-2-enones in moderate to good yields (45 – 87%) and very good enantioselectivities (91 – 95% ee) by a tandem Michael/aldol reaction of α,β-unsaturated ketones with 1-(phenylsulfonyl)propan-2-one, catalysed by 9-amino-(9-deoxy)epiquinine (20 mol%) **XI** with benzoic acid (40 mol%) in dioxane at 35 ºC (Scheme 59).[62]



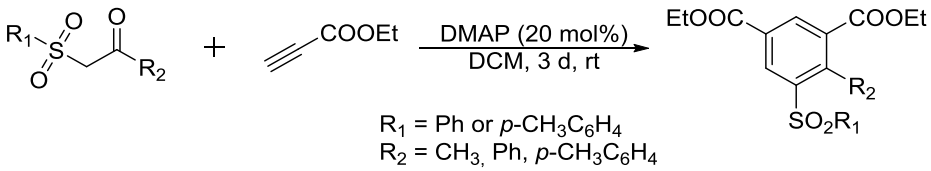
Scheme 59

Perumal *et al.* reported the synthesis of *cis*-1,4-cyclohexa-1,4-dienes employing a catalytic amount of ammonium acetate (Scheme 60).[63]



Scheme 60

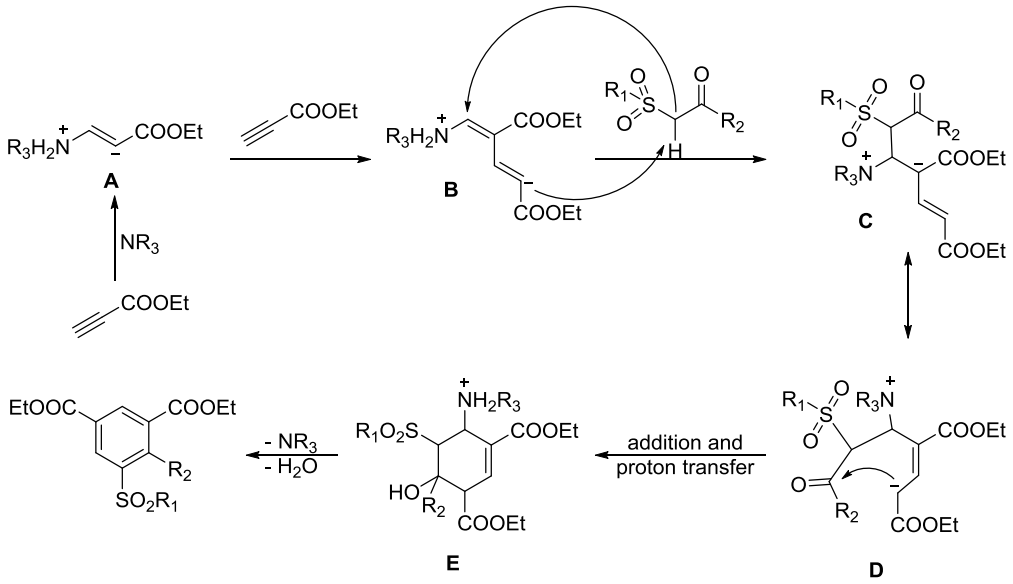
Aromatic structures can also be achieved using this methodology. Xue *et al*. obtained benzannulation products in moderate yields (50 – 76%) *via* DMAP catalysed Michael reaction of β-ketosulfones with ethyl propiolate (Scheme 61).[64]



Scheme 61

[62] Sun, X.; Yu, F.; Ye, T.; Liang, X. and Ye, J. *Chem. Eur. J.* **2011**, *17*, 430. (10.1002/chem.201002418)
[63] Sokkan Harikrishnan, P.; Michael Rajesh, S. and Perumal, S. *Tetrahedron Lett.* **2012**, *53*, 3880. (10.1016/j.tetlet.2012.05.071)
[64] Zhou, Q.-F.; Yang, F.; Guo, Q.-X. and Xue, S. *Synlett* **2007**, 2073. (10.1055/s-2007-984904)

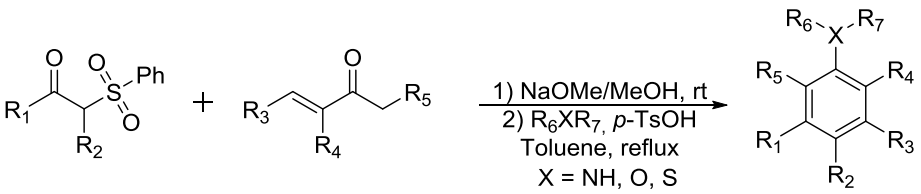
The mechanism proposed by the authors is depicted in Scheme 62.



Scheme 62

DMAP acted as a nucleophilic promoter to initiate the reaction and produced a zwitterionic intermediate **A**, which then added to a second ethyl propiolate to give the intermediate **B**. This intermediate then deprotonates the active methylene proton of the β-ketosulfone to generate a stabilised anion **C**, which after addition and electron transfer steps gives the intermediate **D** and subsequent generation of **E** through intramolecular nucleophilic attack and proton transfer. DMAP and H_2O are eliminated from the intermediate **E** to afford final product.

Padwa *et al.* found a useful benzoannulation method that afforded substituted aryl amines, ethers and thioethers. The key step consisted of a Michael-aldol reaction of β-ketosulfones with enones followed using MeONa in MeOH by a subsequent condensation of the initial adduct with an amine, alcohol or thiol. The Michael-aldol cascade proceeded with a number of β-ketosulfones and enones, affording adducts as single diastereomers in low to excellent yields (17–98%, Scheme 63).[65]

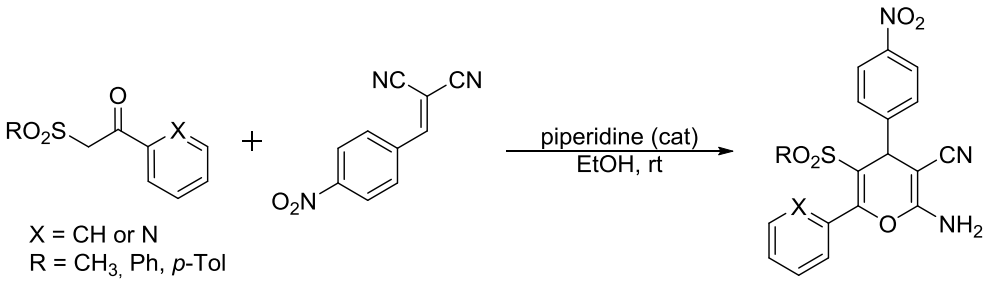


Scheme 63

[65] Kiren, S. and Padwa, A. *J. Org. Chem.* **2009**, *74*, 7781. (10.1021/jo9017793)

Michael addition methodology has also been employed for the synthesis of different heterocycles. For instance, molecules with a pyran heterocycle in their structure, which are very interesting due to their biological activities and applications in medicine.[66,67] Some examples are benzopyrans, such as daurichromenic acid, an anti-HIV agent,[68] seselin, an antinociceptive along with other activities,[69] or privileged structures, such as 2-pyrones, an essential pharmacophore in many naturally occurring and biologically active compounds.[70]

As an extension of their work on the synthesis of enantiomerically pure, polyfunctionalised 2-amino-4*H*-pyrans,[71] Marco *et al.* designed an approach based on the 1,4-conjugate additions of sulfinyl carbanions derived from β-ketosulfoxides and β-ketosulfones with highly stabilised Michael acceptors. Thus, this group described the first successful examples of the Michael addition of β-ketosulfones to Michael acceptors using piperidine as catalyst in ethanol at room temperature, in moderate to good yields (27 – 81%, Scheme 64).[72]

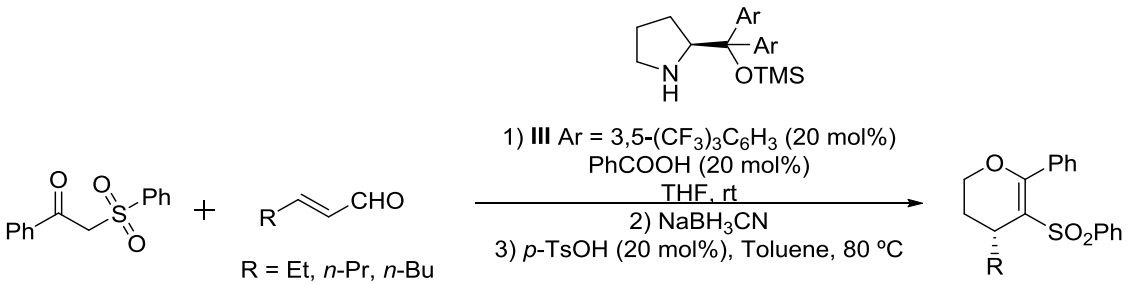


Scheme 64

Alemán and Ruano *et al.* studied the influence of reaction conditions on the conjugated addition of β-ketosulfones to α,β-unsaturated aldehydes catalysed by silyl prolinol ethers and found that small changes in the starting material and/or in the experimental protocol can produce significant variations in the structures of the final products. Furthermore, these compounds can be used in a variety of tandem and one-pot reactions to afford polysubstituted cyclic products bearing multiple chiral centres (see

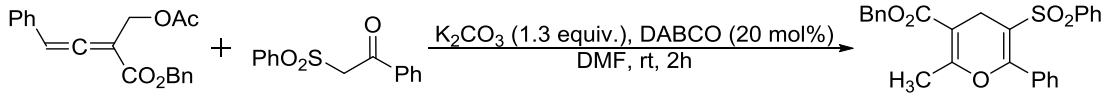
Scheme **58**, page 63). Within these studies, this group found the conditions to obtain hydropyrans in moderate yields (41 – 46%) and very good enantioselectivity (90 – 91% ee) after intramolecular ketalisation and subsequent dehydration steps (Scheme 65).[73]

[66] Yang, D.; Shi, L.; Huang, H.; Zhang, J. and Gan, L. *J. Org. Chem.* **2010**, *75*, 4567. (10.1021/jo100799x)
[67] Larrosa, I.; Romea, P. and Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (10.1016/j.tet.2007.11.092)
[68] Lee, Y. R.; Choi, J. H. and Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539. (10.1016/j.tetlet.2005.08.159)
[69] Lima, V.; Silva, C. B.; Mafezoli, J.; Bezerra, M. M.; Moraes, M. O.; Mourão, G. S. M. M.; Silva, J. N. and Oliveira, M. C. F. *Fitoterapia* **2006**, *77*, 574. (10.1016/j.fitote.2006.09.005)
[70] Peng, W.; Hirabaru, T.; Kawafuchi, H. and Inokuchi, T. *Eur. J. Org. Chem.* **2011**, 5469. (10.1002/ejoc.201100780) and references cited herein.
[71] Marco, J.-L.; Fernández, I.; Khiar, N.; Fernández, P. and Romero, A. *J. Org. Chem.* **1995**, *60*, 6678. (10.1021/jo00126a014)
[72] Marco, J. L. *J. Org. Chem.* **1997**, *62*, 6575. (10.1021/jo9705982)
[73] Alemán, J.; Marcos, V.; Marzo, L. and García Ruano, J. L. *Eur. J. Org. Chem.* **2010**, 4482. (10.1002/ejoc.201000502)



Scheme 65

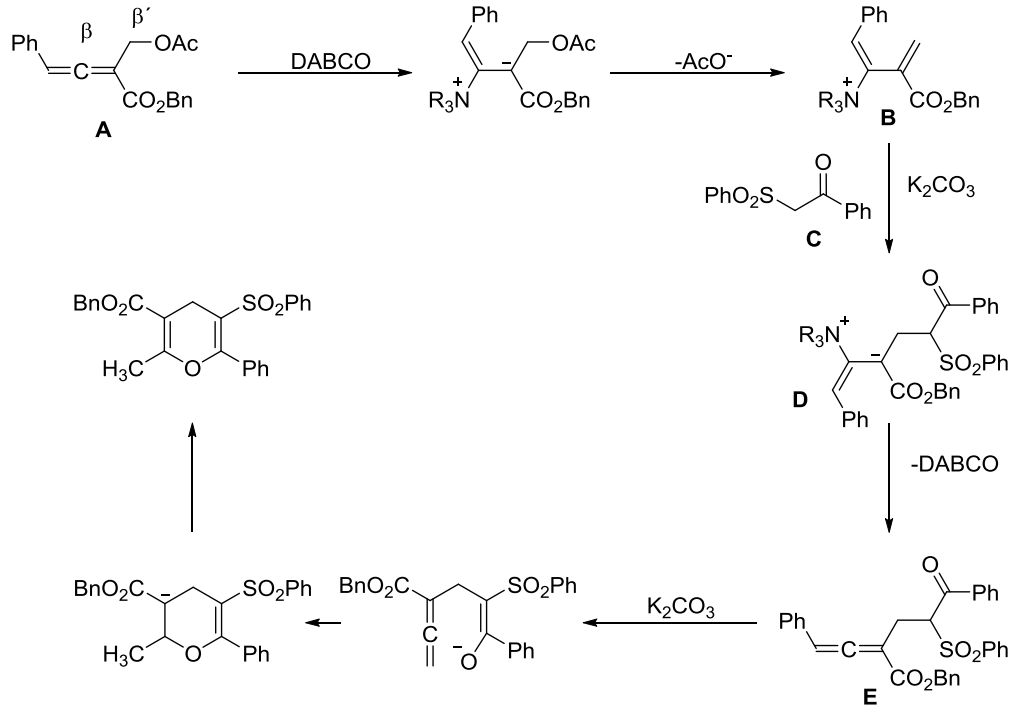
Tong *et al.* realised a tertiary amine-catalysed [*3+3*] annulations of 2-(acetoxymethyl)buta-2,3-dienoate with 1,3-binucleophiles (among them a β-ketosulfone also worked in good yield, 83%) for the synthesis of 4*H*-pyrans in the presence of K_2CO_3 and DABCO (20 mol%) in DMF at room temperature (Scheme 66).[74]



Scheme 66

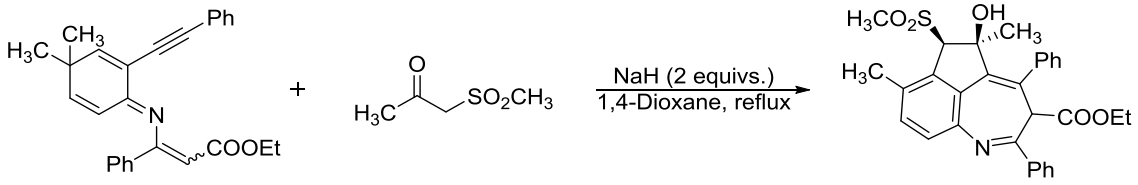
The mechanism proposed by the authors is depicted in Scheme 67. Addition of DABCO to the β-carbon of allenoate **A** initiates the addition–elimination process to yield intermediate **B**. Apparently this process can destroy the stereogenic center of the β´-carbon and enhance its electrophilicity. Consequently, Michael-type addition of **C** to the β´-position of **B** occurs with the help of a base to generate intermediate **D**, which is followed by 1,2-elimination of DABCO catalyst to deliver intermediate **E**. This reaction pathway can be described as a tandem $S_N2´–SN_2´$ substitution process. In the end, compound final product can be obtained *via* continuous isomerisation and protonation, furnishing a formal [*3+3*] annulation.

[74] Li, C.; Zhang, Q. and Tong, X. *Chem. Commun.* **2010**, *46*, 7828. (10.1039/C0CC01966F)



Scheme 67

Other nitrogen-containing heterocyclic structures have been obtained from Micahel addition of β-ketosulfones. Tang and Fan *et al.* used NaH to promote a tandem Michael addition/polycyclisation to construct indenoazepine derivatives from activated methylene compounds and cyclohexadienimine. One β-ketosulfone was also tested, affording the corresponding indenoazepine in a moderate 48% yield (Scheme 68). This structure could be confirmed by its single-crystal diffraction analysis.[75]



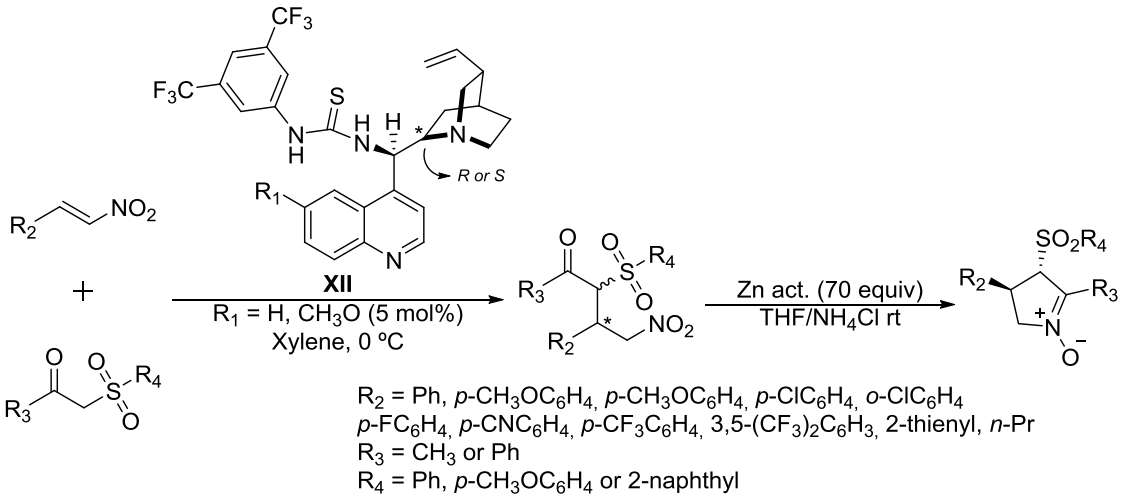
Scheme 68

Nitrones[76] are very useful intermediates in synthesis, especially five-membered cyclic nitrones, which have been used as starting materials for the construction of different natural products (*e.g.*, pyrrolizidines or indolizine alkaloids).[77] The main strategy for the preparation of these cyclic compounds typically implies a relatively long synthetic sequence that starts from different compounds of the chiral pool (*e.g.*, D-malic acid esters). These methods usually incorporate only oxygen functionalities at 3- and/or 4-positions and generate the cyclic skeleton in the last steps through an

[75] Yang, M.; Tang, J. and Fan, R. *Org. Lett.* **2013**, *15*, 3464. (10.1021/ol401553n)
[76] Nájera, C. and Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567. (10.1039/B913066G)
[77] Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M. and Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (10.1002/chem.200900707)

amine or oxime cyclisation followed by oxidation. Conversely, the syntheses of chiral cyclic nitrones with non-oxygenated substituents are scarce because most of them are non-asymmetric versions.

Mancheño and Alemán *et al.* have recently reported the first organocatalytic addition of β-ketosulfones to nitroalkenes catalysed by thiourea cinchona alkaloids **XII** in xylene at 0 ºC that lead to the formation of 1,4-addition products in good to excellent yields and enantioselectivity (50–99%, e.r. up to 99:1). The obtained enantiomerically enriched active products were selectively transformed into cyclic nitrones in low to good yields (34 – 87%) by partial reduction of the nitro group using activated Zn (70 equiv) in THF/NH_4Cl (sat. aq.) at room temperature (Scheme 69).[78] Moreover, the utility of this method has additionally been demonstrated by further transformation to functionalised *N*-hydroxypyrrolidines that possess a quaternary center.



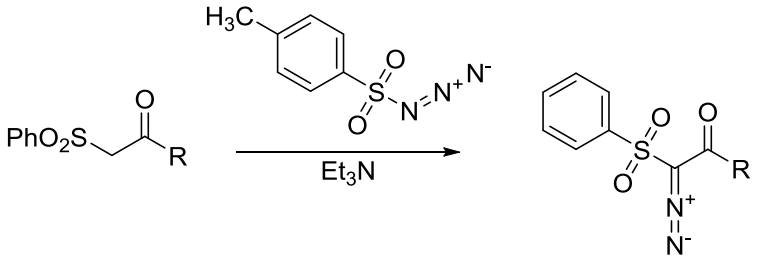
Scheme 69

If both partners in Michael reaction are active enough, there is no need for a base or catalyst to promote the reaction. For instance, Shirakawa *et al.* developed a catalyst-free Michael addition of active methylene compounds, including a β-ketosulfone, to methyl vinyl ketone (MVK) in ethanol at 90 ºC in 83% yield.[79]

[78] García Mancheño, O.; Tangen, P.; Rohlmann, R.; Fröhlich, R. and Alemán, J. *Chem. Eur. J.* **2011**, *17*, 984. (10.1002/chem.201001914)
[79] Shirakawa, S. and Shimizu, S. *Synlett* **2007**, 3160. (10.1055/s-2007-992377)

2.1.i.3. Carbene chemistry.

The transformation of β-ketosulfones into α-diazo-β-ketosufones has opened new ways to obtain many cyclisation products. The synthesis of this diazo-derivatives is tipically achieved by reaction with TsN_3 and Et_3N (Scheme 70).[80]



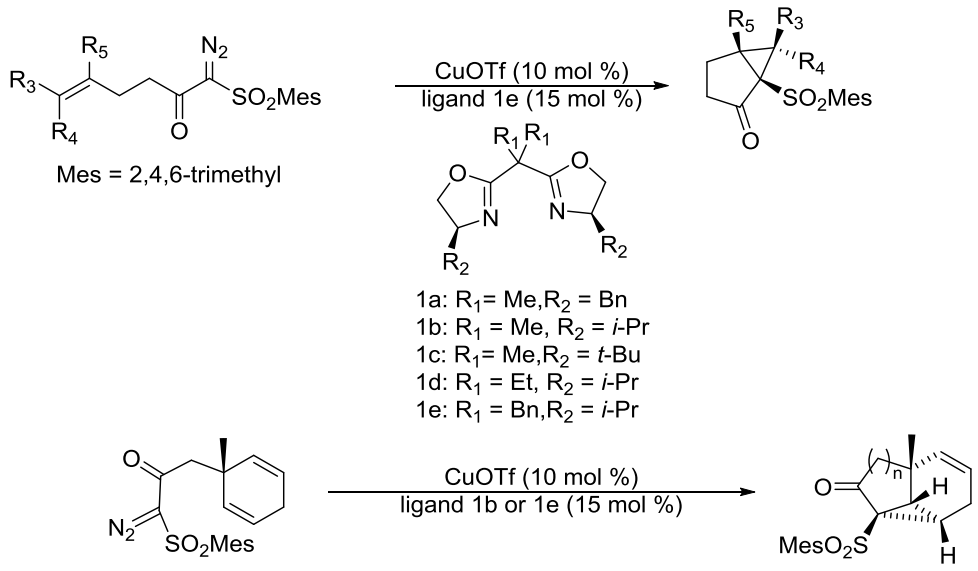
Scheme 70

α-Diazo-β-ketoaryl sulfones have been used as carbenes in many cyclopropanation and/or different X-Y bond insertion (where X/Y can be C, H, O, N, etc.) mainly catalysed by metals or organometallic catalyst. This section will briefly review this type of reactivity and it is divided in two parts: (1) intramolecular cyclopropanation reactions, and (2) insertion reactions.

2.1.i.3.1. Intramolecular cyclopropanation reactions.

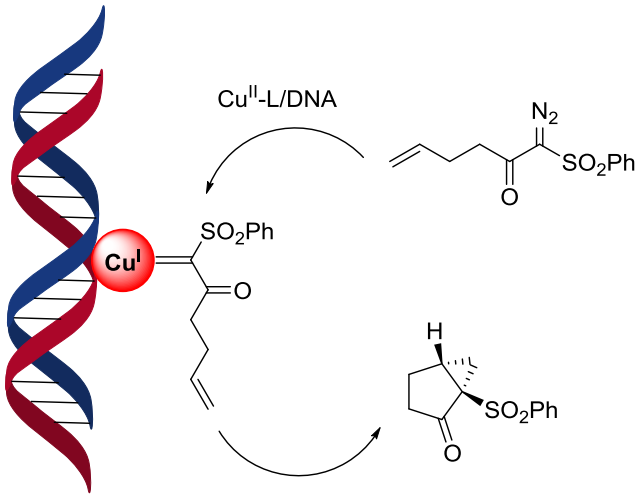
The catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-ketoaryl sulfones has been very often utilised for natural product synthesis by the group of Nakada *et al.* and has promoted related studies, proving the potential utility and wide applicability of the CAIMCP approach. This group has reported the CAIMCP of α-diazo-β-keto aryl sulfones, which proceeds in a high yield and with excellent enantioselectivity. During these studies, this group found that the bisoxazoline ligand with two benzyl groups at the linkage was effective in improving the enantioselectivity of the CAIMCP of α-diazo-β-keto aryl sulfones (Scheme 71). Various other novel bisoxazoline ligands possessing bulky substituents at the bisoxazoline linkage have been successfully prepared by this group.[81]

[80] Honma, M. and Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007. (10.1016/j.tetlet.2003.09.215)
[81] Sawada, T. and Nakada, M. *Tetrahedron: Asymmetry* **2012**, *23*, 350. (10.1016/j.tetasy.2012.02.021) and references cited herein.



Scheme 71

The stability of these compounds and the fact that they readily form metal carbene complexes with CuI at room temperature was used by Roelfes *et al.* to achieve the asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones with moderate yields but good ee using DNA as chiral inductor (Scheme 72).[82]

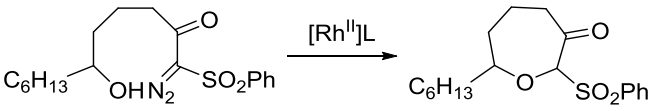


Scheme 72

[82] Oelerich, J. and Roelfes, G. *Chem. Sci.* **2013**, *4*, 2013. (10.1039/C3SC00100H)

2.1.i.3.2. Insertion reactions.

While the exploration of chiral copper catalysts in cyclopropanation has been described, in general enantioselective catalysis in other X-Y (where X/Y = C, H, O, N, etc.) bond-forming reactions of α-diazocarbonyls has concentrated almost exclusively on rhodium-based systems. Moody *et al.* developed one of the first catalytic systems for carbenoid O-H insertion reactions which they used for the synthesis of a range of 2-substituted 3-oxepanones prepared from 2-tetrahydropyranones (δ-lactones) *via* rhodium(II) acetate or trifluoroacetamide catalysed cyclisations of intermediate ω-hydroxy-α-diazo-β-ketoarylsulfones (Scheme 73).[83,84]



Scheme 73

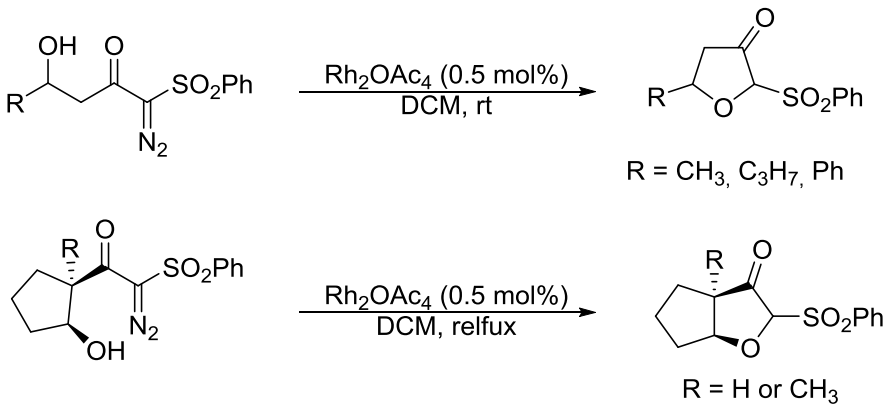
This group found that the nature of the group in *beta* with respect to the carbonyl group markedly affected the rate of the cyclisation reaction.[85] Thus, after carrying out a detailed study of the rhodium(I) carboxylate catalysed decomposition of various diazo compounds in the presence of hydroxylic compounds they found that the stability of the diazo compounds towards rhodium catalysts in 2-propanol decreases in the order:

$$PO(OEt)_2 > Ph_2PO > EtO_2C \approx \mathbf{PhSO_2} > Me_2NCO > CN > PhCH_2 > Ph \approx H$$

So, α-diazophosphonates are markedly less prone to rhodium carbenoid mediated O-H insertion reactions than the corresponding α-diazosulfones and carbonyl compounds.

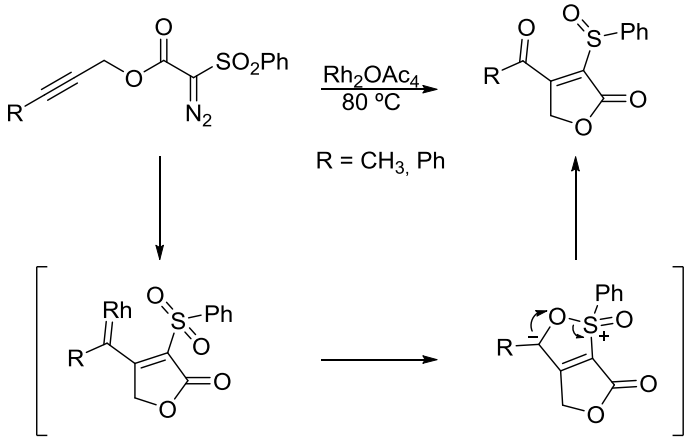
This methodology was applied to the preparation of furanyl derivatives by Doutheau *et al.* using rhodium(II) acetate in dichloromethane (Scheme 74).[86]

[83] Davies, M. J.; Moody, C. J. and Taylor, R. J. *Synlett* **1990**, *2*, 93. (10.1055/s-1990-20997)
[84] Cox, G. G.; Kulagowski, J. J.; Moody, C. J. and Sie, E.-R. H. B. *Synlett* **1992**, *12*, 975. (10.1055/s-1992-21551)
[85] Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E.-R. H. B. and Kulagowski, J. J. *Tetrahedron* **1994**, *50*, 3195. (10.1016/S0040-4020(01)81117-0)
[86] Lacrampe, F.; Léost, F. and Doutheau, A. *Tetrahedron Lett.* **2000**, *41*, 4773. (10.1016/S0040-4039(00)00724-3)



Scheme 74

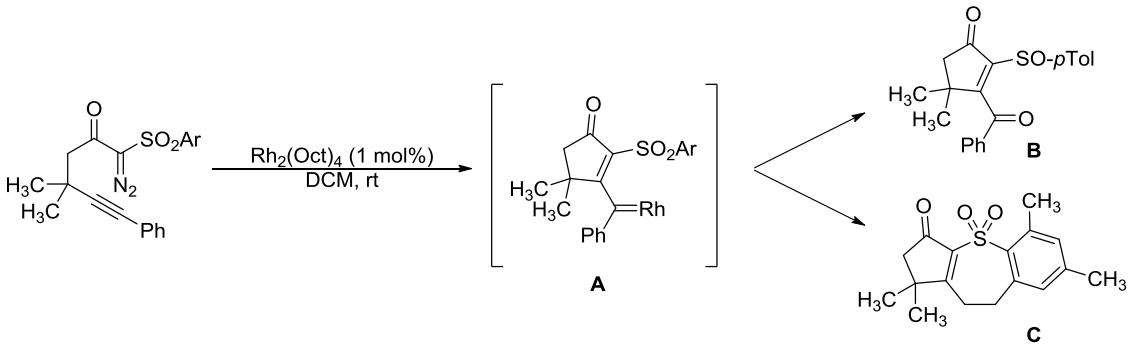
Padwa *et al.* disclosed how diazo alkynyl sulfones undergo an oxygen transfer reaction when treated with rhodium(II) acetate at 80 ºC in good yields (60 – 90%)**.** The cyclised product is formed by sulfone oxygen attack onto the vinyl carbenoid producing a dipolar species which subsequently collapses to give the butenolide sulfoxide (Scheme 75).[87]



Scheme 75

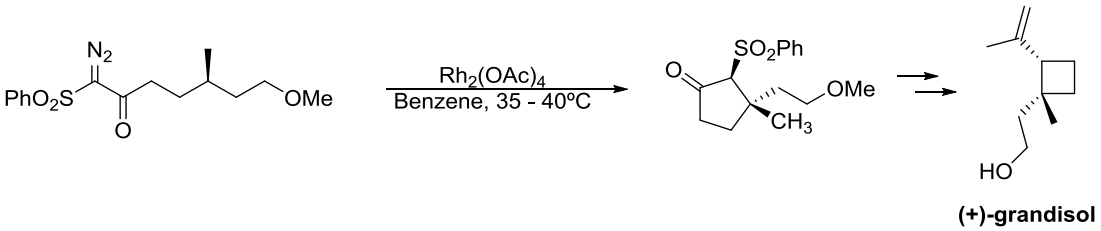
More recently Doyle *et al.* have reported how diazo alkynyl sulfones can provide different outcomes depending on the sulfone aryl substituent in the presence of $Rh_2(Oct)_4$ (1 mol%, Oct = *n*-octanoate) in dichloromethane at room temperature. Thus, when Ar is *p*-tolylsulfonyl, secondary carbene **A** reacted with the sulfone to provide an intermediate sulfoxonium ylide that underwent O atom transfer to deliver racemic sulfoxide **B** in 90% yield. On the other hand, if the arylsulfone was changed to mesityl-substituted system, secondary carbene **A** underwent benzylic 1,7-C–H insertion, instead of O-atom transfer, to provide benzothiepine ring system **C** in 80% yield (Scheme 76).[88]

[87] Padwa, A. and Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21. (10.1021/jo00053a009)
[88] Qian, Y.; Shanahan, C. S. and Doyle, M. P. *Eur. J. Org. Chem.* **2013**, 6032. (10.1002/ejoc.201301000)



Scheme 76

The importance of the rhodium-mediated intramolecular carbenoid cyclisation of α-diazo-β-ketosulfones was demonstrated by Monteiro *et al.* who used this procedure as key step in a 10 step synthesis of (1*S*,2*R*)-2-acetyl-1-methylcyclobutaneacetic acid which was converted into (+)-grandisol, the major optically active pheromone of the cotton boll-weevil *Anthonomus grandis* (Scheme 77).[89] This group has recently disclose a new protocol for the synthesis of this compound using the same strategy but starting from (cyclobutylsulfonyl)benzene.[90]

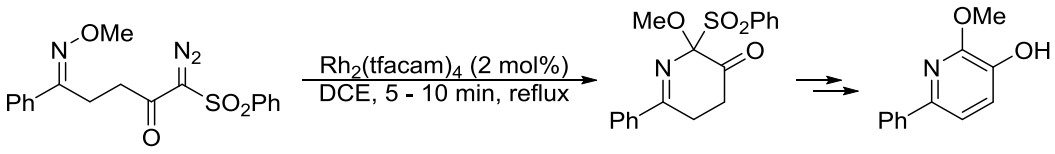


Scheme 77

A novel chiral version of this procedure was achieved by Maguire *et al*. through a combination of rhodium acetate catalysed carbenoid C-H insertion and baker's yeast mediated kinetic resolution.[91] Intramolecular C–H insertion reactions, in view of their mild and neutral reaction conditions and high functional group tolerance, appeared to be an attractive strategy for the synthesis of highly functionalised cyclopentanone derivatives (Scheme 77), and some other groups as Sengupta *et al*. have made important progresses on this area.[92] The first asymmetric induction in the cycloadditions of sulfone-substituted carbonyl ylides using chiral rhodium catalysts was observed by Hodgson *et al.*, with the *N*-phthaloyl-amino acid-based rhodium catalyst at room temperature in dichloromethane, giving affording the desired cycloaddition products in good yield but moderate enantioselectivity (up to 75% and 43% ee).[93] More recently, Park *et al.* have developed a carbenoid-mediated N–O bond insertion for the synthesis of 3-hydroxypyridines by treatment of δ-diazo oxime ethers with dirhodium

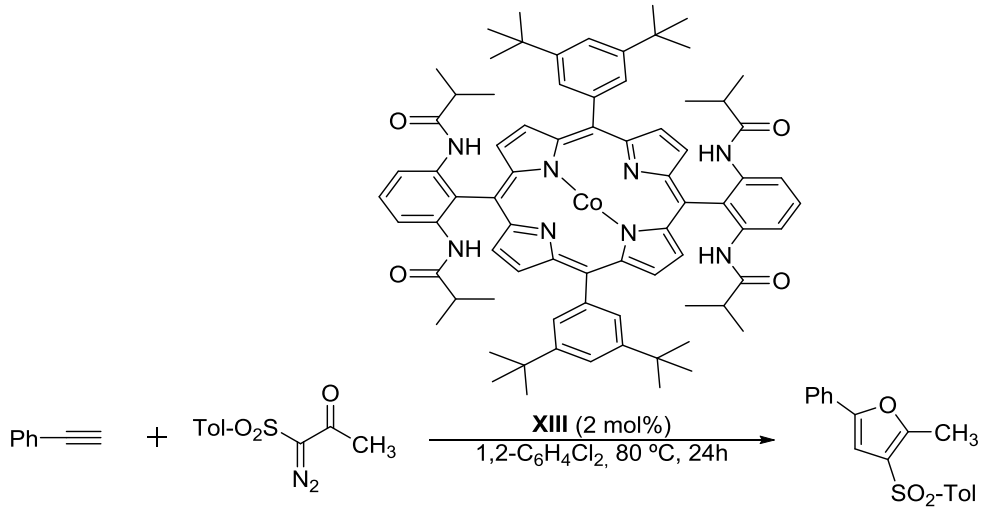
[89] Monteiro, H. J. and Zukerman-Schpector, J. *Tetrahedron* **1996**, *52*, 3879. (10.1016/S0040-4020(96)00175-5)
[90] Sousa, G.; Monteiro, H.; Resck, I.; Gatto, C.; Ellena, J. and Sabino, J. *J. Chem. Crystallogr.* **2013**, *43*, 240. (10.1007/s10870-013-0411-4)
[91] Maguire, A. R. and Kelleher, L. L. *Tetrahedron Lett.* **1997**, *38*, 7459. (10.1016/S0040-4039(97)01756-5)
[92] Sengupta, S. and Mondal, S. *Tetrahedron Lett.* **2003**, *44*, 6405. (10.1016/S0040-4039(03)01619-8)
[93] Hodgson, D. M.; Glen, R. and Redgrave, A. J. *Tetrahedron: Asymmetry* **2009**, *20*, 754. (10.1016/j.tetasy.2009.02.031)

trifluoroacetamide complex $Rh_2(tfacam)_4$. In addition, this protocol provided access to 2-alkoxy-3-hydroxypyridines by employing a α-diazo-β-keto-ε-oxime sulfone substrate (Scheme 78).[94]



Scheme 78

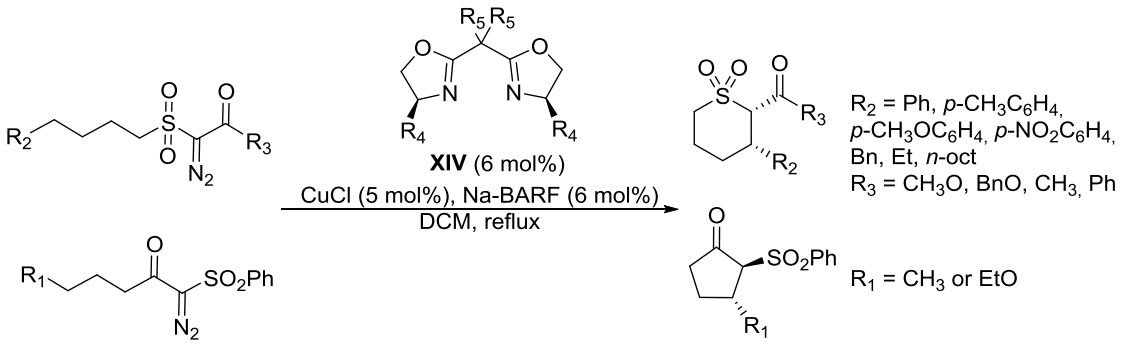
As shown, highly enantioselective diazo decompositions are possible in the presence of chiral rhodium(II) catalysts, of which rhodium(II) carboxylates and carboxamidates have found particular success. However, direct access to furans with sensitive functionalities remains challenging in Rh(II) cycloaddition systems, which share common reaction mechanisms that are intrinsically ionic in nature. To meet the need to develop new catalytic systems for general and effective syntheses of polyfunctionalised furans from different alkynes and α-diazocarbonyls, the group of Zhang *et al.* have developed a Co(II) complex of the amidoporphyrin 3,5-di-*t*-Bu-IbuPhyrin **XIII** radical catalysed system for the regioselective synthesis of furans by cyclisation of alkynes with diazocarbonyls, among them one α-diazoβ-ketosulfone was used affording the corresponding furan in a 87% yield (Scheme 79).[95]



Scheme 79

[94] Qi, X.; Dai, L. and Park, C.-M. *Chem. Commun.* **2012**, *48*, 11244. (10.1039/C2CC36009H)
[95] Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M. and Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981. (10.1021/ja309446n)

The application of other asymmetric metal catalysts in C–H insertion reactions has not been widely exploited in recent times. Application of asymmetric copper catalysts to asymmetric C-H insertion has been very limited, in contrast to cyclopropanation, for example, and has resulted in modest enantioselectivities.[96] However, groups as Maguire *et al.* have recently investigated the potential of copper-based catalyst systems for such transformations, offering a more cost-effective and potentially environmentally benign catalytic alternative.[97] In particular, the application of copper-bis(oxazoline) catalysts for enantioselective C–H insertion and aromatic addition reactions of various α-diazo-β-ketosulfones, with high levels of enantiocontrol achieved for both processes by a careful choice of the catalytic system (tipically with catalysts generated using additives possessing weakly coordinating counterions such as Na-BARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) and $NaPF_6$, and carrying the reaction in DCM at reflux). The choice of bis(oxazoline) ligands **XIV** was also found to be important. For C–H insertion reactions of α-diazo-β-keto sulfones leading to cyclopentanones, benzyl- and indane-substituted ligand systems were found to provide the highest levels of enantioselectivity, while phenyl-substituted ligands were the most effective in terms of enantiocontrol for C–H insertion reactions of α-diazosulfones forming thiopyrans and aromatic addition reactions of α-diazoketones (Scheme 80).

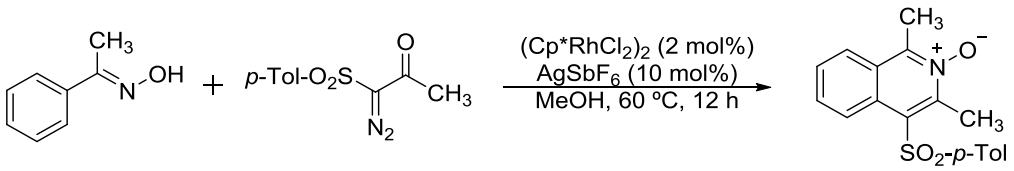


Scheme 80

Their most recent work has been the synthesis of a range of aryl-substituted bis(oxazolines), including four novel ligands, and the observations arisen from these experiments contributed to the understanding of the nature of the interactions between the bis(oxazoline) ligands and the substituents on the copper-carbene in the transition state for the C–H insertion and aromatic addition processes.

[96] Davies, H. M. L. and Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (10.1021/cr0200217)
[97] Slattery, C. N.; O'Keeffe, S. and Maguire, A. R. *Tetrahedron: Asymmetry* **2013**, *24*, 1265. (10.1016/j.tetasy.2013.09.009) and references cited herein.

Isoquinoline *N*-oxides are commonly occurring structural motifs found in numerous pharmaceuticals, biologically active compounds,[98] and chiral ligands.[99] Traditional methods have been reported for the *N*-oxidation of isoquinoline by different oxidants such as *m*-CPBA, H_2O_2, CF_3CO_3H, and CH_3ReO_3/H_2O_2. However, their parent heterocycles need to be prepared in advance and suffer from the potential over-oxidation of the functionalised substituents. Electrophilic cyclisations of oximes are available methods for the preparation of isoquinoline *N*-oxides.[100] Glorius *et al.* reported the Rh(III)-catalysed cyclisation of oximes with carbonyl-containing diazo compounds (among them one β-ketosulfone derivative was also effective in moderate yield, 65 %, Scheme 81) for the synthesis of isoquinoline *N*-oxides. This intermolecular annulation procedure involving tandem C−H activation, cyclisation, and condensation steps proceeds without the need for oxidants, releases H_2O and N_2 as byproducts, and constitutes the first example of a Rh-catalysed synthesis of isoquinoline *N*-oxides in which aryl and vinylic C−H activation serves as the cyclisation-initiating event.[101]

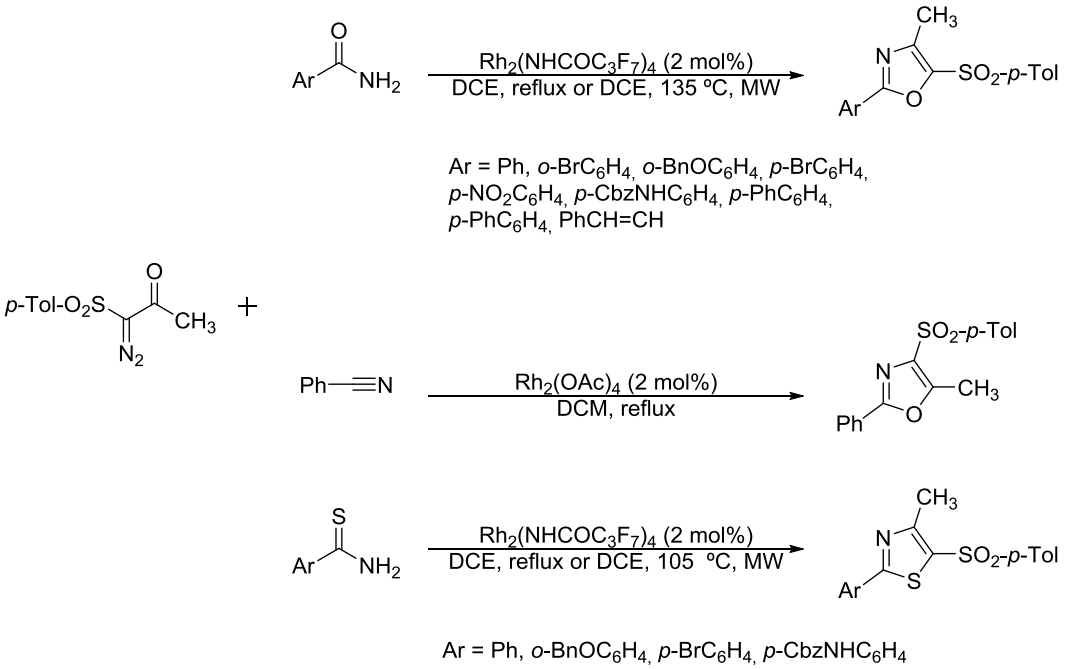


Scheme 81

Oxazoles and thiazoles occur widely in a range of bioactive natural products, particularly the non-ribosomal peptides.[171] The biological activity of relatively simple synthetic oxazoles and thiazoles and the structural diversity of complex naturally occurring derivatives have combined to ensure that new methods continue to be developed for their synthesis. Of the intermediates available for the synthesis of five-membered heteroaromatic rings, 1,4-dicarbonyl compounds are preeminent. In the field of 1,3-azole synthesis, the cyclodehydration of such a 1,4-dicarbonyl compound (an α-acylaminoketone) is the basis of the Robinson-Gabriel oxazole synthesis.[102] Oxazoles can also be obtained by the rhodium-catalysed reaction of diazocarbonyl compounds with nitriles,[103] however, this reaction usually requires the use of nitrile as solvent and therefore is only applicable to simple nitriles. Hence the ready availability of carboxamides, combined with the robustness of the rhodium carbene N-H insertion chemistry, renders the methodology highly suitable for the synthesis of a wide range of oxazoles. Indeed Janda *et al.* developed a solid-phase variant of the reaction and applied it in the synthesis of oxazole arrays.[104]

[98] Nicholas, G. M.; Blunt, J. W. and Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341. (10.1021/np000408+)
[99] Malkov, A. V. and Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. (10.1002/ejoc.200600474)
[100] Ding, Q. and Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850. (10.1002/adsc.200800301)
[101] Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M. and Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (10.1021/ja406338r)
[102] Palmer, D. C. and Venkatraman, S. In *Oxazoles: Synthesis, Reactivity and Spectroscopy. Part A*; Palmer, D. C., Ed.; John Wiley & Sons Inc.: Hoboken, NJ: **2003**, 1.
[103] Moody, C. J. and Doyle, K. J. *Prog. Heterocycl. Chem.* **1997**, *Volume 9*, 1. (10.1016/S0959-6380(97)80003-7)
[104] Clapham, B.; Lee, S.-H.; Koch, G.; Zimmermann, J. and Janda, K. D. *Tetrahedron Lett.* **2002**, *43*, 5407. (10.1016/S0040-4039(02)01076-6)

In continuation of their work, Moody *et al.* first developed a solution-phase, one-pot method that was applicable to the synthesis of oxazoles,[105] and carried out a comprehensive study of the conversion of carboxamides and thiocarboxamides into 4- and 5-substituted oxazole-carboxylates, -phosphonates, and -sulfones, and the corresponding thiazoles (Scheme 82).[106]

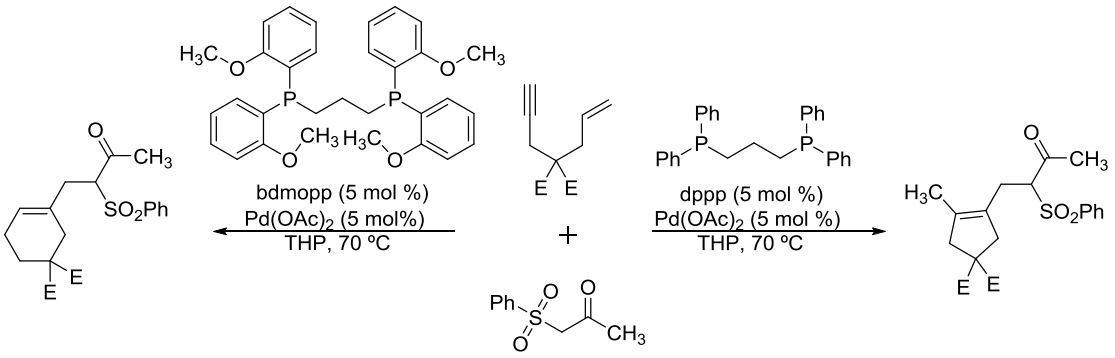


Scheme 82

[105] Shi, B.; Blake, A. J.; Campbell, I. B.; Judkins, B. D. and Moody, C. J. *Chem. Commun.* **2009**, 3291. (10.1039/B903878G)
[106] Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D. and Moody, C. J. *J. Org. Chem.* **2009**, *75*, 152. (10.1021/jo902256r)

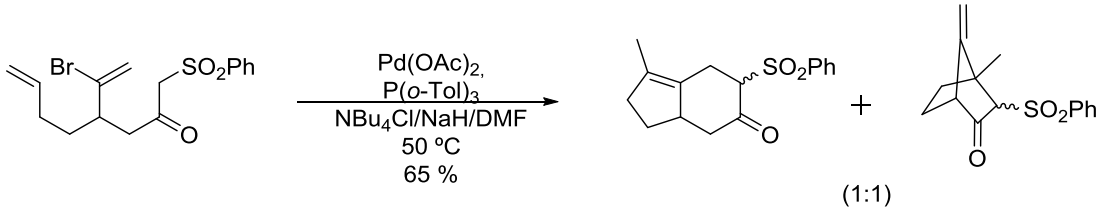
2.1.i.4. Organometallic chemistry.

Organometallic catalysts based mainly in palladium or ruthenium have been used as promoters for the nucleophilic addition of β-ketosulfones to a number of diverse electrophiles. Imi *et al*. developed one of the first formations of five and six membered rings in good yields (59 – 86%) exposing a 1:1 mixture of an enyne and a β-ketosulfone to a palladium catalyst derived from $Pd(OAc)_2$ and a bidentate ligand, 1,3-bis(diphenylphosphino)propane (dppp) or 1,3-bis(di-2-methoxyphenylphosphino)propane (bdmopp) (Scheme 83).[107]



Scheme 83

Weinreb *et al.* demonstrated that an intramolecular tandem Heck reaction-nucleophilic addition to π-allylpalladium species was a useful method for the consecutive formation of two C-C bonds and the construction of functionalised carbobicyclic systems, which is a very useful tool for the synthesis of natural products (Scheme 84).[108]

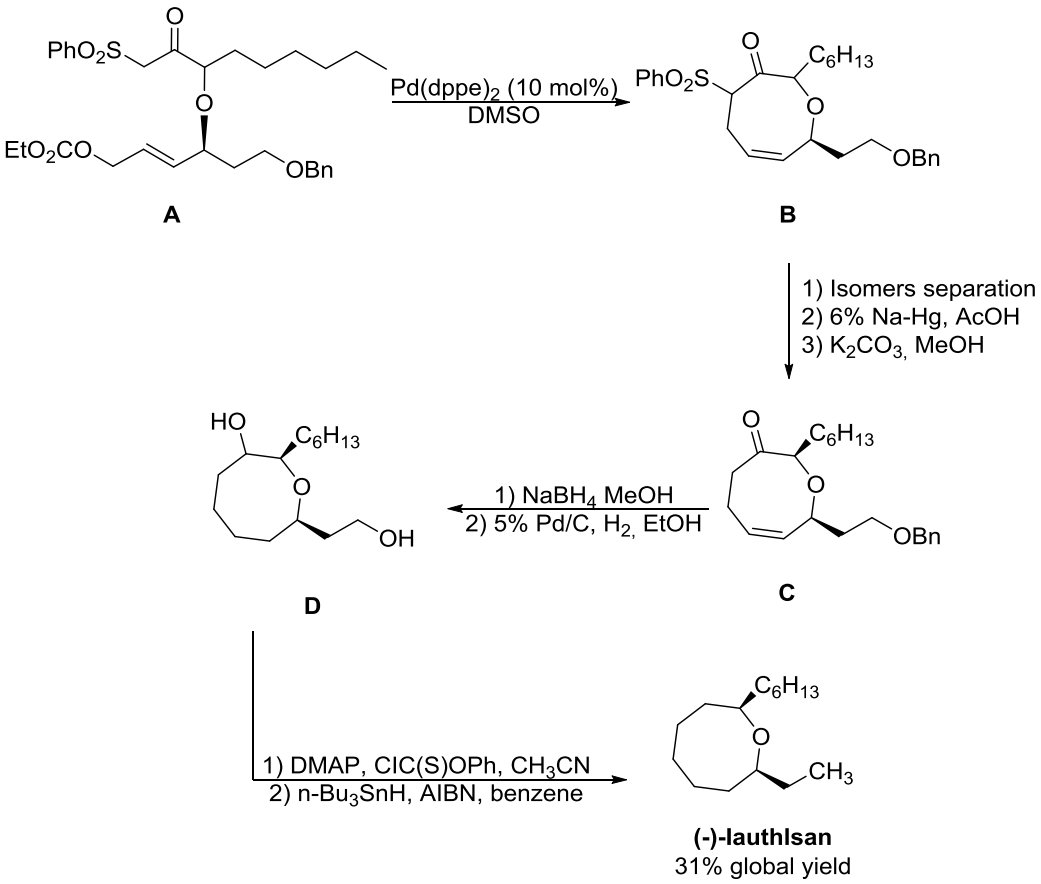


Scheme 84

Suh *et al.* carried out the total synthesis of (-)-lauthisan from β-ketosulfone **A** which was transformed into cyclic ether **B** by treatment with bis[1,2-bis(diphenylphosphino)ethane]Pd(0) ($Pd(dppe_2)$) to give a 6 : 1 mixture of 8 and 6-membered cyclic ethers. Finally $NaBH_4$ reduction, hydrogenation and

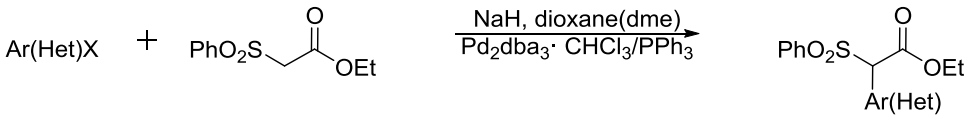
[107] Trost, B. M.; Zhi, L. and Imi, K. *Tetrahedron Lett.* **1994**, *35*, 1361. (10.1016/S0040-4039(00)76218-6)
[108] Nylund, C. S.; Klopp, J. M. and Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 4287. (10.1016/S0040-4039(00)73335-1)

hydrogenolysis of **C** afforded diol **D** in 95% yield. The synthesis of (-)-lauthisan was completed by double deoxygenation of diol **D** (Scheme 85).[109]



Scheme 85

Beletskaya *et al.* reported a method of functionalised arylmethylsulfone synthesis based on palladium catalysed arylation of strongly CH-acidic sulfones. This methodology was further studied by the same group to carry out the monoarylation of a series of more functionalised sulfones by aryl halides in moderate to high yields (25 – 90%) in the presence of $Pd_2dba_3 \cdot CHCl_3$ (dba=dibenzylideneacetone), PPh_3 and NaH as a base.[110,111]

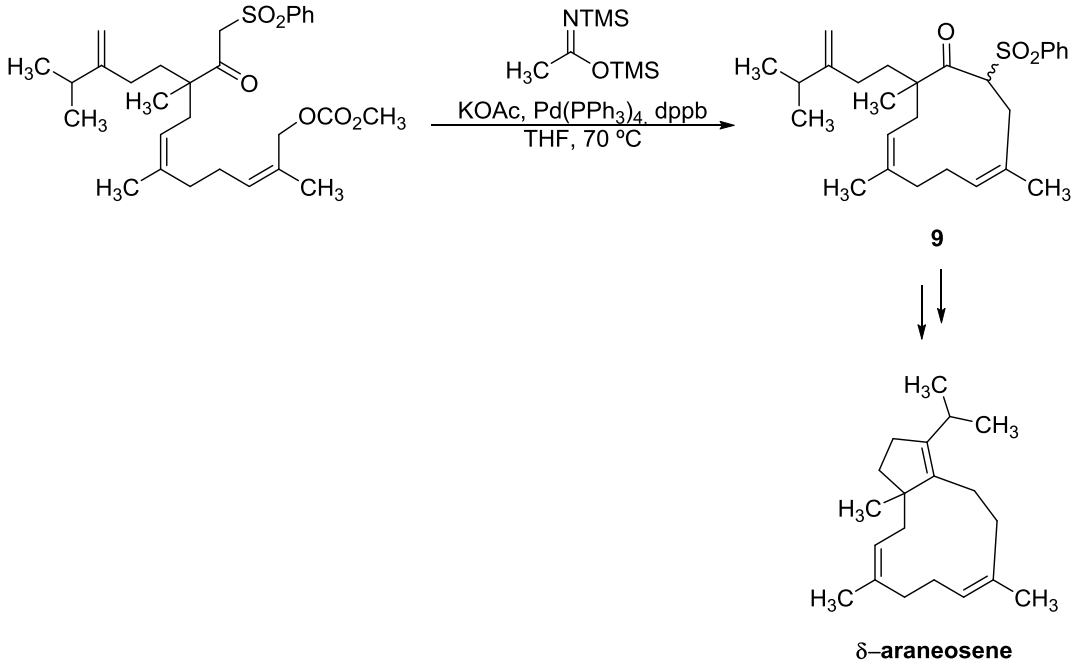


Ar(Het)X = *p*-$CF_3C_6H_4Br$, C_6H_4Br, *p*-$CH_3C_6H_4Br$, *m*-FC_6H_4Br, *p*-$CF_3C_6H_4Cl$, *p*-$CH_3OC_6H_4I$, 1-Br-naphtyl, 3-Br-pyridine, (*E*)-(2-Br-vinyl)benzene

Scheme 86

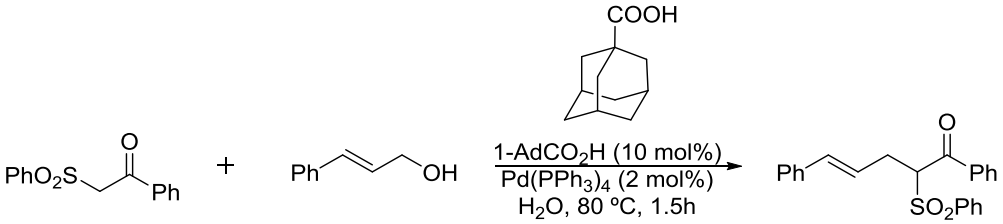
[109] Suh, Y.-G.; Koo, B.-A.; Kim, E.-N. and Choi, N.-S. *Tetrahedron Lett.* **1995**, *36*, 2089. (10.1016/0040-4039(95)00217-Z)
[110] Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P. and Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539. (10.1016/S0040-4039(02)00321-0)
[111] Mitin, A. V.; Kashin, A. N. and Beletskaya, I. P. *Russ. J. Org. Chem.* **2004**, *40*, 802. (10.1023/B:RUJO.0000044542.70121.04)

Corey *et al.* disclosed the syntheses of δ-araneosene through a 11-membered ketone **9**, prepared using as key step the nucleophilic addition of a β-ketosulfone system with $Pd(PPh_3)_4$ with 1,4-bis-(diphenylphosphine)butane ($Pd(PPh_3)_4$, dppb)) in moderate yield (40% global, Scheme 87).[112]



Scheme 87

Kobayashi *et al.* developed a catalytic system that enables reactions of carbon nucleophiles with allylic alcohols as allylating agents in water, among them, a β-ketosulfone system was present affording the corresponding product in a 99% yield. For this purpose this group did proper modifications of catalytic systems based on Pd(0) observing that a carboxylic acid such as 1-adamantanecarboxylic acid (1-$AdCO_2H$) accelerated the palladium-catalysed allylic substitution (Scheme 88).[113]

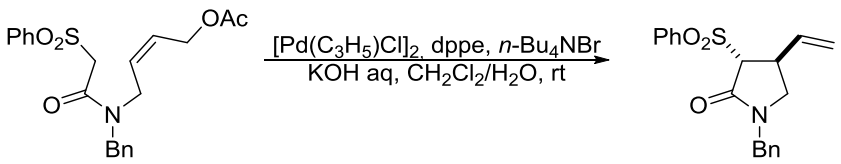


Scheme 88

[112] Hu, T. and Corey, E. J. *Org. Lett.* **2002**, *4*, 2441. (10.1021/ol026205p)
[113] Manabe, K. and Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241. (10.1021/ol035126q)

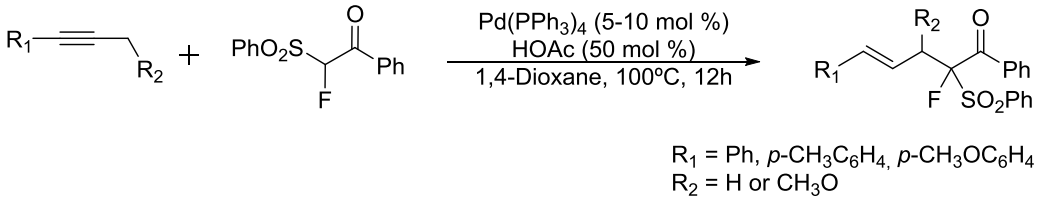
In the same time Yamamoto *et al.* found that this same reaction could be completed without an organic solvent and without water as the solvent, in the presence of a catalytic amount of $Pd(PPh_3)_4$/carboxylic acid under neat conditions.[114]

Madec and Poli *et al.* disclosed new conditions to provide a palladium-catalysed intramolecular allylic alkylation of a β-ketosulfone to form a vinylpyrrolidone (78%, Scheme 89).[115]



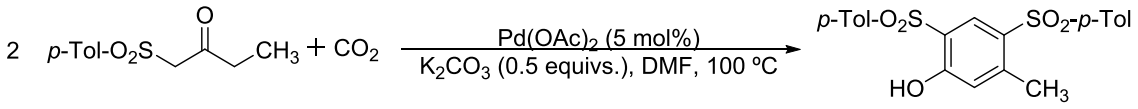
Scheme 89

Hu *et al.* accomplished a palladium-catalysed fluoroalkylation of alkynes with a α-fluoro-β-ketosulfone in the presence of acetic acid to afford the corresponding fluorinated homoallyl ketones in excellent yields (89 – 97%, Scheme 90).[116]



Scheme 90

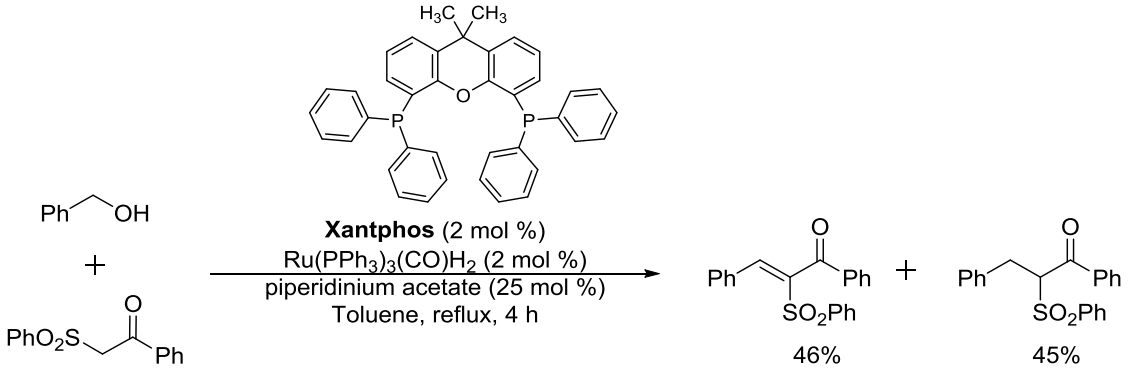
More recently Pan and Liang *et al.* have reported a palladium-catalysed benzannulation by reaction of carbonyl compounds with carbon dioxide in the presence of $Pd(OAc)_2$ (5 mol%), K_2CO_3 (0.5 equiv.) in DMF at 100 ºC. One β-ketosulfone was also tolerated affording the corresponding phenolic compound in an 80% yield (Scheme 91).[117]



Scheme 91

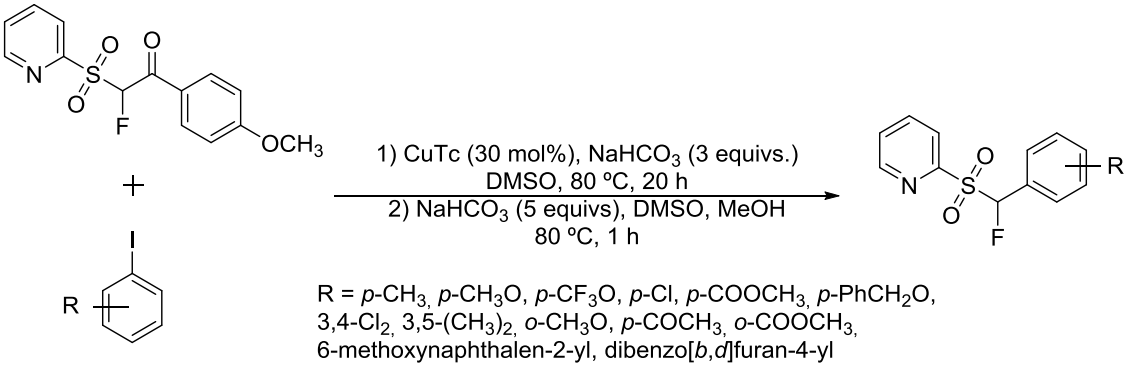
[114] Patil, N. T. and Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 3101. (10.1016/j.tetlet.2004.02.094)
[115] Maitro, G.; Prestat, G.; Madec, D. and Poli, G. *Synlett* **2006**, 1055. (10.1055/s-2006-939702) and references cited herein.
[116] Ni, C. and Hu, J. *Tetrahedron Lett.* **2009**, *50*, 7252. (10.1016/j.tetlet.2009.09.126)
[117] Gao, Q.; Tan, X.-c.; Pan, Y.-m.; Wang, H.-s. and Liang, Y. *Chem. Commun.* **2012**, *48*, 12080. (10.1039/C2CC37194D)

Besides palladium, other metals can be used to promote the nucleophilic addition of β-ketosulfones. Williams *et al.* demonstrated that alcohols could be used to alkylate a β-ketosulfone instead of conventional, often toxic, alkyl halides, using a ruthenium complex of **Xantphos**, although a mixture of compounds with no selectivity was achieved (Scheme 92).[118]



Scheme 92

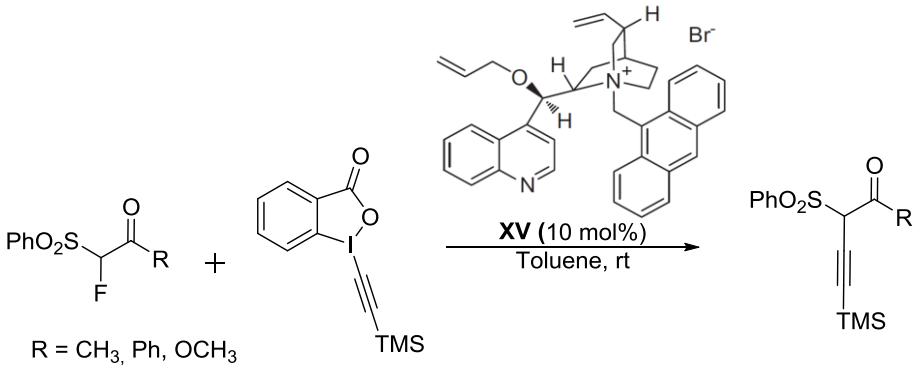
Continuing with their investigations, the group of Hu *et al.* (Scheme 90) has recently developed the monofluoromethylation of aryl iodides in moderate to good yields (63−85%) in the presence of CuTc (copper thiophene-2-carboxylate) and $NaHCO_3$ *via* a Hurtley-type[119] debenzoylative fluoroalkylation and subsequent desulfonylation (Scheme 93).[120]



Scheme 93

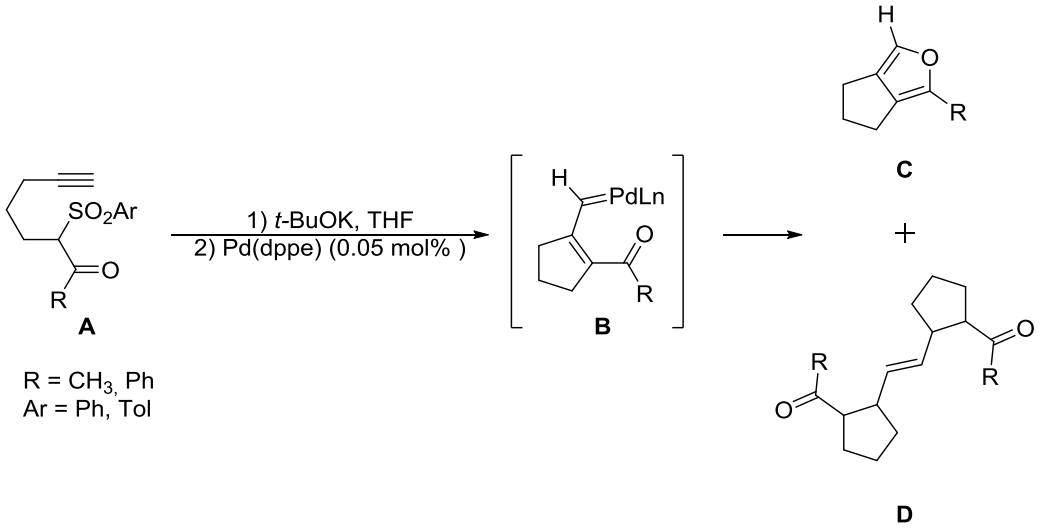
Recently, the group of Veselý *et al.* has developed an alkynylation of α-fluoro-β-ketosulfones using hypervalent iodine compounds under cinchona-based catalysis. The reaction afforded the products in moderate to very good yields (58 – 91%) but with moderate enantioselectivities (58 – 83%, Scheme 94).[121]

[118] Slatford, P. A.; Whittlesey, M. K. and Williams, J. M. J. *Tetrahedron Lett.* **2006**, *47*, 6787. (10.1016/j.tetlet.2006.07.069)
[119] Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870. (10.1039/JR9290001870)
[120] Zhao, Y.; Ni, C.; Jiang, F.; Gao, B.; Shen, X. and Hu, J. *ACS Catal.* **2013**, *3*, 631. (10.1021/cs4000574)
[121] Kamlar, M.; Putaj, P. and Veselý, J. *Tetrahedron Lett.* **2013**, *54*, 2097. (10.1016/j.tetlet.2013.02.023)



Scheme 94

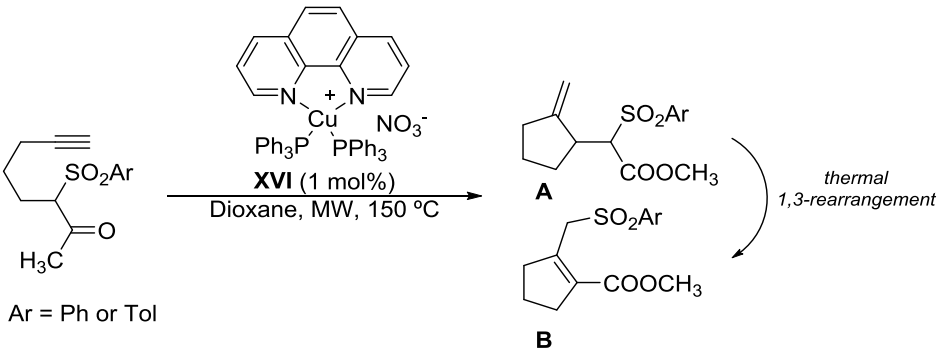
The evidence for the existence of a vinylalkylidene rhodium (Scheme 75) which was formed during the rhodium(II)-catalysed cyclisation led Balme *et al.* to study the existence of alkylidene palladium species of type **B** (Scheme 95) which gave some of the reactions typical of carbenoids: cyclopropanation, attack by a carbonyl group or alkaline sulfinate and dimerisation. Thus, after treating β-keto-ε´-alkynylarylsulfones **A** with potassium *tert*-butoxide in the presence of a Pd(0) complex, bicyclic furans **C** were formed in moderate to good yields (21 – 72%) besides some byproducts **D** . This observation is consistent with the existence of the electrophilic palladium carbenoid **B**. Moreover, this reaction provides an efficient one pot synthesis of 3,4-annulated furans from simple acetylenic β-ketosulfones.[122]



Scheme 95

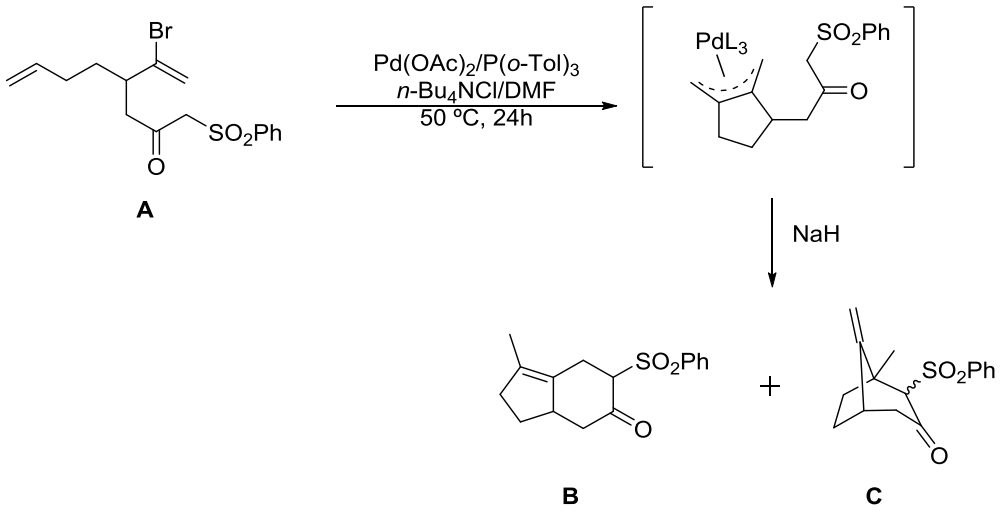
[122] Monteiro, N.; Goré, J.; Van Hemelryck, B. and Balme, G. *Synlett* **1994**, 447. (10.1055/s-1994-22885)

More recently, this group reported a copper-catalysed Conia-ene cyclisation[123] of alkynes bearing a stabilising carbon nucleophile under neutral conditions and microwave irradiation. Among these alkynes, β-ketosulfones were also tested affording predominantly the primary allylic sulfone **B** (9 – 24%) arising from a thermal 1,3-rearrangement of the initially formed tertiary sulfone **A** (44 – 56%) which was isolated as the minor compound (Scheme 96).[124]



Scheme 96

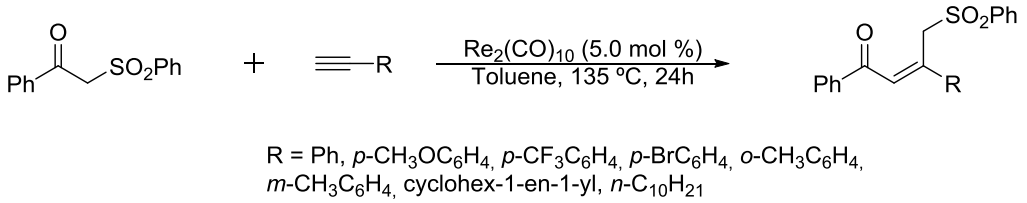
Weinreb *et al.* published the synthesis of byciclic products **B** and **C** from cyclisation of β-keto-ε´-alkenylsulfone **A** using Pd(0) and sodium hydridide to promote the last nucleophilic step (Scheme 97).[125]



Scheme 97

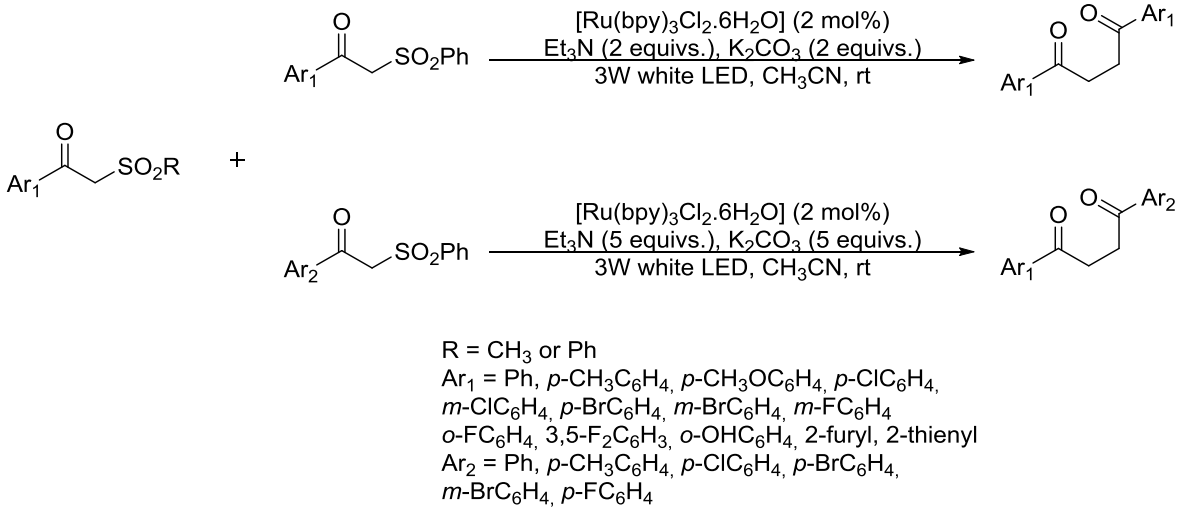
[123] Wang, Z. *Comprehensive Organic Name Reactions and Reagents* **2010**, 37. (10.1002/9780470638859.conrr010)
[124] Montel, S.; Bouyssi, D. and Balme, G. *Adv. Synth. Catal.* **2010**, *352*, 2315. (10.1002/adsc.201000351)
[125] Nylund, C. S.; Smith, D. T.; Klopp, J. M. and Weinreb, S. M. *Tetrahedron* **1995**, *51*, 9301. (10.1016/0040-4020(95)00518-D)

More recently, Kuninobu and Takai *et al.* have reported the use of a rhenium based catalyst for the treatment of β-ketosulfones in the presence of terminal alkynes to form unsaturated δ-ketosulfones in moderate to good yields (31 – 86%, Scheme 98).[126]



Scheme 98

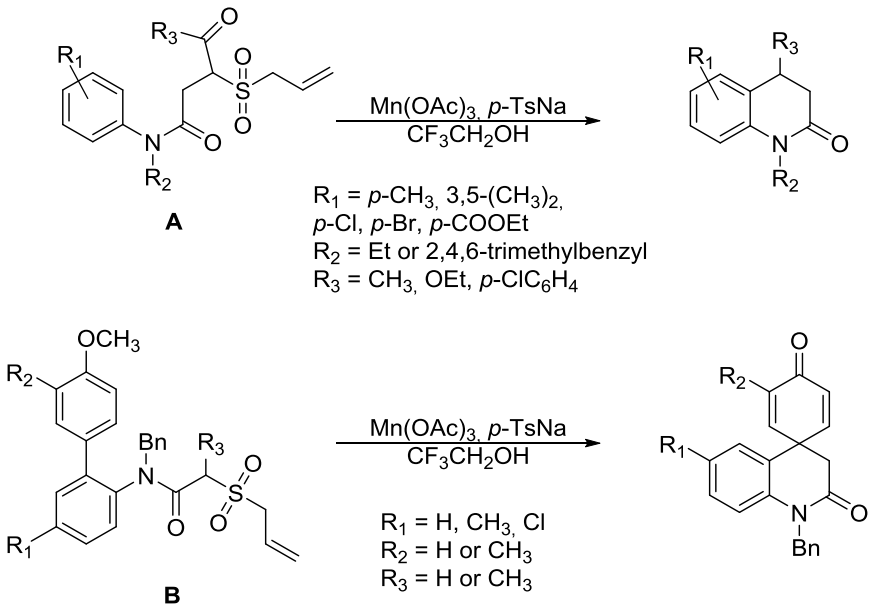
Lu and Xiao *et al.* have very recently developed a visible light-induced C-S bond activation reaction of β-ketosulfones in the presence of a catalytic amount of $[Ru(bpy)_3Cl_2 \cdot 6H_2O]$, Et_3N (2 equivs.), K_2CO_3 (2 equivs.) using a 3W white LED in acetonitrile at room temperature to produce various symmetrical and unsymmetrical 1,4-diketones (Scheme 99).[127]



Scheme 99

Chuang *et al.* have found that *p*-toluenesulfonyl radicals generated by the manganese(III) acetate oxidation of sodium *p*-toluenesulfinate radical can induce the free radical reaction of allylsulfonyl substituted *N*-aryl amides. These alkyl radicals underwent 5-*exo*-trig, 6-*endo*-trig, or 6-*exo*-trig cyclisation onto the aromatic ring effectively. With β-allylsulfonylpropanamides **A**, this reaction provides a method for the synthesis of dihydroquinolinones and azaspirocyclic cyclohexadienes dependening on the substituent of aromatic ring and the stability of radical intermediate. With α-allylsulfonylethanamides **B**, spirodihydroquinolinones were obtained as major products (Scheme 100).

[126] Kuninobu, Y.; Matsuzaki, H.; Nishi, M. and Takai, K. *Org. Lett.* **2011**, *13*, 2959. (10.1021/ol2008507)
[127] Xuan, J.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q. and Xiao, W.-J. *Chem. Eur. J.* **2014**, *20*, 3045. (10.1002/chem.201304898)


R1
R3
O
S
O
O
N
O
R2
A
Mn(OAc)3, p-TsNa
CF3CH2OH
R1 = p-CH3, 3,5-(CH3)2,
p-Cl, p-Br, p-COOEt
R2 = Et or 2,4,6-trimethylbenzyl
R3 = CH3, OEt, p-ClC6H4
OCH3
R2
Bn
R3
N
O
S
O
O
R1
B
Mn(OAc)3, p-TsNa
CF3CH2OH
R1 = H, CH3, Cl
R2 = H or CH3
R3 = H or CH3
O
R2
R1
N
O
Bn

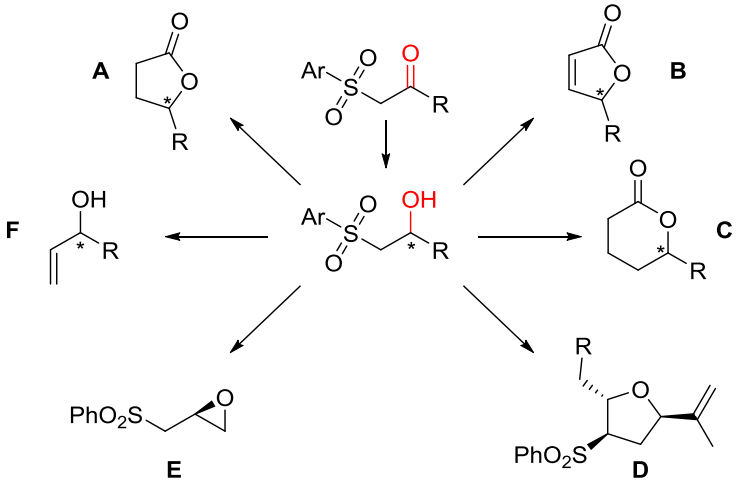
Scheme 100

2.1.ii Reactivity at position 2.

Reactions at position 2 of the β-ketosulfone system typically involves the reactivity as electrophile in addition reactions with other nucleophiles, however, there is many works dealing with the non-racemic reduction of the carbonyl group to a hydroxyl group due to the potential usefulness of optically active β-hydroxysulfones as chiral synthons in organic synthesis. This chapter is divided into the next sections: (1) reduction (by hydrogenation, by reaction with hydrides or by biological reductions), (2) adittion of nucleophiles, (3) reactivity *via* enol (for the synthesis of furanyl derivatives) and (4) reactivity *via* enamine (for the synthesis of pyrrole and pyridine derivatives).

2.1.ii.1. Reduction.

β-Hydroxysulfones have been used as starting materials for the synthesis of many different products such as optically active γ-butenolides (**A,** Scheme 101), γ-butyrolactones (**B**), [128,129] δ-valerolactones (**C**),[130] 2,5-disubstituted tetrahydrofurans (**D**), chiral epoxides (**E**),[131] or allylic alcohols (**F**).[132]



Scheme 101

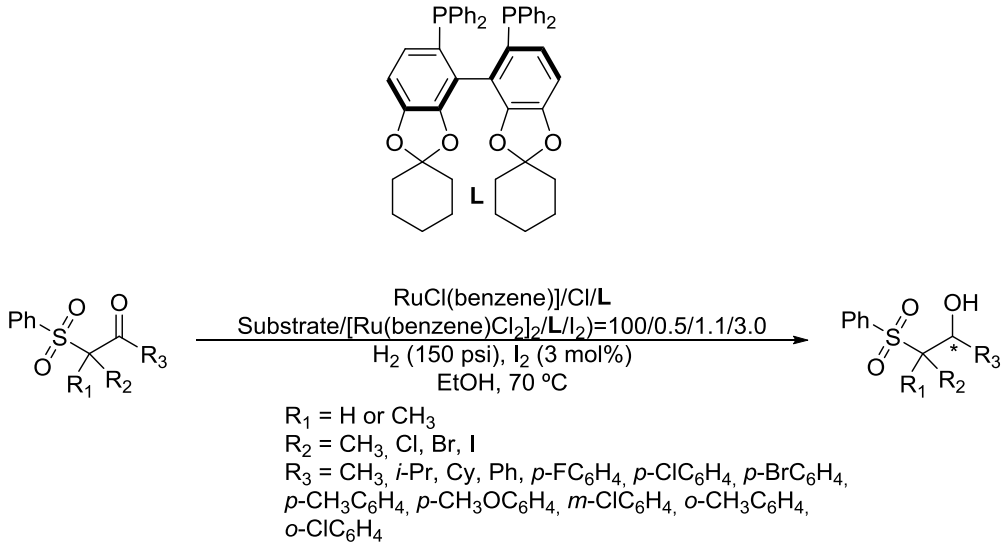
As a result, many methods have been developed for the enantioselective synthesis of optically active β-hydroxysulfones, which can be divided into hydrogenation, reaction with hydrides and biological reductions.

[128] Bertus, P.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Touati, A. R.; Homri, T. and Hassine, B. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1369. (10.1016/S0957-4166(99)00113-5)
[129] Robin, S.; Huet, F.; Fauve, A. and Veschambre, H. *Tetrahedron: Asymmetry* **1993**, *4*, 239. (10.1016/S0957-4166(00)82344-7)
[130] Kozikowski, A. P.; Mugrage, B. B.; Li, C. S. and Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817. (10.1016/S0040-4039(00)85071-6)
[131] Tanikaga, R.; Hosoya, K. and Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1799. (10.1039/P19870001799)
[132] Tanikaga, R.; Hosoya, K. and Kaji, A. *Chem. Lett.* **1987**, *16*, 829.

2.1.ii.1.1. Hydrogenation.

Genêt *et al*. reported enantioselective hydrogenation of β-ketosulfones with chiral Ru(II) catalysts (mainly (*R*) and (*S*)-MeO-BIPHEP = (*R*)-(+)-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,l'-biphenyl and CODRu(2-methylallyl)$_2$ = cyclooctadieneRu(methylallyl)2), in MeOH at different hydrogen pressures and temperatures.[128,133] Later this group reported the *in situ* preparation of chiral ruthenium-diphosphine catalysts from anhydrous $RuCl_3$, based on the fact that $RuCl_3 \cdot nH_2O$ is the readily available source for most of the multistep preparations of chiral diphosphine ruthenium complexes. Thus, hydrogenation using $RuCl_3$ + (*S*)-MeO-BIPHEP or *in situ* generated $RuBr_2$[(*S*)-MeO-BIPHEP] reduced prochiral C=O and C=C bonds with high enantioselectivities. Among the substrates studied, a β-ketosulfone was also hydrogenated in comparable yields and enantioselectivities to the previously reported by the group.[134]

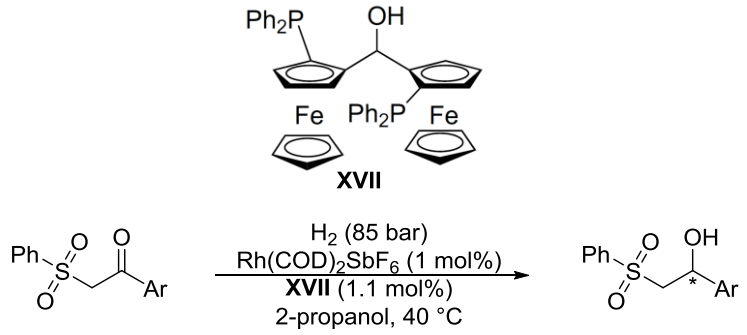
Zhang *et al.* focused on the design and application of new biaryl phosphine ligands for this reaction and they reported a highly enantioselective hydrogenation (90 – 99% ee) of β-ketosulfones in the presence of iodine with full conversion (Scheme 102).[135]



Scheme 102

[133] Bertus, P.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Touati, A. R.; Homri, T. and Hassine, B. B. *Tetrahedron Lett.* **1999**, *40*, 3175. (10.1016/S0040-4039(99)00453-0)
[134] Madec, J.; Pfister, X.; Phansavath, P.; Ratovelomanana-Vidal, V. and Genêt, J. P. *Tetrahedron* **2001**, *57*, 2563. (10.1016/S0040-4020(01)00067-9)
[135] Wan, X.; Meng, Q.; Zhang, H.; Sun, Y.; Fan, W. and Zhang, Z. *Org. Lett.* **2007**, *9*, 5613. (10.1021/ol702565x)

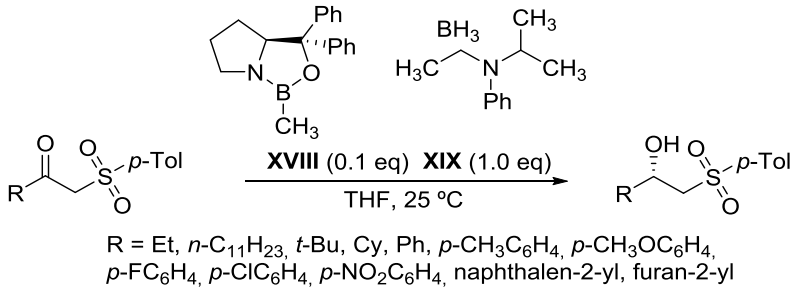
Hou and Dai *et al.* developed a bisferrocenyl diphosphine ligand with planar chirality for the Rh-catalysed enantioselective hydrogenation of aromatic β-ketosulfones with full conversion and good to excellent enantioselectivity (72 – 98 % ee, Scheme 103).[136]



Scheme 103

2.1.ii.1.2. Reaction with hydrides.

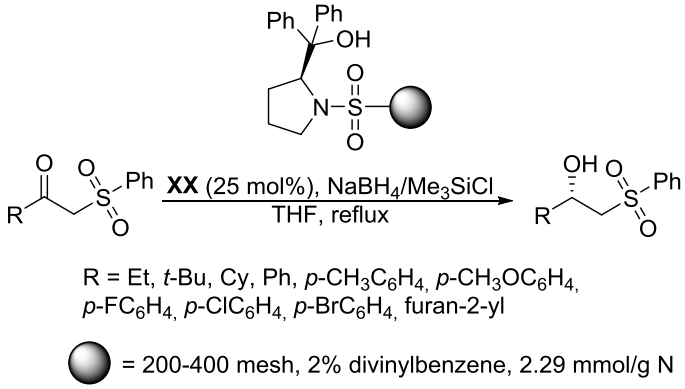
One of the most successful reduction reactions involves the use of borane in the presence of homogeneous catalysts derived from chiral amino alcohols. Cho *et al.* reported a Corey-Bakshi-Shibata (CBS)–oxazaborolidine-catalysed asymmetric borane (**XVIII**) reduction of β-ketosulfones using *N*-ethyl-*N*-iso-propylaniline–borane complex **XIX** as the borane carrier. The corresponding β-hydroxysulfones were obtained in excellent yields (96 – 99%) and good to excellent enantioselectivity (73 – 99% ee, Scheme 104).[137]



Scheme 104

[136] Zhang, H.-L.; Hou, X.-L.; Dai, L.-X. and Luo, Z.-B. *Tetrahedron: Asymmetry* **2007**, *18*, 224. (10.1016/j.tetasy.2007.01.009)
[137] Cho, B. T. and Kim, D. J. *Tetrahedron: Asymmetry* **2001**, *12*, 2043. (10.1016/S0957-4166(01)00359-7)

However, the recovery and purification of these catalysts are usually problematic. Immobilisation of chiral catalysts or reagents on insoluble polymers offers a solution to the problem. Zhao *et al.* reported the enantioselective synthesis of optically active β-hydroxysulfones in excellent yields (96 – 99%) and moderate to excellent enantioselectivity (56 – 97% ee, Scheme 105) by asymmetric reduction of β-ketosulfones using the $NaBH_4/Me_3SiC$ system in the presence of 25 mol% of polymer-supported sulfonamide **XX** (200–400 mesh, 2% divinylbenzene, 2.29 mmol/g N).[138]



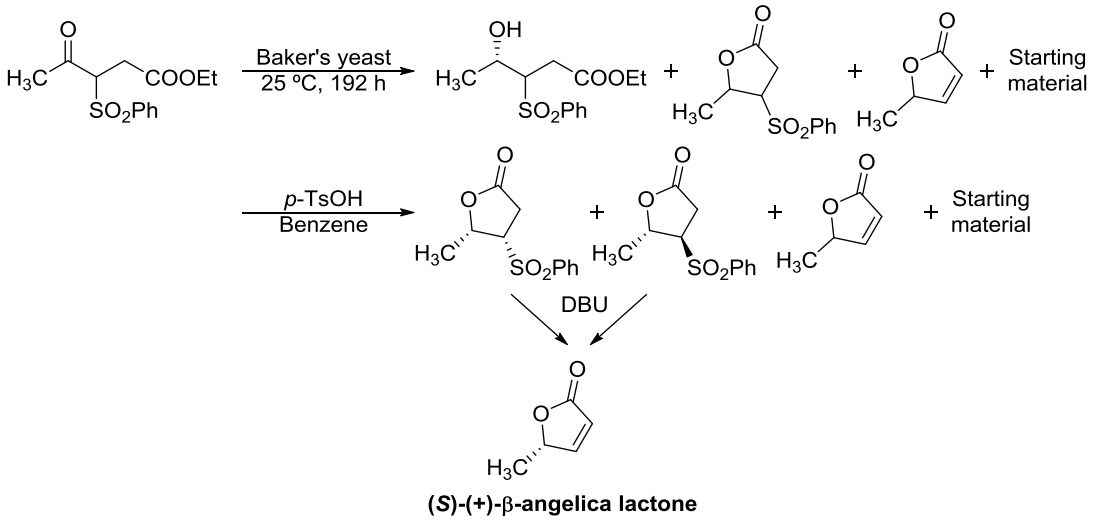
Scheme 105

Later, this group developed a recoverable homogeneous dendrimer-supported catalyst for the enantioselective borane reduction of prochiral ketones (among them one β-ketosulfone was also compatible affording the corresponding β-hydroxysulfone in 99% yield and 98% ee).[139] More recently Singaram *et al.* reported the asymmetric reduction of different α-substituted ketones with 3-nitrophenylboronic acid L-tartaric acid ester (L-TarB-NO_2) and $NaBH_4$ in THF. However, most of the products were obtained with poor to modest enantioselectivity although in moderate to excellent yields. Only one β-ketosulfone was tested obtaining the corresponding β-hydroxysulfone in 86% yield but only with 35% ee.[140]

[138] Zhao, G.; Hu, J.-B.; Qian, Z.-S. and Yin, W.-X. *Tetrahedron: Asymmetry* **2002**, *13*, 2095. (10.1016/S0957-4166(02)00546-3)
[139] Wang, G.-Y.; Liu, X.-Y. and Zhao, G. *Synlett* **2006**, 1150. (10.1055/s-2006-926253)
[140] Eagon, S.; Ball-Jones, N.; Haddenham, D.; Saavedra, J.; DeLieto, C.; Buckman, M. and Singaram, B. *Tetrahedron Lett.* **2010**, *51*, 6418. (10.1016/j.tetlet.2010.09.146)

2.1.ii.1.3. Biological reductions.

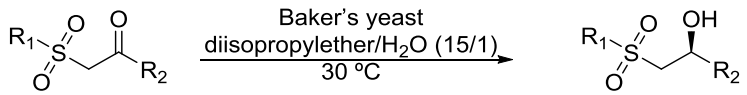
One of the most useful strategies to access chiral β-hydroxysulfones has been the baker's yeast alcohol dehydrogenase mediated asymmetric reduction of β-ketosulfones.[141,142] In 1993 Huet *et al.* reported the microbiological reductions of β-ketosulfones. A three step synthesis of (*S*)-(+)-β-angelica lactone, a useful synthetic intermediate in enantioselective synthesis,[143] was also reported (Scheme 106).[144]



Scheme 106

Employing whole-cell biocatalysts, Sugai *et al.* developed different yeast strains (*Candida floricola* IAM 13115 and *Trichosporon cutaneum* IAM 12206, with *Si*-face hydride attack and *Pichia angusta* IAM 12895 and *Pichia minuta* IAM 12215 with *Re*-face hydride attack) for the synthesis of sterically hindered optically active 3-methyl-1-(phenylsulfonyl)butan-2-ol in moderate to very good yields (32 – 93%) and very good enantioselectivity (92 – 97% ee).[145] This bioreduction system suffers from the same intrinsic limitations of biotransformations in water, *i.e.*, a relatively large volume of water is required as the solvent, which makes the work-up procedure more difficult, particularly since the product is difficult to isolate from the huge amounts of biomass. Yuan *et al.* reported the synthesis of chiral β-hydroxysulfones in modereate to excellent yields (35 – 99%) and good to excellent enantioselectivity (70 – 99% ee) using baker's yeast and and *Candida Antarctica* lipase B in a diisopropyl ether (as a substitute for water)/limited water solvent (Scheme 107).[146]

[141] Servi, S. *Synthesis* **1990**, 1. (10.1055/s-1990-26775)
[142] Csuk, R. and Glaenzer, B. I. *Chem. Rev.* **1991**, *91*, 49. (10.1021/cr00001a004)
[143] Ortuño, R. M.; Alonso, D.; Cardellach, J. and Font, J. *Tetrahedron* **1987**, *43*, 2191. (10.1016/S0040-4020(01)86801-0)
[144] Robin, S.; Huet, F.; Fauve, A. and Veschambre, H. *Tetrahedron: Asymmetry* **1993**, *4*, 239. (10.1016/S0957-4166(00)82344-7)
[145] Hiraoka, C.; Matsuda, M.; Suzuki, Y.; Fujieda, S.; Tomita, M.; Fuhshuku, K.-i.; Obata, R.; Nishiyama, S. and Sugai, T. *Tetrahedron: Asymmetry* **2006**, *17*, 3358. (10.1016/j.tetasy.2006.12.013)
[146] Chen, Q.; Wang, K. and Yuan, C. *New J. Chem.* **2009**, *33*, 972. (10.1039/B820192G)



R_1= Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$, *p*-ClC_6H_4
R_2 = CH_3, Et, *n*-Pr, Ph

Scheme 107

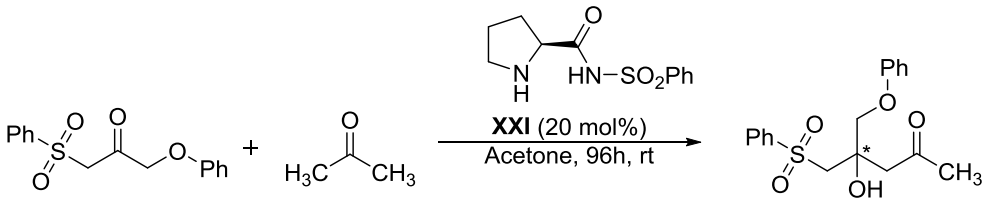
Besides baker's yeast, fungus as *Curvularia lunata* CECT 2130 has also been used to reduce β-ketosulfones to the corresponding β-hydroxysulfones in very good yields (89 – 92%) and good to excellent enantioselectivity (87 – 97% ee). Moreover, these cells could be re-used without loss of their catalytic activity as reported by Rebolledo *et al.*[147]

Pandey *et al.* have recently developed the syntheses of *cis*-1,2-diaminocyclohexane derivatives and 7-azabicyclo[2.2.1]hept-2-amines, starting with the racemic reduction of an azabicyclo β-ketosulfone with $LiBH_4$ in THF.[148] 1,2-Diamines are important scaffolds in organic chemistry and are routinely used as ligands in asymmetric organic transformations.[149]

[147] Gotor, V.; Rebolledo, F. and Liz, R. *Tetrahedron: Asymmetry* **2001**, *12*, 513. (10.1016/S0957-4166(01)00048-9)
[148] Pandey, G.; Dey, D. and Fernandes, R. *Eur. J. Org. Chem.* **2013**, 4319. (10.1002/ejoc.201300253)
[149] Zhang, L. and Luo, S. *Synlett* **2012**, 1575. (10.1055/s-0031-129068)

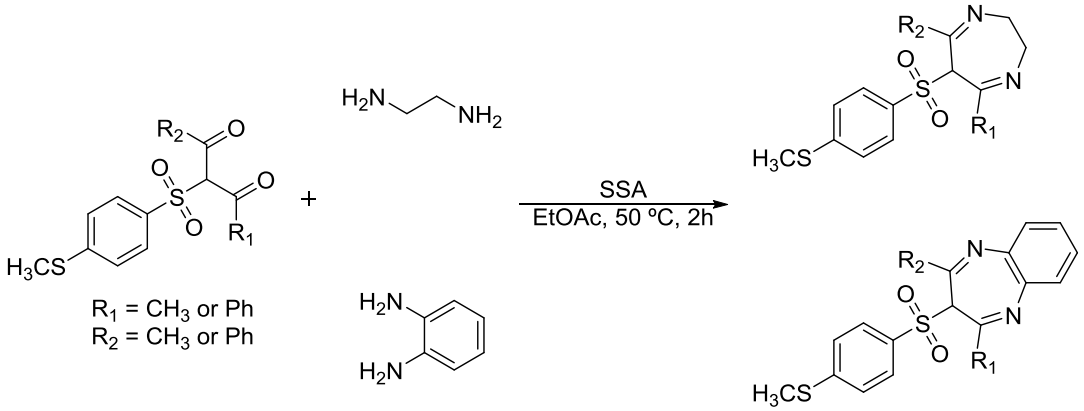
2.1.ii.2. Addition of nucleophiles.

As mentioned at the beginning of this chapter, the position 2 of the β-ketosulfone system can react as electrophile in addition reactions with other nucleophiles. Hence, Frongia *et al*. reported the cross aldol reaction of two β-ketosulfones (phenylsulfonylacetone and phenylsulfonylphenoxyacetone) with acetone catalysed by an L-proline amide derivative. However, phenylsulfonylacetone did not react under these conditions and phenylsulfonylphenoxyacetone only yielded a 60% of the corresponding aldol with a 70% ee after 96 hours of reaction (Scheme 108).[150]



Scheme 108

More recently, Joshi *et al.* reported the synthesis of 1*H*-1,4-diazepines and 3*H*-1,5-benzodiazepines in moderate to good yields (63 – 83%) using silica sulfuric acid (SiO_2-OSO_3H, SSA)[151] in ethyl acetate from the heterocyclisation reaction of 2-(4-methylthio benzenesulfonyl)-propane-1,3-diones with ethylenediamine (EDA) and *o*-phenylenediamine (*o*-PDA), respectively (Scheme 109)[152]. Synthesised compounds were biologically evaluated, finding antimicrobial and antifungal activities.



Scheme 109

[150] Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. and Spiga, M. *Tetrahedron Lett.* **2008**, *49*, 3037. (10.1016/j.tetlet.2008.03.066)
[151] Veisi, H. *Tetrahedron Lett.* **2010**, *51*, 2109. (10.1016/j.tetlet.2010.02.052)
[152] Joshi, Y. C.; Saingar, S.; Kavita, J. P. and Kumar, R. *J. Korean Chem. Soc.* **2011**, *55*, 638. (10.5012/jkcs.2011.55.4.638)

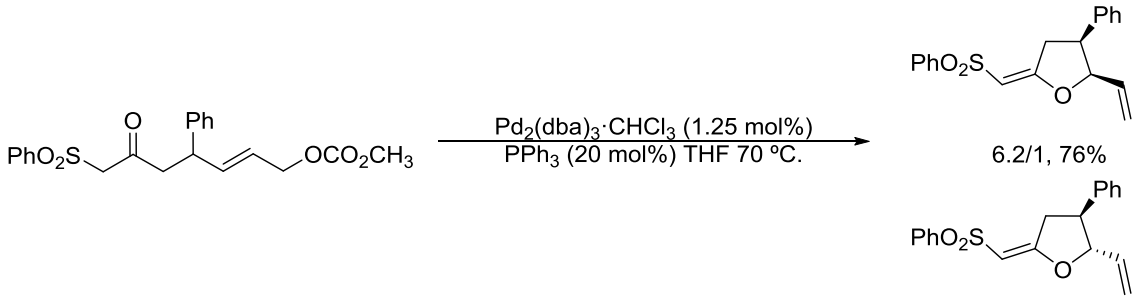
Using this methodology, Eweas *et al.* reported the synthesis of a series of 8-hydroxyquinoline-5-sufonyl 1,4-diazepine derivatives[153] and found that these compounds have *in vitro* schistosomicidal[154] activity against *S. mansoni* adult worms and may be novel broad-spectrum anti-schistosomal drug candidates. Also starting from a β,β´-diketosulfone, Wisner and Zysman-Colman *et al*. reported the synthesis and characterisation of an iridium complex bearing a 2-pyridyl-6-methylthiazine dioxide ligand used in spectroscopic and photophysical studies.[155] This ligand was synthesised in three steps including cyclisation using NH_4OAc in refluxing dimethylformamide.

[153] Eweas, A. F.; Allam, G.; Abuelsaad, A. S. A.; Alghamdi, A. H. and Maghrabi, I. A. *Bioorg. Chem.* **2013**, *46*, 17. (10.1016/j.bioorg.2012.10.003)
[154] Utzinger, J.; Raso, G.; Brooker, S.; De Savigny, D.; Tanner, M.; Ørnbjerg, N.; Singer, B. H. and N'Goran, E. K. *Parasitology* **2009**, *136*, 1859. (10.1017/S0031182009991600)
[155] Ladouceur, S.; Donato, L.; Romain, M.; Mudraboyina, B. P.; Johansen, M. B.; Wisner, J. A. and Zysman-Colman, E. *Dalton Trans.* **2013**, *42*, 8838. (10.1039/c3dt33115f)

2.1.ii.3. Reactivity *via* enol.

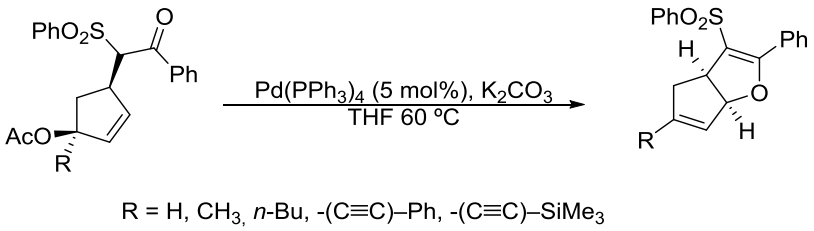
Carbonyl group of β-ketosulfones participates in many reactions in the enol form for the synthesis of furan derivatives.

Since the synthetic and pharmacological potentials of furan compounds have been widely recognised,[156] the new and efficient synthetic method for the construction of furan nucleus has been attracting extensive interest.[157] For the mild construction of furan nucleus, transition metal-catalysed cyclisations of ε-alkenyl, or cyclopropyl β-ketosulfones have been developed, in particular, Pd-catalysed reactions of such substrates with electrophiles in tandem approaches. In 1991, Trost *et al*. published the cyclisation of a β-ketosulfone in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, and triphenylphosphine in THF at 70 ºC (Scheme 110).[158]



Scheme 110

Bisht *et al*. studied the Pd (0) catalysed intramolecular cyclisation of β-ketosulfones acetyl derivatives in the presence of K_2CO_3 and $Pd(PPh_3)_4$ in THF at 60 ºC to obtain optically pure dihydrofurans in good diasteromeric ratios and yields (61 -73%, Scheme 111).[159]

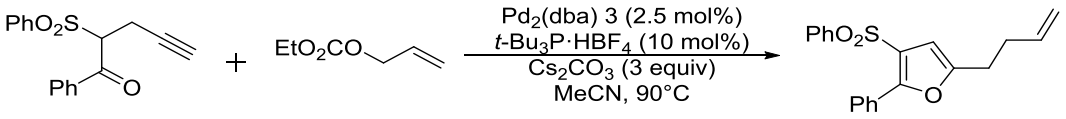


Scheme 111

[156] Wright, D. L. *Prog. Heterocycl. Chem.* **2005**, *Volume 17*, 1. (10.1016/S0959-6380(05)80323-X)
[157] Hou, X.-L.; Yang, Z.; Yeung, K.-S. and Wong, H. N. C. *Prog. Heterocycl. Chem.* **2008**, *Volume 19*, 176. (10.1016/S0959-6380(08)80009-8)
[158] Trost, B. M. and Lee, P. H. *J. Am. Chem. Soc.* **1991**, *113*, 5076. (10.1021/ja00013a062)
[159] Khan, P. M.; Wu, R. and Bisht, K. S. *Tetrahedron* **2007**, *63*, 1116. (10.1016/j.tet.2006.11.066)

According to the authors, this reaction starts with base deprotonation of the methine proton between the two electron-withdrawing groups. The carbanion thus generated results in the formation of dihydrofurans *via* electron-flow through enolate oxygen. The stereochemical outcome of the reaction is the result of two sequential steps. First is the formation of the Pd π-allyl complex formed on the opposite side of the OAc leaving group because of steric control. In the second step, the attack of the nucleophile proceed in an *anti*-fashion with respect to metal resulting in a highly stereoselective reaction.

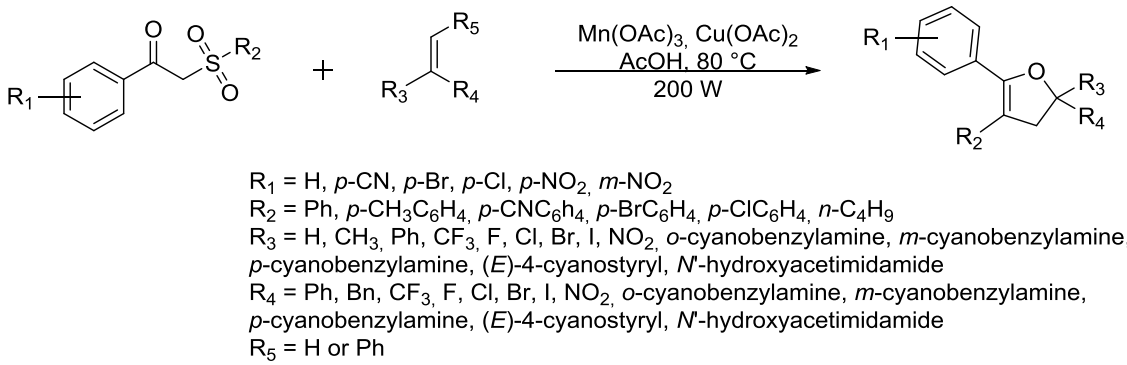
As a part of the study of Hanzawa *et al.* on the synthesis of heterocyclic compounds based on Pd-catalysed 5-*exo* cyclisation reactions this group recently reported the formation of 5-homoallylfuran derivatives from 4-alkynones with allyl carbonates in the presence of $Pd_2(dba)_3$, *t*-$Bu_3P{\cdot}HBF_4$, and Cs_2CO_3 in CH_3CN at 90 ºC. Among them, one β-ketosulfone was also reactive affording the expected 5-homoallyl furan in 91% yield (Scheme 112).[160]



Scheme 112

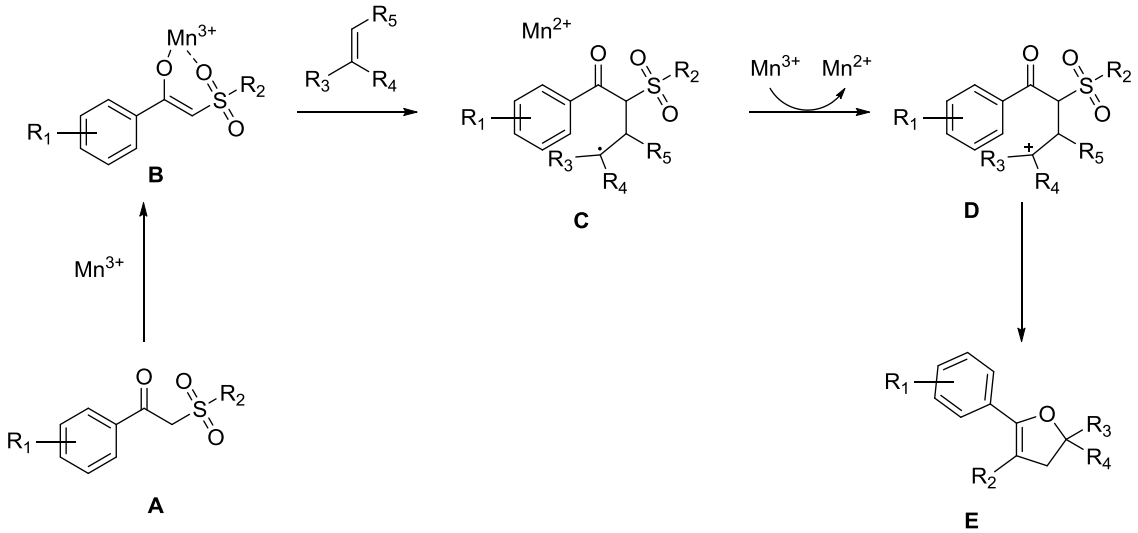
Other metals rather than palladium can be used for the synthesis of furans from β-ketosulfones *via* enol activation. Manganese derivatives have been developed and used by Vanelle *et al.* for the radical cyclisation of β-ketosulfones to synthesise dihydrofurans (Scheme 113).[161,162,163] Recently this group has reported the reactivity of two alkenes, α-methylstyrene and *trans*-stilbene[164], extending previous works.[165,166,167]

[160] Saito, A.; Enomoto, Y. and Hanzawa, Y. *Tetrahedron Lett.* **2011**, *52*, 4299. (10.1016/j.tetlet.2011.06.037)
[161] Paloque, L.; Bouhlel, A.; Curti, C.; Dumètre, A.; Verhaeghe, P.; Azas, N. and Vanelle, P. *Eur. J. Med. Chem.* **2011**, *46*, 2984. (10.1016/j.ejmech.2011.04.026)
[162] Bouhlel, A.; Curti, C.; Dumètre, A.; Laget, M.; Crozet, M. D.; Azas, N. and Vanelle, P. *Bioorg. Med. Chem.* **2010**, *18*, 7310. (10.1016/j.bmc.2010.06.099)
[163] Bouhlel, A.; Curti, C.; Khoumeri, O. and Vanelle, P. *Tetrahedron Lett.* **2011**, *52*, 1919. (10.1016/j.tetlet.2011.02.049)
[164] Bouhlel, A.; Curti, C.; Tabele, C. and Vanelle, P. *Molecules* **2013**, *18*, 4293. (10.3390/molecules18044293)
[165] Curti, C.; Crozet, M. D. and Vanelle, P. *Tetrahedron* **2009**, *65*, 200. (10.1016/j.tet.2008.10.080)
[166] Qian, C.-Y.; Nishino, H. and Kurosawa, K. *J. Heterocycl. Chem.* **1993**, *30*, 209. (10.1002/jhet.5570300136)
[167] Qian, C.-Y.; Hirose, J.-I.; Nishino, H. and Kurosawa, K. *J. Heterocycl. Chem.* **1994**, *31*, 1219. (10.1002/jhet.5570310519)



Scheme 113

The plausible reaction mechanism for this oxidative cyclisation suggested by the authors is depicted in Scheme 114. According to this mechanism, the interaction of $Mn(OAc)_3$ with the enol form of **A** could afford manganese(III)-enolate complex **B**. Then the reaction of structure **B** and the alkene formed a C–C bond with a benzylic radical **C**. A second equivalent of $Mn(OAc)_3$ could be used to oxidise the newly formed radical in order to give rise to a carbocation **D**. Finally, an intramolecular cyclisation gives the 2,3-dihydrofuran **E**.

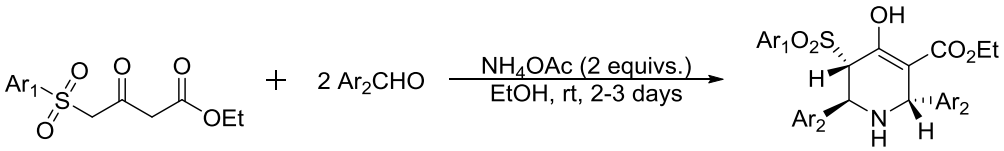


Scheme 114

Perumal *et al*. also reported the use of manganese for a diasteroselective synthesis of tetrasubstituted *cis* 4,5-dihydrofurans by oxidative addition of 1,3-dicarbonyl compounds with chalcones in the presence of $Mn(OAc)_3$ and NaOAc in acetic acid at 80 ºC. Among the examples studied, one β-ketosulfone was tolerated affording the corresponding furan in 44% yield.[168] In the previously shown work of this group for the synthesis of *cis*-1,4-cyclohexa-1,4-dienes (Scheme 60, page 64) this group also reported the synthesis of 1,2,5,6-tetrahydropyridines in moderate to very good yields (60 – 91%)

[168] Shanmugam, P. N.; Kumar, K. I. H. and Perumal, P. N. T. *J. Heterocycl. Chem.* **2007**, *44*, 827. (10.1002/jhet.5570440412)

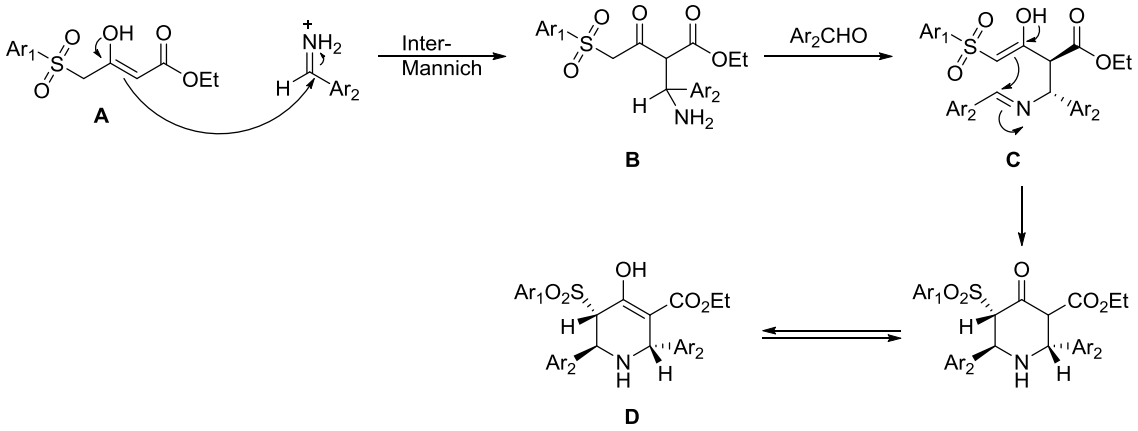
from the domino reactions of ethyl 3-oxo-4-(arylsulfonyl)butanoates, aromatic aldehydes (2 equivs.) and using this time an excess of ammonium acetate (2 equivs.) instead of catalytic amount (Scheme 115).



Ar_1 = Ph, *p*-ClC_6H_4 or *p*-$CH_3C_6H_4$
Ar_2 = Ph, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *o*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, *o*-BrC_6H_4, *m*-ClC_6H_4, *m*-BrC_6H_4, *o*,*p*-$Cl_2C_6H_3$, *m*-$NO_2C_6H_4$ or *m*-FC_6H_4

Scheme 115

The mechanism proposed by the authors is depicted in Scheme 116. After formation of intermediate **B** by the Mannich reaction of enol form of **A** with aryliminium ion, this would react with aromatic aldehyde forming imine **C** and its subsequent intramolecular Mannich reaction. The relative configuration of the stereocentres in **D** is presumably fixed during the Mannich reactions.



Scheme 116

In contrast to metal-mediated processes, other methods as phase-transfer catalysed (PTC) or organocatalytic approaches to the construction of furans are scarce. Arai and Shioiri *et al.* used a PTC reaction system to produce dihydrofurans *via* both intermolecular C-C and intramolecular C-O bond formations. The reaction of a cyclic enone such as α-chlorocyclohexenone with a β-ketosulfone was carried out in the presence of rubidium carbonate with a catalytic amount of quaternary ammonium salt tetrahexylammonium bromide (THAB) as the PTC at room temperature, affording the corresponding furan in 81% yield and faster than in the absence of PTC.[169]

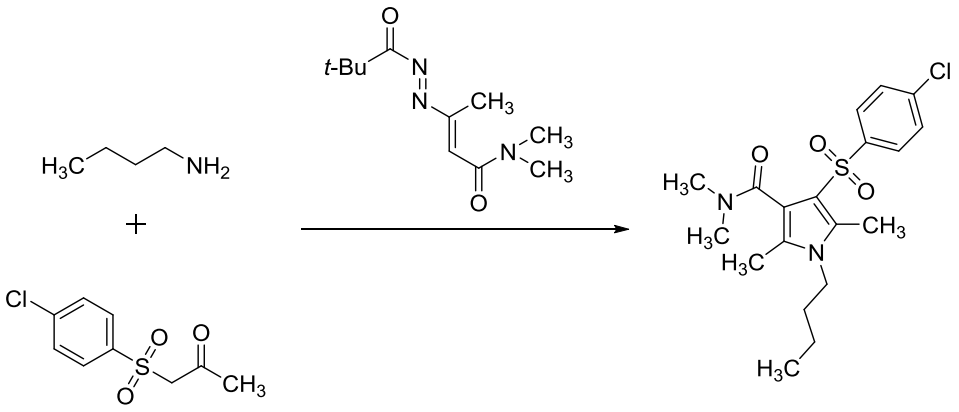
[169] Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.-i. and Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739. (10.1016/S0040-4039(98)02239-4)

2.1.ii.4. Reactivity *via* enamine.

Natural products that contain saturated five- or six-membered nitrogen heterocycles, such as pyrrole,[170] nitrone, oxazol, thiazol, pyridone,[171] pyridine,[172] quinoline, isoquinoline and indolizidine have been popular synthetic targets due to the array of potent biological activities of these compounds, and the variety of structural challenges that are encountered in their construction. A general approach to the preparation of these ring systems, which has had numerous applications, has been the azaannulation with imines and various acrylate derivatives. Unfortunately, the initial use of acid chlorides for these annulation reactions often produced low yields due to the generation of side products and the use of acrylate esters or other acrylic acid anhydride derivatives was necessary for optimum annulation. In a recent study of azaannulation with imine substrates, a number of alternative acrylate derivatives were used for efficient preparation of δ-lactams. However, restrictions to this methodology include the lack of alkene regioselectivity, poor yields that result from the imines of aldehydes, and limited methods for reduction of the resultant double bond. Cyclic enamines, which have carbonyl substituents at the nucleophilic enamine carbon, have been used to overcome these limitations in the construction of nitrogen heterocycles.

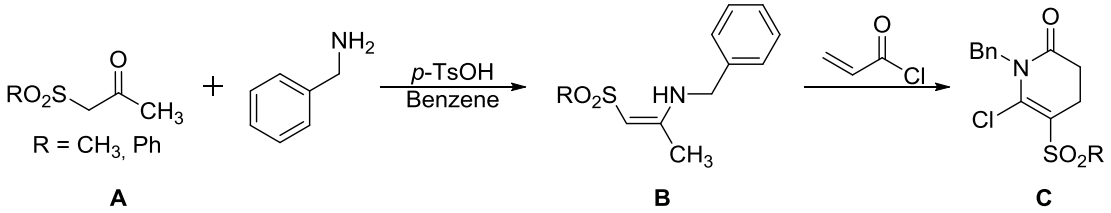
Pyrrole is one of the most important simple heterocycles, which is found in a broad range of natural products and drug molecules, and is also of growing relevance in materials science.[170] The most frequently used methods for their syntesis include the classical Hantzsch procedure,[173] the cyclocondensation of α-aminoketones with β-ketoester or β-diketones (Knorr synthesis), the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal-Knorr synthesis),[174] and various cycloaddition and transition-metal-catalysed cyclisation strategies. Many of these procedures, however, have certain restrictions in terms of the scope and placement of the substitution pattern around the heterocyclic core. Favi *et al.* have reported a catalyst- and solvent-free, one-pot procedure at room temperature, for the preparation of functionalised pyrroles through a sequential three-component reaction of primary aliphatic amines, active methylene compounds (among them one β-ketosulfone was also supported although in low yield, 26%, Scheme 117), and 1,2-diaza-1,3-dienes. This approach avoids transition-metal catalysts and occurs with complete control of pathway selectivity.[175]

[170] Estevez, V.; Villacampa, M. and Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (10.1039/B917644F)
[171] Hughes, R. A. and Moody, C. J. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 7930. (10.1002/anie.200700728)
[172] Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052. (10.1002/chem.201001100)
[173] Wang, Z. *Comprehensive Organic Name Reactions and Reagents* **2010**, 1326. (10.1002/9780470638859.conrr295)
[174] Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A. and Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924. (10.1021/jo00024a040) and references cited herein.
[175] Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G. and Santeusanio, S. *J. Org. Chem.* **2011**, *76*, 2860. (10.1021/jo200287k)



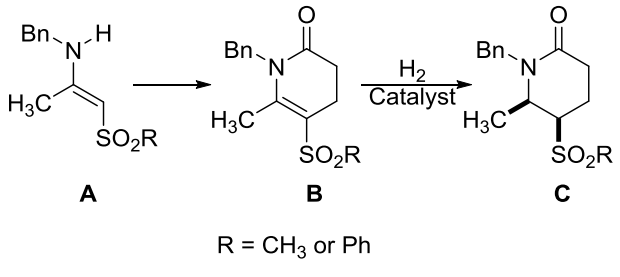
Scheme 117

The reaction of acyclic β-ketosulfones with acryloyl chloride resulted in the formation of six membered nitrogen heterocycles in moderate yield (45 – 69%), as Stille *et al*. found. In general, condensation of **A** with $BnNH_2$ produced regio- and stereoselective formation of **B**, and subsequent treatment of **B** with acryloyl chloride regioselectively generated **C** (Scheme 118).[176]



Scheme 118

This group reported studies of the aza-annulation of enamine substrates **A** with acryloyl chloride to form **B**, with an emphasis on: (1) the use of acyclic enamines, (2) the stereochemically controlled incorporation of ring substituents by reduction to **C**, and (3) the application of this methodology for the stereoselective synthesis of indolizidine natural products (Scheme 119).[177]

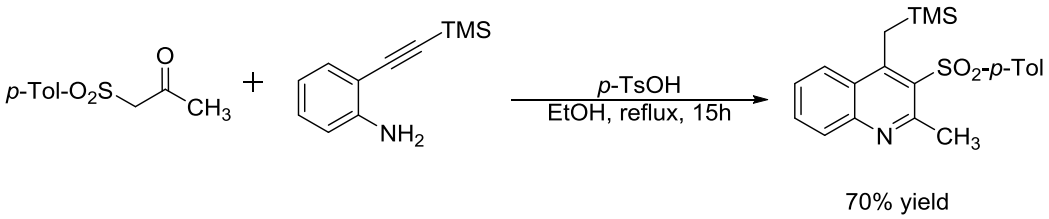


Scheme 119

[176] Paulvannan, K. and Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197. (10.1016/S0040-4039(00)61389-8)
[177] Paulvannan, K. and Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (10.1021/jo00086a009)

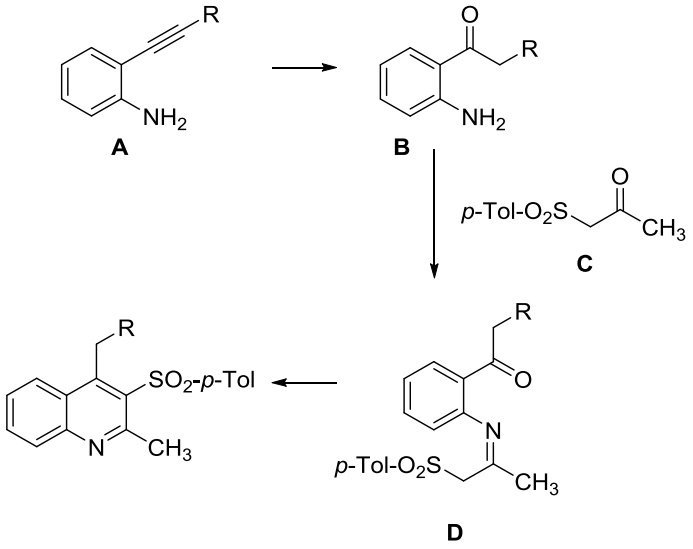
Pyridine, and more specifically, 2,6-disubstituted-1,2,5,6-tetrahydropyridine skeleton is present in natural products, such as (+)-cannabisativine,[178] (–)-palustrine,[179] and (–)-sedacrine.[180]

Zhu *et al.* demonstrated a single-step procedure for the conversion of 2-alkynylanilines and activated ketones, among them one β-ketosulfone, into the corresponding 4-alkylquinolines (Scheme 120).[181]



Scheme 120

The mechanism proposed by the authors is based on an indirect Friedländer reaction,[182] *i.e.*, in the presence of *p*-TsOH, **A** is hydrated to **B** first, and then enamine **D** is formed with ethyl acetoacetate **C** before cyclisation and dehydration to furnish the final product (Scheme 121).



Scheme 121

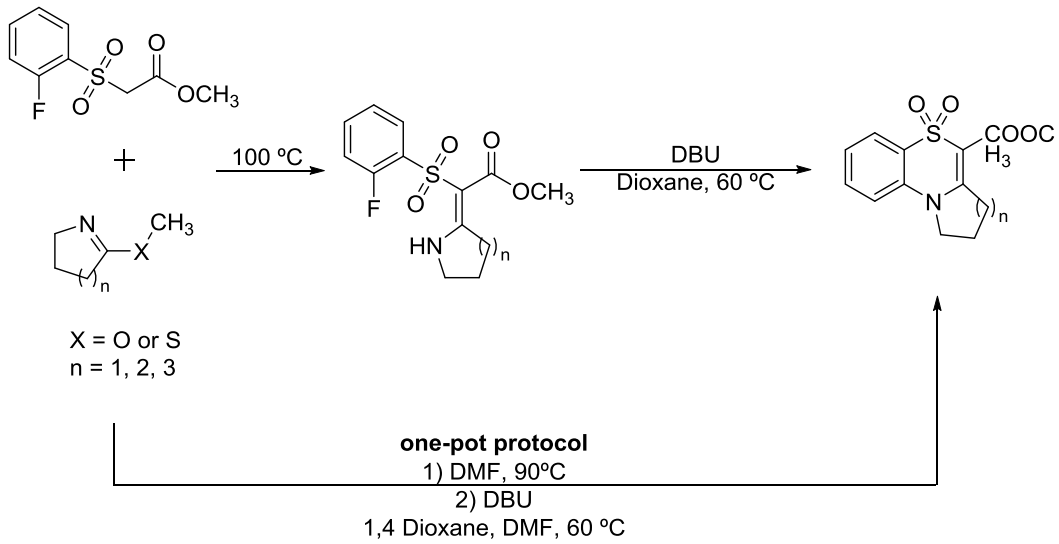
[178] Latter, H. L.; Abraham, D. J.; Turner, C. E.; Knapp, J. E.; Schiff Jr, P. L. and Slatkin, D. J. *Tetrahedron Lett.* **1975**, *16*, 2815. (10.1016/S0040-4039(00)75003-9)
[179] Bates, R. W. and Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957. (10.1016/S0040-4020(02)00584-7)
[180] Beeler, A. B.; Gadepalli, R. S. V. S.; Steyn, S.; Castagnoli Jr, N. and Rimoldi, J. M. *Bioorg. Med. Chem.* **2003**, *11*, 5229. (10.1016/j.bmc.2003.08.002)
[181] Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J. and Zhu, Q. *Eur. J. Org. Chem.* **2010**, 818. (10.1002/ejoc.200901257)
[182] Cheng, C.-C. and Yan, S.-J. *The Friedländer Synthesis of Quinolines*; Organic Reactions, **2004**. (10.1002/0471264180.or028.02)

2.2. Reactivity of α-alkyliden- and α-cyclopropyl/cyclopropenyl-β-ketosulfones.

α-Alkyliden- and α-cyclopropyl- or α-cyclopropenyl-β-ketosulfones have been used for the synthesis of many cyclic systems. This section will be subdivided depending on whether these compounds are synthesised and used as starting materials or if they are generated *in situ* during the reaction pathway.

2.2.i As starting materials.

Drushlyak *et al*. have developed the synthesis of 2,3-dihydro-1*H*-pyrrolo[2,1-c][1,4]benzothiazines by interaction of methylene active (2-fluorophenyl)sulfones with homologues of either 5-methoxy-3,4-dihydro-2*H*-pyrrole or 5-(methylthio)-3,4-dihydro- 2*H*-pyrrole (Scheme 122). Among the reported examples, β-ketosulfones were also tolerated affording 2-[(2-fluorophenyl)sulfonyl]methylene pyrrolidines in moderate to good yields (42 – 85%) by mixing with the corresponding *S*-methyl-lactim at 100°C for 10 to 20 hours. The compounds were isolated as the mixture of *E* and *Z* isomers and eventually transformed into the corresponding benzothiazines in moderate yields (33 – 68%) using DBU in dioxane at 60 ºC. This protocol afforded better yields in one-pot version (53 – 73%).[183]

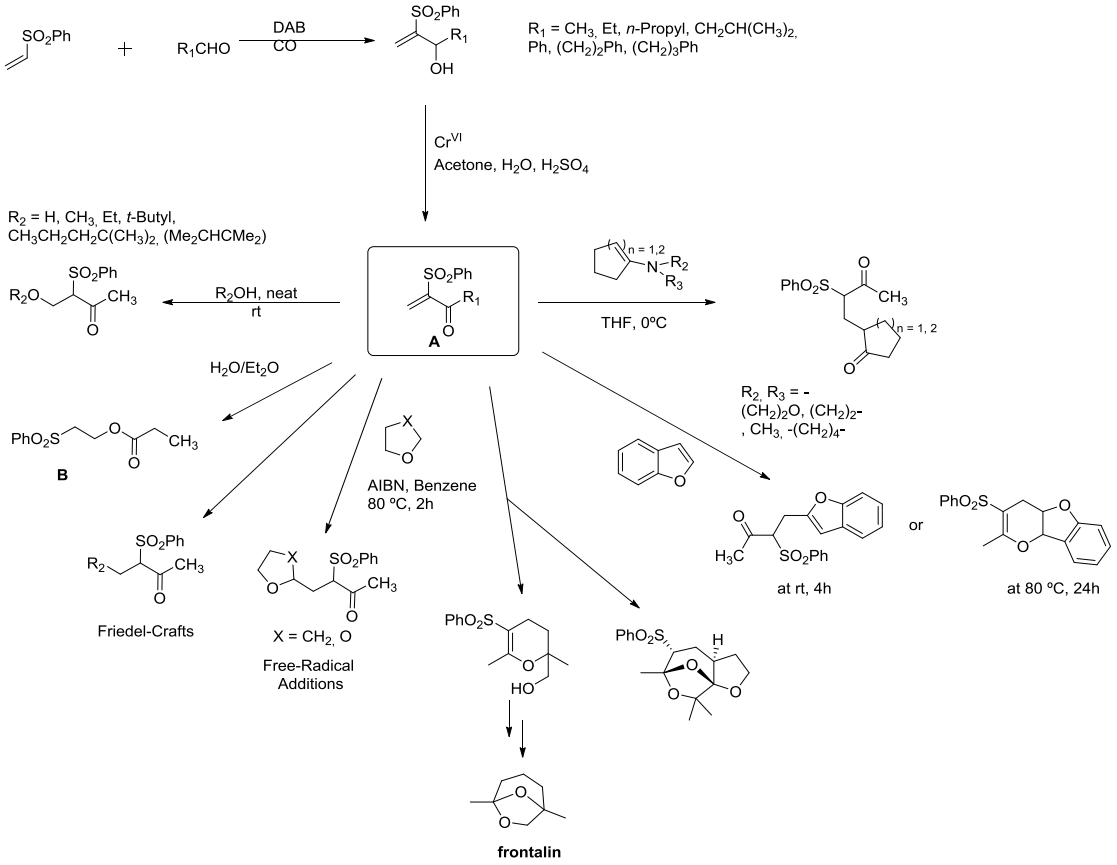


Scheme 122

Hoffman *et al*. developed a facile synthesis of a variety of α-methylene-β-keto sulfones **A**, which afforded selective cross-reactions (Scheme 123). With alcohols, including sterically hindered tertiary alcohols and also with 2-(ethoxycarbonyl)cyclopentanone**,** the compounds function as efficient Michael acceptors, even in the absence of base catalysis. In moist ether, 2-(benzenesulfonyl)-1penten-3-one suffers rearrangement to 2-(benzenesulfonyl)ethyl propanoate **B**. Toward electron-rich aromatics and heteroaromatics, α-methylene-β-ketosulfones **A** behave as electrophiles in Friedel-

[183] Grevtsov, O. Y.; Zaremba, O. V.; Bondarenko, A. B.; Drushlyak, O. G.; Kovalenko, S. M. and Chernykh, V. P. *International Journal of Organic Chemistry* **2013**, *3*, 125.

Crafts-type functionalisations**.** Prototype 3-(benzenesulfonyl)-3-buten-2-one is a crystalline methyl vinyl ketone (MVK) equivalent which, unlike MVK, undergoes controlled free-radical additions with nucleophilic radicals. In hetero-Diels-Alder reactions, 3-(benzenesulfonyl)-3-buten-2-one serves as a l-oxa-l,3-butadiene unit, combining with a wide range of alkenes of graded nucleophilicity. Electron deficient 3-(benzenesulfonyl)-3-buten-2-one also reacts as an enophile toward 1,l-dialkylated ethylenes. In further applications to natural products chemistry, the synthesis of frontalin and novel trioxatricyclics were described.[184]



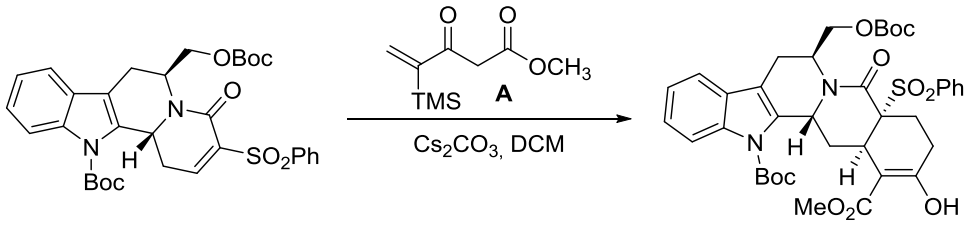
Scheme 123

Yamazaki and Yamabe *et al.* showed a new usage of α-methylene-β-keto sulfones in the presence of Lewis acids when 1-seleno-2-silylethene and 2-sulfonylacrylates underwent $SnCl_4$-promoted [*2+1*] cycloaddition reactions stereoselectively but in moderate yields (26 – 56%, Scheme 124).[185]

[184] Weichert, A. and Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098. (10.1021/jo00013a007)
[185] Yamazaki, S.; Yanase, Y.; Tanigawa, E.; Yamabe, S. and Tamura, H. *J. Org. Chem.* **1999**, *64*, 9521. (10.1021/jo9911591)

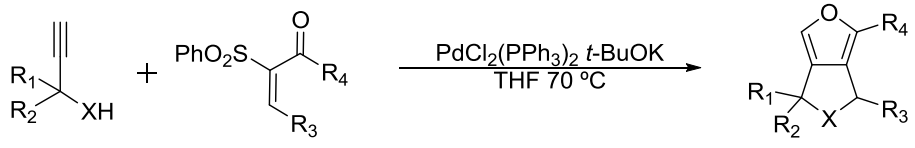
Scheme 124

Recently, Amat *et al.* have developed a synthetic Nazarov reagent equivalent, the silyl derivative **A** (Scheme 125), which was able to participate in Cs_2CO_3-promoted double Michael annulations with α-methylene-β-ketosulfones. Using this methodology and starting from unsaturated indolo[2,3-*a*]-quinolizidine lactams, this silylated Nazarov reagent allows the construction of pentacyclic yohimbinone-type systems.[186]



Scheme 125

A study of the synthetic utility of sulfone-based activated olefins as versatile multi-coupling reagents for the construction of more elaborate heterocycles was undertaken by Balme *et al.* based on their previous work[122] which suggested that the particular ability of the sulfonyl group to act as a leaving group may change the reaction pathway by generating carbene palladium complexes. Thus, this group developed a single-step synthesis of furofurans and furopyrroles from propargyl alcohols (or amines) and arylidene (or alkylidene) β-ketosulfones using $PdCl_2(PPh_3)_2$ and *t*-BuOK in THF at 70 ºC (Scheme 126).[187]

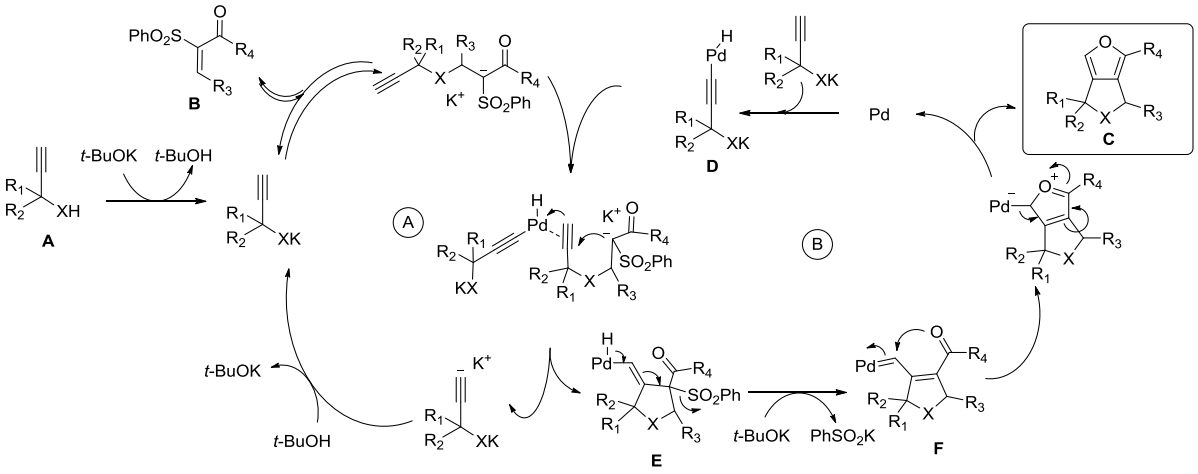


$R_1 = R_2 = H$ or CH_3
R_3 = Ph, *p*-FC_6H_4 or cyclohexyl or benzo[*d*][1,3]dioxol-5-yl
R_4 = Ph, $CH(CH_3)_2$, *p*-$NO_2C_6H_4$, *p*-$CH_3OC_6H_4$
XH = OH, $NHCH_3$, $NHCH_2Ph$

Scheme 126

[186] Amat, M.; Arioli, F.; Pérez, M.; Molins, E. and Bosch, J. *Org. Lett.* **2013**, *15*, 2470. (10.1021/ol400934c)
[187] Monteiro, N. and Balme, G. *J. Org. Chem.* **2000**, *65*, 3223. (10.1021/jo991817h)

According to the mechanism proposed by the authors, the arylidene β-ketosulfone behaves here as a multi-coupling reagent. It acts initially as a Michael acceptor and then as a nucleophilic ionic centre. The cyclisation would be promoted by a σ-alkynyl Pd(II) (or IV) hydride species **D** resulting from insertion of the metal into the C-H bond of the terminal acetylene (Scheme 127). This would lead to an intermediate species **E**. At this stage, the well-known ability of the sulfonyl moiety to act as a leaving group would trigger the generation of a palladium carbene **F** *via* a sulfinic acid elimination. As illustrated in the first catalytic cycle A (Scheme 127), the first cyclisation reaction would require only catalytic quantities of *t*-BuOK in order to proceed, as this base should be continuously regenerated during this process. The base intervenes also in the second cyclisation reaction B abstracting the hydrogen of the intermediate Pd(II or IV)-H species to form the palladium carbene. This would produce potassium sulfinate as a side product, hence the need for stoichiometric quantities of base. The electrophilic vinylidene palladium **F** is then attacked by the oxygen of the adjacent ketone, leading to **C** in a 6π-electrocyclisation process at the end of which the catalyst is recycled (Scheme 127).

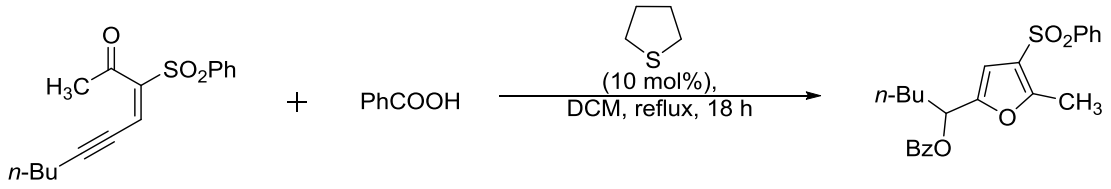


Scheme 127

Another simple method, dehydration of a couple of β-keto-γ′-sulfones with TsOH in benzene, was used by Gopalan *et al.* for the intramolecular cyclisation of acyl derivatives of these sulfones for the preparation of functionalised dihydrofurans and dihydropyrans.[188]

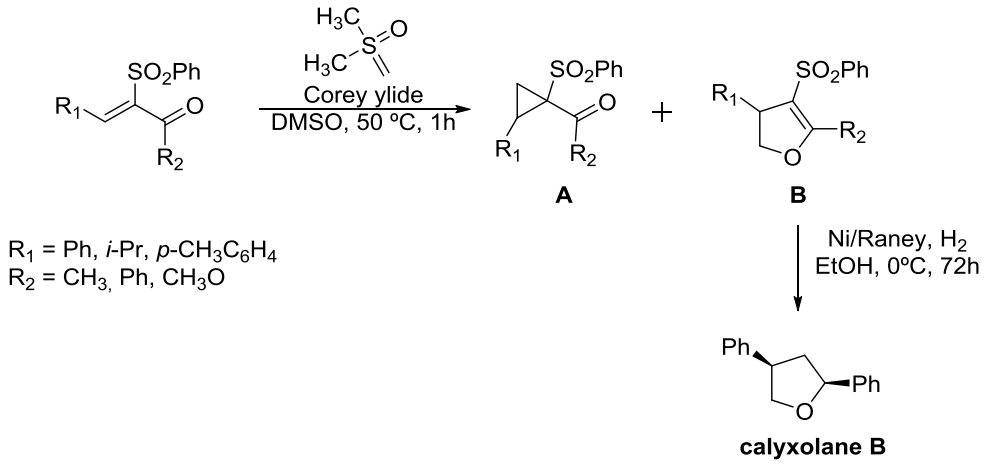
An organocatalytic synthesis of substituted furans using tetrahydrothiophene (THT, 10 mol%) as the organocatalyst, under neutral conditions was developed by Clark *et al.*. This reaction proceeded in excellent yield (98%) with a α-methylene-β-keto-sulf-γ′-yne and $PhCO_2H$ in DCM at reflux during 18 h affording the corresponding furan (Scheme 128).[189]

[188] Jin, C.; Ramirez, R. D. and Gopalan, A. S. *Tetrahedron Lett.* **2001**, *42*, 4747. (10.1016/S0040-4039(01)00856-5)
[189] Clark, J. S.; Boyer, A.; Aimon, A.; Engel García, P.; Lindsay, D. M.; Symington, A. D. and Danoy, Y. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 12128. (10.1002/anie.201207300)



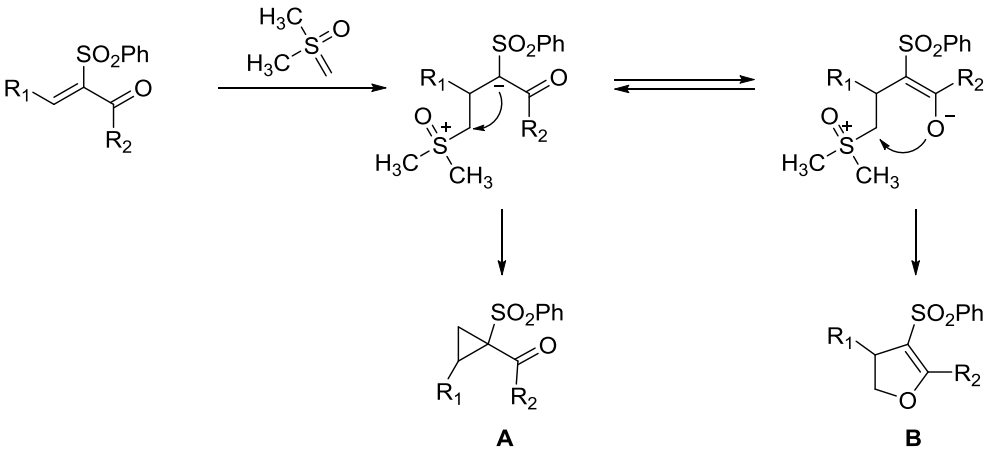
Scheme 128

Piras *et al*. realised a regioselective synthesis of 3,4,5-trisubstituted 2,3-dihydrofurans by a Corey ylide reaction with β-ketosulfones. The method allowed a straightforward synthesis of the natural product calyxolane B (Scheme 129).[190]



Scheme 129

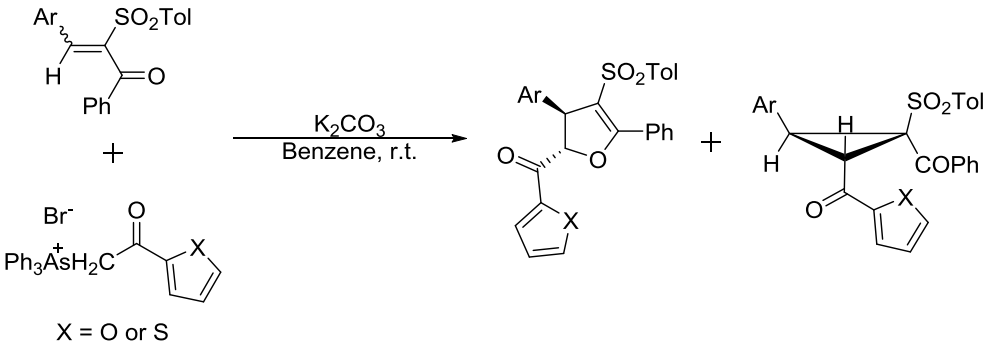
Cyclopropanes **A** and dihydrofurans **B** are formed very likely through the intermediate enolate, which can react either through the carbon or the oxygen atom (Scheme 130).



Scheme 130

[190] Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. and Spiga, M. *Org. Lett.* **2005**, *7*, 4565. (10.1021/ol0514606)

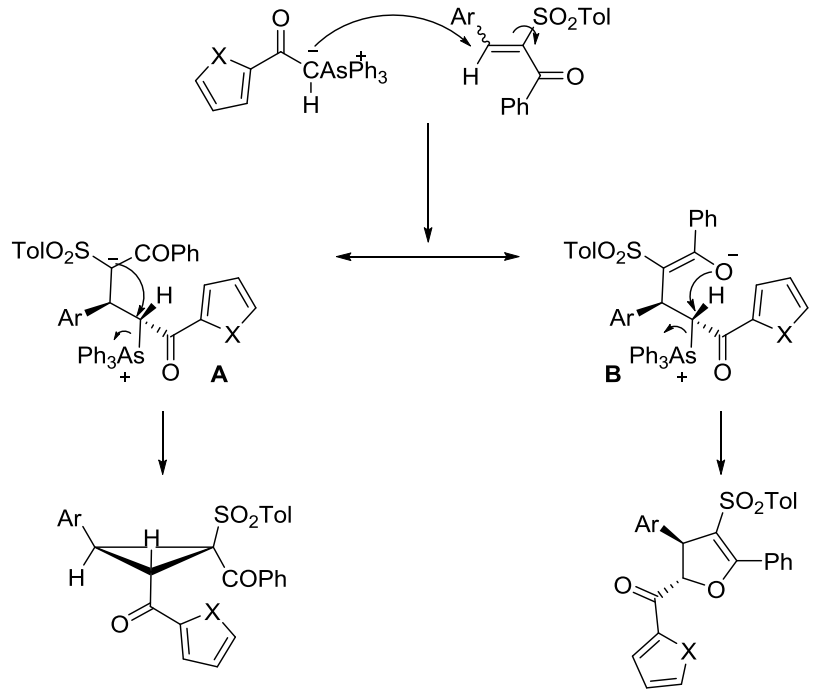
Similarly, Cao and McMills *et al.* developed the synthesis of *trans*-2,3-dihydrofuran derivatives and *trans*-1,2-cyclopropane derivatives but using α-methylen-β-ketosulfones with arsonium bromides in the presence of potassium carbonate (3 equivalents) in benzene at room temperature (Scheme 131).[191]



Scheme 131

The proposed reaction mechanism of the authors is shown in Scheme 132. Initial attack of the α,β-unsaturated sulfone *via* the carbanion derived from arsonium bromide and base produces two intermediates, stabilised carbanion **A** and sulfonyl stabilised enolate **B**. An intramolecular substitution reaction occurred at intermediate **A** to form the *trans*-cyclopropane, whereas the intramolecular attack of the oxygen enolate to the pendent arsenium-containing carbon resulted in the occurrence of a substitution reaction of **B**. Two possible scenarios occur when the enolate oxygen attacks C2 from the backside of leaving group ($Ph3As^{+}$). The resulting product conformation comes from the one in which the repulsion of two large groups (Ar and CO-furyl) exists. Reaction through this conformation is preferred, producing the *trans*-dihydrofuran. Generally, enolate intermediate **B** is much more stable than carbanion **A**, so dihydrofuran is produced to the near exclusion of cyclopropane.

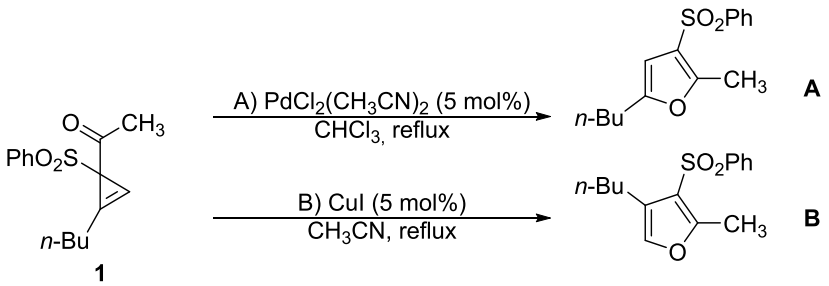
[191] Cao, W.; Zhang, H.; Chen, J.; Zhou, X.; Shao, M. and McMills, M. C. *Tetrahedron* **2008**, *64*, 163. (10.1016/j.tet.2007.10.073)



Scheme 132

More recently Reddy *et al.* have developed a DBU-promoted [3 +2]-annulation reaction in acetonitrile at 85 ºC for the synthesis of substituted furans from (*E*)-2-alken-4-yn-1-ones with keto-active methylenes through a tandem Michael addition/5-*exo*-dig-cycloisomerisation.[192] One β-ketosulfone was used in the scope of the reaction (73%), adding one more example to the synthesis of 3-sulfonyl furans from alkynones (Scheme 128)[189] to the literature.

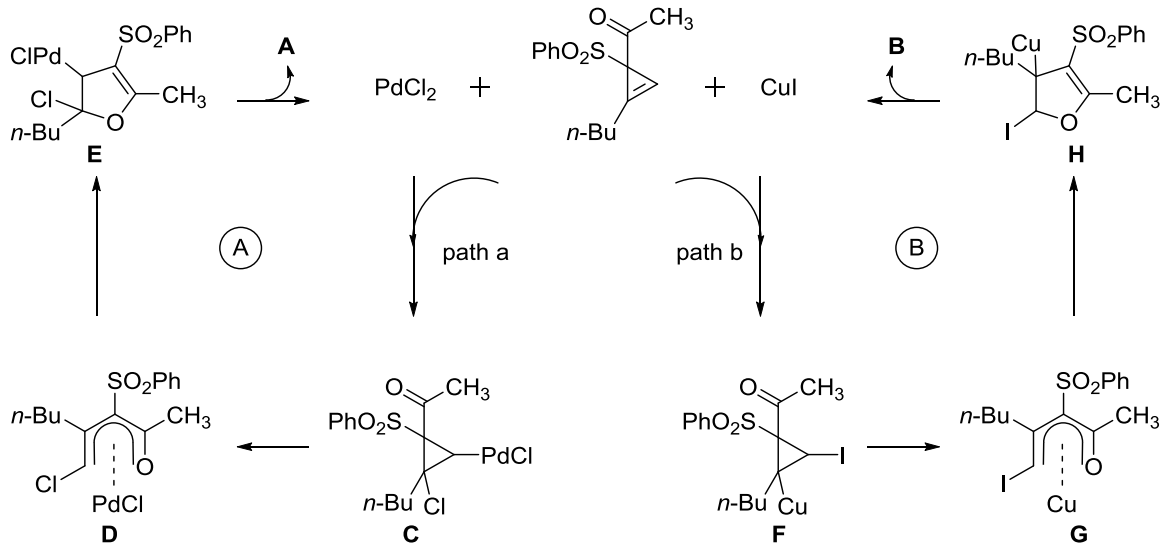
Ma *et al.* developed a regioselective cycloisomerisation of cyclopropenyl ketones, among them a β-ketosulfone was also reported, leading to 2,3,4-trisubstituted furan **A** or 2,3,5-trisubstituted furan **B** in good yield by using the catalyst $PdCl_2(CH_3CN)_2$ in chloroform at reflux or CuI in CH_3CN at reflux, respectively (Scheme 133).[193]



Scheme 133

[192] Raji Reddy, C. and Damoder Reddy, M. *J. Org. Chem.* **2013**, *79*, 106. (10.1021/jo4023342)
[193] Ma, S. and Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (10.1021/ja036616g)

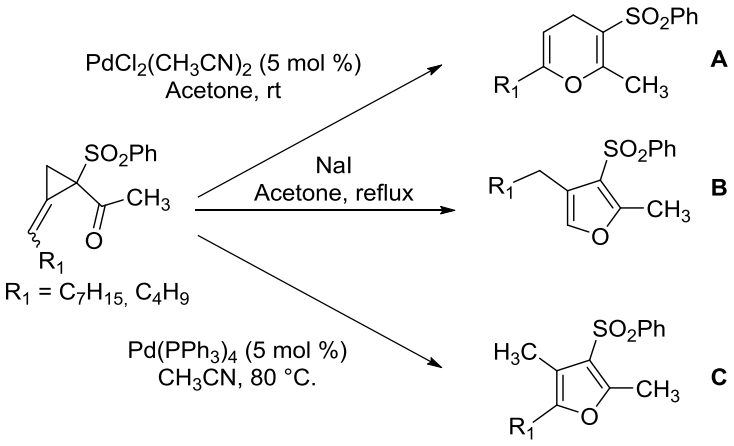
The mechanism proposed by the authors is depicted in (Scheme 134). In the presence of a catalytic amount of $PdCl_2(CH_3CN)_2$ (cycle A), the regioselective chloropalladation of the C-C double bond of the cyclopropenyl ketone (path a) would afford the palladium intermediate **C**, which would undergo β-decarbopalladation to afford delocalised intermediate **D**. Subsequent intramolecular *endo*-mode insertion of the C-C double bond into the oxygen-palladium bond of intermediate **D** would afford a cyclic palladium intermediate **E**, which would undergo β-halide elimination to afford **A** and regenerate Pd(II) species. On the other hand, in the presence of a catalytic amount of CuI, it would proceed according to cycle B. The opposite regioselective iodocupration of the C-C bond of cyclopropenyl ketone (path b) and subsequent β-decarbocupration gave delocalised intermediate **F**. The intramolecular *endo*-mode insertion of the C-C double bond into the oxygen-copper bond of intermediate **G** and subsequent β-halide elimination of intermediate **H** afforded **B** and regenerated CuI.



Scheme 134

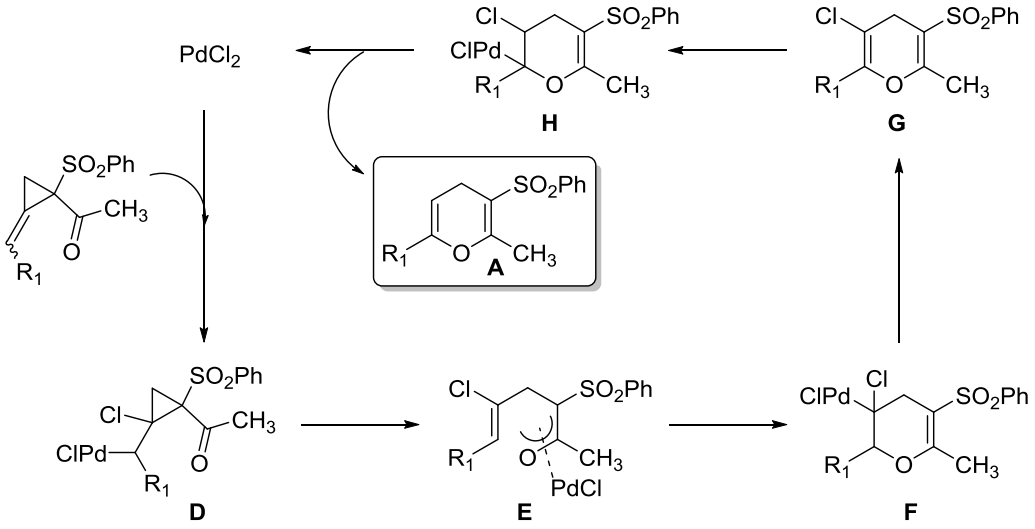
Three new different types of reactions for ring-opening cycloisomerisation of methylene- or alkylidenecyclopropyl ketones[194] were found by Ma *et al.* when they were continuing with their previous work.[193] With the application of different reaction conditions and catalysts, a highly selective formation of 4*H*-pyrans, 3-alkylidene-2,3-dihydrofurans (or 2,4- or 2,3,4-trisubstituted furans), and 2,3,4,5-tetrasubstituted furans (or 3-alkylidene-2,4,5-trisubstituted- 2,3-dihydrofurans) could be realised, showing a great utility in organic synthesis (Scheme 135).

[194] Ma, S.; Lu, L. and Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (10.1021/ja0494860)



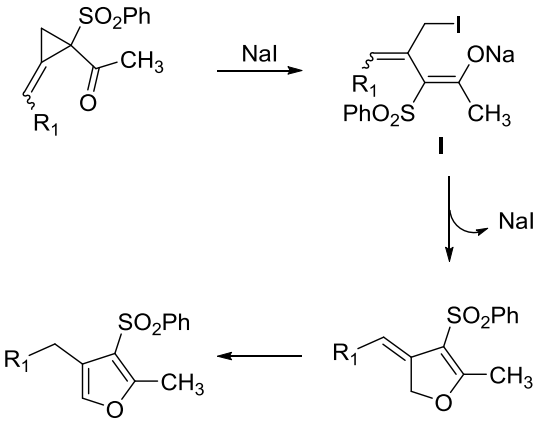
Scheme 135

The different mechanisms proposed by the authors to explain the formation of pyran **A** and furans **B** and **C** are depicted in the next Schemes.



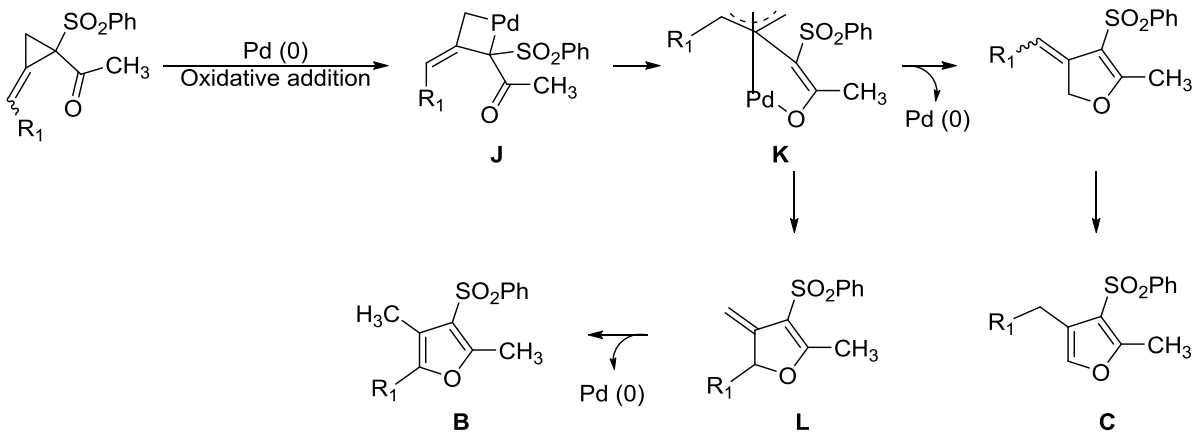
Scheme 136

Regioselective chloropalladation of cyclopropenyl ketone with $PdCl_2$ affords intermediate **D**, which would undergo β-decarbopalladation forming palladium enolate **E**. *Endo*-mode insertion of the C-C double bond into the oxygen-palladium bond in **E** would generate **F**. The regiospecific β-H elimination of **F** and hydropalladation with a reversed regioselectivity of **G** would afford **H**. After these steps, 4*H*-pyrans **A** would be formed *via* β-dechloropalladation (Scheme 136).



Scheme 137

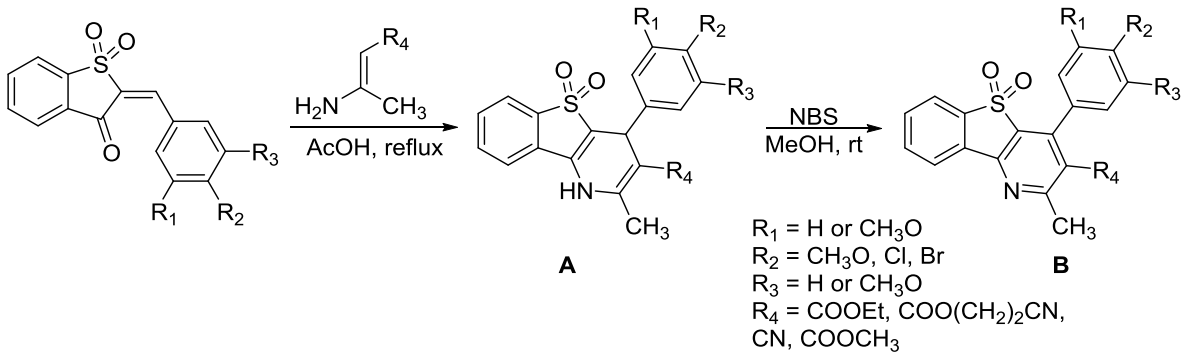
As compared to what is shown in Scheme 136, iodine may attack on the non-substituted carbon atom of the cyclopropane ring generating 2-alkylidenehomoallylic halide intermediate **I**, which can then undergo a 5-*exo*-tet cyclisation, just as shown in Scheme 137.



Scheme 138

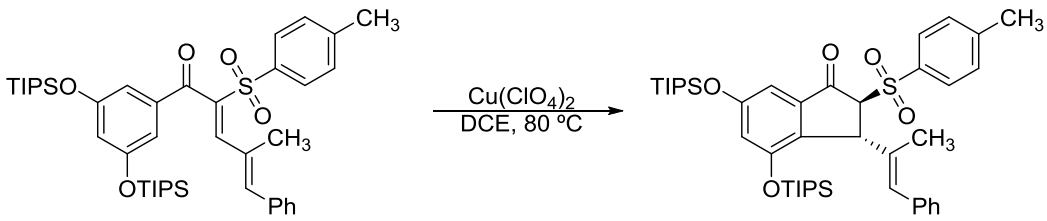
The regiospecific oxidative addition of the distal C-C bond of cyclopropenyl ketone would afford palladacyclobutane intermadiate **J**, which may be transformed into enolate-type allylic palladium intermediate **K**. Reductive elimination or intramolecular allylic substitution of **K** at the more substituted terminal would lead to **L**, which can be aromatised to give tetrasubstituted furans **B** (Scheme 138).

Recently, Sobolev *et al.* have reported the synthesis of 4-aryl-2-methyl-1,4-dihydrobenzothieno[3,2-*b*]pyridine 5,5-dioxides **A** in moderate yields (52 – 82%) from 2-arylidenebenzo[b]thiophen-3(2*H*)one 1,1-dioxides and 3-aminocrotonates by refluxing in acetic acid, and their oxidation to 4-aryl-2-methylbenzothieno[3,2-*b*]pyridine 5,5-dioxides **B** in moderate to very good yields (81 – 95%) with NBS in MeOH at room temperature (Scheme 139).[195]



Scheme 139

More recently Frontier *et al.* synthesised a series of Nazarov substrates bearing electron-donating substituents at C-2 and electron-withdrawing substituents at C-4 which, after treatment with catalytic amounts of Lewis acid $Cu(OTf)_2$ (2 mol%) afforded high yields of the corresponding Nazarov products *via* cyclisation of "polarised" pentadienyl cation intermediates. Among the different examples studied, a β-ketosulfone was made to react but changing the reaction conditions to $Cu(ClO_4)_2$ in dichloroethane at 80 ºC (Scheme 140).[196]



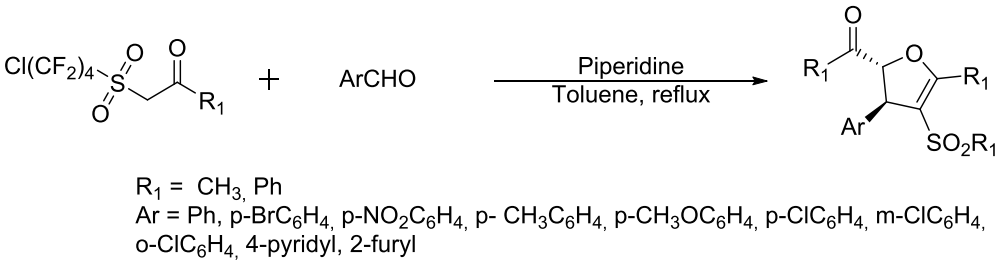
Scheme 140

[195] Cekavicus, B.; Vigante, B.; Rucins, M.; Birkmane, K.; Petrova, M.; Belyakov, S.; Zuka, L.; Plotniece, A.; Pajuste, K.; Gosteva, M. and Sobolev, A. *Tetrahedron* **2013**, *69*, 5550. (10.1016/j.tet.2013.04.060)

[196] He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A. and Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *130*, 1003. (10.1021/ja077162g)

2.2.ii Generated *in situ*.

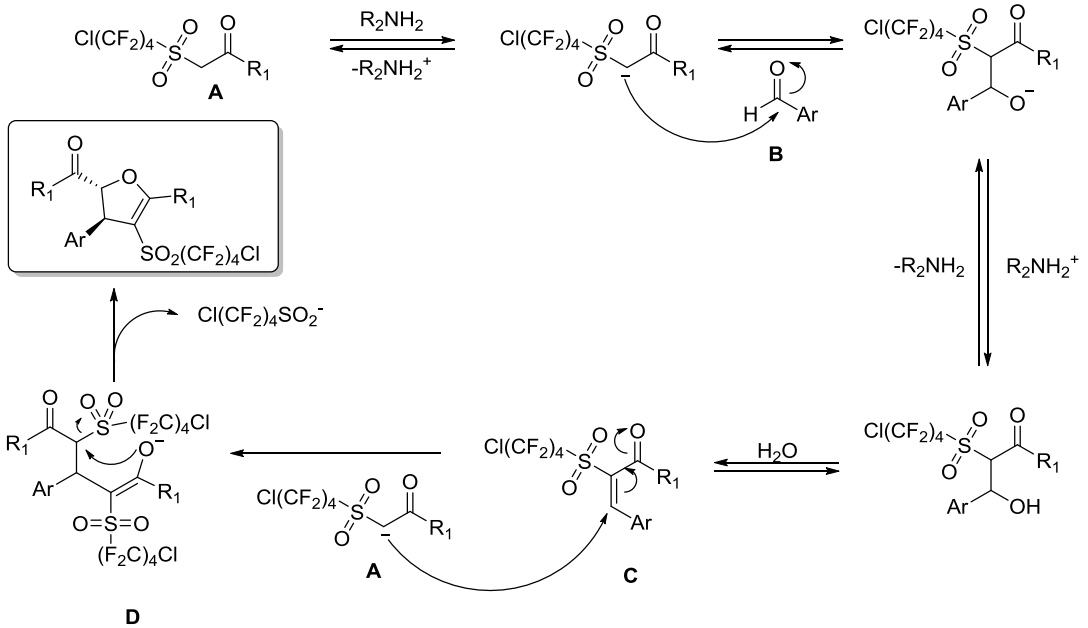
Zhu *et al*. found an unexpected result in the reaction between β-ketopolyfluoroalkanesulfones and aldehydes in the presence of piperidine in toluene at reflux. Instead of the traditional Knoevenagel condensation reaction, this reaction proceeded past the initial condensation product to provide the synthesis of fluorine-containing tetrasubstituted *trans*-2,3-dihydrofurans (Scheme 141).[197]



R_1 = CH_3, Ph
Ar = Ph, p-BrC_6H_4, p-$NO_2C_6H_4$, p- $CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-ClC_6H_4, m-ClC_6H_4, o-ClC_6H_4, 4-pyridyl, 2-furyl

Scheme 141

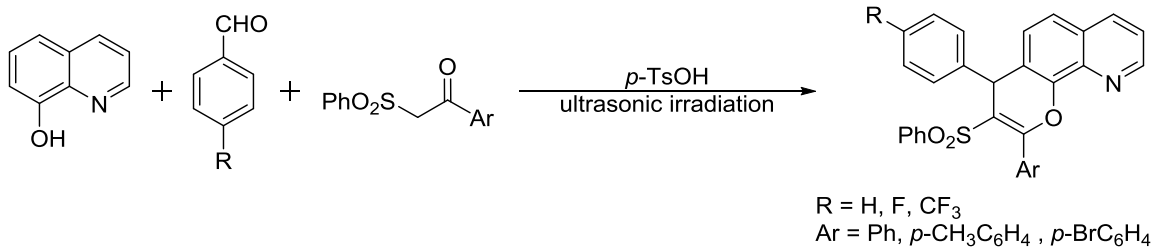
The mechanism proposed by the authors is depicted in Scheme 142. First, the reaction of **A** with **B** gives the Knoevenagel condensation product α-polyfluoroalkanesulfonyl-α,β-unsaturated ketone **C** as the intermediate. The newly formed C–C double bond is readily attacked by the anion of **A**. This Michael addition affords the enolate anion **D**. Finally, the subsequent intramolecular nucleophilic displacement of **D** gave the final product. During ring closure, the two large neighboring groups (Ar and ArCO) preferably formed *trans* conformation for the sake of stereohindrance.



Scheme 142

[197] Xing, C. and Zhu, S. *J. Org. Chem.* **2004**, *69*, 6486. (10.1021/jo049317y)

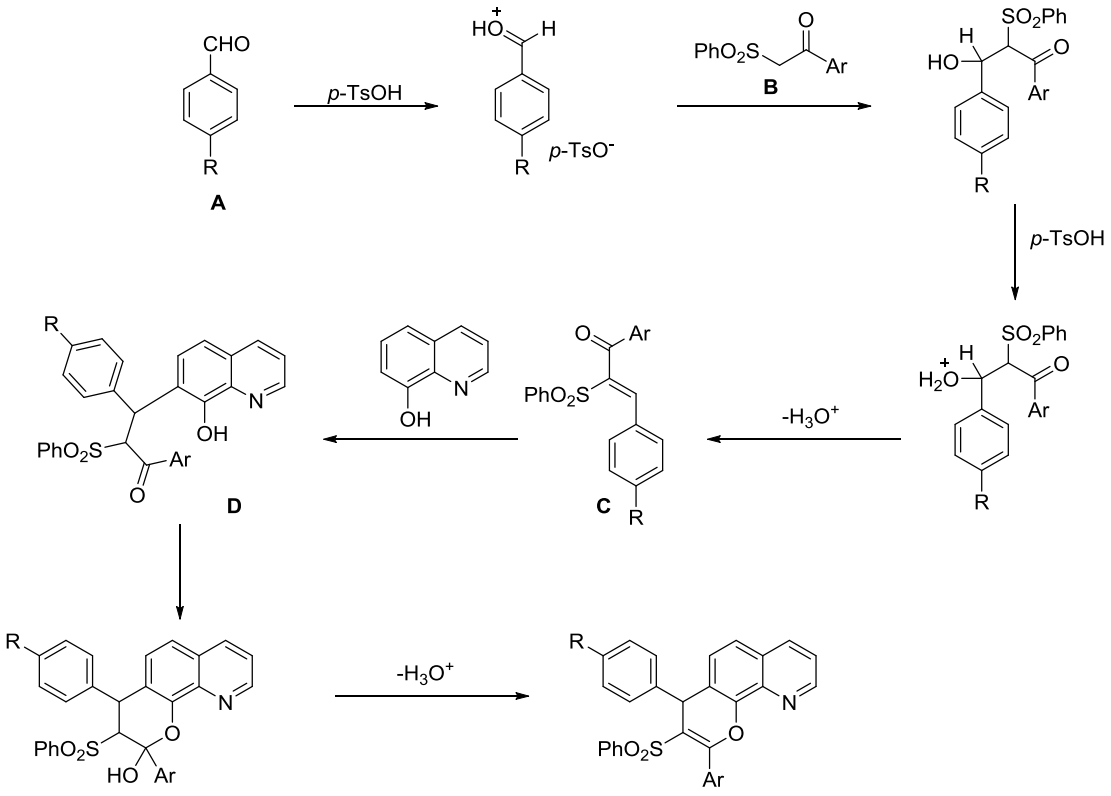
More recently, Saleh *et al*. have developed a novel green protocol three-components condensation reaction of 8-hydroxy quinoline, aldehydes and β-ketosulfones for the synthesis of 4*H*-pyrano [3,2-*h*] quinoline derivatives in moderate yields (58 – 70%, Scheme 143) under ultra-sonic irradiation *via* utilisation of *p*-TsOH as a catalyst in EtOH. Moreover, this work evidences an example to that sometimes ultrasound irradiations enable some reactions to occur which could not be carried out under silent conditions.[198]



Scheme 143

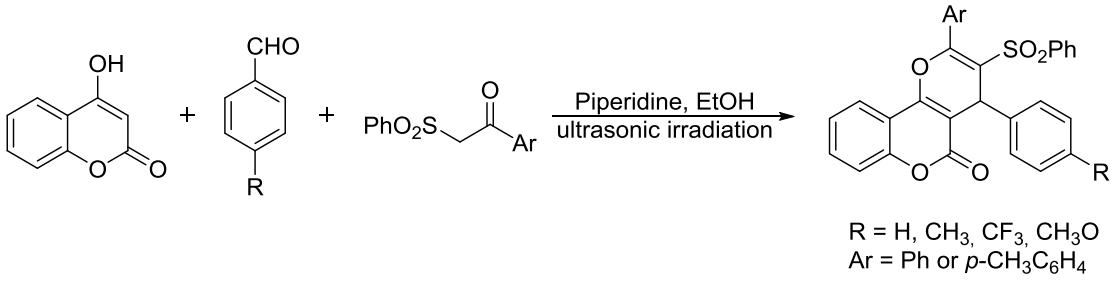
The mechanism proposed by the authors is depicted in Scheme 144. The reaction starts with intermolecular condensation between benzaldehyde **A** and 1-phenyl-2- (phenylsulfonyl)ethanone **B** to form α,β-unsaturated carbonyl intermediate **C**. Then, Michael addition of the quinolinyl C-7 to the activated double bond in **C** yields the corresponding acyclic intermediates **D** followed by cyclisation to afford the finalproduct.

[198] Al-Bogami, A. S.; Saleh, T. S. and Zayed, E. M. *Ultrason. Sonochem.* **2013**, *20*, 1194. (10.1016/j.ultsonch.2013.03.003)



Scheme 144

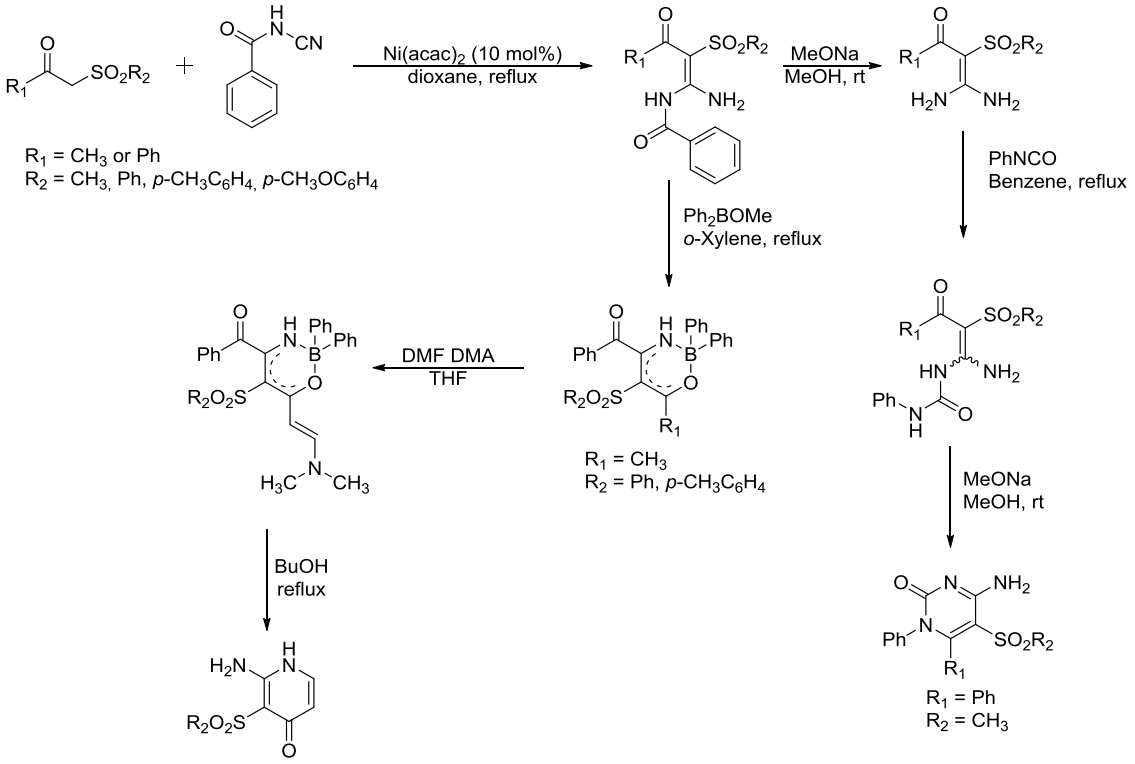
Al-bogami used a similar multi-component reaction with 4-hydroxy coumarin, aromatic aldehydes, and β-ketosulfone derivatives for the synthesis of pyrano[3,2-*c*]coumarin derivatives in modereate yields (67 – 80%) catalysed by piperidine in EtOH under ultrasonic irradiation (Scheme 145).[199]



Scheme 145

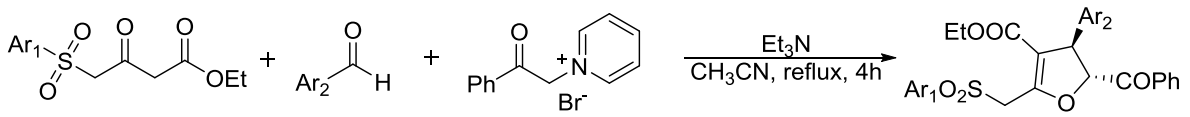
[199] Al-bogami, A. *Res. Chem. Intermed.* **2013**, 1. (10.1007/s11164-013-1171-7)

Dorokhov *et al*. found that active methylene β-ketosulfones add to the nitrile bond of benzoylcyanamide in the presence of catalytic amounts of $Ni(acac)_2$ (acac = acetylacetonate), which after debenzoylation under the action of MeONa in MeOH afforded *N,N´*-unsubstituted diaminomethylidene derivatives (acyl(R-sulfonyl)ketene aminals), which were used as reagents for the syntheses of 2-amino-3-arylsulfonylpyridin-4(1*H*)-ones and 5-sulfonylcytosine derivatives (Scheme 146).[200]



Scheme 146

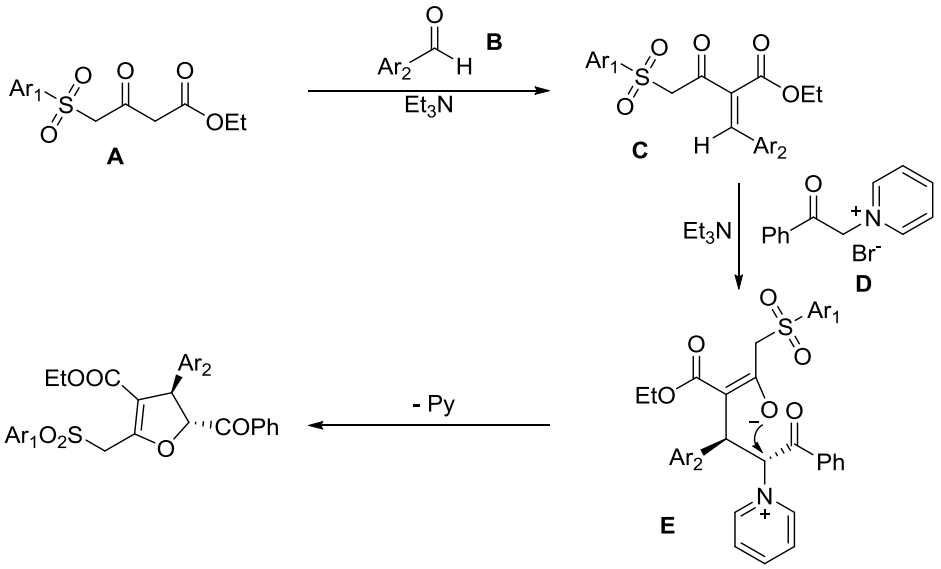
Perumal *et al.* reported the synthesis of a series of dihydrofuran-3-carboxylates in good yields (70 – 82%) using *N*-phenacyl pyridinium, bromides instead of diamides, in presence of Et_3N in acetonitrile at reflux (Scheme 147).[201]



Scheme 147

[200] Voronkova, V. A.; Baranin, S. V.; Prezent, M. A.; Vasil'ev, L. S. and Dorokhov, V. A. *Russ. Chem. Bull.* **2010**, *59*, 1937. (10.1007/s11172-010-0337-3)
[201] Harikrishnan, P. S.; Rajesh, S. M.; Perumal, S. and Almansour, A. I. *Arkivoc* **2013**, *4*, 1. (10.3998/ark.5550190.p007.921)

According to the authors, this transformation generates C–O, C–C and C=C bonds *via* an α,β-unsaturated ketosulfonyl ester generation/Michael addition/intramolecular cyclisation domino sequence (Scheme 148).

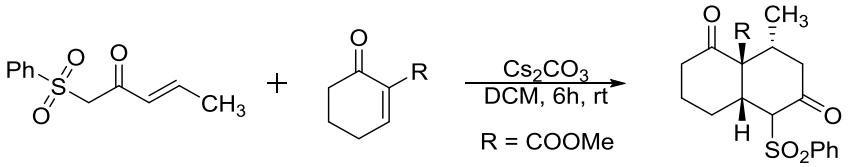


Scheme 148

Thus, this transformation is presumably triggered by an initial regioselective condensation of ketosulfonyl ester **A** with aromatic aldehyde **B** affording **C**. This regioselectivity might probably arise from the steric hindrance posed by the bulky arylsulfonyl moiety to the condensation of the aromatic aldehyde with the methylene flanked by the sulfonyl and keto groups, which is likely to impede the formation of the other double bond stereochemistry. Subsequent Michael addition of the pyridinium ylide **D** to the acceptor **C** furnishes the enolate **E**, which undergoes intramolecular cyclisation by the displacement of pyridine to afford final product.

2.3. Reactivity of γ-alkyliden-β-ketosulfones.

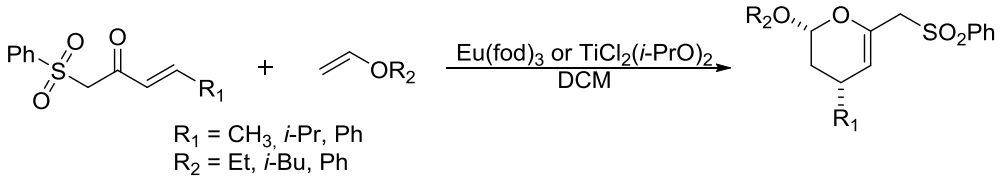
Since the main reactivity of β-ketosulfones occurs at positions 1 and 2, *i.e.*, the active methylene and carbonyl, it is not very common to find reactions where these two positions are not involved. There are a few examples where the double bond of a γ-alkyliden-β-ketosulfone participates. However, Deslongchamps *et al.* found in 1990 a double Michael addition-cyclisation of a β-ketosulfone and 2-carbomethoxy-2cyclohexenone using Cs_2CO_3 in DCM affording a single bicyclic adduct in 45% yield (Scheme 149).[202]



Scheme 149

More usually observed is a Diels-Alder or hetero-Diels-Alder reaction catalysed by a Lewis acid such as ZnI_2, $TiCl_2(i\text{-}PrO)_2$, $Eu(fod)_3$ ((tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium) or chiral versions of titanium catalysts.

For instance, sulfonyl-functionalised α,β-unsaturated ketones have been used as prochiral electrophilic substrates in catalysed asymmetric C–C bond formations. Wada *et al*. reported the stereoselective formation of 2,4-*cis*-3,4-dihydro-2*H*-pyrans in good to excellent yields (71 – 97%) by a sequence based on the hetero-Diels-Alder reactions of β-keto-γ,δ-unsaturated sulfones with vinyl ethers in the presence of a catalytic amount (0.5 – 10 mol%) of $Eu(fod)_3$ or $TiCl_2(i\text{-}PrO)_2$ in DCM at different temperatures (Scheme 150).[203]

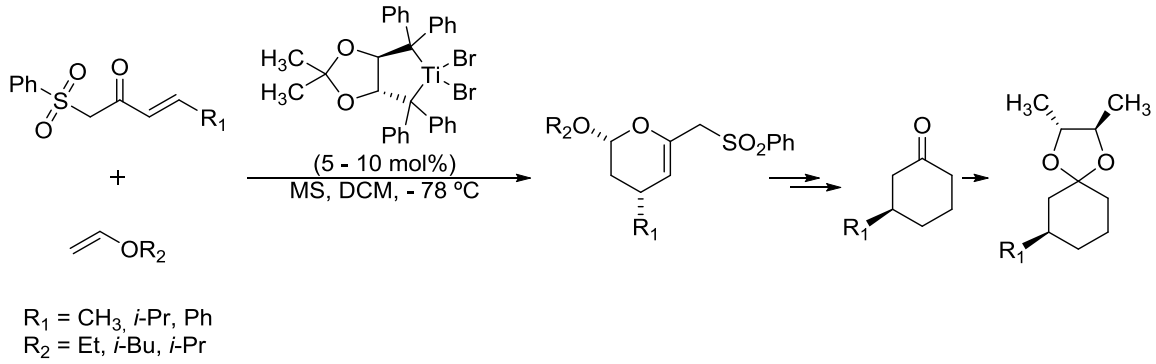


Scheme 150

These results led the same group to further investigate this Lewis acid catalysed hetero-Diels-Alder reaction and thus reported the first example of catalysed asymmetric intermolecular hetero-Diels-Alder reaction between β-keto-γ,δ-unsaturated sulfones and excess amounts of vinyl ethers in the presence of a catalytic amount (5 – 10 mol%) of a Titanium chiral Lewis acid and molecular sieves in DCM at – 78 ºC. The corresponding 4-substituted 2,4-*cis*-2-alkoxy-3,4-dihydro-2*H*-pyrans were

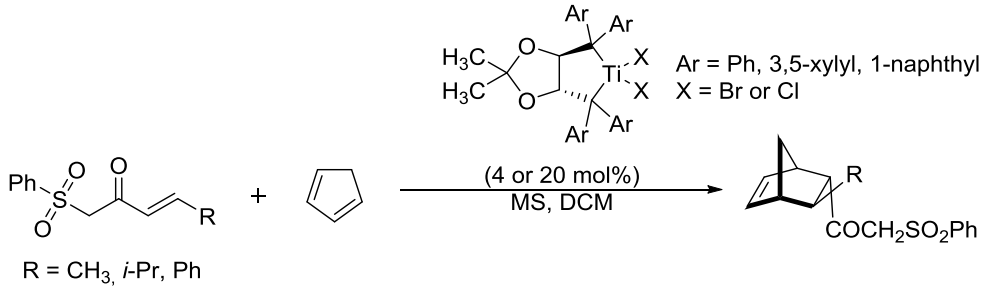
[202] Spino, C. and Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969. (10.1016/S0040-4039(00)94474-5)
[203] Wada, E.; Yasuoka, H. and Kanemasa, S. *Chem. Lett.* **1994**, *23*, 145. (10.1246/cl.1994.145)

obtained in good to excellent yields (77 – 96%) and moderate to excellent enantioselectivity (59 – 97% ee). Furthermore, the absolute configurations of the major enantiomers were determined by ^{13}C NMR after conversion of these compounds to the corresponding cyclohexenones and acetals (Scheme 151).[204]



Scheme 151

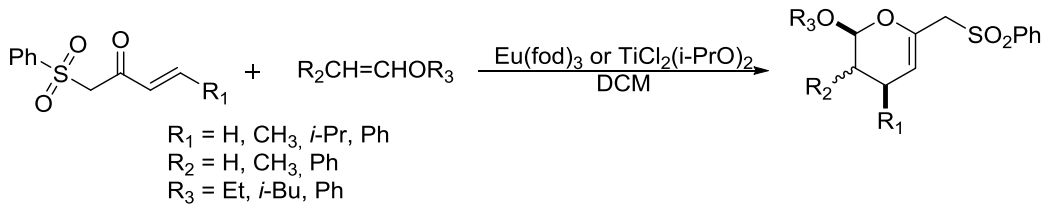
In the presence of a catalytic amount of a chiral titanium catalyst, 2,6-substituted-5-(phenylsulfonylacetyl)bicyclo[2.2.1]hept-2-enes were also obtained by this group by ordinary asymmetric Diels–Alder reaction of β-keto-γ,δ-unsaturated sulfones as dienophiles with cyclopentadiene in moderate to excellent yields (29 – 97%) and good to excellent enantiocontrol (78 – 100% ee, Scheme 152).[205]



Scheme 152

This group reported that β-keto-γ,δ-unsaturated sulfones as sulfonyl functionalised chelating enones, also worked effectively as hetero-1,3-dienes in Lewis acid ($Eu(fod)_3$ or $TiCl_2(i\text{-}PrO)_2$) catalysed hetero-Diels–Alder reactions with vinyl ethers, in the presence of a titanium catalyst in DCM at different temperatures, stereoselectively affording 2,4-*cis*-3,4-dihydro-2*H*-pyrans in moderate to excellent yields (41 – 97%, Scheme 153).[206]

[204] Wada, E.; Yasuoka, H. and Kanemasa, S. *Chem. Lett.* **1994**, *23*, 1637. (10.1246/cl.1994.1637)
[205] Wada, E.; Pei, W. and Kanemasa, S. *Chem. Lett.* **1994**, *23*, 2345. (10.1246/cl.1994.2345)
[206] Wada, E.; Pei, W.; Yasuoka, H.; Chin, U. and Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205. (10.1016/0040-4020(95)00980-9)



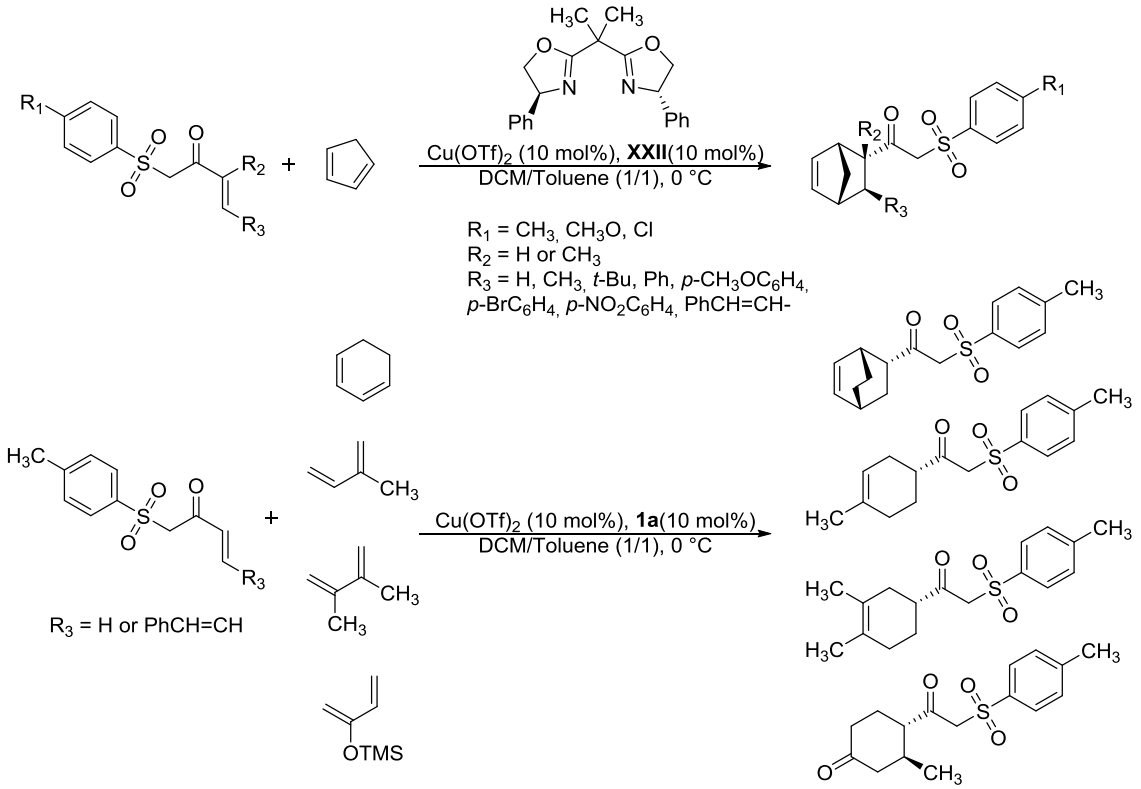
Scheme 153

Despite all these works, the reaction mechanism of the asymmetric Diels–Alder reaction was not discussed because no crystals of the cycloadducts were available. More recently, Pei *et al*. prepared crystals of (5*R*,6*R*)-6-phenyl-5-(phenylsulfonylacetyl)bicyclo[2.2.1]hept-2-ene with >99% ee and found the reaction proceeded with (*S*)-*cis* conformation in the position of the α,β-unsaturated ketone moiety in the transition state of the reaction of 4-phenyl-1-phenylsulfonyl-3-buten-2-ones with cyclopentadiene.[207]

More recently this group reported their study on the asymmetric Diels–Alder reaction mechanism of β-keto-γ,δ-unsaturated sulfones, and the hetero-Diels–Alder reaction of same substrate as hetero 1,3-dienes in a chiral titanium reagent. Furthermore, they summarise their results on the Diels–Alder reactions of β-keto-γ,δ-unsaturated sulfones catalysed by a chiral titanium reagent.[208]

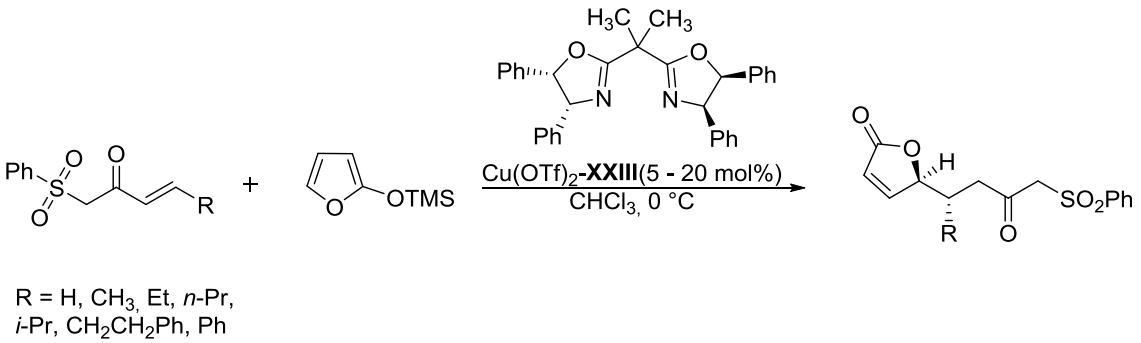
Position 3 of β-ketosulfones can also play its role in the reaction right after position 1 or 2 have participated in it. Moreover, there are some examples in literature in which only position 3 takes part, normally by reaction over a C-C double bond in a β-keto-γ,δ-unsaturated sulfone. These compounds have been used by Blay and Pedro *et al.* as bidentate dienophiles for asymmetric Cu(II)-bis(oxazoline) (Cu(II)-BOX) **XXII** catalysed Diels-Alder reaction with cyclopentadiene and other reactive dienes affording the corresponding products (mainly *endo*) in moderate to excellent yields (35 – 99%) and moderate to excellent enantioselectivity (69 – 97% ee, Scheme 154).[209]

[207] Pei, W.; Shao, Y. and Sun, L. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2004**, *60*, o374. (doi:10.1107/S1600536804002089)
[208] Pei, W.; Wang, Y.-G.; Wang, Y.-J. and Sun, L. *Synthesis* **2008**, 3383. (10.1055/s-0028-1083167)
[209] Barroso, S.; Blay, G.; Al-Midfa, L.; Muñoz, M. C. and Pedro, J. R. *J. Org. Chem.* **2008**, *73*, 6389. (10.1021/jo8009227)



Scheme 154

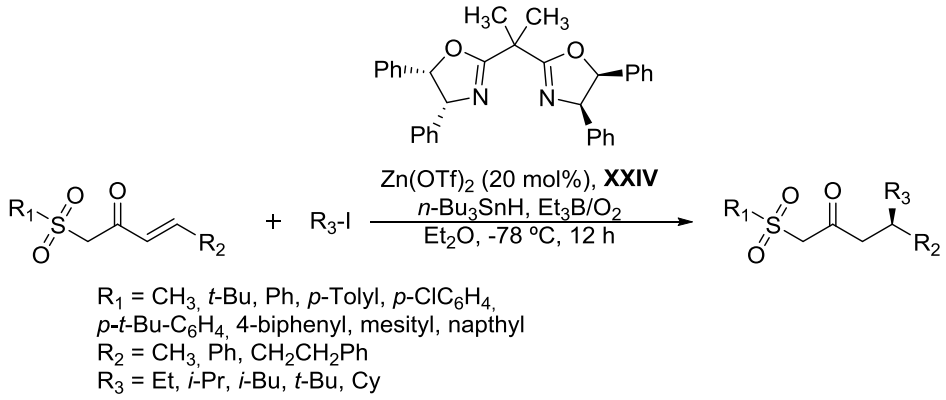
β-keto-γ,δ-unsaturated sulfones have been utilised by Kim *et al.* in Mukaiyama–Michael reactions with 2-(trimethylsilyloxy)furan using a different Cu(II)-BOX complex **XXIII** (5 – 20 mol%), in $CHCl_3$ at 0 ºC, to afford γ-butenolides in good to excellent yields (75 – 99%), excellent enantioselectivity (95 – 99% ee) and high anti/syn selectivity (75:25 to >99:1%, Scheme 155).[210]



Scheme 155

[210] Yang, H. and Kim, S. *Synlett* **2008**, 555. (10.1055/s-2008-1032074)

The effect of various Lewis acids along with BOX ligands was further examined by this group in the enantioselective conjugate addition reactions of alkyl *radicals* to β-keto-γ,δ-unsaturated sulfones and a bis-oxazoline-Zn triflate complex **XXIV** proved to be an effective catalyst leading to moderate to very good yields (58 – 94%) and enantioselectivity (42 – 95% ee, Scheme 156).[211]



Scheme 156

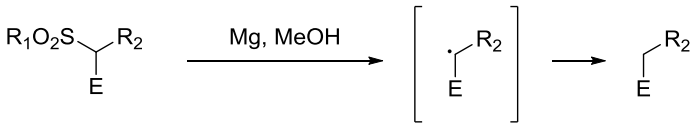
[211] Lee, J. Y.; Kim, S. and Kim, S. *Tetrahedron Lett.* **2010**, *51*, 4947. (10.1016/j.tetlet.2010.07.014)

2.4. Desulfonylation and other reactivity.

In this chapter, tipically used desulfonylation reaction conditions and other type of reactivity presented by β-ketosulfones is briefly reviewed.

2.4.i Desulfonylation.

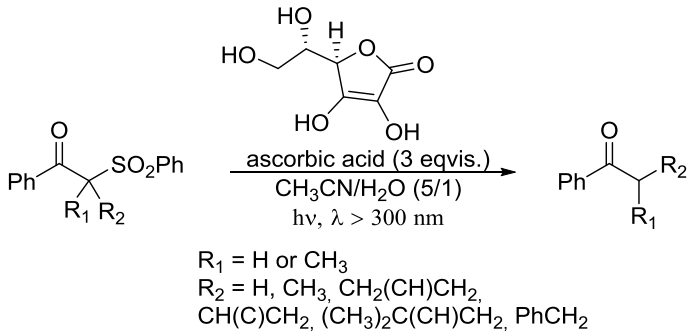
To remove the sulfone moiety further functional group transformations are needed. One of the most widely used methods is the replacement of sulfone group with hydrogen, which is traditionally achieved by reductive desulfonylation[212,213] using metal-containing reducing agents (Scheme 157), such as Al(Hg),[214] $Zn/TiCl_4$,[215] $Bu_3SnCl/NaBH_3CN$,[216] Mg/EtOH[217] or Mg/MeOH[218], SmI_2[219] or Sm/HOAc.[220]



Scheme 157

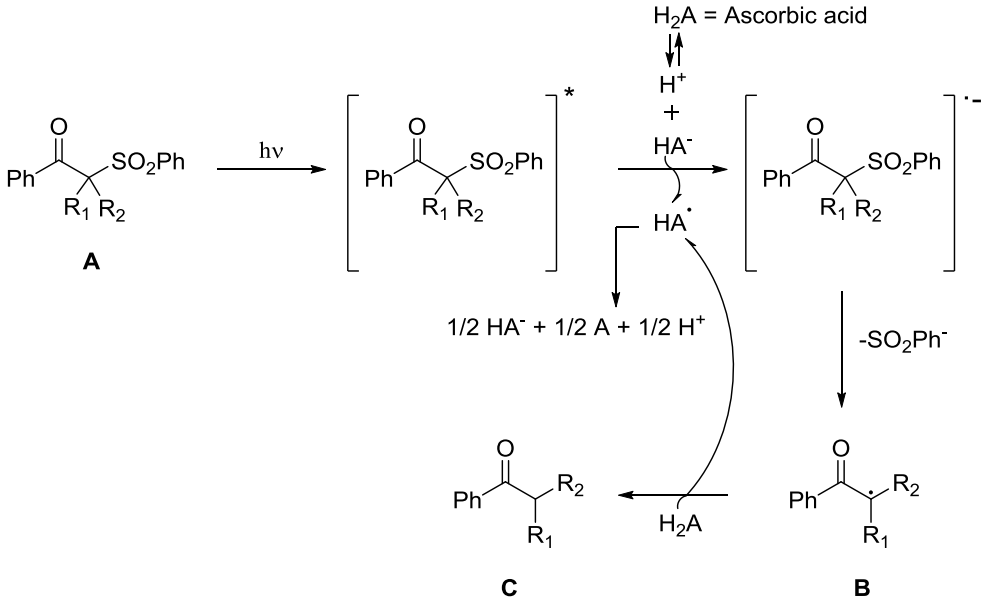
Despite the effectiveness of most of these methods, use of metals and amalgams is not very environmentally friendly and hence, chemists are trying to develop new techniques which allow desulfonylation under green conditions. Thus, Liu and Yu *et al.* reported a photochemical reduction of β-ketosulfones in good to excellent yields (75 – 98%) employing 3 equivalents of ascorbic acid (vitamin C) as the reducing agent in acetonitrile/H_2O (5/1), irradiating with high-pressure mercury lamp ($\lambda > 300$ nm) at room temperature (Scheme 158).[221]

[212] Nájera, C. and Yus, M. *Tetrahedron* **1999**, *55*, 10547. (10.1016/S0040-4020(99)00600-6)
[213] Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W. and Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 2668. (10.1002/anie.200906340)
[214] Sengupta, S.; Sen Sarma, D. and Mondal, S. *Tetrahedron* **1998**, *54*, 9791. (10.1016/S0040-4020(98)00533-X)
[215] Guo, H.; Ye, S.; Wang, J. and Zhang, Y. *J. Chem. Research (S)* **1997**, 114. (10.1039/A606405A)
[216] Giovannini, R. and Petrini, M. *Synlett* **1995**, 973. (10.1055/s-1995-5118)
[217] Hyeong Lee, G.; Bok Choi, E.; Lee, E. and Siek Pak, C. *Tetrahedron Lett.* **1993**, *34*, 4541. (10.1016/0040-4039(93)88080-3)
[218] Benedetti, F.; Berti, F. and Risaliti, A. *Tetrahedron Lett.* **1993**, *34*, 6443. (10.1016/0040-4039(93)85066-6)
[219] Lygo, B. and Rudd, C. N. *Tetrahedron Lett.* **1995**, *36*, 3577. (10.1016/0040-4039(95)00564-S)
[220] Guo, H. Z. Y. *J. Chem. Res. (S)* **2001**, 26. (10.3184/030823401103168172)
[221] Liu, Q.; Han, B.; Liu, Z.; Yang, L.; Liu, Z.-L. and Yu, W. *Tetrahedron Lett.* **2006**, *47*, 1805. (10.1016/j.tetlet.2006.01.023)



Scheme 158

The photoinduced electron-transfer mechanism proposed by the authors is depicted in Scheme 159. The electron transfer from ascorbate to the excited β-ketosulfone **A** produces ascorbic acid radical HA· and the radical anion of **A**. After desulfonylation, the α-ketone radical **B** abstracts a hydrogen atom from ascorbic acid, producing the corresponding ketone **C**. HA· disproportionates to dehydroascorbic acid (A).



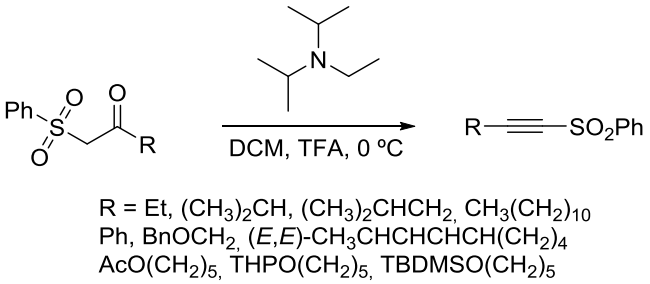
Scheme 159

Despite the advantages of this metal-free process, the method was limited by the necessity of high-energy UV radiation. More recently, this group has developed a visible-light-driven method combining an eosin Y dye bis(tetrabutylammonium salt) (TBA-eosin Y) and *i*Pr_2EtN, affording the desired desulfonylated products in moderate to excellent yields (55 – 99%).[222]

[222] Yang, D.-T.; Meng, Q.-Y.; Zhong, J.-J.; Xiang, M.; Liu, Q. and Wu, L.-Z. *Eur. J. Org. Chem.* **2013**, 7528. (10.1002/ejoc.201301105)

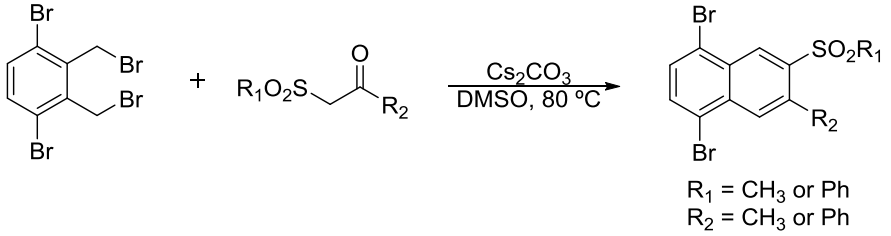
2.4.ii Other reactivity.

A method to access 1-(phenylsulfonyl)-1-alkynes in good yields (69 – 82%) using β-ketosulfones and Hünig's base (*N*,*N*-diisopropylethylamine)-triflic anhydride (Scheme 160) was developed by Craig *et al*.[223]



Scheme 160

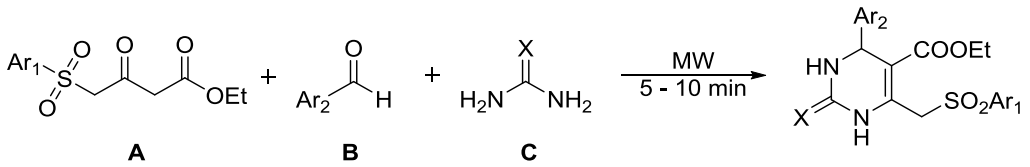
Recently, Wu *et al*. have reported the synthesis of β-substituted sulfonyl naphthalenes derivatives in moderate yields (43 – 68%) *via* the rearrangement aromatisation of benzo[c]oxepine (Scheme 161).[224]



Scheme 161

Besides the Diels-Alder or hetero-Diels-Alder reactions of β-ketosulfones, these compounds have been recently used in the synthesis of tetrahydropyrimidines in good yields (74 – 93%) by the Biginelli reaction[225] of ethyl β-ketosulfone **A**, aromatic aldehyde **B** and diamide (urea/thiourea) **C** under microwave irradiation and solvent- and catalyst-free conditions (Scheme 162).[226]

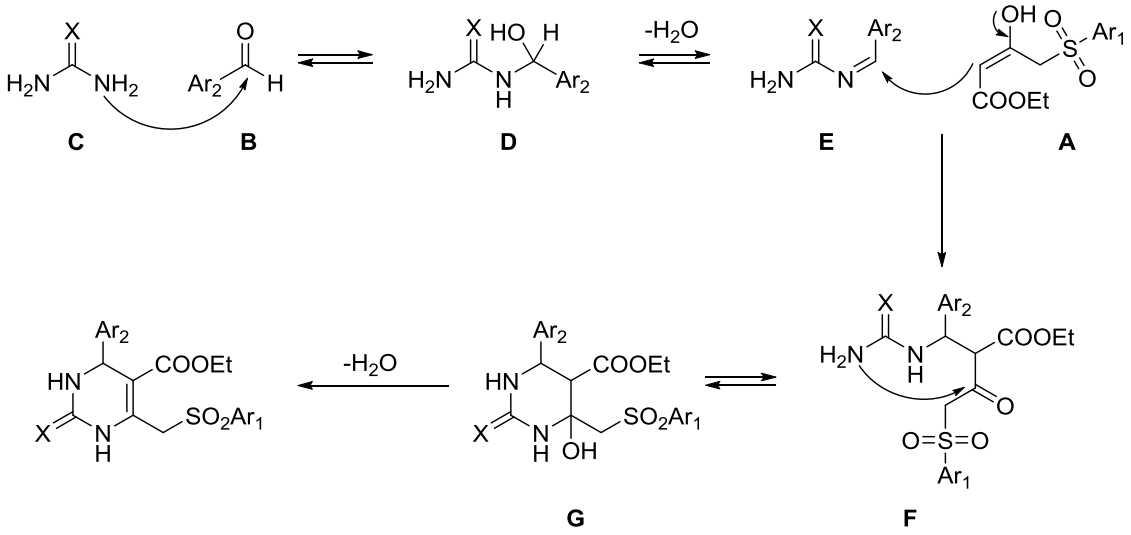
[223] Clasby, M. C. and Craig, D. *Synlett* **1992**, 825. (10.1055/s-1992-22017)
[224] Wang, J.; Xiang, J.; Wang, M.; Guan, J. and Wu, A. *Tetrahedron* **2014**, *70*, 1412. (10.1016/j.tet.2014.01.005)
[225] Kappe, C. O. and Stadler, A. *The Biginelli Dihydropyrimidine Synthesis*; Organic Reactions, **2004**. (10.1002/0471264180.or063.01)
[226] Harikrishnan, P. S.; Rajesh, S. M.; Perumal, S. and Almansour, A. I. *Tetrahedron Lett.* **2013**, *54*, 1076. (10.1016/j.tetlet.2012.12.034)



Ar_1 = *p*-ClC_6H_4 or *p*-$CH_3C_6H_4$
Ar_2 = *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-FC_6H_4
X = O or S

Scheme 162

The mechanism proposed by the authors is depicted in Scheme 163.



Scheme 163

The formation of ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates involves the formation of *N*-arylideneurea intermediate **E** generated by the dehydration of intermediate **D**, which is formed from the reaction of aldehyde **B** and urea/thiourea **C**. Subsequent reaction of *N*-arylideneurea **E** with the enol form of ethyl 3-oxo-4-(arylsulfonyl)butanoate **A** produces an open-chain ureide **F**, which undergoes condensative annulation to afford final product.

AIMS

This work is focused in the field of organocatalysis, in which our group has been working during the last years. From this research we started the study of the reactivity of β-ketosulfones in organocatalytic conditions.

Hence, the main aims of this work are:

1. Synthesis of sulfonyl Nazarov reagents **I-A**, **I-B**, **I-C** and **I-D** (Figure 3).

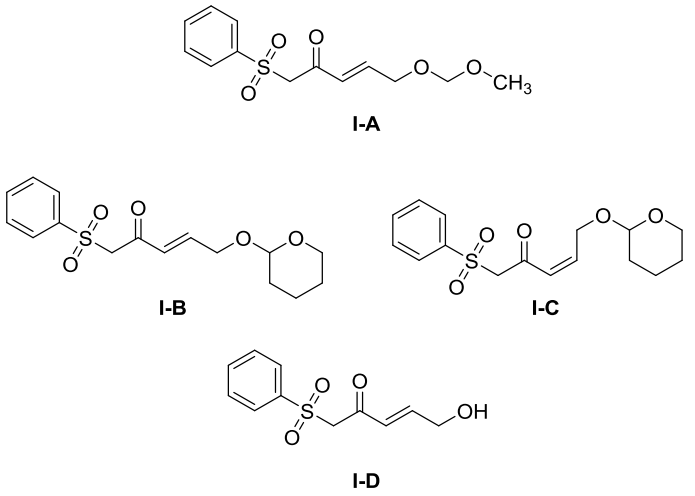


Figure 3

2. Study of the reactivity of sulfonyl Nazarov reagents **I-A**, **I-B**, **I-C** and **I-D** in the reaction with differently substituted aldehydes under organocatalytic conditions (Figure 4). In this way we will study the reactivity with (1) β-monosubstituted, (2) β-methyl-β-disubstituted, (3) complex β,β-disubstituted, and (4) cyclic α,β-unsaturated aldehydes.

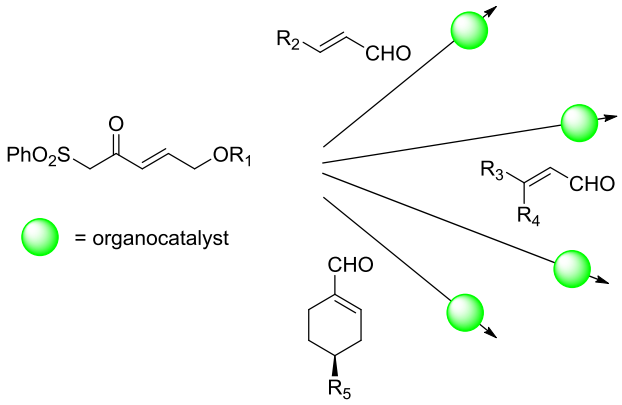


Figure 4

3. Study of the reactivity of obtained products for diversity oriented synthesis.
4. Translate this chemistry to solid support using polyethyleneglycol derivatives.

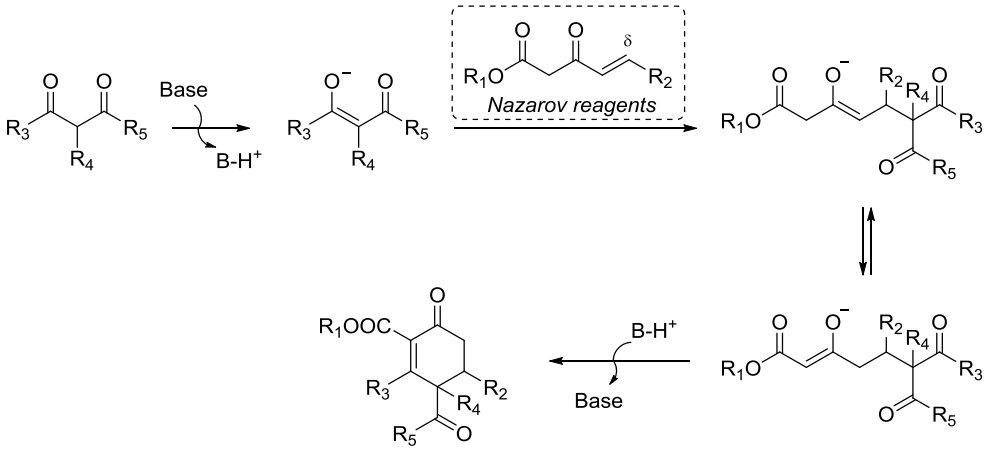
RESULTS AND DISCUSSION

RESULTS AND DISCUSSION. TABLE OF CONTENTS.

1. Introduction.

In 1953 Nazarov[227] proposed a new reagent, a vinyl ketone that had been activated as a β-keto ester, and since known as the Nazarov reagent. Ethyl and methyl 3-oxo-4-pentenoate have been used in synthesis since the work of Nazarov and Zav'yalov, who were the first to show their usefulness in the annulation of cyclic β-diketones.

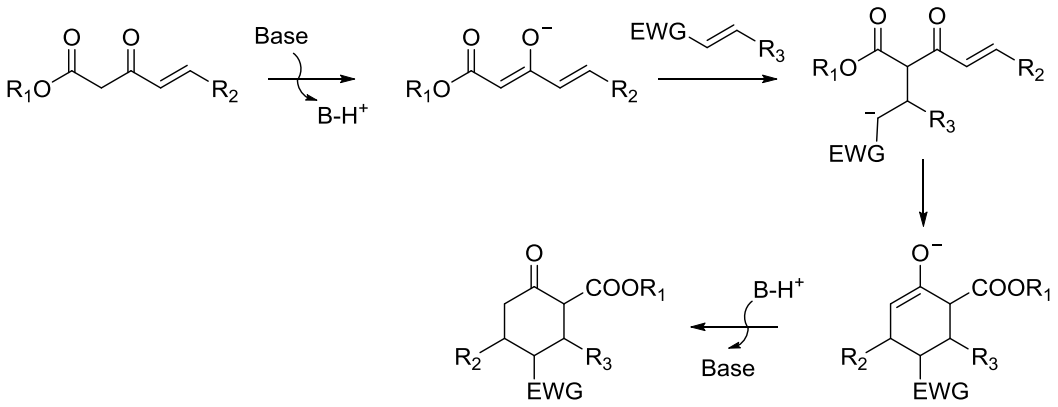
Nazarov reagents lead to a cycle according to two processes. In the first process described by Nazarov, a stabilised carbanion induces a Michael addition on the vinyl ketone moiety of the reagent (Scheme 164). Then an intramolecular aldolisation ends the cyclisation. In this way, the Nazarov reagent appears, in the first step, as an electrophilic reagent and the overall reaction resembles to the Robinson annulation.[228] Its reactivity as electrophilic reagent depends on the substitution at the δ carbon atom, and when a disubstitution occurs the Michael addition step is disfavoured.



Scheme 164 Nazarov reaction pathway (I).

In the second process, the enolisation of the β-keto ester moiety of the reagent leads to a stabilised carbanion, which can react with an electrophilic Michael acceptor. In this case, it first reacts as a nucleophilic reagent (Scheme 165).

[227] Bergelson, L. D. *Tetrahedron* **1959**, *6*, 161. (10.1016/0040-4020(59)85010-9)
[228] Gawley, R. E. *Synthesis* **1976**, 777. (10.1055/s-1976-24200)

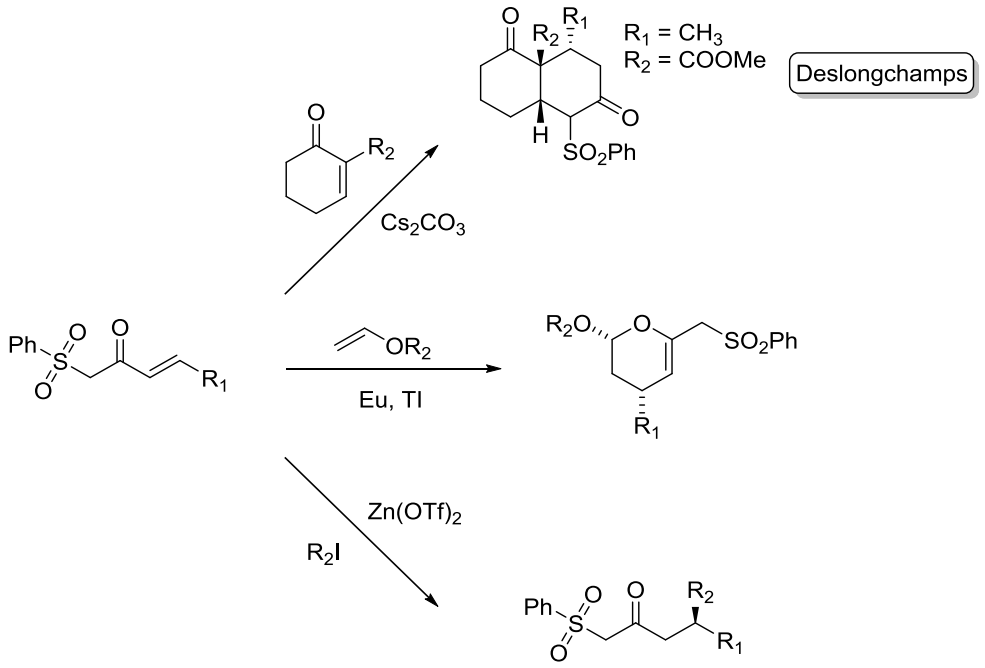


Scheme 165 Nazarov reaction pathway (II).

Two successive Michael additions occur, and some papers invoke a tandem Michael addition or Michael-Michael addition. But for selected cases, the stereochemistry of the products resulting from this hypothetical tandem Michael addition suggests a concerted Diels-Alder reaction. More recent syntheses of functionalised *cis*-decalines based on the so-called Deslongchamps annulation involve this mechanism.[229]

Although there are many examples of reactions of α,β-unsaturated esters used as Nazarov reagents in literature, the presence of ester functionality is not always possible or desired in a synthetic route. For this reason some Nazarov analogues (mainly sulfoxide, sulfone or phosphonate) preparations and applications have also been reported.[229] However, the reactivity of sulfonyl Nazarov reagents has not been widely explored, and most of papers in literature describe nucleophilic additions to the double bond or Diels-Alder reactions (see Introduction chapter 2.3). Only Deslongchamps *et al*. have reported a double Michael addition-cyclisation of a β-ketosulfone using Cs_2CO_3 without stereoselectivity control (Scheme 166).[202]

[229] Audran, G.; Brémond, P.; Feuerstein, M.; Marque, S. R. A. and Santelli, M. *Tetrahedron* **2013**, *69*, 8325. (10.1016/j.tet.2013.06.065) and references cited herein.

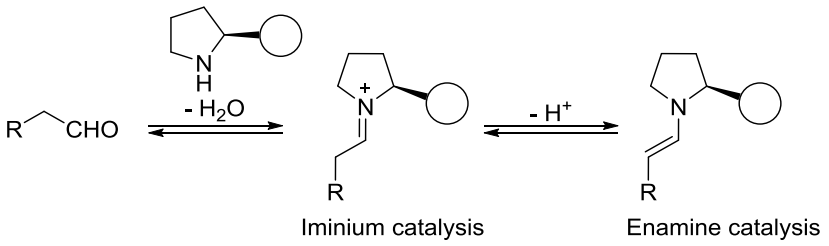


Scheme 166 Examples of typical reactivity of sulfonyl Nazarov analogues.

Since the turn of the millennium, the field of asymmetric organocatalysis has been the focus of immense research and development.[230] It has evolved through the "gold rush" and has emerged as a powerful tool for asymmetric synthesis, which has become increasingly suitable in a range of synthetic disciplines such as target- and diversity oriented synthesis (DOS).[231] Important for this development has been the application of a variety of functional groups, such as sulfones, as reaction partners,[232] which have greatly contributed to the overall synthetic applicability of asymmetric organocatalysis. The strong inductive ability of the sulfone group makes it ideal for various types of organocatalysed reactions, and the many possible transformations of the sulfone functionality make the subsequent intermediates suitable for the generation of a range of important products which are otherwise difficult to obtain. Considering the many newly developed transformations, asymmetric organocatalysis employing sulfone-containing reagents should be regarded as a contribution to the emerging area of stereoselective organocatalytic DOS.

[230] Bertelsen, S. and Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (10.1039/B903816G)
[231] Trabocchi, A. *Diversity-oriented synthesis : basics and applications in organic synthesis, drug discovery, and chemical biology*; Hoboken, New Jersey : Wiley, **2013**.
[232] Alba, A.-N. R.; Companyo, X. and Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018. (10.1039/B911852G)

Among other activation modes, enamine catalysis[233] and iminium catalysis[234] have been the main modes established in organocatalysis. Condensation of an aldehyde substrate and a secondary amine catalyst initially generates an inimium ion, which is in equilibrium with an enamine (Scheme 167). Therefore, the activated carbonyl group can be nucleophilic or electrophilic depending on reaction conditions. Most of the transformations that have been developed to date are based on these two similar, yet complementary modes of activation.



Scheme 167 Enamine/iminium oraganocatalysis.

Our group has been interested in this kind of chemistry using different organocatalysts. In this work we plan to study the reactivity of new sulfonyl Nazarov reagents with differently substituted aldehydes making use of commercial organocatalysts (Figure 5). First we will examine the reactivity with β-monosubstituted α,β-unsaturated aldehydes (Figure 5, route A). Then we will increase the complexity of the α,β-unsaturated aldehyde using β-methyl-β-disubstituted α,β-unsaturated aldehydes (Figure 5, route B), other more complex β,β-disubstituted α,β-unsaturated aldehydes (Figure 5, route C), and cyclic α,β-unsaturated aldehydes (Figure 5, route D). Furthermore, we plan to study the reactivity of the so-obtained products for DOS and translate these results to solid-support chemistry.

[233] Notz, W.; Tanaka, F. and Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. (10.1021/ar0300468)
[234] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. and Pesquera, A. *Synthesis* **2010**, 701. (10.1055/s-0029-1218645)

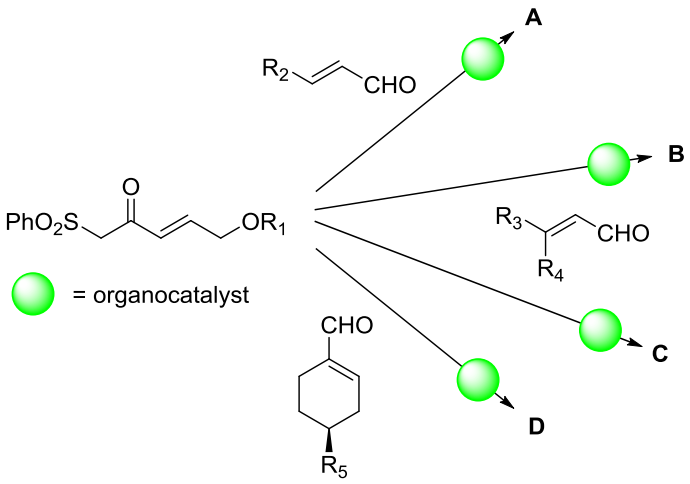


Figure 5 Reactivity of our sulfonyl Nazarov reagents with differently substituted aldehydes in organocatalytic conditions.

2. Synthesis of sulfonyl Nazarov reagents I-A, I-B, I-C and I-D.

As shown in the introduction of this thesis, the reactivity of β-keto-γ,δ-unsaturated sulfones has been widely explored. However, most of the examples in literature only consider the reactivity at the active methylene, the carbonyl group or the double bond separately. We wanted to test the reactivity of these sulfones as Nazarov analogues, where at least two of the three functionalities participate in the reaction. Furthermore, we decided to have an extra function at the end of these sulfonyl Nazarov reagents, where we placed a hydroxyl group (protected or free), which can be further employed for the synthesis of diversity oriented compounds or as a linker in solid support chemistry.[235] In this way we developed the synthesis of four new sulfonyl Nazarov reagents namely, **I-A**, **I-B**, **I-C** and **I-D** (Figure 6).

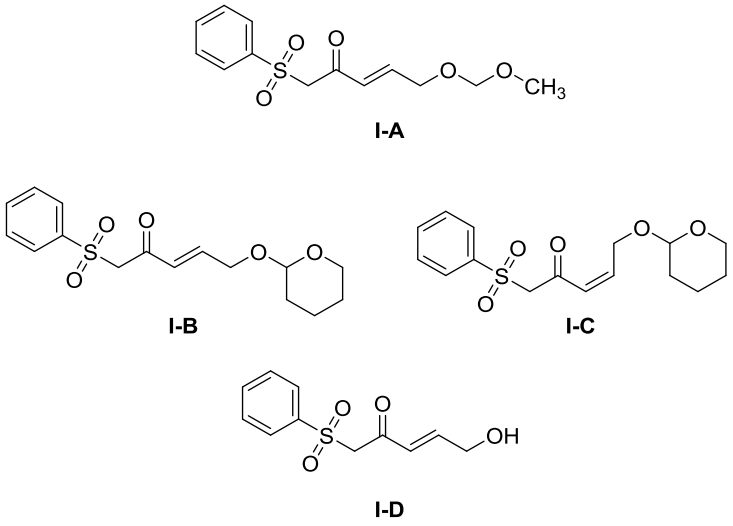
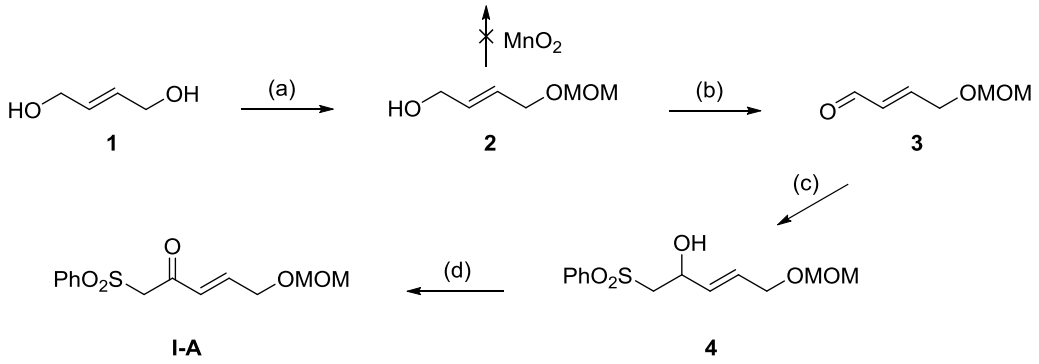


Figure 6 Sulfonyl Nazarov reagents sinthesised in this work.

Here we describe the synthesis of these sulfonyl Nazarov reagents.

[235] Arboré, A.; Dujardin, G. and Maignan, C. *Eur. J. Org. Chem.* **2003**, 4118. (10.1002/ejoc.200300417)

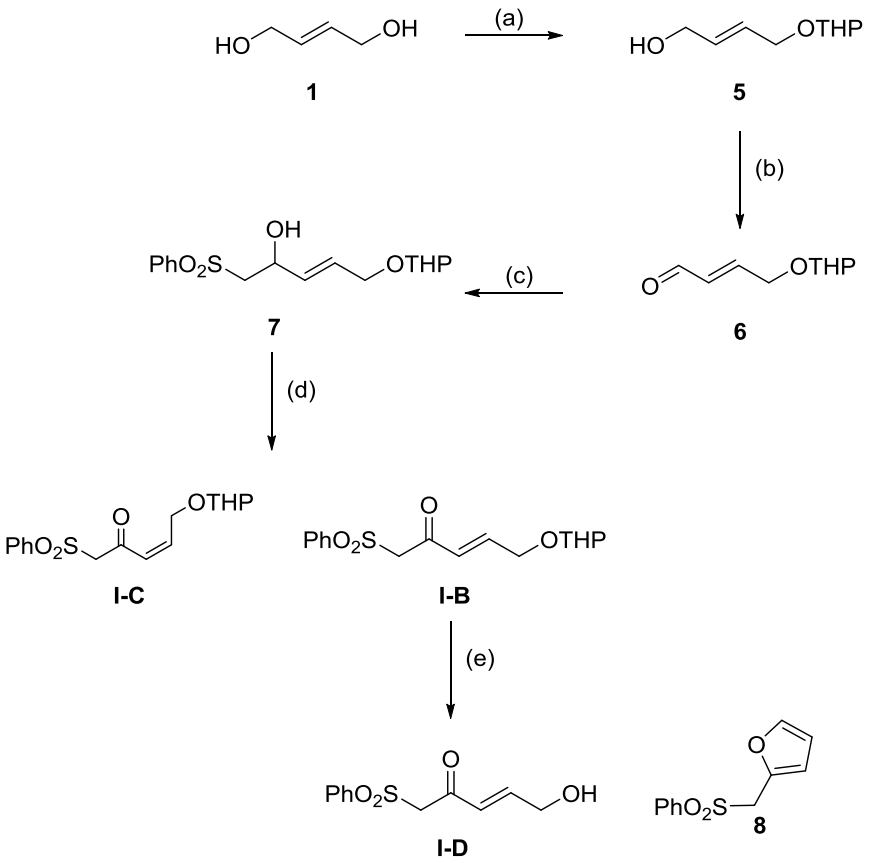
First, sulfonyl Nazarov analogue **I-A** was easily synthesised in high yield from commercially available diol **1** in four steps (Scheme 168).



Scheme 168. (a) MOMCl, NaH, THF, 0 ºC, 87%; (b) PDC (2 equivs.), MS, DCM, rt, 72%; (c) Methylphenylsulfone (0.9 equivs.), *n*-BuLi (0.9 equivs.), THF, -78 ºC, 63%; (d) PDC (2 equivs.), MS, DCM, rt, 50 %.

(*E*)-But-2-ene-1,4-diol **1** was protected under standard conditions to obtain the MOM protected derivative **2**; this compound was oxidised with PDC in DCM to give aldehyde **3** in good yield over two steps (other oxidation conditions such as manganese dioxide did not work). Addition of the lithium derivative of methylphenylsulfone to aldehyde **3** gave alcohol **4** that was oxidised to the corresponding ketone **I-A** using PDC as before.

The synthesis of β-ketosulfones **I-B, I-C** and **I-D** is depicted in Scheme 169. Monoprotection product **5**, obtained using DHP under standard conditions, was oxidised with PDC and condensed with the lithium derivative of methylphenylsulfone to afford the corresponding alcohol **7**, which oxidation gave the corresponding mixture of β-ketosulfones **I-B** and **I-C** in a 99/1 ratio respectively. Use of other oxidising conditions including the use of catalytic TPAP led to a decrease in the yield of the oxidations steps. These sulfones were separated by flash chromatography on silica gel and the deprotection of the major compound with *p*-TsOH·H_2O in THF/H_2O led to β-ketosulfone **I-D**. Deprotection in 2-propanol only afforded a 28% of the desired product and a 27% of intramolecular cyclisation product **8.**



Scheme 169 (a) DHP, *p*-TsOH·H_2O (1 mol%), DCM, rt, 96%; (b) PDC (2 equivs.), MS, DCM, rt, 91%; (c) Methylphenylsulfone (0.9 equivs.), *n*-BuLi (0.9 equivs.), THF, -78 ºC, 61%; (d) PDC (2 equivs.), MS, rt, 58%, (ratio **I-B**/**I-C**: 99/1); (e) *p*-TsOH·H_2O (10%), THF/H_2O (1/1), rt, 88%.

3. Study of the reactivity of sulfonyl Nazarov reagents I-A, I-B, I-C and I-D in organocatalytic reactions.

Since β-keto-γ,δ-unsaturated sulfones have been mainly used in Diels-Alder reactions, we wanted to study their behaviour as Nazarov analogues in the reaction with differently substituted aldehydes under organocatalytic conditions. Thus, here we describe the different organocatalityc conditions and reactions screened with β-ketosulfones **I-A, I-B, I-C** and/or **I-D**, and differently α,β-unsaturated aldehydes. This study has led us to obtain the structures depicted in Figure 7.

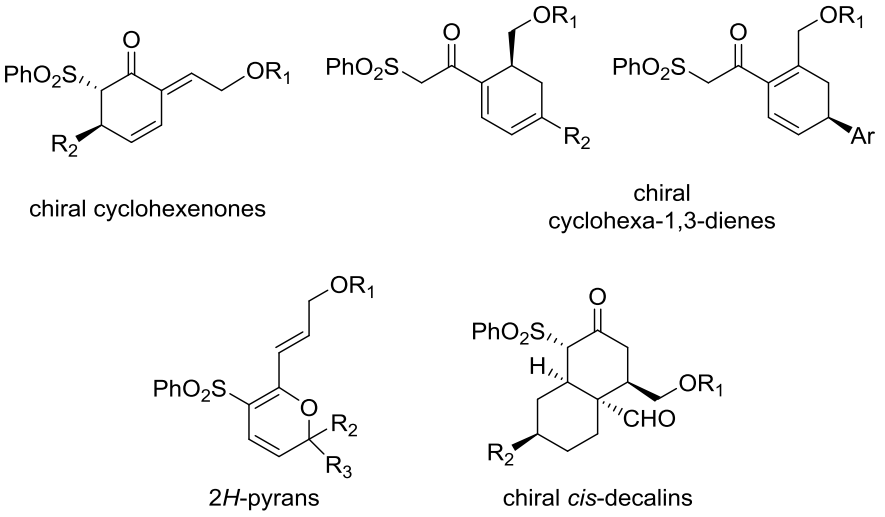
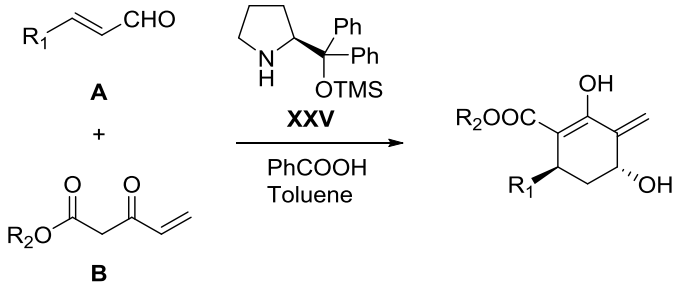


Figure 7 Structures obtained in this work.

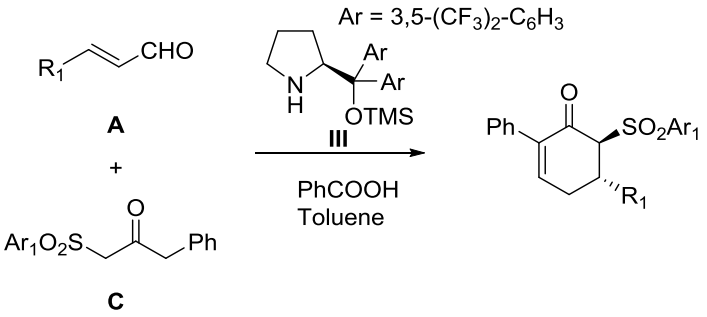
3.1. Reactivity with β-monosubstituted α,β-unsaturated aldehydes.

As shown in the introduction, examples of the use of Nazarov reagents for the synthesis of chiral cyclohexenones are scarce. Jørgensen *et al.* used a Nazarov reagent in the reaction with β-monosubstituted α,β-unsaturated aldehydes, however, 2-alkylidene cyclohexanones were obtained instead (Scheme 170).[236,237] This group described that the tandem reaction between compound **A,** and the Nazarov reagent **B**, when substituted with a methyl group at the alkene´s γ or δ positions did not take place, and only a sluggish Michael addition was observed due to the steric hindrance associated with the Morita-Baylis-Hillman reaction.



Scheme 170 Synthesis of 2-alkylidene cyclohexanones by Jørgensen *et al.*

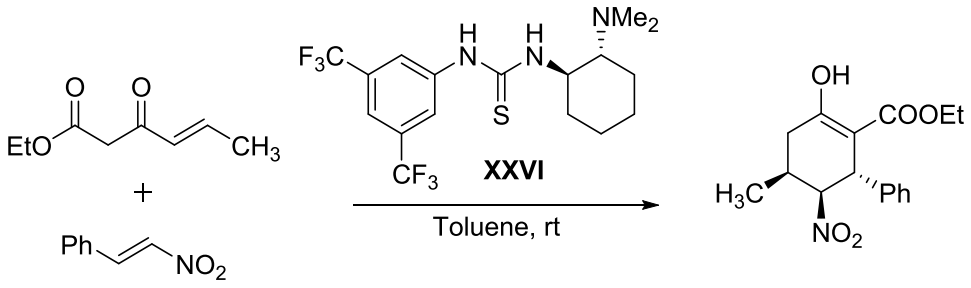
Ruano and Alemán *et al.* were able to obtain chiral cyclohexenones employing β-monosubstituted α,β-unsaturated aldehydes but using simple β-ketosulfones and not Nazarov reagents or analogues (Scheme 171).[238]



Scheme 171 Synthesis of chiral cyclohexenones by Ruano and Alemán *et al.*

[236] Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S. and Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 121. (10.1002/anie.200704076)
[237] Albrecht, Ł.; Richter, B.; Vila, C.; Krawczyk, H. and Jørgensen, K. A. *Chem. Eur. J.* **2009**, *15*, 3093. (10.1002/chem.200802285)
[238] García Ruano, J. L.; Alvarado, C.; Díaz-Tendero, S. and Alemán, J. *Chem. Eur. J.* **2011**, *17*, 4030. (10.1002/chem.201003267)

In 2006 and using bifunctional thiourea **XXVI** instead of proline-like organocatalysts, Takemoto *et al.* reported a tandem Michael addition of β-keto-γ,δ-unsaturated-esters to a nitroalkane affording the corresponding chiral cyclohexenones (Scheme 172).[239]



Scheme 172 Synthesis of chiral cyclohexenones by Takemoto *et al.*

More recently, research has focused on the development of cascade and multicomponent reactions (MCR), particularly organocatalysed reactions.[240] Nature uses this principle for the efficient construction of multiple bonds in the biosynthesis of many natural products with the aid of enzymes. In this regard, organocatalytic cascade reactions resemble natural biosynthetic processes that are highly chemo-, regio-, and stereoselective.[241] According to Tietze, a domino reaction is a process in which two or more bond-forming events occur under the same reaction conditions based on the functionalities formed in the previous step.[242] Domino or cascade reactions constitute a powerful subgroup of the broader category of one-pot reactions. These transformations are atom-economical and avoid time-consuming protection/deprotection steps and isolation of intermediates. In addition, they are recognised as processes with minimal waste generation. In this way, cascade reactions fall under the category of green chemical transformations. In contrast to classical multistep sequences, in the case of cascade reactions, numerous pathways are possible. These pathways can compete, leading to undesired routes; nevertheless, by careful selection of the catalyst, exceptional levels of control can be achieved, as only a few of these possible pathways are facilitated, resulting in high selectivities for the overall transformation. Organocatalysis provides an alternative to metal- and enzyme-catalysed cascade reactions for creating molecular complexity from simple starting materials in an expedient manner. Organocatalytic cascade reactions are distinguished especially by the fact that a single organocatalyst activates relatively unreactive organic molecules such as carbonyl compounds. Organocatalytic tandem reaction was found to be an efficient tool for the synthesis of chiral cyclohexenones. However, for the development of successful asymmetric synthesis, many crucial issues had to be addressed.

[239] Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H. and Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (10.1016/j.tet.2005.08.109)
[240] Dömling, A.; Wang, W. and Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (10.1021/cr100233r)
[241] Clardy, J. and Walsh, C. *Nature* **2004**, *432*, 829. (10.1038/nature03194)
[242] Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (10.1021/cr950027e)

Firstly, we started our study using our sulfonyl Nazarov reagent **I-A** with β-monosubstituted α,β-unsaturated aldehydes. The first aldehyde tested was (*E*)-2-pentenal **9a** (Table 1).

When the reaction was done in 2-propanol without catalyst (entry 1), or even with LiOAc as the additive (entry 2), nothing happened. So an organocatalyst was necessary for this reaction to take place. When pyrrolidine was used as catalyst, only decomposition was observed (entry 3). L-Proline has been, since the leading paper of List, Lerner and Barbas,[243] one of the most employed organocatalysts, not only for simple reactions as aldol,[244] Mannich,[245] Michael,[246] Biginelli,[247] Diels-Alder/Knoevenagel,[248] Baylis-Hillman,[249] aza-Morita-Baylis-Hillman,[250] α-selenylation,[251] α-halogenation[252] and oxidation reactions,[253] among others, but also in tandem or multicomponent reactions.[254] When we used L-Proline, a new structure was observed by ^{1}H-NMR experiments. In this spectrum we saw what it seemed to be the starting sulfone, although some signals had changed. The olefinic hydrogen in α to the carbonyl had changed or disappeared and the two hydrogens between the sulfone and the carbonyl groups had changed too. There was no signal of aldehyde by ^{1}H-NMR. From ^{13}C-NMR we could observe the presence of a CO group besides four olefinic carbon signals, three CH and one tetrasubstituted carbon. No hydroxyl group was observed by IR experiments. Next to the sulfone there seem to be only one hydrogen but it was not coupled to any other. Furthermore, we could see an allylic hydrogen (close to the CH_3O group of the MOM protecting group) which was joined to an ethyl group. All these data pointed to the same fact, a cyclohexenone had been formed, but it was a mixture of two cyclohexenones, actually, two diasteromers at the *exo*-double bond, *i.e.*, *trans* or *cis*, in a 2/1 ratio as shown in (Figure 8). Flash chromatography of the mixture afforded both separated isomers, as we suspected. The *anti*-relative stereochemistry for the sulfone and the ethyl group was established since no coupling was observed between H5 and H6, in both compounds. In the case of the olefin, by the nOe coupling observed for both compounds (Figure 8).

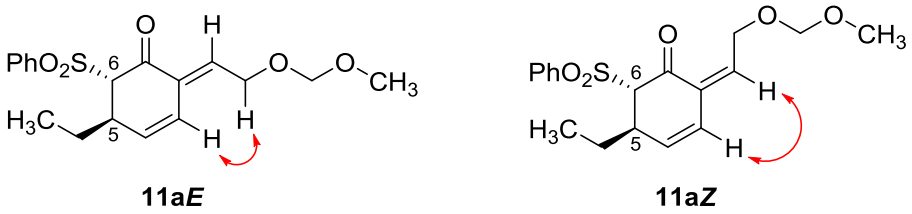


Figure 8 Observed nOe´s that establish configuration of exocyclic double bond for **11a**.

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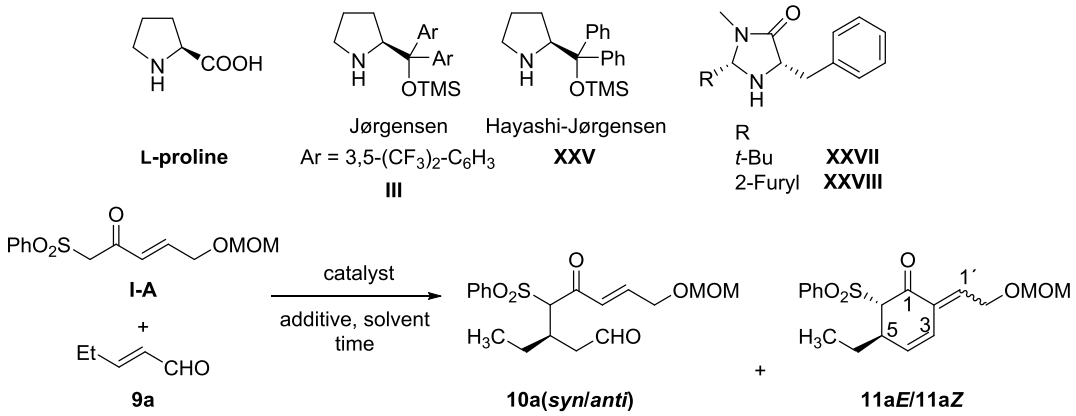
Table 1 Screening of the reaction between Nazarov reagent **I-A** and (*E*)-2-pentenal **9a**, using different catalysts and conditions.[a]



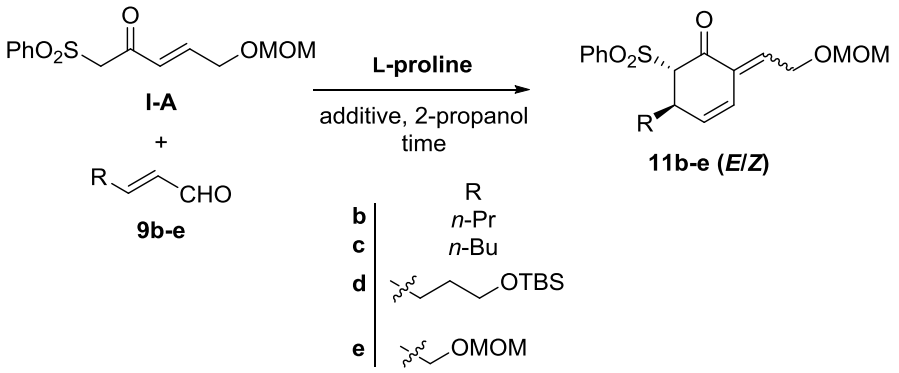
Entry	Catalyst	Additive	Solvent	Time (h)[b]	Yield (%)[c] **10a(*syn*/*anti*)**	Yield (%)[c] **11a*E*/11a*Z***	ee (%)[d]	d.r.[e]
1	-	-	2-propanol	6	S.M.		-	-
2	-	LiOAc	2-propanol	6	S.M.		-	-
3	Pyrrolidine	LiOAc	2-propanol	3	Decomposition		-	-
4	**L-proline**	LiOAc	2-propanol	3		40	0	2/1
5	**L-proline**	LiOAc	EtOH	69		11	0	2/1
6	**L-proline**	LiOAc	$CDCl_3$	13		60	0	2/1
7	**L-proline**	B.A.	$CDCl_3$	120	60		N.D.	1/1
8	**L-proline**	-	$CDCl_3$	63		33	0	2/1
9	**L-proline**	-	2-propanol	22		32	0	2/1
10	**(±)-proline**	LiOAc	2-propanol	9		38	0	2/1
11	**XXV**	LiOAc	$CDCl_3$	120	40		N.D.	1/1
12	**XXV**	B.A.	$CDCl_3$	120	30		N.D.	1/1
13	**III**	LiOAc	$CDCl_3$	42	38		N.D.	1/1
14	**III**	B.A.	$CDCl_3$	23	32		N.D.	1/1
15	**III**	LiOAc	2-propanol	5	23		N.D.	1/1
16	**XXVII**	LiOAc	$CDCl_3$	120	S.M.		-	-
17	**XXVII**	B.A.	$CDCl_3$	120	S.M.		-	-
18	**XXVIII**	LiOAc	$CDCl_3$	120	35		N.D.	1/1
19	**XXVIII**	B.A.	$CDCl_3$	120	30		N.D.	1/1

[a]All the reactions were carried out at room temperature, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol% of catalyst, and 20 mol% of additive. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored either by TLC or by ^{1}H-NMR spectroscopy when $CDCl_3$ is used as the solvent). [c] Yield referring to the mixtures of compounds **10a(*syn*/*anti*)** and to the mixtures of compounds **11a*E*** and **11a*Z*** respectively (both with identical stereochemistry at C5 and C6). [d] Enantiomeric excess referred to the compounds **11a*E*** and **11a*Z***, provided to be the same. The ee was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm. [e] Diastereomeric ratio referred to the *syn*/*anti*-ratio in the case of compounds **10a(*syn*/*anti*)** or to the *E*/*Z* ratio in the case of **11a*E*/11a*Z***. B.A. = Benzoic acid; S.M. = Starting material; N.D. = Not determined due to stability issues.

So after using L-proline as catalyst, we obtained desired cyclohexenone **11a** in a diastereomeric ratio of 2/1 of the olefins but without enantioselectivity.

The use of lithium acetate as additive accelerated the reaction when 2-propanol was used as the solvent (entries 4-6). When benzoic acid is used as the additive, the reaction proceeded with a different outcome (entry 7). The obtained product was similar to the starting sulfone except for the CH_2 between the sulfonyl and the carbonyl groups, which now seemed to be a CH. Moreover, now there were two carbonyl groups (CO and CHO) as observed by ^{13}C-NMR. By ^{1}H-NMR, only two olefinic hydrogens were present and the aldehyde signal corresponded to a non-conjugated aldehyde. All these data fitted well with the Michael addition of our sulfonyl Nazarov reagent to *E*-2-pentenal (**10a**) and again, we observed a diastereomeric mixture corresponding to the *syn* and *anti*-dispositions derived from this reaction. Although the use of benzoic acid as the additive stopped the cyclisation and gave a mixture of diastereomeric aldehydes **10a-*syn*** and **10a-*anti*** in a 1/1 ratio, the reaction proceeded in good yield, but we were unable to establish the enantiomeric excess (entry 7). Without any additive (entries 8 and 9), yield decreased slightly and the reaction was slower, but the same cyclisation products were obtained in the same diastereomeric ratio, with no enantioselectivity. Racemic proline was used to establish the conditions for the enantiomeric excess determination by HPLC, giving the cyclisation product as the same mixture of diastereomeric olefins (entry 10). Once we have tested proline, we continued with the study of Hayashi-Jørgensen's catalyst XXV and Jørgensen's catalyst **III** using lithium acetate and benzoic acid as the additives (entries 11-15). Both catalysts gave good results in the Michael addition step affording the mixture of diastereoisomeric aldehydes **10a** (*syn*/*anti*, 1/1) at the carbon flanked by the carbonyl and sulfonyl group, but no cyclisation product was produced. MacMillan catalyst **XXVII** gave no reaction at all (entries 16 and 17) and **XXVIII** afforded similar result as Jørgensen's catalyst **III**, but in longer time (entries 18 and 19).

Table 2 Proline as catalyst for the synthesis of 2-alkylidene cyclohexenones.[a]



Entry	Aldehyde	Additive	Product	Time (h)[b]	Yield (%)[c]	ee (%)[d]	d.r.[e]
1	**9b**	LiOAc	**11b**	8	69	0	2/1
2	**9c**	LiOAc	**11c**	8	80	0	2/1
3	**9d**	LiOAc	**11d**	6	51	0	2/1
4	**9e (3)**	LiOAc	**11e**	16	31	0	2/1

[a]All the reactions were carried out at room temperature, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, 20 mol% of **L-proline**, and 20 mol% of additive. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Yield referring to the mixtures of isomers ***E*** and ***Z***. [d] Enantiomeric ratio referred to compounds ***E*** and ***Z***, provided to be the same. The ee was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm. [e] *E*/*Z* diastereomeric ratio.

Although proline gave no enantioselectivity, the synthesis of 2-alkylidene cyclohexenones **11** in a domino process in an easy and convenient manner is very significant. For this reason, and in order to check this reaction and extend its versatility, a variety of aldehydes **9b-e** (caution: aldehyde **9e** is aldehyde **3** in Scheme 168. Number is changed here for simplicity) were screened.

The results observed in Table 2 indicated that this domino reaction could be extended to several aldehydes providing different 2-alkylidene cyclohexenones. The reaction affords a 2/1 diastereomeric mixture of olefins in favour of the *E*-compound with no enantioselectivity. It is remarkable that bulkier alkyl chains led to better yields. In no case did this reaction proceed to the phenol structure under these reaction conditions.

Proline afforded cyclohexenones with no enantioselectivity. However, we knew how this organocatalyst had been employed in tandem with other catalysts,[254] so we decided to use Jørgensen's catalyst **III** (instead of **XXVIII,** due to the reaction speed and better yields observed, entries 13, 14 and 18, 19, Table 1) and proline in tandem, where **III** would be used for the enantiomeric Michael addition step, as previously shown, and successively, we would add proline to produce the cyclisation. In this way we expected to afford our cyclohexenones with the good yields given by proline and enantioselectively thanks to the use of Jørgensen's catalyst.

Thus, we started using catalyst **III** for the asymmetric Michael addition of our Nazarov reagent **I-A** to different β-monosubstituted α,β-unsaturated aldehydes (Table 3).

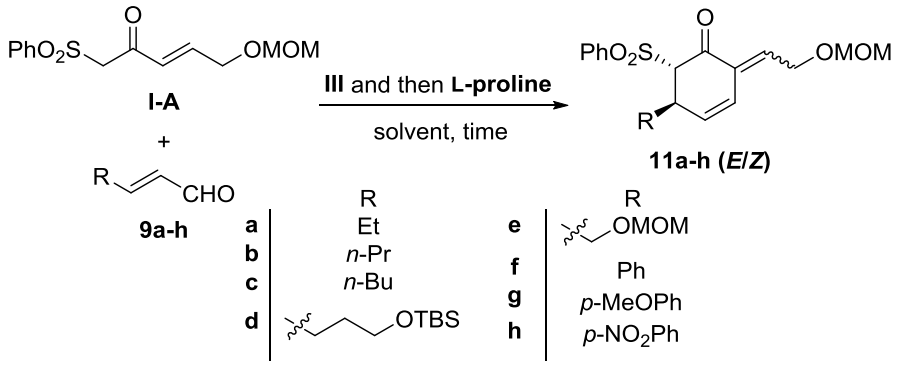
Chiral HPLC analysis showed that we have obtained our cyclohexenones with high enantioselectivity and with the usual 2/1 d.r. ratio for the *exo*-double bond. In this tandem way we obtained chiral cyclohexenones in better yields and enantioselectivites than using only proline.

As shown in Table 3, entry 1, if 2-propanol is used as solvent without any additive the reaction takes place in very good yield with good enantiomeric ratio. Although there is slight difference between chloroform and 2-propanol as solvents (entries 1 and 2), $CDCl_3$ was the option selected in order to monitor the reaction by ^{1}H-NMR, attending to the disappearance of the sulfone and the starting aldehyde employed. The reaction under the same conditions gives identical results using $CHCl_3$ as the solvent. Reaction conditions were established using pentenal, hexenal and heptenal as aldehydes and extended to other alkyl aldehydes as **9d** and **9e**. Optimal conditions to obtain 2-alkylidene cyclohexenones were found to be $CDCl_3$, no additives, **III** as the first catalyst, allowing to react until all starting materials have been consumed, followed by the addition of proline.

In this manner we have been able to obtain 2-alkylidene cyclohexenones in good yield and with good enantiomeric ratio. The absolute configuration of the products was established tentatively according to the results obtained by Ruano and Alemán *et al.*[255] with similar sulfones and aldehydes. When bulkier alkyl aldehydes are employed, increased yields are obtained with excellent enantiomeric ratios. On the contrary, the use of aryl aldehydes does not produce any reaction. This behaviour was reported by Ruano and Alemán *et al.* in a similar case in which no reaction with cinnamaldehyde and other activated aldehydes was observed. In our case, oppositely only the Michael reaction in very poor yield with deactivated aryl aldehydes as **9h** is observed, although the addition step took more time.

[255] Alemán, J.; Marcos, V.; Marzo, L. and García Ruano, J. L. *Eur. J. Org. Chem.* **2010**, 4482. (10.1002/ejoc.201000502)

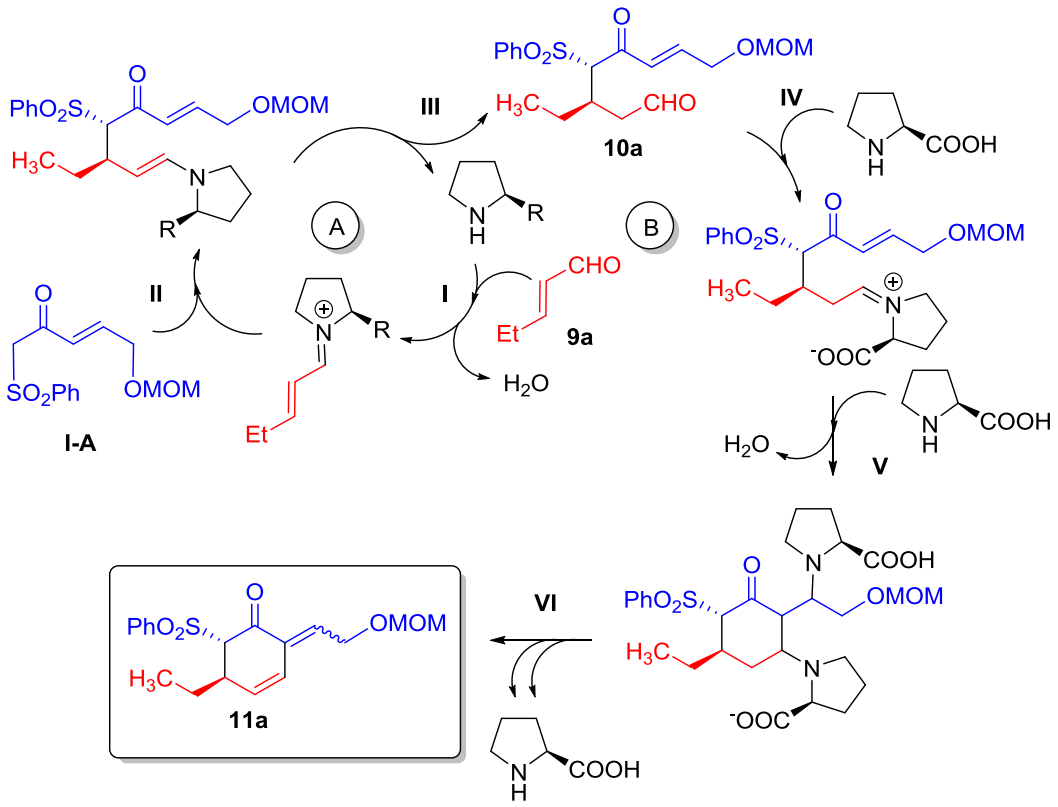
Table 3 Synthesis of chiral 2-alkylidene cyclohexenones *via* tandem catalysis.[a]



Entry	Aldehyde	Solvent[b]	Product	Time (h)[c]	Time Proline (h)[d]	Yield (%)[e]	ee (%)[f]	d.r.[g]
1	**9a**	2-propanol	**11a*E*/11a*Z***	10	96	77	82	2/1
2	**9a**	$CDCl_3$	**11a*E*/11a*Z***	10	48	73	90	2/1
3	**9b**	$CDCl_3$	**11b*E*/11b*Z***	26	48	75	96	2/1
4	**9c**	$CDCl_3$	**11c*E*/11c*Z***	26	48	50	96	2/1
5	**9d**	$CDCl_3$	**11d*E*/11d*Z***	30	115	46	N.D.	2/1
6	**9e**	$CDCl_3$	**11e*E*/11e*Z***	2	42	41	90	2/1
7	**9f**	$CDCl_3$	-	63	-	S.M.	-	-
8	**9g**	$CDCl_3$	-	73	-	S.M.	-	-
9[h]	**9h**	$CDCl_3$	Michael	73	-	-	-	-

[a] All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol% of **III**, and 20 mol% of **L-proline**. [b] Identical results are obtained when $CHCl_3$ is used as the solvent. [c] Time in which intermediate aldehyde is formed (monitored either by TLC or by ^{1}H-NMR spectroscopy when $CDCl_3$ is used as the solvent). [d] Extra time after the addition of proline. [e] Yield referring to the mixtures of isomers ***E*** and ***Z***. [f] Enantiomeric ratio referred to the compounds ***E*** and ***Z***, provided to be the same. The ee was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm. [g] *E*/*Z* diastereomeric ratio. [h] This reaction does not proceed completely to the Michael addition product, being observed a 50% yield after 73 hours; for this reason proline was not added.

To explain the results obtained, we postulate the mechanism depicted in Scheme 173. First the organocatalyst forms an iminium intermediate with the α,β-unsaturated aldehyde promoting the Michael addition of the sulfonyl Nazarov analogue **I-A** (standard catalytic cycle **A** reported in the literature).[236,237] Once aldehydes **10** are formed after elimination of organocatalyst, we understand that they enter in a new catalytic cycle **B**, in which an intramolecular MBH reaction takes place with a concomitant Knoevenagel condensation to form chiral cyclohexenones **11**, after elimination of two organocatalyst molecules.



Scheme 173 Proposed mechanism for the Michael/Morita–Baylis–Hillman/Knoevenagel tandem reaction.

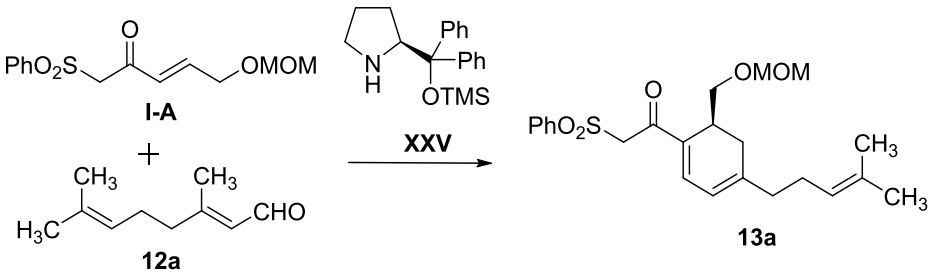
In this way we have demonstrated how it is possible to obtain chiral cichohexenones from sulfonyl Nazarov analogues as **I-A** and β-monosubstituted α,β-unsaturated aldehydes using organocatalytic and green conditions.

3.2. Reactivity with β-methyl-β-disubstituted α,β-unsaturated aldehydes.

Monosubstituted unsaturated aldehydes have been widely used in organocatalysis for the synthesis of very interesting compounds.[256] However, β-methyl-β-disubstituted unsaturated aldehydes have been much less used in organocatalysis. For this reason and due to the good results obtained previously, we decided to study more complex aldehydes so, instead of the previous monosubstituted aldehydes, this time we used β-methyl-β-disubstituted α,β-unsaturated aldehydes.

A tentative reaction was carried out using sulfone **I-A** and readily commercially available citral **12a**. We started using Hayashi-Jørgensen's catalyst **XXV** since it gave similar results compared to **III** in the Michael addition step to simple α,β-unsaturated aldehydes (Table 1), it was easier to handle and furthermore, this catalyst is non-fluorinated and more soluble in 2-propanol.

After addition of **XXV** we would add proline in tandem. Surprisingly, the only addition of **XXV** did not produce just the Michael adduct we were expecting, but a new structure. ^{1}H-NMR spectrum was much more different to the starting sulfone this time. We could observe two coupled doublets corresponding to olefinic hydrogens 5 and 6 (Scheme 174), conjugated with a carbonyl group due to the observed shielding. The two hydrogens of the CH_2 between the sulfonyl and the carbonyl group remained at the same chemical shift, so the "$PhSO_2CH_2CO$-'' structure was still present. No CHO group was observed either by ^{1}H- or ^{13}C-NMR, but only one CO group was present, also visible in the IR spectrum. All these data made us think that this new structure was cyclohexa-1,3-diene **13a**, constituting the first time that a Nazarov reagent acted as dienophile using organocatalysis. Absolute stereochemistry was determined by X-ray diffraction experiments for an analogue, as shown later on. Chiral HPLC analysis showed that compound **13a** was obtained in a good ee of 82%.

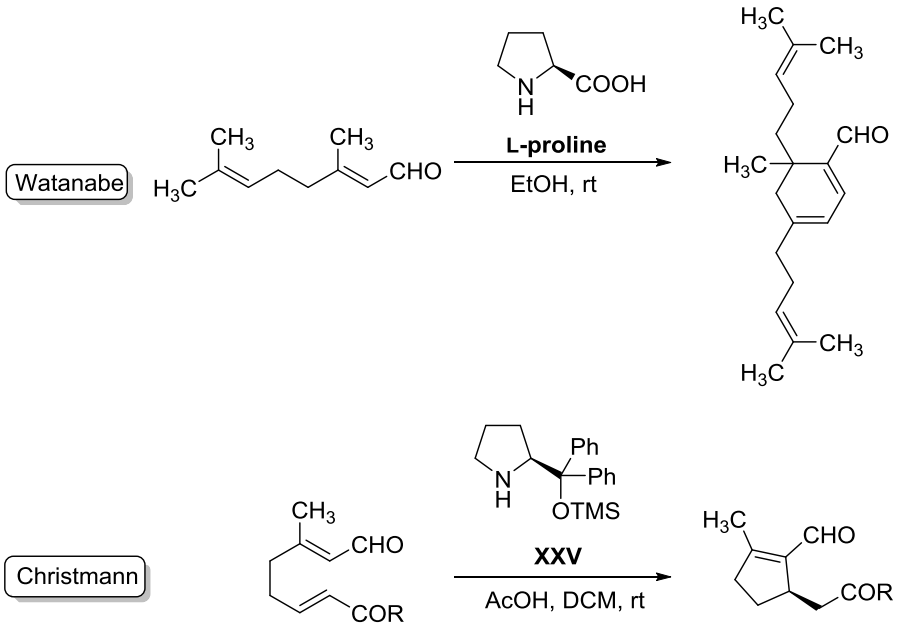


Scheme 174 Reactivity of Nazarov reagent **I-A** with citral.

[256] Giacalone, F.; Gruttadauria, M.; Agrigento, P. and Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406. (10.1039/C1CS15206H)

Substituted cyclohexa-1,3-dienes and their derivatives are structurally important since they are versatile intermediates for the synthesis of natural products and biologically active compounds,[257] including terpenes, carotenoids, and steroids. Cyclohexa-1,3-diene itself has been used as the starting material for the stereoselective synthesis of 11-deoxyprostaglandines.[258] It is a promising monomer for the manufacture of aromatisable polymers, and both the diene itself and the vast majority of its derivatives are obtained solely by synthesis. Despite the importance of this class of compounds, the principal methods for their synthesis have as starting material the cyclohexane ring and many of the synthetic methods result in the formation of side products, including isomeric dienes. The high reactivity of cyclohexadienes, particularly their tendency to dimerise, polymerise, aromatise, and oxidise, may also be the cause of the reduced yield of the desired products and the appearance of impurities.[259]

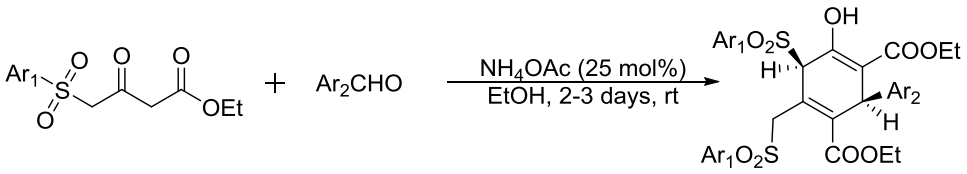
Serebryakov *et al.* developed the asymmetric synthesis of cyclohexa-1,3-dienes from prenal and unsaturated esters or derivatives.[260] Watanabe *et al.*, using proline as organocatalyst, made citral to dimerise through a Diels-Alder reaction[261] and Christmann *et al.* reported an intramolecular Rauhut-Curier-type reaction *via* dienamine activation (Scheme 175).[262]



Scheme 175 Watanabe and Christmann *et al.* cyclisation works.

[257] Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F. and Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459. (10.1021/jo701477v)
[258] Corey, E. J. and Ravindranathan, T. *Tetrahedron Lett.* **1971**, *12*, 4753. (10.1016/S0040-4039(01)87545-6)
[259] V A Mironov, A. D. F. A. A. A. *Russian Chemical Reviews* **1983**, *52*, 61.
[260] Serebryakov, E. P.; Shcherbakov, M. A.; Gamalevich, G. D. and Struchkova, M. I. *Russ. Chem. Bull.* **2003**, *52*, 734. (10.1023/A:1023987613185)
[261] Bench, B. J.; Liu, C.; Evett, C. R. and Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458. (10.1021/jo061763t)
[262] Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M. and Christmann, M. *Org. Lett.* **2009**, *11*, 4116. (10.1021/ol901614t)

As shown in the introduction, there is no examples of the synthesis of cyclohexa-1,3-dienes using β-ketosulfone systems nor sulfonyl Nazarov analogues. Only Perumal *et al.* used β-ketosulfones in a Michael reaction with aldehydes using NH_4OAc but they obtained cyclohexa-1,4-dienes instead (Scheme 176).[263]



Scheme 176 Synthesis of cyclohexa-1,4-dienes by Perumal *et al.*

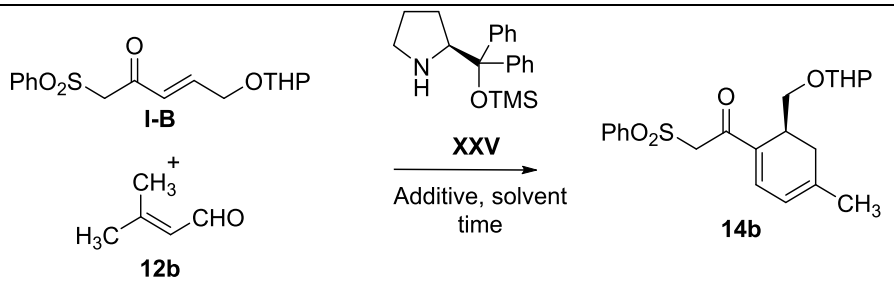
Considering all these facts, we decided to develop a new synthetic procedure for the synthesis of chiral cyclohexa-1,3-dienes using sulfonyl Nazarov analogues and β-methyl-β-disubstituted α,β-unsaturated aldehydes under organocatalytic and environmentally friendly conditions.

After the first reaction studied with sulfone **I-A** and citral **12a**, we continued using commercially available 3-methyl-butenal **12b** and sulfonyl Nazarov analogue **I-B** since, as we previously demonstrated, it behaves exactly the same as **I-A** but the THP protecting group is much more easily removable.

First of all we started our study to set up the conditions to obtain the corresponding cyclohexadiene in the best yield. A screening of different sulfone/aldehyde ratios, solvents and additives was carried out in order to test the importance of the β-substituent. As shown in Table 4, the sulfone/aldehyde ratio did not change the reaction yield substantially, (entries 1-2). Use of different acid additives (entries 3-5) decreased yields comparing to initial conditions except for benzoic acid (entry 3).

[263] Sokkan Harikrishnan, P.; Michael Rajesh, S. and Perumal, S. *Tetrahedron Lett.* **2012**, *53*, 3880. (10.1016/j.tetlet.2012.05.071)

Table 4 Reaction of Nazarov reagent **I-B** with **12b**.[a]



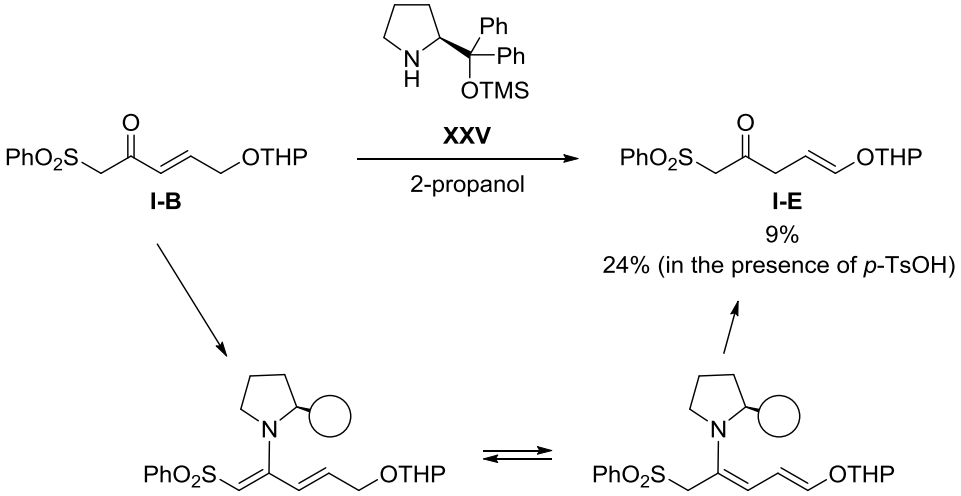
Entry	**I-B/12b** ratio	Additive	Solvent	Time[b]	Yield (%)[c]
1	2/1	-	2-propanol	47 h	42
2	1/2	-	2-propanol	44 h	49
3	2/1	B.A.	2-propanol	47 h	50
4	2/1	BinapOH	2-propanol	46 h	27
5	2/1	*p*-TsOH·H_2O	2-propanol	40 h	13
6	2/1	Na_2CO_3	2-propanol	7 days	17
7	2/1	K_2CO_3	2-propanol	6 days	31
8	2/1	$CsCO_3$	2-propanol	2 days	60
9	2/1	LiOAc· H_2O	2-propanol	3 days	65
10	2/1	NaOAc	2-propanol	6 days	63
11	2/1	$FeCl_3·6H_2O$	2-propanol	42 h	S.M.
12	2/1	$ZnCl_2$	2-propanol	47 h	S.M.
13	2/1	-	*n*-Hexane	80 h	23
14	2/1	-	Toluene	79 h	66
15	2/1	-	CH_2Cl_2	74 h	67
16	2/1	-	$CHCl_3$	71 h	73
17	2/1	-	Et_2O	30 h	26
18	2/1	-	THF	46 h	32
19	2/1	-	MeOH	56 h	Decomposition
20	2/1	-	EtOH	49 h	75[d]
21	1/2	-	EtOH	24 h	40
22	1/1	-	EtOH	45 h	7
23	**2/1**	**B.A.**	**EtOH**	**48 h**	**79[e]**

[a] All the reactions were carried out at rt., in the corresponding solvent at 0.18 M, 20 mol% additivie and 50 mol% **XXV**.[b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).[c] Isolated yield after chromatography on silica gel.[d] 89% ee determined by HPLC.[e] 92% ee determined by HPLC. B.A. = benzoic acid. BinapOH = (*S*)-(+)-1,19-binaphthyl-2,29-diyl hydrogenphosphate. S.M. = Starting Material.

Brønsted bases had similar effect, and although lithium or sodium acetate made a good improvement, the reaction time increased (entries 6-10). Lewis acids did not produce any reaction (entries 11-12). Solvent screening (entries 13-20) proved EtOH to be the best solvent. After testing the sulfone/aldehyde ratio (entries 21-22) and the use of benzoic acid (entry 23) in EtOH, we found the best conditions were sulfone/aldehyde ratio of 2/1 and 20 mol% of benzoic acid in EtOH. The ee was

measured for the best conditions (entries 20 and 23) observing that the use of benzoic acid slightly increased the yield and the enantiomeric excess as before.

When no aldehyde was present in the reaction the β-keto-γ,δ-unsaturated sulfone **I-B** isomerised to β-keto-δ,ε-unsaturated sulfone **I-E**, probably due to greater stability of allyl *versus* viniyl sulfones (Scheme 177). This result was favoured in the presence of *p*-TsOH·H_2O.



Scheme 177 Isomerisation of sulfone **I-B** to **I-E** in the presence of no aldehyde.

Finally we carried out a study of catalyst loading (Table 5), finding that a 50 mol% catalyst was the optimum amount needed for the best yield and enantioselectivity. The absolute stereochemistry was determined by X-ray analysis of an analogue (Figure 9, page 163).

Table 5 Catalyst load screening[a]

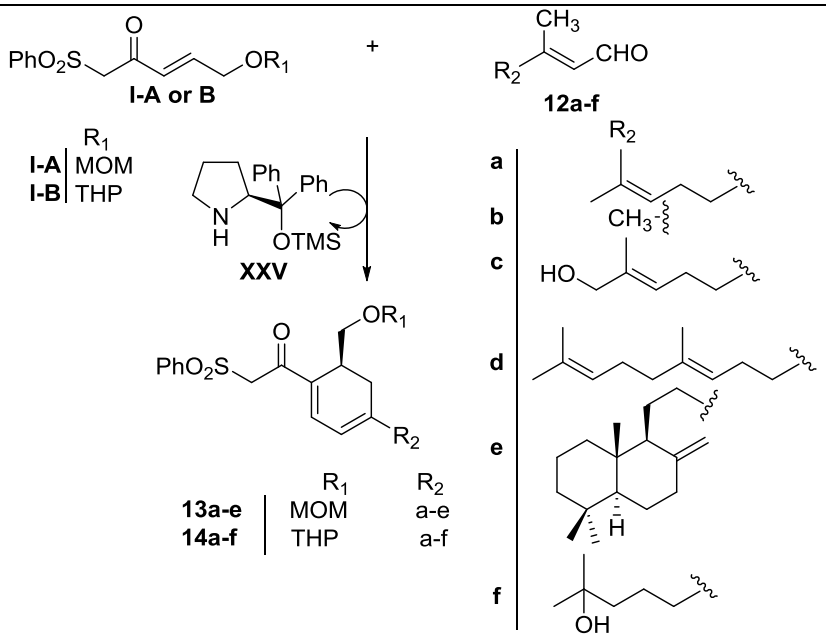
Entry	Catalyst **XXV** (mol%)	Yield[b] (%)	ee[c] (%)
1	5	S.M.	-
2	10	S.M.	-
3	20	39	89
4	50	79	92
5	100	75	90

[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of **I-B**/**12b** and 20 mol% benzoic acid.[b] Isolated yield of **14b** after chromatography on silica gel.[c] *ee* determined by HPLC analysis, carried out on a CHIRALCEL IC column; *n*-hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min.

Once the best conditions were established for this reaction, several β-methyl-β-alkylsubstituted aldehydes **12a-f** were tested with protected sulfonyl Nazarov reagents **I-A** and **I-B** (Table 6).

When sulfone **I-A** was used, yields were from moderate to good except for aldehydes **12c** and **12d** (entries 3 and 4) due to a possible oxo-Michael reaction.[13] The enantiomeric excess measured by chiral HPLC varied from good to excellent in all cases. Similar behaviour was observed when using β-ketosulfone **I-B**. In this case and in order to corroborate the obtained results, enantiomeric catalyst ***ent*-XXV** was used (entries 7, 9 and 13) obtaining the corresponding enantiomers with identical or similar ee, adding more versatility to this procedure. It can be concluded that when both *β*-substituents are alkyl groups, cyclohexa-1,3-diene derivatives **13**/**14** are obtained from low to good yields (16-79%) and in good to very good ee (75-92%).

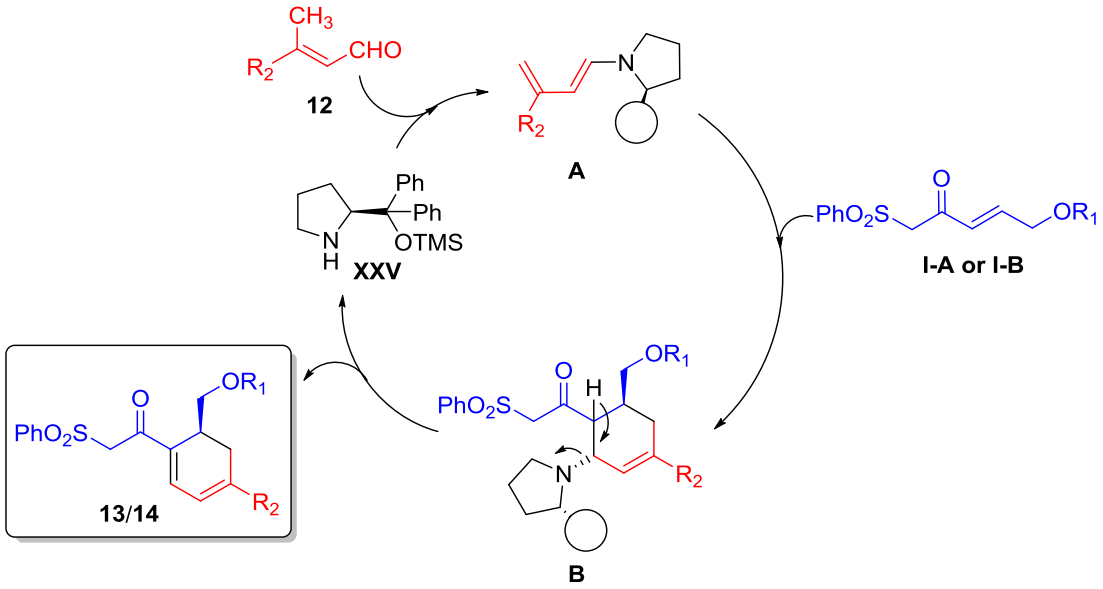
Table 6 Reaction of Nazarov reagents **I-A**, **I-B** with prenals **12a-f**.[a]



Entry	Sulfone	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1	**I-A**	**12a**	**13a**	69	82
2	**I-A**	**12b**	**13b**	62	79
3	**I-A**	**12c**	**13c**	20	80
4	**I-A**	**12d**	**13d**	24	39
5	**I-A**	**12e**	**13e**	58	75
6	**I-B**	**12a**	**14a**	62	90
7[d]	**I-B**	**12a**	***ent*-14a**	65	-91
8	**I-B**	**12b**	**14b**	**79**	**92**
9[d]	**I-B**	**12b**	***ent*-14b**	75	-92
10	**I-B**	**12c**	**14c**	49	80
11	**I-B**	**12d**	**14d**	33	89
12[d]	**I-B**	**12d**	***ent*-14d**	36	-89
13	**I-B**	**12e**	**14e**	16	88
14	**I-B**	**12f**	**14f**	32	91

[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of sulfone/aldehyde, 50 mol% **XXV** and 20 mol% benzoic acid.[b] Isolated yield after chromatography on silica gel.[c] *ee* determined by HPLC analysis, carried out on a CHIRALCEL IC column; *n*-hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min.[d] Using catalyst ***ent*-XXV**.

Formation of compounds **13**/**14** can be understood through a Diels-Alder mechanism between dienamine **A** (Scheme 178) formed between the catalyst and the α,β-unsaturated aldehyde,[264] and the Nazarov reagent acting as dienophile similarly as in the cases of Serebryakov *et al.*[260] It is noteworthy that in this reaction the diene is established with the methyl group and not with the methylene group as in the case of the Rauhut-Curier-type reaction of Christmann *et al.*[262]



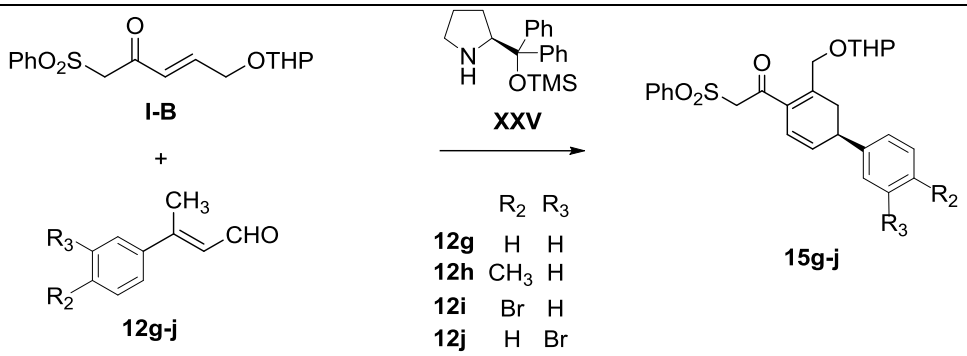
Scheme 178 Proposed Diels-Alder mechanism for the synthesis of **13**/**14**.

With these results in hand we decided to test the behaviour when the alkyl group is changed to an aromatic ring, leaving the methyl group *cis* to the aldehyde group.

When Nazarov reagent **I-B** and different aromatic aldehydes were treated under the same conditions, a similar but yet different structure was observed by ^{1}H-NMR. Now, we could see two olefinic hydrogens coupled to each other as before but they appeared more deshielded and presented one extra coupling with a third hydrogen, allylic hydrogen. Moreover, no coupling of the CH_2 group joined to the OTHP was observed and these hydrogens appeared now at a higher chemical shift, indicating that they are now in an allylic position. All the other signals remained similarly at the same positions and ^{13}C and IR spectra were almost the same except for the carbonyl group (now more deshielded) and for the presence of the aromatic signals. With all these data we suggested that a new cyclohexadiene has been formed, but now it is a non-conjugated cyclohexa-1,3-diene **15** (Table 7). As shown, yields and enantiomeric excesses are good in all cases.

[264] Ramachary, D. B. and Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865. (10.1002/ejoc.201101157)

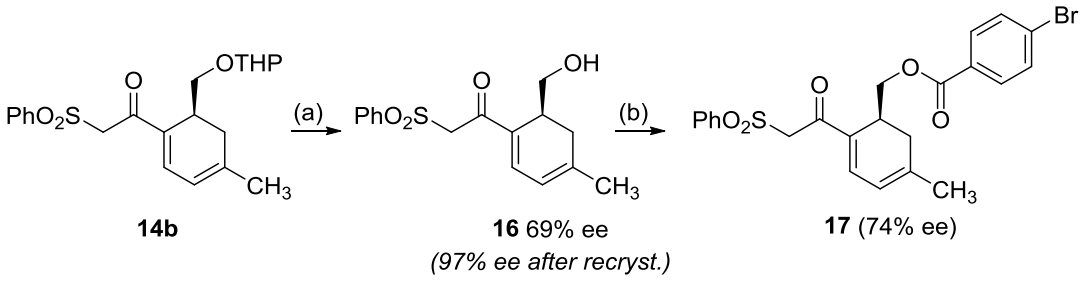
Table 7 Reaction of Nazarov reagent **I-B** with aromatic-*β*-susbtituted unsaturated aldehydes [a]



Entry	Aldehyde	Product	Yield (%) [b]	ee (%) [c]
1	**12g**	**15g**	59	91
2	**12h**	**15h**	69	90
3	**12i**	**15i**	59	91
4	**12j**	**15j**	**81**	**93**

[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of **I-B**/**12g-j**, 50 mol% **XXV** and 20 mol% benzoic acid.[b] Isolated yield after chromatography on silica gel.[c] ee determined by HPLC analysis, carried out on a CHIRALCEL AD-H column; *n*-hexane/2-propanol [80/20 – 70/30 (v/v)]; flow rate: 1.0 mL/min.

In order to determinate the absolute stereochemistry of these cyclohexadienes we decided to obtain the *p*-bromobenzoic ester derivative after deprotection of the THP group in **14b** (Scheme 179). However and for our delight, the hydroxyl-derivative **16** obtained right after deprotection turned out to be crystalline already.



Scheme 179 (a) *p*-TsOH·H_2O (50 mol%), THF/H_2O (1/1), rt, 48 h, 96%; (b) *p*-Br-benzoic acid, DMAP, DCC, DCM, rt, 15 h, 60%.

Thus compound **14b** was deprotected affording **16**, although with some racemisation (69% ee), but we were able to crystallise it (increasing the ee up to 97% ee). The ee for this crystalline product was measured by chiral HPLC which, together with X-ray diffraction experiments, allowed us to establish the absolute configuration of cyclohexadienes **13**, **14** and **15** formed in the organocatalytic reaction (Figure 9). The stereochemistry at the new chiral centre in **15** is proposed to come from a *1,5-H* sigmatropic rearrangement, since the formation of the same intermediate **B** (Scheme 178) is observed with both aliphatic and aromatic substituents.

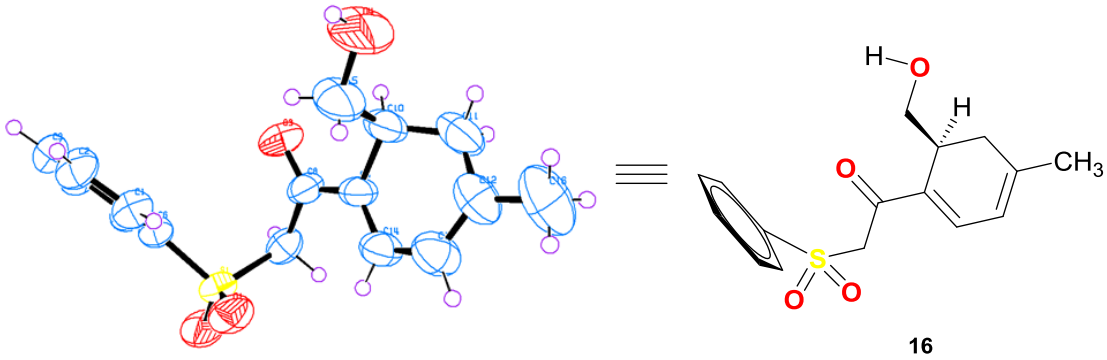


Figure 9 ORTEP diagram for compound **16**.

Therefore, we have demonstrated for the first time how a sulfonyl Nazarov reagent can react in a Diels-Alder manner in organocatalytic and environmentally benign conditions. This reaction has made possible to obtain diverse chiral highly functionalised cyclohexa-1,3-dienes, depending on whether the aldehyde substitution group is alkyl or aryl.

3.3. Reactivity with more complex β,β-disubstituted α,β-unsaturated aldehydes.

Since reactivity of β-methyl-β-disubstituted α,β-unsaturated aldehydes was different with the Hayashi-Jørgensen's catalyst **XXV**, we decided to try a tandem methodology. We started screening different organocatalysts, from simple bases such as DABCO, DBU, Et_3N, piperidine, pyrrolidine or pyridine to more complex organocatalysts, in order to make the enamine intermediate. Then we would add **XXV** to produce cyclisation. In this way we expected to improve both yield and enantioselectivity of the reaction.

First of all we decided to screen different bases, organocatalysts and additives (Figure 10 and Table 8) in the reaction between Nazarov reagent **I-A** and the *E*/*Z* mixture of citral **12a** in 2-propanol, as it was the best solvent used in our previous studies for the synthesis of chiral 2-alkylidene cyclohexenones.

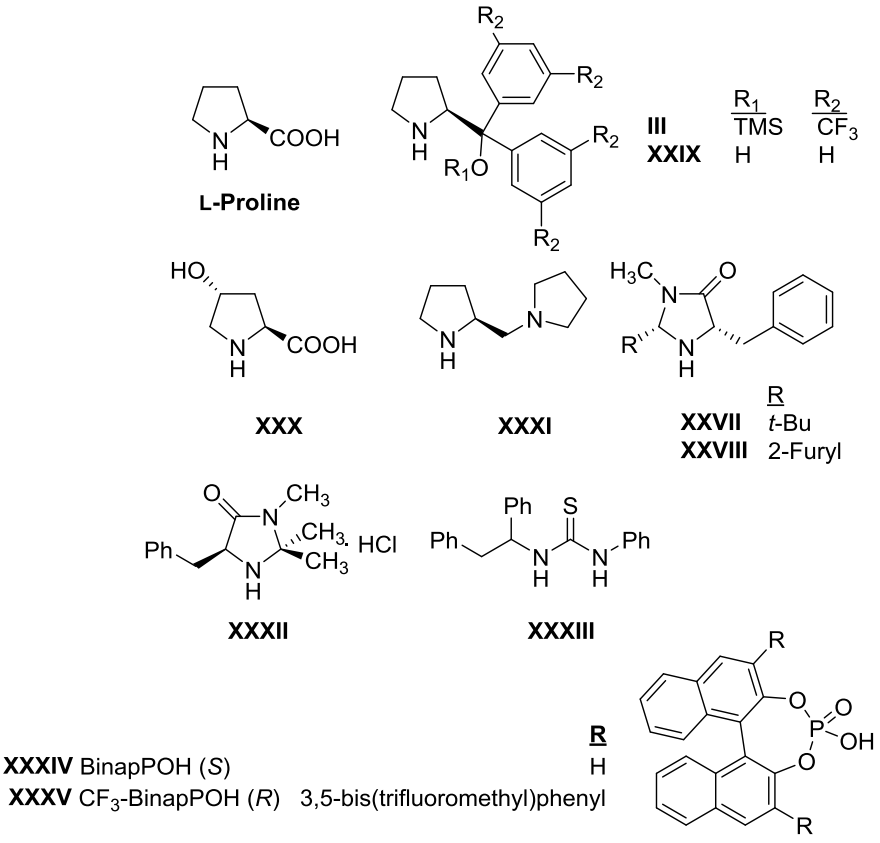
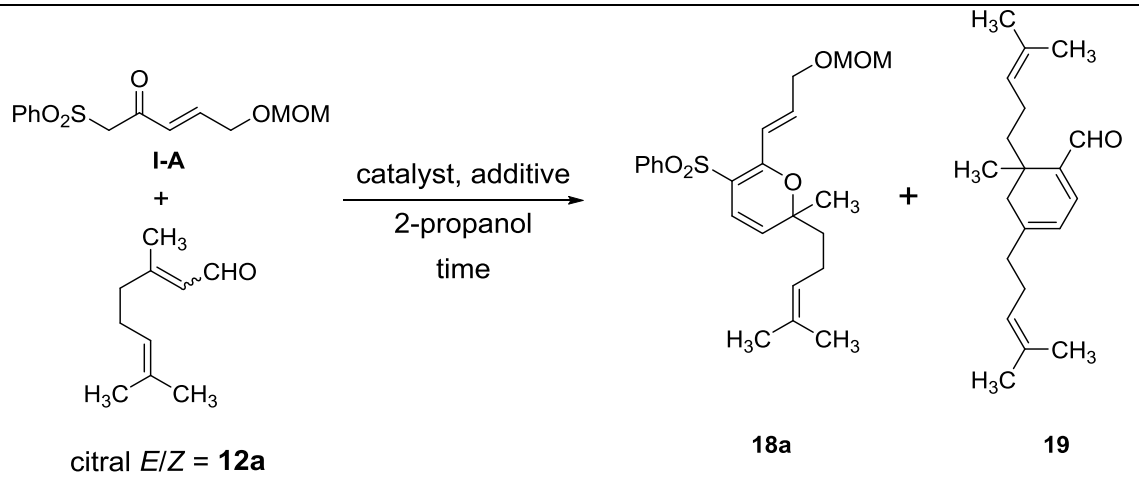


Figure 10 Catalysts and additives for use in the synthesis of 2*H*-pyrans.

We first used usual Brønsted bases but these led to Knoevenagel adduct in low yields, decomposition or simply no reaction after several days (Table 8, entries 1–6). Benzoic acid or even chiral acids, *i.e.* **XXXIV** and **XXXV**, were tested, as they can be used as additives, and thioureas, *i.e.* **XXXIII**, were also tested, but the reaction either did not proceed at all or did not proceed in a reasonable time (entries 7–10). Only the citral dimer **19** was formed in very low yield after 45 days with benzoic acid, previously obtained by Watanabe *et al.* in the reaction of citral with proline (entry 7).[261] Then several organocatalysts (Figure 10) were tested, with and without additives. When L-proline was used with and without additives (entries 11–15), no Knoevenagel adduct was formed, but a new different structure instead. ^{1}H-NMR analysis showed many changes compared to starting materials. Both hydrogens of the CH_2 between the sulfonyl and carbonyl groups had disappeared. There were five olefinic hydrogens. Two of them were coupled similarly to those from starting sulfone but they seemed to belong to a more conjugated system. Other two olefinic hydrogens were forming a couple of doublets and they were only coupled to each other. The fifth olefinic hydrogen would belong to the citral chain. There was no aldehyde signal in ^{1}H-NMR spectrum and ^{13}C-NMR and IR spectra did not show any signal of carbonyl group. All these data together with a very deshielded ^{13}C signal at 80.6 ppm corresponding to a quaternary carbon atom made us think in a pyran structure as **18a**. The obtained pyran was a racemic mixture as ascertained by chiral HPLC and specific rotation measures so use of chiral additives as **XXXIV** or **XXXV** is not worth. Other proline-realted organocatalyst as **III** and **XXIX** were studied but only starting materials were recovered (entries 16 and 17). Citral dimer **19** was only observed after 60 days when catalyst **III** and additive **XXXIV** were used together (entry 18). We tried a tandem procedure using catalyst **5** and proline in the presence of lithium acetate or benzoic acid but poor yields of pyran or citral dimer were obtained (entries 19 and 20). More proline derivative catalyst suchs as **XXX** or **XXXI**, Macmillan imidazolidinones **XXVII**, **XXVII** or **XXXII** and thiourea **XXXIII** were also tested but again only starting materias or citral dimer were observed after long reaction times (entries 21-25).

Table 8 Screening of catalysts and additives for the reaction between β-ketosulfone **I-A** and *E/*Z-citral **12a** in 2-propanol.[a]

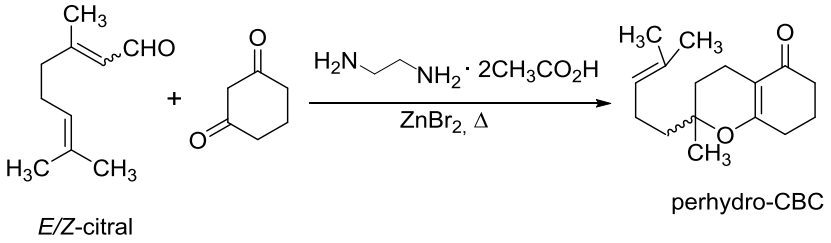


Entry	Catalyst	Additive	Time[b]	Yield (%)[c]	
				18a	**19**
1	DABCO	-	21 h	S.M.	
2	DBU	-	3 d	S.M.	
3	Et_3N	-	3 d	S.M.	
4	Piperidine	-	3 d	Decomposition	
5	Pyrrolidine	-	2 h	Decomposition	
6	Pyridine	-	3 d	16	-
7	-	B.A.	45 d	-	<5
8	-	**XXXIV**	10 h	S.M.	
9	-	**XXXV**	12 h	S.M.	
10	**XXXIII**	B.A.	8 d	S.M.	
11	**L-Proline**	-	6 h	63	11
12	**L-Proline**	LiOAc	13 h	44	29
13	**L-Proline**	B.A.	17 h	62	9
14	**L-Proline**	**XXXIX**	24 h	96	4
15	**L-Proline**	**XXXV**	**17 h**	**99**	**1**
16[d]	**XXIX**	B.A.	8 d	S.M.	
17[e]	**III**	B.A.	8 d	S.M.	
18[f]	**III**	**XXXIV**	60 d	-	15
19[e,g]	**III** + **L-Proline**	LiOAc	39 h	10	-
20[e,g]	**III** + **L-Proline**	B.A.	39 h	7	33
21	**XXX**	-	6 d	-	60
22	**XXXI**	-	13 h	-	33
23	**XXVII**	-	25 d	S.M.	
24	**XXVIII**	-	10 d	-	11
25[h]	**XXXII**	B.A.	8 d	S.M.	

[a] All the reactions were carried out at rt, in 2-propanol, at 0.18M, with 2/1 ratio of sulfone and *E/Z*-citral **12a**, 20 mol% of catalyst and 20 mol% of additive. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).[c] Isolated yield after chromatography on silica gel.[d] Benzoic acid was added 6 days after catalyst **XXIX**.[e] Benzoic acid was added 6 days after catalyst **III**.[f] Catalyst **5** was added 10 hours after BinapPOH.[g] L-Proline was added 26 hours after catalyst **III**.[h] Benzoic acid was added 6 days after catalyst **XXXII**. S.M. = Starting material; B.A. = Benzoic acid; **XXXIV** = BinapPOH = (*S*)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate; **XXXV** = CF_3-BinapPOH = (*R*)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate.

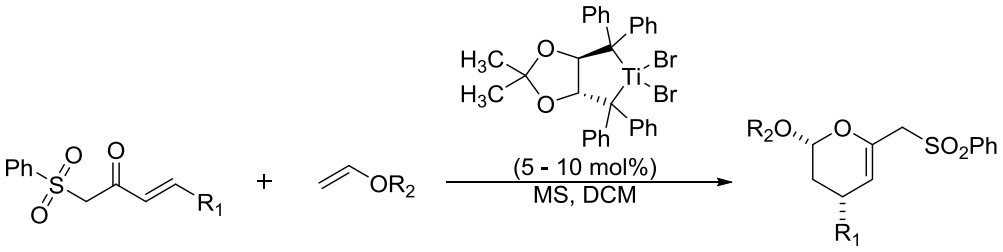
Other organocatalysts did not give any good results with or without additives (entries 16–25).

As shown at the introduction, molecules with a pyran heterocycle in their structure are very interesting due to their biological activities and applications in Medicine. However, there is not a great variety of starting materials to synthesise them, being usually made by iminium activation of a carbonyl group and a 1,3-dicarbonyl compound.[265] As an example, Chang and Marsella *et al.* described the reaction of the *E*/*Z* mixture of citral with 1,3-cyclohexanodione to yield perhydro-CBC (cannabichromene) that later on was transformed into a Δ^1-tetrahydrocannabinol analogue using ethylenediamine diacetate (Scheme 180).[266]



Scheme 180 Synthesis of *perhydro*-CBC by Profs. Chang and Marsella.

The use of β-ketosulfones over 1,3-dicarbonyl compounds adds the extra versatility of the sulfone moiety, mainly due to its easy elimination and reactivity. Although β-ketosulfones have been employed for the synthesis of pyranyl derivatives (see Introduction, pages 66, 67 for some examples), sulfonyl Nazarov analogues, *i.e.* β-keto-γ,δ-unsaturated sulfones, have only been used by Wada *et al.* to produce pyran structures by an hetero-Diels-Alder reaction with vinyl ethers (Scheme 181).[267]



Scheme 181 Wada *et al.* previous synthesis of 3,4-dihydro-2*H*-pyrans.

[265] Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y.; You, L.-F. and Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105. (10.1016/j.tet.2011.09.111)
[266] Garcia, A.; Borchardt, D.; Chang, C.-E. A. and Marsella, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 16640. (10.1021/ja907062v)
[267] Wada, E.; Yasuoka, H. and Kanemasa, S. *Chem. Lett.* **1994**, *23*, 1637.

The best reaction conditions of this procedure required (i) a complex organometallic catalyst, (ii) a chlorinated solvent (DCM), (iii) an activated enol ether and that (iv) the sulfonyl Nazarov analogue was deactivated and not very hindered. Furthermore, this procedure always yields 2-alkoxy-3,4-dihydro-2*H*-pyrans, where certain reaction conditions during a synthetic route can cleavage the acetal bond. Furthermore, Inokuchi *et al.* established that 2-alkylsubstituted enals favour the formation of (*E*)-Knoevenagel adducts for the ensuing electrocyclisation.[268]

Considering all this and the good results we had obtained with proline, we decided to develop this new method for the synthesis of pyran structures using sulfonyl Nazarov analogues under organocatalytic conditions in more environmentally friendly solvents (or in solvent free conditions). We became interested in doing the reaction with our β-ketosulfones, β-methyl- and other β,β-disubstituted α,β-unsaturated aldehydes, for its profusion in nature,[269] as in the case of Chang and Marsella *et al.*, using organocatalysts in order to develop environmentally benign processes for the synthesis of 2*H*-pyrans.

As L-Proline was found to be the best organocatalyst (Table 8), we then screened different solvents (Table 9) in order to find more environmentally friendly conditions. This reaction was found to work in low to moderate yields in most of solvents tested except for *n*-hexane (entry 1) where a good yield was obtained (72%) or water (entry 9) where reaction did not work. After observing the reaction in *n*-hexane we thought that this solvent was not actually dissolving all the reaction components but still the pyran structure was being formed at the end. Thus we decided to test this reaction in solvent-free conditions (entries 10-12) and for our delight it worked in good yield without additives. Surprisingly the use of additives **XXXIV** or **XXXV** did not lead to any increase in the yield, but suppressed the production of the citral dimer in no solvent conditions (entries 11 and 12).

[268] Peng, W.; Hirabaru, T.; Kawafuchi, H. and Inokuchi, T. *Eur. J. Org. Chem.* **2011**, 5469. (10.1002/ejoc.201100780)
[269] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G. and Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144. (10.1039/C2NP00090C)

Table 9 Screening of solvents for the synthesis of 2*H*-pyrans with L-proline and additives.[a]

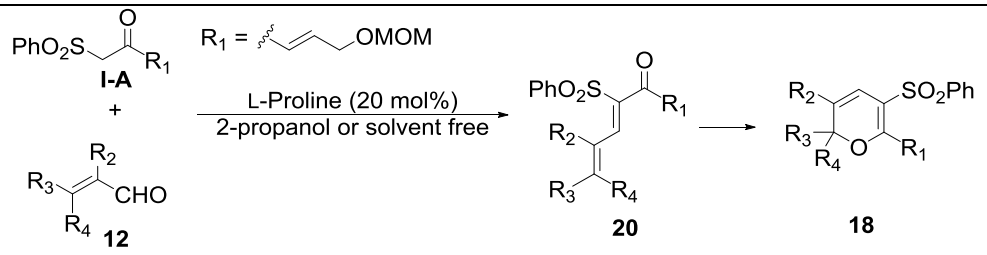
Entry	Solvent	Time (h)[b]	Yield (%)[c]	
			18a	**19**
1	*n*-Hexane	54	72	12
2	Toluene	29	32	-
3	CH_2Cl_2	29	34	13
4	$CHCl_3$	29	42	-
5	Diethyl ether	29	37	-
6	THF	29	20	-
7	MeOH	8	28	-
8	EtOH	8	39	-
9	H_2O	56	S.M.	
10[d]	**NO SOLVENT**	**22**	**87**	**13**
11	NO SOLVENT	24	58	-
12[e]	NO SOLVENT	21	49	-

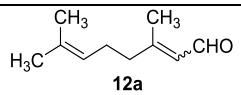
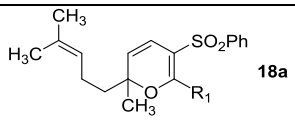
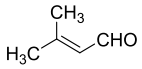
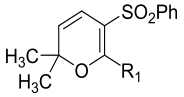
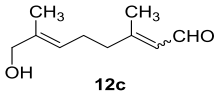
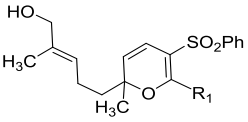
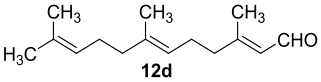
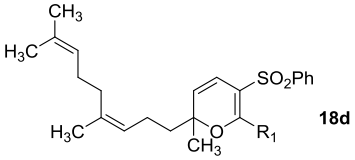
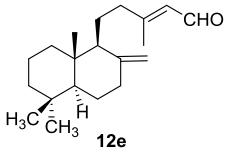
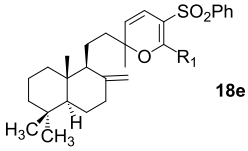
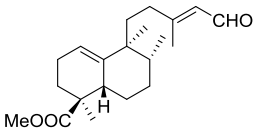
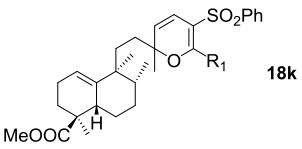
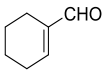
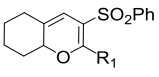
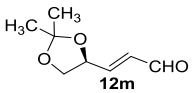
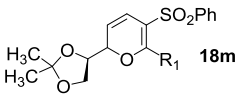
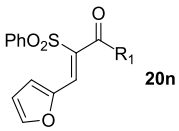
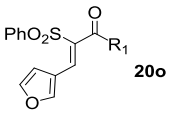
[a] All the reactions were carried out at rt, at 0.18 M, with a 2/1 ratio of **I-A**/**12a**, 20 mol% L-proline and 20 mol% **XXXIV**. [b] Time in which the highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] No additives used. [e] 20 mol% **XXXV** added to the reaction as additive instead of **XXXIV**. S.M. = Starting material.

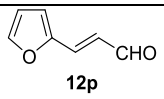
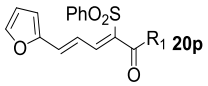
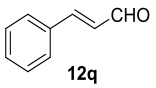
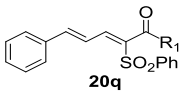
From this study, solvent free conditions with no additive turned out to be the best conditions (entry 10). In all cases racemic mixtures were obtained, ascertained by HPLC and specific rotation, even when additives **XXXIV** or **XXXV** were used in order to induce chirality. Although the yield was excellent when 2-propanol and additive **XXXV** were used (Table 8, entry 15) the use of no solvent and no expensive additives makes this procedure to obtain 2*H*-pyrans easier and more environmentally efficient than the previous ones. In case of reagents solubility problems, the use of 2-propanol is a green alternative too. These conditions are not exclusive to β-ketosulfones and can be applied to 1,3-diketones, β-ketoesters or β-ketoamides.

Having established the best reaction conditions, we decided to evaluate our method with different aldehydes, using firstly the same starting material, the β-ketosulfone **I-A**, as shown in Table 10. In all cases where the unsaturated aldehyde was β,β-dialkylsubstituted, the corresponding 2*H*-pyran **18** was obtained in a very good yield but as a racemic mixture, ascertained by HPLC and specific optical rotation (entries 1–6). Other differently substituted substrates were screened in order to study the scope of the reaction. When cyclohexenal **12l** or chiral aldehyde **12m** was used (entries 7 and 8), the corresponding 2*H*-pyrans were obtained in moderate or low yield respectively. The enantiomeric excess for the latter was not determined for this reason. Other aromatic aldehydes were screened to extend this methodology but, as expected, only the Knoevenagel adducts were formed (entries 9–12), with no cyclisation, probably due to the high stability of such conjugated systems formed. These results can be explained by the proposed mechanism (Scheme 182).

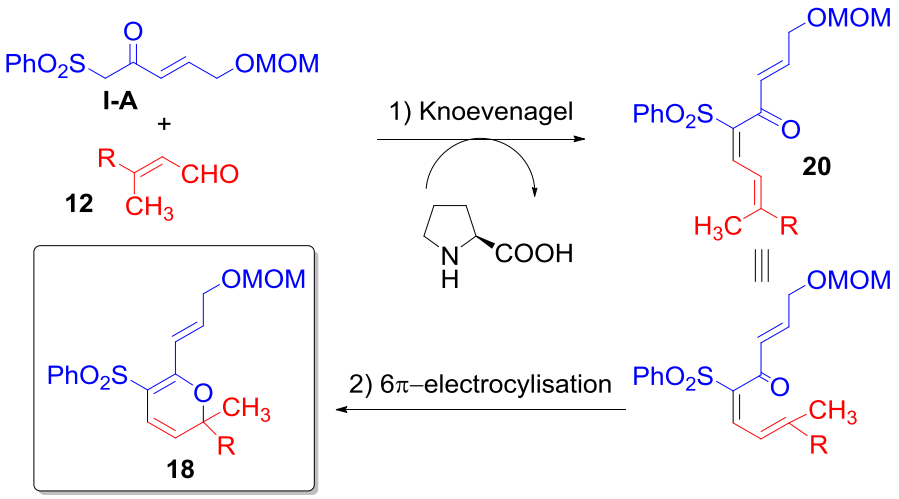
Table 10 Screening of α,β-unsaturated aldehydes.[a]



Entry	α,β-unsaturated aldehyde	Product	Time[b]	Yield (%)[c]
1	 **12a**	 **18a**	6 h	63
2	 **12b**	 **18b**	4.5 h	82
3	 **12c**	 **18c**	15 h	58
4[c]	 **12d**	 **18d**	15 h	58
5	 **12e**	 **18e**	3 d	63
6	 **12k**	 **18k**	7 h	38
7	 **12l**	 **18l**	5 d	43
8[d]	 **12m**	 **18m**	28 h	19
9	 **12n**	 **20n**	21 h	87
10	 **12o**	 **20o**	1 d	99

Entry	α,β-unsaturated aldehyde	Product	Time[b]	Yield (%)[c]
11	 12p	 20p	15 h	56
12[e]	 12q	 20q	15 h	22

[a] All the reactions were carried out at rt, in 2-propanol at 0.18 M, with a 2:1 ratio of sulfone **I-A** to aldehyde and 20 mol% **L-proline** or under solvent free conditions. In all cases the yields were similar. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] 20 mol% of BinapPOH, **XXXIV**, added to the reaction. [e] In $CDCl_3$ with LiOAc (50 mol%) as additive.



Scheme 182 Proposed mechanism for the formation of 2*H*-pyrans.

Initial Knoevenagel condensation leads to intermediate **20**, which after 6π-electrocyclisation produces the corresponding 2*H*-pyran **18**. Other aldehydes, with a different substitution pattern, only gave the corresponding Knoevenagel products (Table 10, entries 9-12), which stereochemistry was established by bidimensional NMR and nOe experiments. A similar result was obtained by Mischne and Riveira *et al.* in polycyclisation reactions of 1,3-dicarbonyl compounds and α,β,γ,δ-unsaturated aldehydes, where the unsubstituted one gives only condensation and no cyclisation.[270] Of special interest are the compounds obtained in entries 5 and 6, analogues of marine natural products, such as the pyranocoumarin ferprenin (Figure 11).[271]

[270] Riveira, M. J. and Mischne, M. P. *Chem. Eur. J.* **2012**, *18*, 2382. (10.1002/chem.201103080)
[271] Irwin, J. J.; Ha, T.-K. and Dunitz, J. D. *Helv. Chim. Acta* **1990**, *73*, 1805. (10.1002/hlca.19900730702)

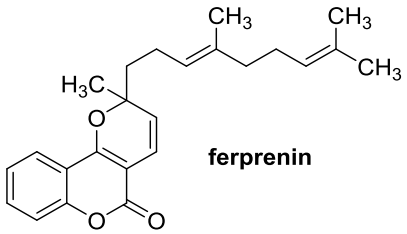
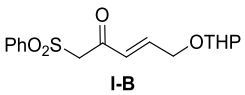
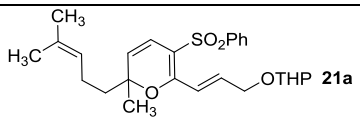
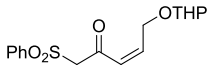
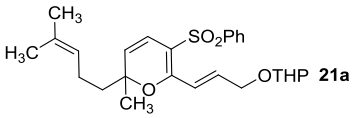
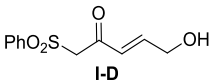
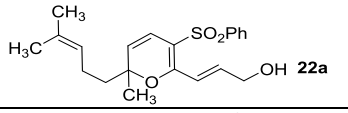


Figure 11 Ferprenin, a pyranocumarin.

Once the procedure for the synthesis of 2*H*-pyrans had been carried out consistently with different aldehydes, it was subjected to a study with other β-ketosulfones in order to define the scope and consistency of the reaction (Table 11).

Table 11 2*H*-pyrans using different β-ketosulfones and *E/Z*-citral **12a**.[a]

Entry	β-ketosulfone	Product	Time (h) [b]	Yield (%) [c]	
				19	**21a/22a**
1	 **I-B**	 **21a**	7	3	97
2	 **I-C**	 **21a**	5	12	88
3	 **I-D**	 **22a**	15	36	64

[a] All the reactions were carried out at rt, in 2-propanol at 0.18M, or under free solvent conditions with 2/1 ratio of sulfone and **12a**, and 20 mol% of **L-Proline**. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).[c] Isolated yield after chromatography on silica gel.

As shown in Table 11, the three sulfones **I-B**, **I-C**, and **I-D** behave exactly as before, yielding the corresponding 2*H*-pyrans in good to excellent yields, when reacted with *E*/*Z*-citral. It is noteworthy that pyran **21a** is formed using *trans* or *cis* β-ketosulfones **I-B** or **I-C**.

We have demonstrated for the first time how a sulfonyl Nazarov analogue participates in a Diels-Alder reaction under organocatalytic and solvent free conditions, making this procedure ideal for the synthesis of highly functionalised 2*H*-pyrans in environmentally safe conditions.

3.4. Reactivity with cyclic α,β-unsaturated aldehydes.

After observing the result obtained with cyclohexenal **12l** (Table 10, entry 7) in the presence of proline, we decided to extend the study with this and other cyclic aldehydes but in the presence of the Jørgensen's catalyst **III**, in order to obtain bicyclic systems.

We started evaluating the reactivity of sulfone **I-B** with cyclohexencarboxaldehyde **12l** in 2-propanol, using organocatalyst **III**. No pyran structure with **12l**, as when using proline as catalyst, was observed by ^{1}H-NMR. Study of ^{1}H-NMR spectrum revealed that a new structure different from cyclohexenones, cyclohexadienes or pyrans had been formed. In this case, one aldehyde hydrogen and no olefinic hydrogen signals were present in the ^{1}H-NMR spectrum. Only one hydrogen signal from the CH_2 group between sulfonyl and carbonyl groups remained and, as in the case of cyclohexenones, this hydrogen was not coupled with any other, indicating that either there was no hydrogen close to it or that it may be inside a cyclic structure and in an *anti*-disposition with the next hydrogen. We were able to see two carbonyl groups in the ^{13}C-NMR spectrum now, corresponding to a CO and a CHO group. The latter was joined to a tetrasubstituted carbon atom. All these facts made us think that we had obtained a decalin system. The result was verified by X-ray experiments of the carboxylic acid derivative **24** (Figure 12) formed by oxidation of aldehyde **22l** under normal air atmosphere. This result also corroborated that we had obtained a *cis*-decalin structure.

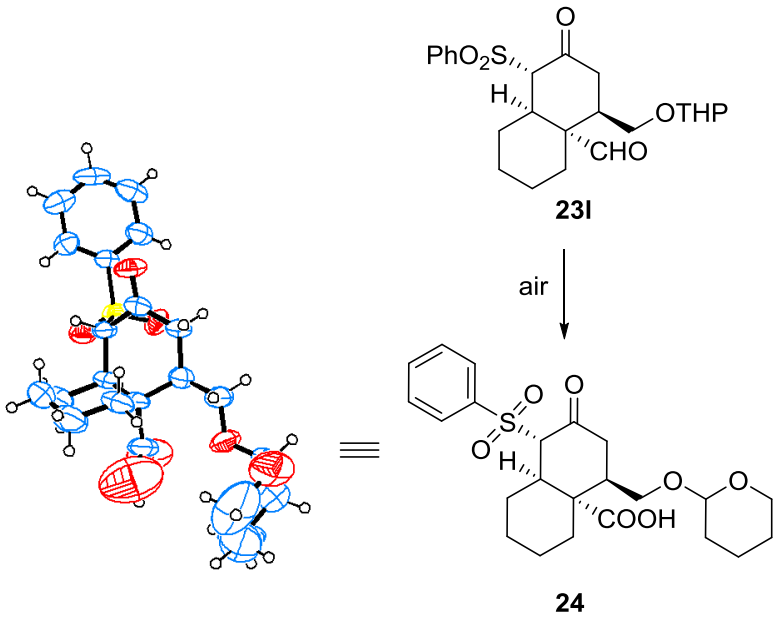


Figure 12 Ortep diagram for compound **24**.

The *cis*-decalin framework is present in the molecular structure of various classes of natural products such as *cis*-clerodanes,[272] kalihinenes,[273] thelepoganes,[274] cadinanes,[275] eremophilanes,[276] and valeranones.[277] These products have been mainly obtained by isolation from natural sources. Many of these *cis*-decalin-based natural products exhibit wide-ranging and interesting biological activities. It is evident that many of these natural products have varying degrees of substitution patterns and four or more contiguous stereogenic centres on the decalin skeleton and, hence, pose a considerable synthetic challenge. The structural complexity of these natural products together with their interesting biological properties have led to significant interest in the development of new and efficient methods for the synthesis of *cis*-decalins and the aforementioned natural products.[278]

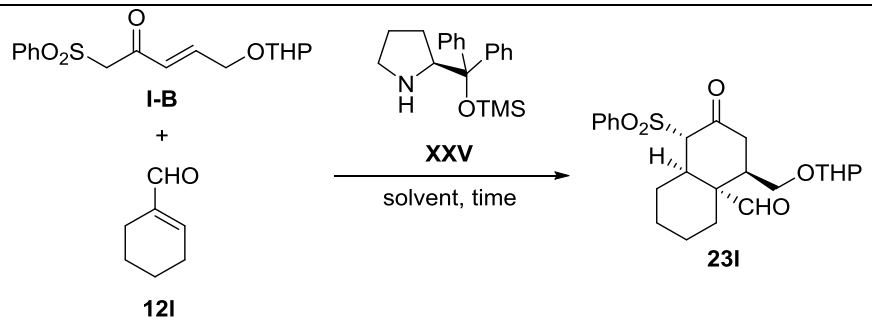
Nazarov reagents have been used for the synthesis of *cis*-decalines based on the so-called Deslongchamps annulation[279] but without control of the absolute stereochemistry (Scheme 166).[229] Furthermore there are no examples in literature where sulfonyl Nazarov reagents have been used for the synthesis of *cis*-decalines.

For these reasons we envisaged the use of our methodology with β-keto-γ,δ-unsaturated sulfones under organocatalytic conditions to synthesise *cis*-decalines using cyclic unsaturated aldehydes as starting materials.

We started carrying out a solvent screening in the reaction of our sulfonyl Nazarov reagent **I-B** and cyclic aldehyde **12l** (Table 12). As shown, this reaction does not work in non-polar or polar aprotic solvents (entries 1 – 3). However, in polar protic solvents or even without solvent (entries 4 – 8), this reaction works affording the corresponding *cis*-decalin **23l** in low to moderate yields, being EtOH the solvent which gave the best results. When benzoic acid was used (entry 6), similar yield was afforded in less time, although, products were harder to purify. Moreover, the sulfone/aldehyde ratio was also tested and, as before, the best results are obtained using a 2/1 ratio. From this study, EtOH proved again to be the best solvent. Next we studied the catalyst load for this reaction (Table 13).

[272] Merritt, A. T. and Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243. (10.1039/NP9920900243)
[273] Okino, T.; Yoshimura, E.; Hirota, H. and Fusetani, N. *Tetrahedron Lett.* **1995**, *36*, 8637. (10.1016/0040-4039(95)01861-B)
[274] Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M. and van Soest, R. W. M. *J. Nat. Prod.* **1998**, *61*, 1310. (10.1021/np980173q)
[275] Ohta, Y. and Hirose, Y. *Tetrahedron Lett.* **1969**, *10*, 1601. (10.1016/S0040-4039(01)87956-9)
[276] Tada, M.; Moriyama, Y.; Tanahashi, Y. and Takahashi, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1999.
[277] Kulkarni, K. S.; Paknikar, S. K. and Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 1289. (10.1016/S0040-4020(01)98993-8)
[278] Singh, V.; Iyer, S. R. and Pal, S. *Tetrahedron* **2005**, *61*, 9197. (10.1016/j.tet.2005.06.102)
[279] Lavallée, J.-F. and Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117. (10.1016/S0040-4039(00)80694-2)

Table 12 Solvent screening for the reaction of Nazarov reagent **I-B** with **12l**.[a]



Entry	**I-B**/**12l** ratio	Solvent	Time (h) [b]	Yield (%) [c]
1	2/1	*n*-Hexane	72	S.M.
2	2/1	Et_2O	72	S.M.
3	2/1	THF	72	S.M.
4	2/1	MeOH	72	20
5	**2/1**	**EtOH**	**72**	**52**
6[d]	2/1	EtOH	48	53
7	2/1	2-propanol	72	35
8	2/1	H_2O	48	6
9	2/1	NO SOLVENT	72	18
10	1/1	EtOH	72	30
11	1/2	EtOH	72	42

[a] All the reactions were carried out at rt, in the corresponding solvent at 0.18 M during the specified time, and catalyst **XXV** (20 mol%).[b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] 20 mol% benzoic acid added. S.M. = Starting material.

Table 13 Catalyst load screening.[a]

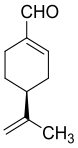
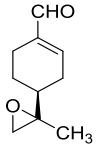
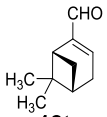
Entry	Catalyst **XXV** (%)	Yield (%) [b]
1	0	S.M.
2	5	28
3	10	29
4	20	52
5	50	60

[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 72 h, with a 2/1 ratio of **I-B**/**12l**.[b] Isolated yield after chromatography on silica gel. S.M. = Starting material.

As shown in Table 13, the reaction does not work without catalyst (entry 1). As the catalyst amount increases, so does the yield (entries 2 – 5), however, the difference between using 20 or 50 mol% is not enough to compensate the catalyst load increment. For this reason, a 20 mol% is taken as the optimal catalyst amount to be used for this transformation.

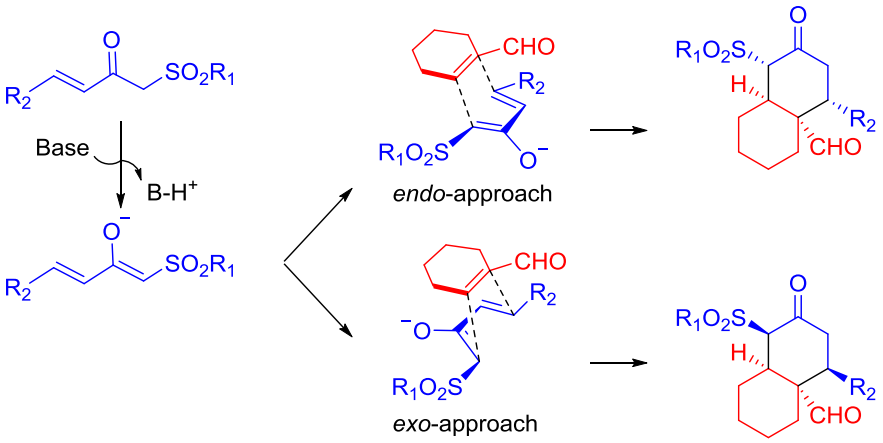
With the best conditions in hand, we tested different cyclic enals. As shown in Table 14, the reaction also worked well with sulfone **I-A** (entry 2). Moderate results were achieved with other more hindered aldehydes such as (*S*)-(−)-perillaldehyde **12r** (entries 3 – 8), although the best yield was achieved adding a 20 mol% of benzoic acid. When enantiomeric catalyst ***ent*-XXV** was used, the reaction worked poorly or did not work at all, perhaps because of a mismatch pair effect between the aldehyde and catalyst substituents (entries 7 and 8). Similar results were obtained with its epoxide **12s** (entries 9 – 11). Reaction with an even more hindered aldehyde such as (1*R*)-Myrtenal **12t** or smaller pentacyclic enal **12u** (entries 12 – 18) did not work.

Table 14 Reaction of Nazarov reagent **I-B** with cyclic enals **12l** and **12r-u**.[a]

Entry	Cyclic enal	Product	Time (h) [b]	Yield (%) [c]	ee (%)[d]
1	 **12l**	**23l**	72	52	96
2[e]	**12l**	***ent*-23l**	72	50	-74
3[f,g]	**12l**	**25l**	48	50	96
4	 **12r**	**23r**	48	63	90
5	**12r**	**23r**	96	15	N.D.
6[g]	**12r**	**23r**	48	85	90
7[e]	**12r**	***ent*-23r**	48	4	N.D.
8[e]	**12r**	**-**	72	-	N.D.
9[h]	**12r**	***ent*-23r**	96	4	N.D.
10	 **12s**	**23s**	48	22	N.D.
11[i]	**12s**	**23s**	48	39	-[j]
12[g,i]	**12s**	**23s**	48	30	N.D.
13	 **12t**	S.M.	96	-	-
14[e]	**12t**	S.M.	120	-	-
15	 **12u**	S.M.[k]	48	-	-
16	**12u**	S.M.[k]	72	-	-
17	**12u**	S.M.[k]	96	-	-
18	**12u**	S.M.[k]	120	-	-
19[g]	**12u**	S.M.[k]	120	-	-

[a] All the reactions were carried out at rt, in EtOH at 0.18 M during the specified time, with a 2/1 ratio of **I-B/cyclic enal** and catalyst **XXV** (20 mol%).[b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] ee determined by HPLC analysis, carried out on a CHIRALPAK IC column; [e] ***ent*-XXV** (20 mol%). [f] Sulfone **I-A** (1 equiv.) used. [g] 20 mol% benzoic acid added. [h] ***ent*-XXV** (50 mol%). [i] **XXV** (50 mol%). [j] Complex HPLC results were obtained and we are currently working on these results. [k] Only starting sulfone **I-B** was recovered; S.M. = Starting material. N.D. = Not determined.

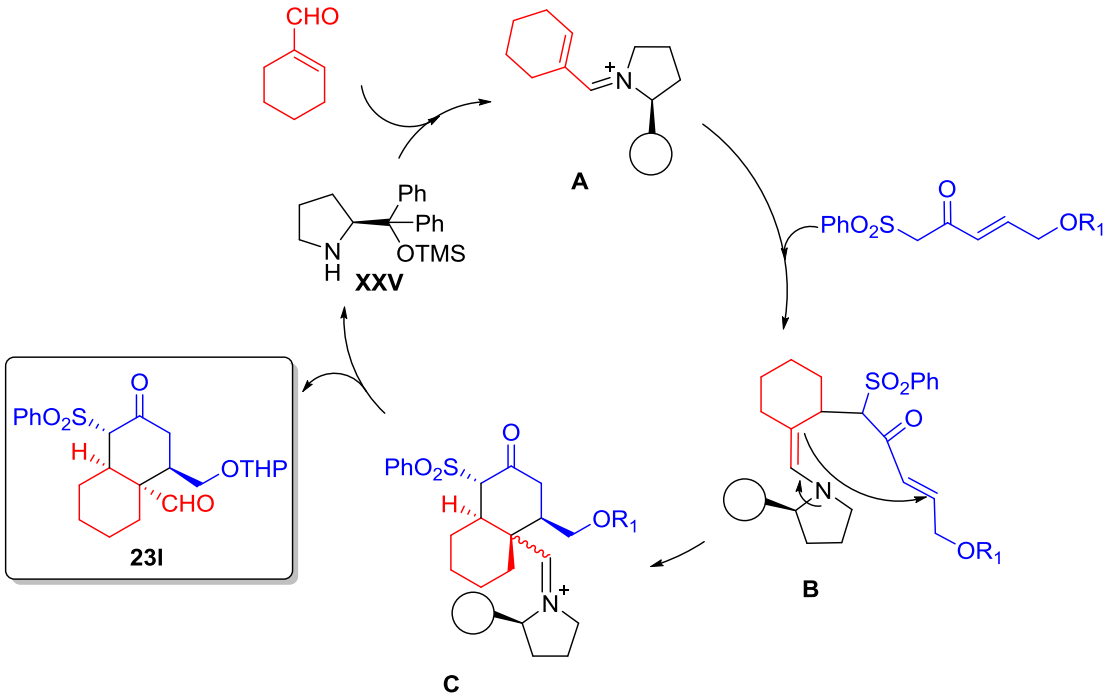
The Diels-Alder mechanism proposed by Deslogchamps *et al.*[280] does not explain the stereochemical outcome of our procedure since, according to this pathway, neither the *endo*- nor the *exo*-approach produce the same stereochemistry (Scheme 183). As shown, with this mechanism the R_1SO_2 group and the δ-substituent R_2 of the sulfonyl Nazarov reagent are always in the same *syn* disposition, but in our results, as ascertained by the X-ray diffraction experiments, these groups are always in *anti*. These result could be explained by a Diels-Alder mechanism only if configuration of any of the double bonds in the diene was *cis*, what seems to be quite unlikely.



Scheme 183 Diels-Alder mechanism proposed by Deslongchamps *et al*.

Hence, we propose the double-Michael mechanism depicted in Scheme 184. First, dienamine **A** is formed between the catalyst and the α,β-unsaturated aldehyde, then the Nazarov reagent acts as nucleophile forming **B**. This enamine reacts with the α,β-unsaturated ketone affording **C** which after elimination of catalyst yields bicycle **23l** with the stereochemistry observed by X-ray experiments.

[280] Audran, G.; Brémond, P.; Feuerstein, M.; Marque, S. R. A. and Santelli, M. *Tetrahedron* **2013**, *69*, 8325. (10.1016/j.tet.2013.06.065)



Scheme 184 Proposed mechanism for the synthesis of bicycles **23**.

Thus, we demonstrated for the first time how *cis*-decalines can be prepared form a sulfone Nazarov reagent in a mechanism different of a Diels-Alder in organocatalytic and environmentally safe conditions. This procedure affords polysubstituted *cis*-decalines in moderate to good yields and good to excellent enantioselectivities, opening a new way for the synthesis of many natural occurring products with important biological activities.

4. Transformation of obtained products for diversity oriented synthesis (DOS).

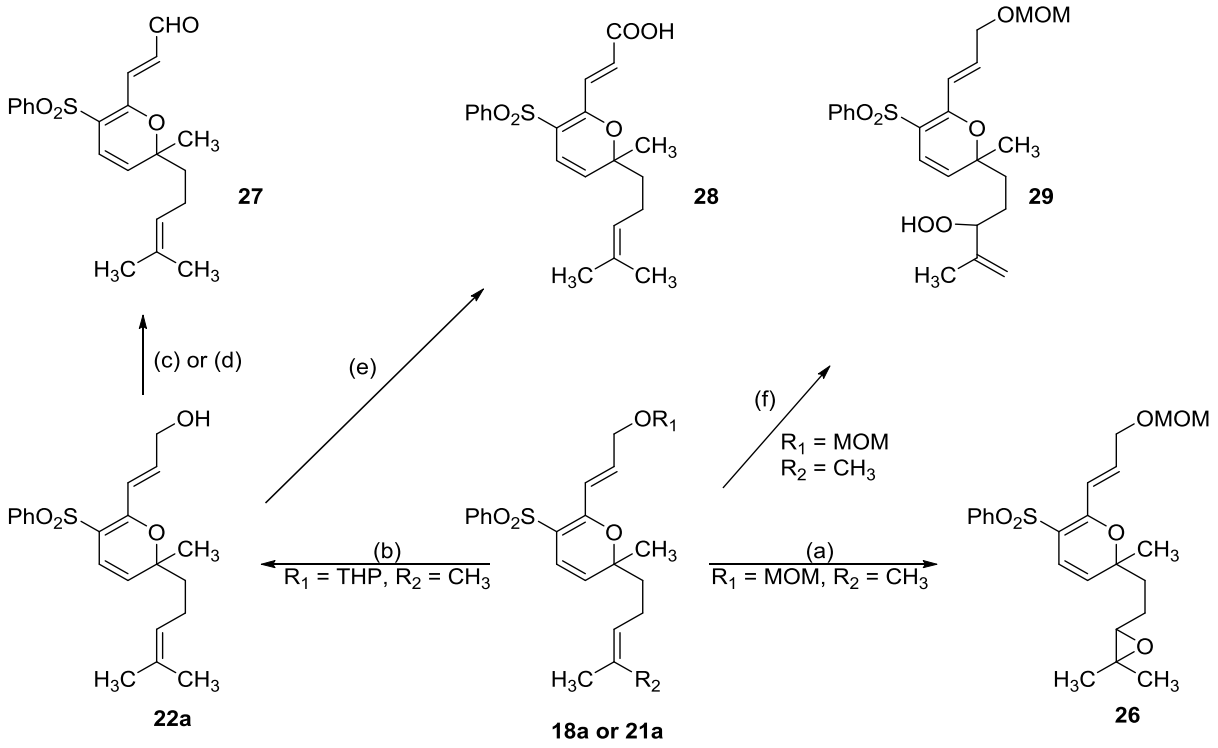
The term diversity oriented synthesis (DOS) first appeared in the chemical literature in the year 2000 in an article written by Stuart Schreiber.[281] Later, Spring *et al.* have redefined this concept saying that "diversity-oriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem".[282] The arrival of diversity-oriented synthesis (DOS) is providing a powerful further incentive for the invention of new reactions. Concise new reaction methodologies leading to the rapid synthesis of novel chemotypes are the most effective source of structurally and stereochemically diverse libraries for biological screening. The use of domino processes can offer several benefits (financial, atom efficiency, environmental) compared to multistep syntheses containing discrete workups and product isolations.[283]

As shown, different structures can be obtained just by tuning the organocatalyst used in the reaction. With these new molecules in hand, we carried out different reactions in order to see the value of these reactions and compounds, obtaining a number of products in diversity oriented strategy. Furthermore, we wanted to use the new obtained products for biological tests or as starting materials for other syntheses.

[281] Schreiber, S. L. *Science* **2000**, *287*, 1964. (10.1126/science.287.5460.1964)
[282] Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (10.1039/B310752N)
[283] Tietze, L.-F.; Brasche, G. and Gericke, K. M. *Domino reactions in organic synthesis*; Wiley-VCH: Weinheim [Germany], **2006**.

4.1. DOS with pyran derivatives.

Thus, in the context of DOS, pyrans such as **18a**, **18c** or **21a** were treated under different conditions as shown in Scheme 185.



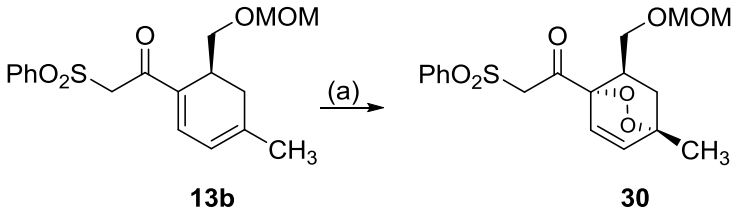
Scheme 185 (a) *m*-CPBA, DCM, 0 ºC – rt, 3 h, 95%; (b) *p*-TsOH·H_2O (10 mol%), MeOH, rt, 14 h, quant.; (c) TPAP (25 mol%), NMO (2 equivs.) MS, DCM, rt, 30 min., 50%; (d) HIO_6, CrO_3, CH_3CN/H_2O (3/1), 0 ºC, 15 h, 76%; (e) PDC (7 equivs.), DMF, rt, 96%; (f) Rose Bengal, MeOH, O_2 atmosphere, - 78 ºC, 26 h, 8%;

When pyran **18a** was treated with *m*-CPBA in DCM, the corresponding epoxide **26** was obtained in excellent yield (Scheme 185). This epoxide was further treated with *N*-bromosuccinimide (NBS) in $CDCl_3$ at room temperature for 19 hours or diisobutylaluminum hydride (DIBAL-H) in dichloromethane at -78 ºC but only complex mixtures were obtained. Deprotection of MOM group was attempted using mild conditions as *p*-TsOH·H_2O (20 mol%) or (±)-10-camphorsulfonic acid in MeOH, or harsher conditions as trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,2′-bipyridyl in DCM at 0 ºC for 1 hour or heating in toluene at 125 ºC for 72 hours, but no good results were obtained.

Diels-Alder reactivity was also tested using phenylvinylsulfone and heating in $CDCl_3$ at 70 ºC or C_6D_6 at 115 ºC for 12 hours, but no reaction happened. These conditions only afforded starting materials or decomposition products. However, when THP protecting group was used instead, deprotection product **22a** was achieved easily and quantitatively using *p*-TsOH·H_2O in MeOH, allowing the reactivity at this position as demonstrated with the oxidation to the corresponding aldehyde **27** under different conditions (TPAP or Jones oxidation) or carboxylic acid **28**. Further reactivity with both **27** and **28** will be studied in near future. Furthermore, pyran **18a** was treated with Rose Bengal in MeOH affording hydroperoxide **29** but in very poor yield.

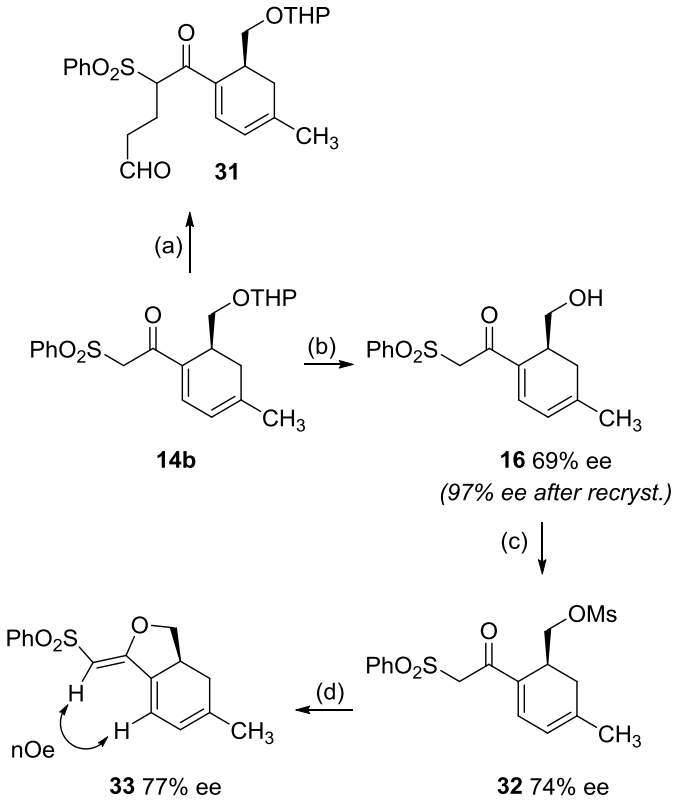
4.2. DOS with chiral cyclohexa-1,3-dienes.

Following the DOS idea, reactivity of cyclohexadienes **13**, **14** and **15** was explored, mainly seeking for Diels-Alder reactivity. Thus, diene **13b** was treated with Rose Bengal catalyst in MeOH under oxygen atmosphere at room temperature and under sunlight affording the corresponding intermolecular hetero-Diels-Alder product with oxygen, but in low yield (Scheme 186).



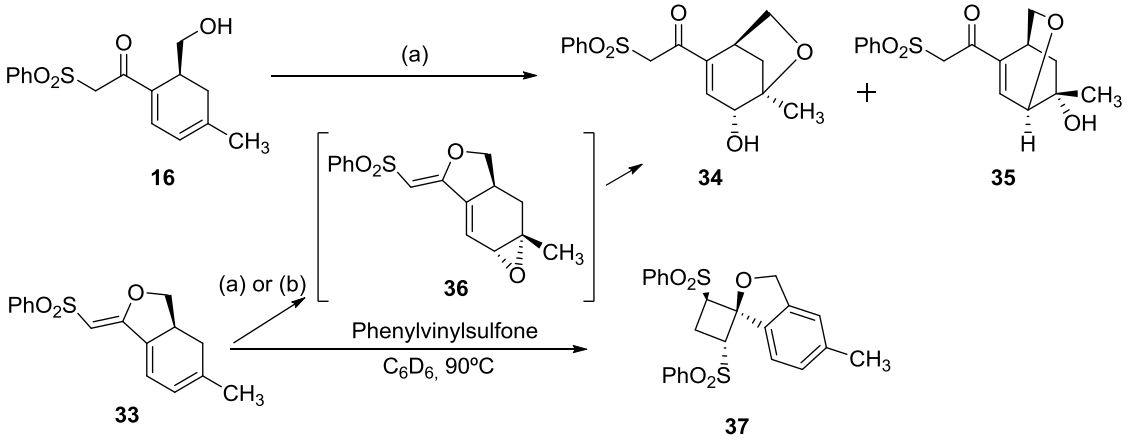
Scheme 186 (a) O_2 atmosphere, Rose Bengal (25 mol%), sunlight, MeOH, rt, 4 h, 33%.

Diene **14b** was made to react with acrolein affording **31** in good yield (Scheme 187). Unfortunately **31** was much less reactive than expected and did not react when submitted to intramolecular hetero-Diels-Alder conditions (heating in THF at 65 ºC during 3 days or using BF_3·Et_2O in DCM at room temperature for 3 hours led to decomposition of starting material), and when compound **14b** was submitted to a variety of dienophiles (dihydropyran, maleimide and *N*-phenylmaleimide, maleic anhydride, 2-pentenal or diphenylmethanimine) only starting materials or degradation products were obtained. Mesylation of **16** afforded **32** which by treatment in basic conditions led to triene **33** in moderate yield after two steps.



Scheme 187 (a) Acrolein (2 equivs.), K_2CO_3 (8 equivs.), THF, rt, 4 h, 48%; (b) *p*-TsOH·H_2O (50 mol%), THF/H_2O (1/1), rt, 48 h, 96%; (c) MsCl, Et_3N, DMAP, DCM, rt, 99%; (d) DBU, DCM, rt, 50%;

More diversity oriented structures were obtained from reactivity studies of diene **16** and triene **33** (Scheme 188, Table 15).



Scheme 188 (a) *m*-CPBA, $CDCl_3$, 0ºC, rt; (b) $CHCl_3$, heat (37ºC).

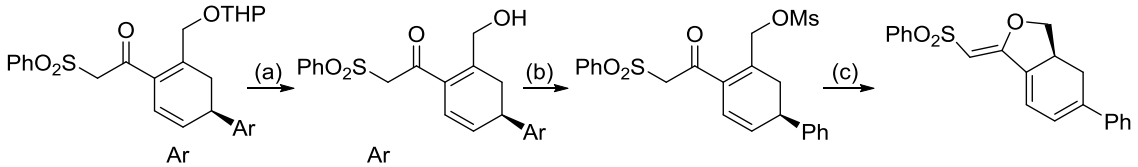
Table 15 Reactivity of compounds **16** and **33** [a]

Entry	S.M.	Conditions	Time (h)	Product	Yield (%) [b]
1	**16**	*m*-CPBA	15	**34** + **35** (1/1)	38
2	**33**	*m*-CPBA	6	**34**	62
3[c]	**33**	Heat (37ºC)	72	**34**	53
4	**33**	PVS[d], 90ºC	2.5	**37**	42

[a] For more details see text and experimental section. [b] Isolated yield after chromatography on silica gel. [c] Under air atmosphere. [d] PVS = Phenylvinylsulfone.

When **16** was treated with *m*-CPBA a 1/1 mixture of tetrahydrofuran and tetrahydropyran **34**/**35** was obtained in moderate yield. However, if compound **33** was submitted to the same conditions, or just heating, only **34** was obtained in better yields in a chemo, regio- and stereocontrolled way. This substructure is present in quinocycline and isoquinocycline compounds with antibiotic and cytotoxic activities.[284] In this case it was possible to isolate intermediate epoxide **36**, corroborating the mechanism of the reaction. Analogues of these compounds have been used for the synthesis of natural products.[285] This kind of compounds is related to bruceantin, an antitumor agent isolated from *Bruceas* species.[286] When compound **33** was heated in C_6D_6 in the presence of phenylvinylsulfone (PVS) cyclobutane **37** was obtained by a *[2+2]* cycloaddition in moderate yield, adding even more versatility to these compounds.

Aromatic derivatives **15g-j** were submitted to the same conditions as **14b**, *i.e.* deprotection and mesylation, but the resulting compounds were more unstable than aliphatic and only mesylated phenyl derivative **39** obtained from **38g** could be isolated. Aromatic triene **40** was observed by NMR, after basic treatment of **39**, but it was not stable enough to be fully characterised (Scheme 189).



Scheme 189 (a) *p*-TsOH·H_2O (50 mol%), THF/H_2O (1/1), rt, 48 h; (b) MsCl, Et_3N, DMAP, DCM, rt; (c) DBU, DCM, rt;

[284] Cordes, J.; Harms, K. and Koert, U. *Org. Lett.* **2010**, *12*, 3808. (10.1021/ol101500k)
[285] Lorbach, V.; Franke, D.; Nieger, M. and Muller, M. *Chem. Commun.* **2002**, 494. (10.1039/B110420A)
[286] Cuendet, M. and Pezzuto, J. M. *J. Nat. Prod.* **2003**, *67*, 269. (10.1021/np030304+)

4.3. DOS with chiral *cis*-decalines.

Natural products obtained from *Amphiachyris dracunculoides* (a North American annual with use as a folk remedy in the treatment of coughs and colds in the southwestern part of the United States)[287] such as gutierolide (I) (Figure 13) or arnphiacrolides are important biological compounds structurally close to our *cis*-decalines.[288]

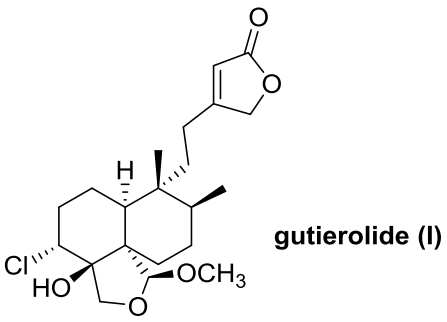
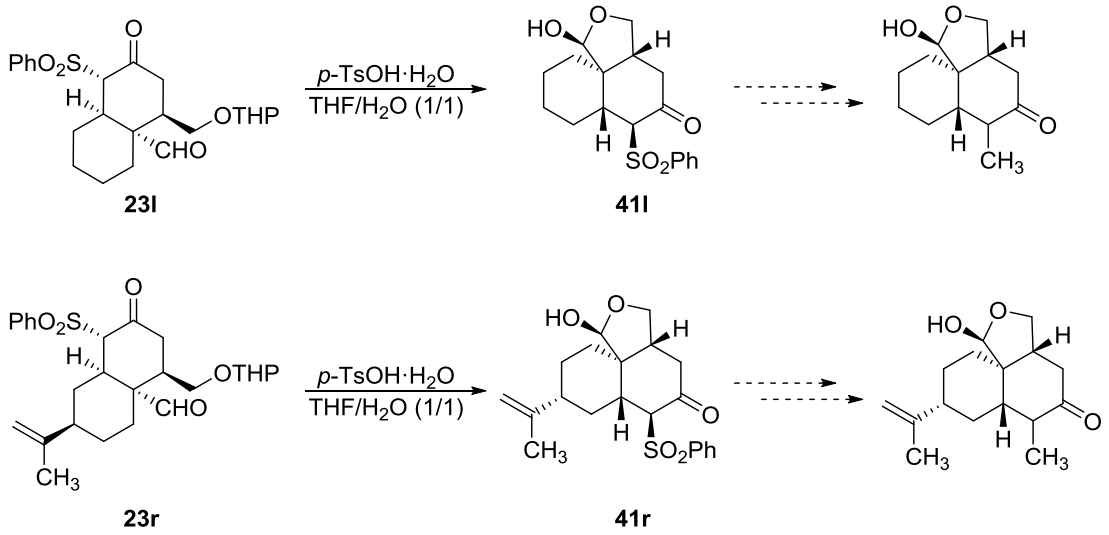


Figure 13

Regarding bicycles **23**, and despite the fact that the reaction for their obtention may not be general for a number of cyclic enals, it is a good manner to obtain these *cis*-decaline derivatives. Thus we decided to transform decalines **23** in order to demonstrate the utility of this methodology.



Scheme 190 Transformations of *cis*-decalines **23l** and **23r**.

[287] Harraz, F. M. and Doskotch, R. W. *J. Nat. Prod.* **1990**, *53*, 1312. (10.1021/np50071a027)
[288] Harraz, F. M. and Doskotch, R. W. *J. Nat. Prod.* **1996**, *59*, 463. (10.1021/np9601263)

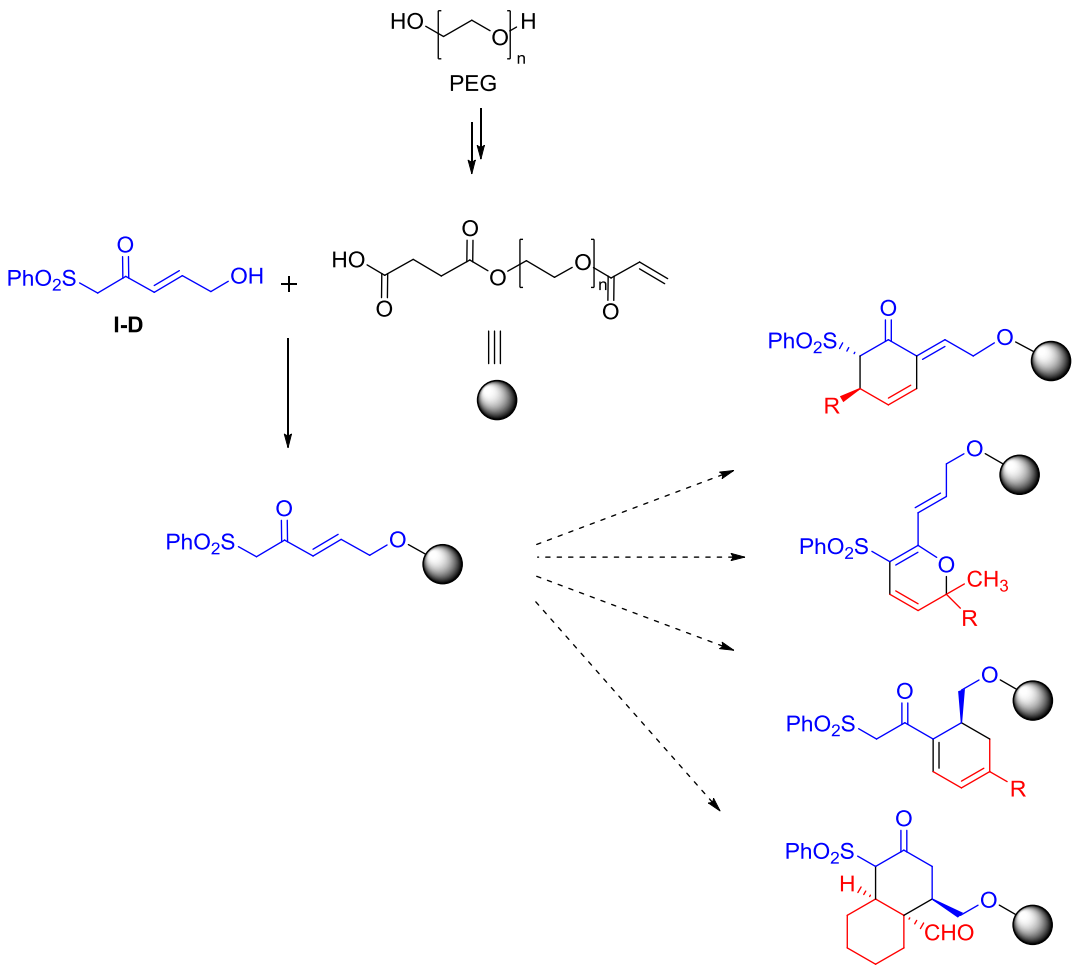
As shown in Scheme 190, decalines **23l** and **23r** were deprotected with *p*-TsOH·H_2O in THF/H_2O affording tricyclic compounds **41l** and **41r** in 90–98% yield. Future transformations as alkylation and desulfonylation, as long with the use of different enantiomeric forms of the Jørgensen's catalyst would afford these tricyclic derivatives, which structure is present in the aforementioned natural products.

4.4. Solid support chemistry.

The use of polymer-supported methodologies in carbon-carbon bond-forming asymmetric reactions has become a more and more attractive strategy.[289] Polymer-immobilised chiral reagents or catalysts offer specific opportunities for the easy recovering and iterative use of expensive chiral sources. A complementary approach, which avoids the prerequisite binding of the polymer to the chiral auxiliary or ligand, consists of supporting a prochiral substrate. Some examples of Diels–Alder and hetero Diels–Alder reactions performed under such heterogeneous conditions have been reported.[235] While the solid-phase synthesis of peptides and oligonucleotides is already well established, the preparation of small organic molecules remains a relatively new and rapidly growing area of research.[290]

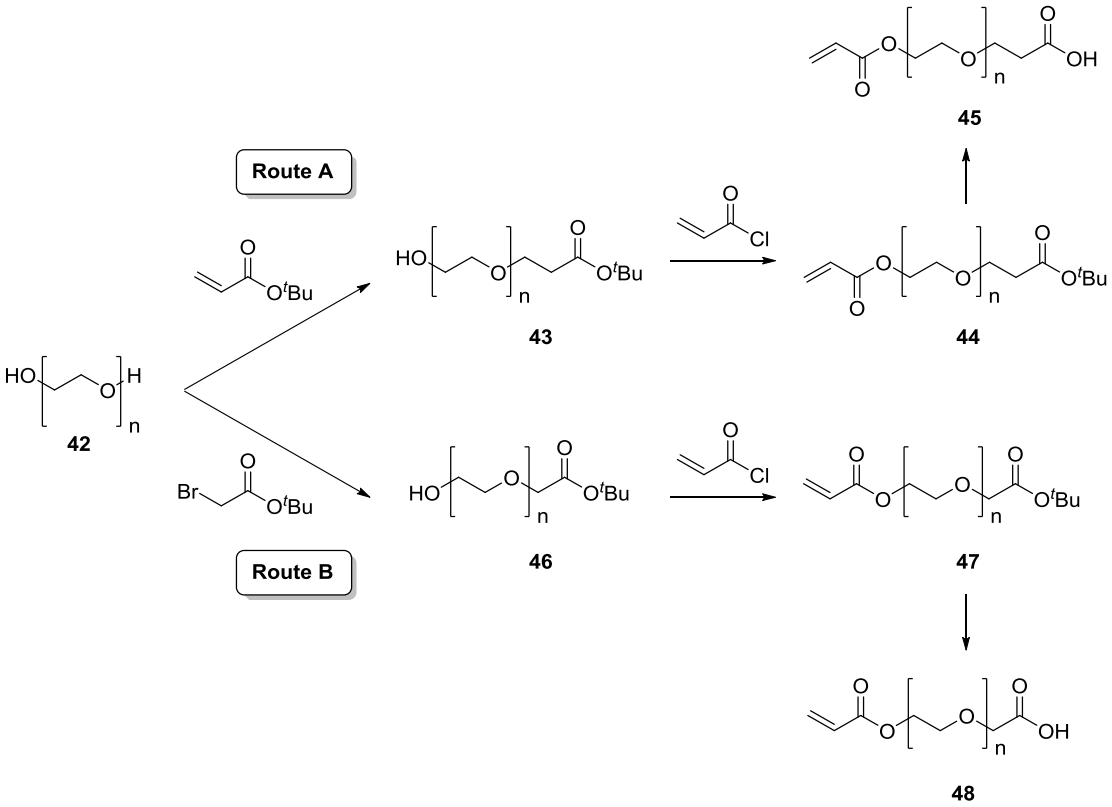
Recently we have been interested in this solid support chemistry employing polyethylene glycol (PEG) derivatives. In this way, a new field can be opened for the synthesis of the compounds we have synthesised hitherto (Scheme 191).

[289] Sammelson, R. E. and Kurth, M. J. *Chem. Rev.* **2000**, *101*, 137. (10.1021/cr000086e)
[290] Boll, E.; Drobecq, H.; Ollivier, N.; Raibaut, L.; Desmet, R.; Vicogne, J. and Melnyk, O. *Chem. Sci.* **2014**. (10.1039/C3SC53509F)



Scheme 191 Design of new solid support chemistry synthesis system.

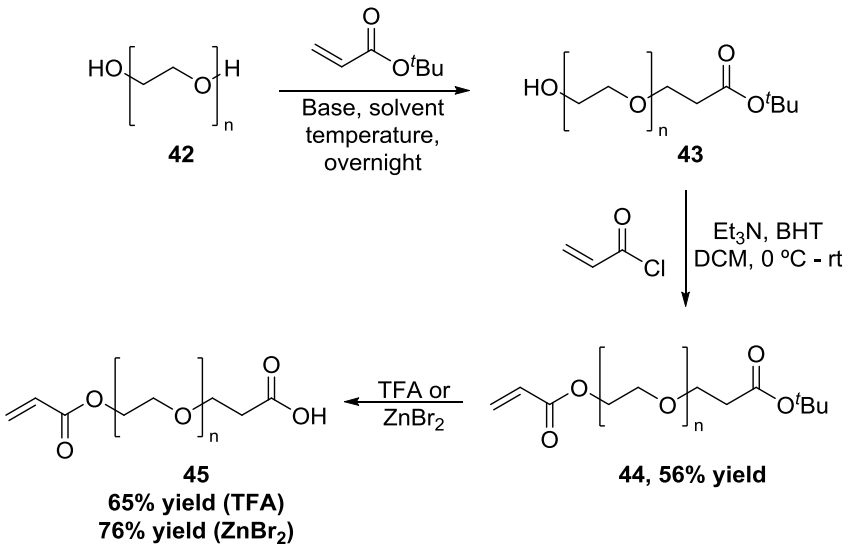
To start with this investigation, we chose PEG-400 (polyethylene glycol with an average molecular weight of 380–420) for its simplicity to handle and we decided to transform this polymer in both ends: one end will hold an acceptor group such as an α,β-unsaturated carbonyl (acrylate-like) and the other end will be a carboxylic acid in order to be eventually esterified with the hydroxyl group of our sulfone **I-D**. Two different routes were studied for the synthesis of Acrylate-Polyethyleneglycol400-COOH (APEG400COOH) as depicted in Scheme 192. Both routes involve the selective synthesis of the carboxylic terminus at only one end of PEG, followed by addition of acrylic acid in the other end.



Scheme 192 Routes studied towards the synthesis of APEG400COOH.

Route A.

First, we studied the reaction of PEG400 **42** with *tert*-butyl acrylate under different conditions (Scheme 193, Table 16).



Scheme 193 Synthesis of APEG400COOH derivative **45**.

Table 16 Conditions screened for the synthesis of **43**.[a]

Entry	Solvent	Base (equivs.)	Temperature	Yield (%)
1[b]	THF	^{t}BuOK (0.003)	rt	S.M.
2[c]	THF	^{t}BuOK (1.0)	rt	S.M.
3	DCM	^{t}BuOK (1.0)	rt	81
4	THF	^{t}BuOK (1.0)	rt	S.M.
5[d]	THF	NaH/60% (1.0)	0 ºC - rt	N.D.

[a] All the reactions were carried out overnight using 1.0 equiv. of PEG-400 and 0.5 equivs. of *tert*-butyl acrylate. [b,c] 1 equiv. of PEG-1000 instead of PEG-400 and 0.5 equivs. of *tert*-butyl acrylate were used in these reactions.[d] 1.0 equiv. of *tert*-butyl acrylate was used in this reaction. S.M. = Starting material. N.D. = Not determined.

As shown in Table 16, using potassium *tert*-butoxide in catalytic amounts, as reported by Kratz *et al.* (entry 1),[291] is not good enough and only starting material was obtained from this reaction. However, the difference observed when DCM is used instead of THF might be the cause for the previous conditions did not work (entries 2 - 4). The use of NaH as the base did not work properly leading to a complicated mixture of compounds (entry 5).

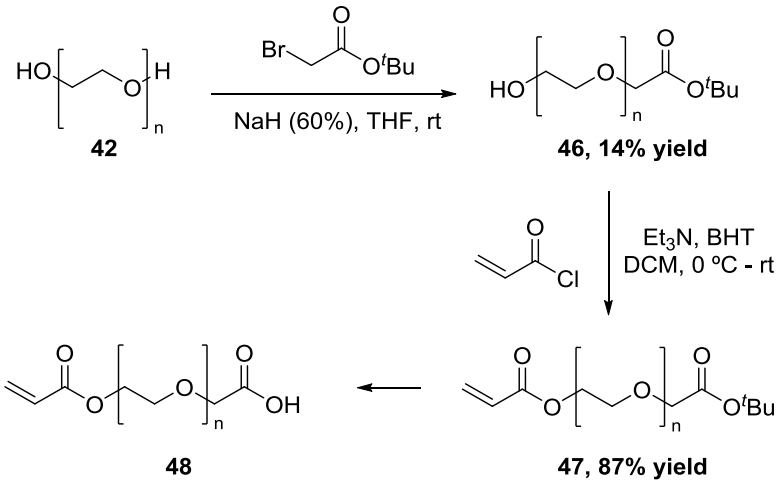
[291] Warnecke, A. and Kratz, F. *Bioconjugate Chem.* **2003**, *14*, 377. (10.1021/bc0256289)

Following standard conditions, using triethylamine in DCM at low temperature and catalytic amounts of 2,6-di-*tert*-butyl-4-methylphenol to avoid polymerisations, the desired product **27** was obtained in moderated yield (56%, Scheme 193).

To perform next hydrolysis, two different approaches were screened. First, typical procedure using trifluoroacetic acid (TFA) in DCM[291] was followed obtaining the desired product **45** in 65% yield although TFA impurities were impossible to separate from the product. The reaction with $ZnBr_2$ in DCM[292] afforded pure **45** in higher yield of 76%.

Route B.

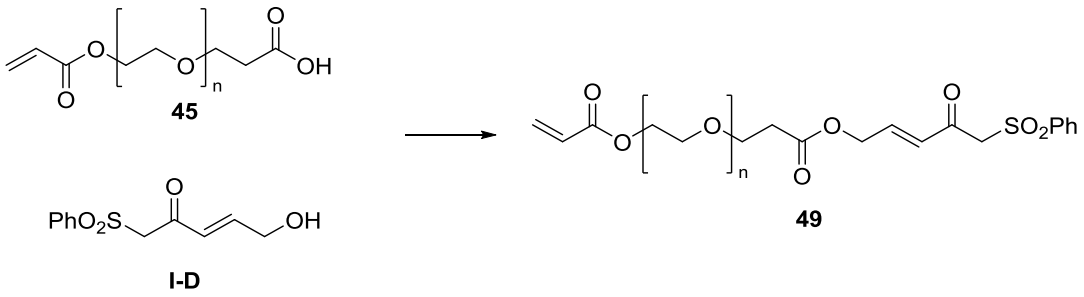
In this route, *tert*-butyl acrylate was changed to *tert*-butyl 2-bromoacetate, shortening one carbon atom the ester terminus (Scheme 194). Following the conditions used by Paduano *et al.*[293] only a 14% of the selective monoester **46** was obtained. Using the aforementioned procedure for the synthesis of **44** (Scheme 193), compound **47** was obtained in a good yield of 87%. Hydrolysis of *tert*-butyl ester to obtain free carboxylic acid **48** was attempted with TFA in dichloromethane but a complex mixture was obtained after workup. Due to the simplicity and higher yielding synthesis of PEG derivative **45**, we decided to work with this polymer instead of **48**.



Scheme 194 Synthesis of APEG400COOH derivative **48**.

The next step in this study was the combination of A-PEG carboxylic derivative with phenylsulfone **I-D** (Scheme 195) in order to obtain a monomer suitable for subsequent organocatalytic reactions or other procedures such as attachment to other polymers, synthesis of nanoparticles etc.

[292] Kaul, R.; Brouillette, Y.; Sajjadi, Z.; Hansford, K. A. and Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 6131. (10.1021/jo0491206)
[293] Simeone, L.; Mangiapia, G.; Irace, C.; Di Pascale, A.; Colonna, A.; Ortona, O.; De Napoli, L.; Montesarchio, D. and Paduano, L. *Mol. Biosyst.* **2011**, *7*, 3075. (10.1039/C1MB05143A)

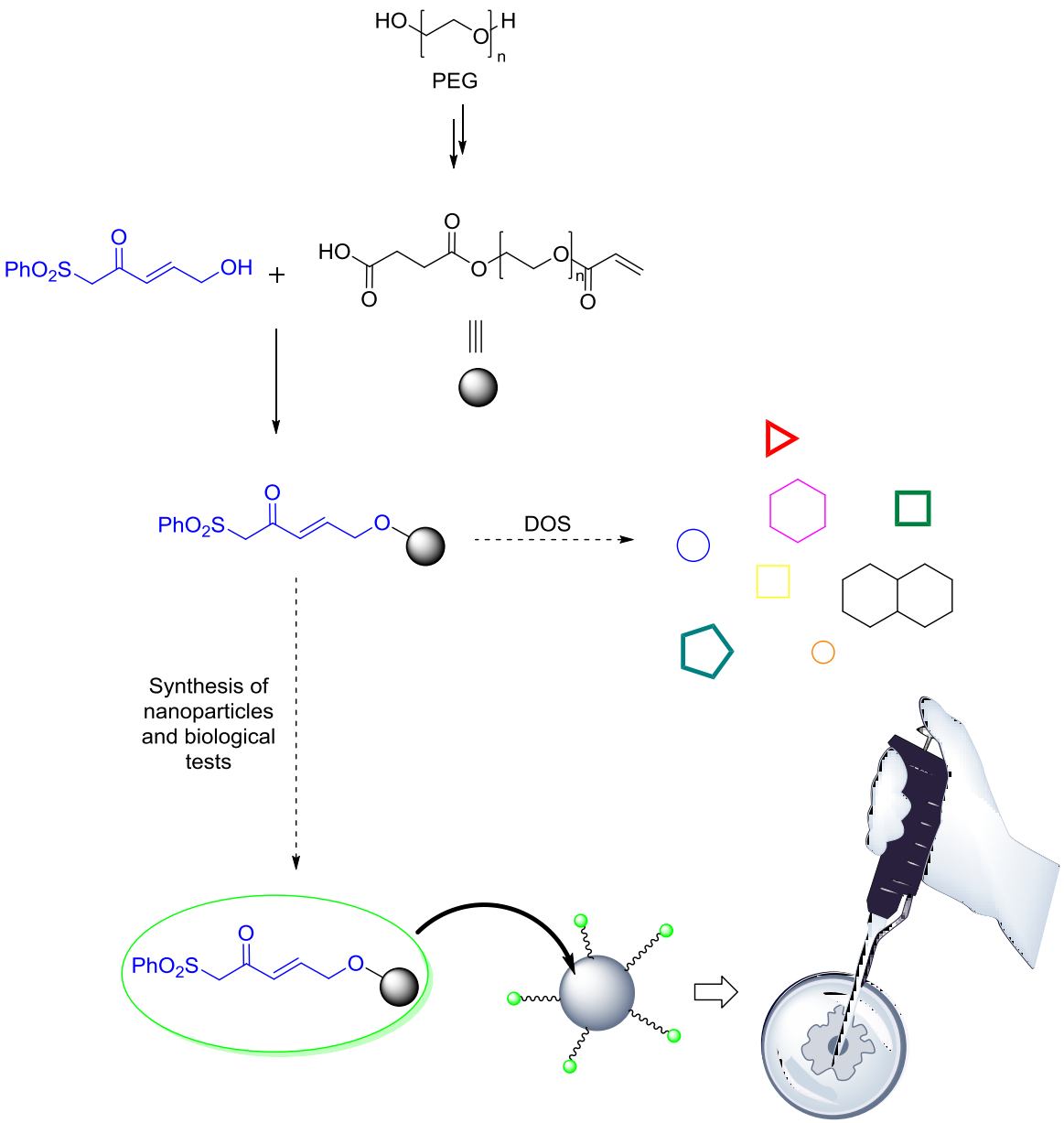


Scheme 195 Esterification with phenylsulfone **I-D** and APEGCOOH **45**.

Two different methods were envisaged for this esterification step. First using *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC·HCl), Et_3N and DMAP.[294] Apparently, these conditions provided the desired product **49** according to crude NMR and mass analyses. However, the use of Et_3N gave a nasty brown semisolid product. Thus we followed a different procedure without this base and using DCC and DMAP as described by J. Liu *et al.*[295] This new method also provided compound **49**, having the crude the same physical characteristics. Crude NMR and mass analyses showed that compound **49** could have been afforded with this method. We are currently working to determine the structure of this polymer.

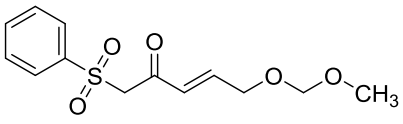
Further studies on the development of new solid-phase synthesis of our described chiral cyclohexenones, cyclohexadienes, pyrans, *cis*-decalins and all the products derived from DOS will be carried out in the future. In this way we pretend to simplify purification of products and improve the facility to carry out biological activity tests on cell lines.

[294] Pla, D.; Francesch, A.; Calvo, P.; Cuevas, C.; Aligué, R.; Albericio, F. and Álvarez, M. *Bioconjugate Chem.* **2009**, *20*, 1100. (10.1021/bc800503k)
[295] Cao, C. R.; Ou, S.; Jiang, M. and Liu, J. T. *Org. Biomol. Chem.* **2014**, *12*, 467. (10.1039/c3ob42093k)

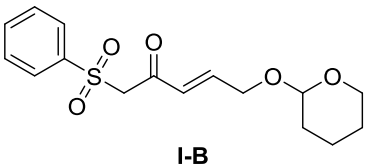

HO
O
H
n
PEG
PhO2S
O
OH
+
HO
O
O
O
n
O
PhO2S
O
O
DOS
Synthesis of
nanoparticles
and biological
tests
PhO2S
O
O

CONCLUSIONS

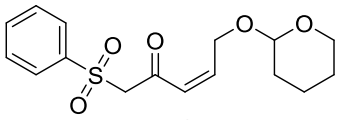
1. Using readily available starting materials, the syntheses of four new sulfonyl Nazarov reagents have been developed and optimised:



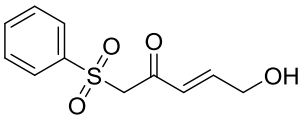
I-A



I-B

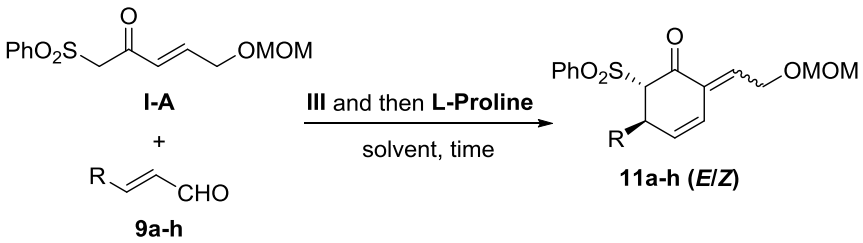


I-C

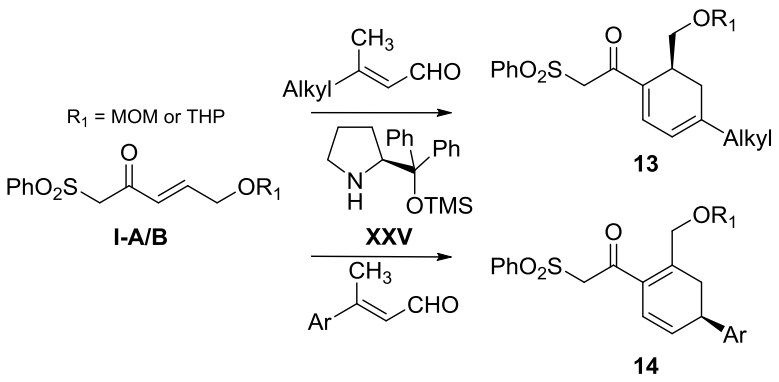


I-D

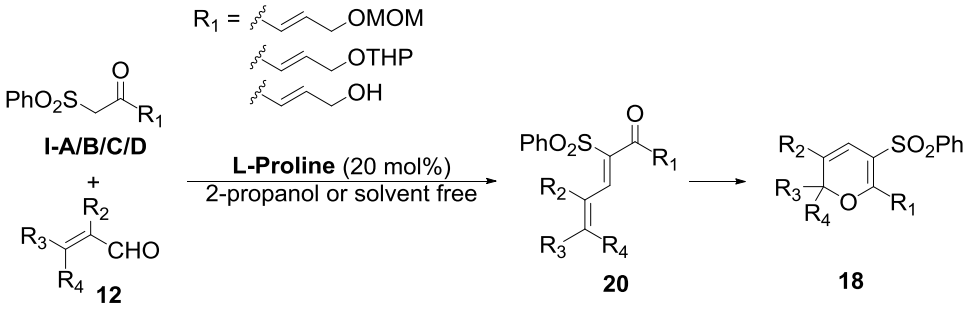
2. From the different catalyst screened, L-proline and Jørgensen's catalyst **III** have been found to be the best for the synthesis of chiral 2-alkylidene cyclohexenones, diastereoselectively and with high enantioselectivity, from Nazarov reagent as **I-A** and β-alkyl monosubstituted α,β-unsaturated aldehydes. All the compounds synthesised were stable and no transformation into phenols was detected.



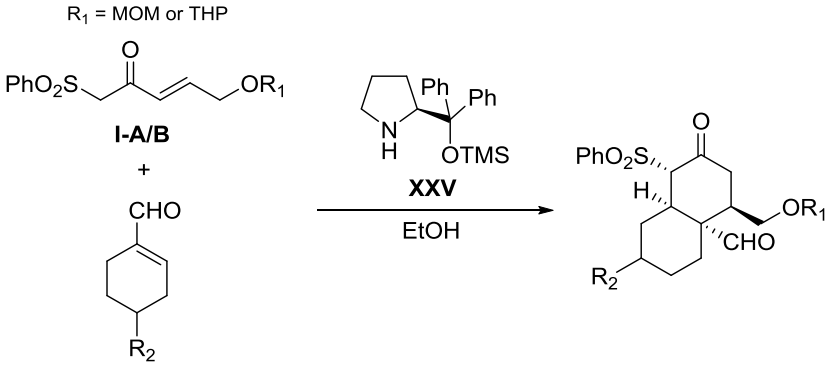
3. From the different oraganocatalyst screened, Hayashi-Jørgensen´s catalyst **XXV** proved to be the only one affording chiral cyclohexa-1,3-dienes. Thus, we demonstrated for the first time how a sulfone Nazarov reagent can react in a Diels-Alder manner in organocatalytic conditions. This reaction has made possible to obtain diverse chiral highly functionalised cyclohexa-1,3-dienes, depending on whether the aldehyde substitution is an alkyl or aryl group.



4. From all the catalyst screened for the synthesis of 2*H*-pyrans, starting from our Nazarov reagents and β,β-disubstituted-α,β-unsaturated aldehydes, proline proved to be the best and the only catalyst that gives this reaction, showing once again its versatility as organocatalyst. The reaction proceeds under solvent free conditions, becoming a green way to obtain compounds of high impact for the synthesis of natural compound analogues with biological activity in diversity oriented synthesis. Moreover, Knoevenagel adducts have been achieved in good yields.

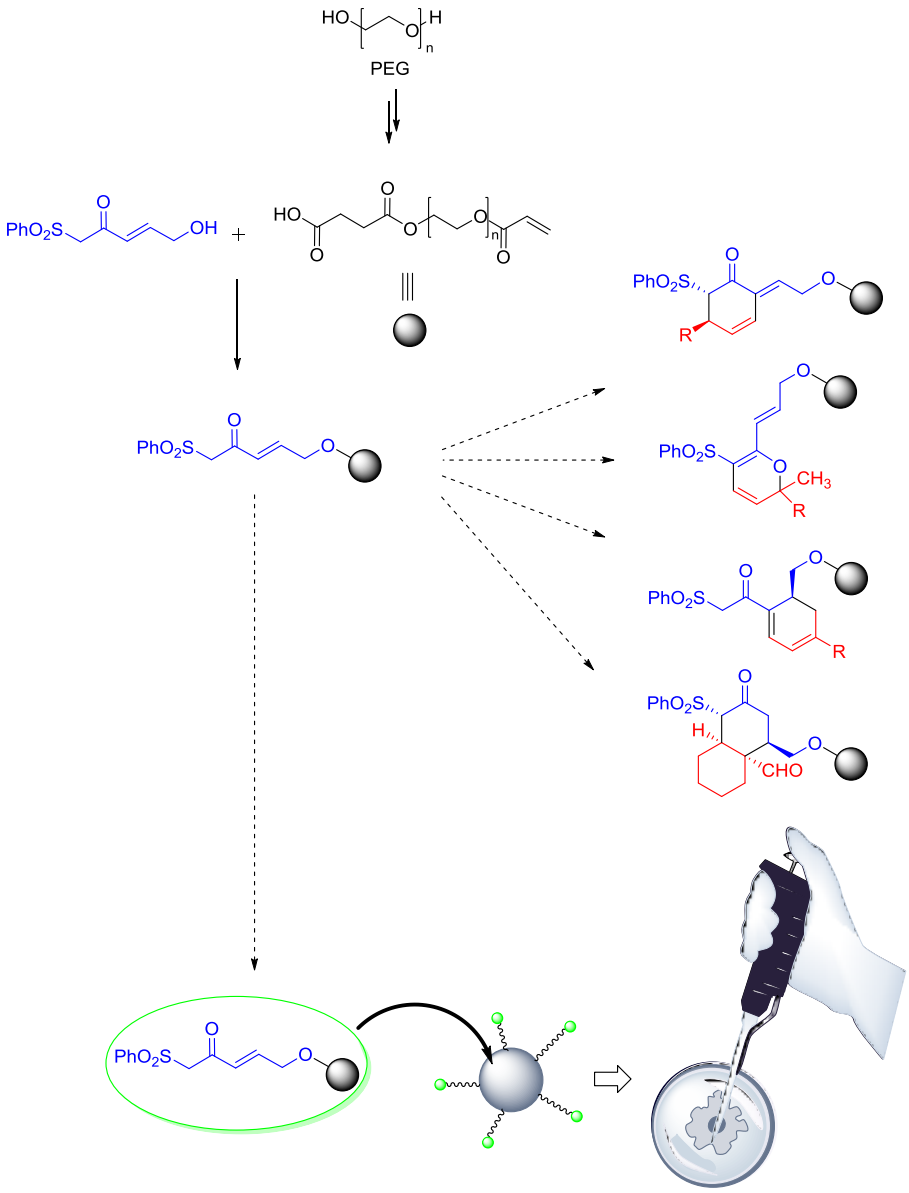


5. Hayashi-Jørgensen's catalyst **XXV** has been re-explored for the reaction of Nazarov reagent with cyclic enals producing *cis*-decalines stereospecifically and in good enantioselectivity.



6. The new products obtained are high valuable compounds which can be used as starting materials or building blocks for the synthesis of different chemical skeletons. Their reactivity has also been applied to diversity oriented synthesis to achieve many diverse skeletons.

7. A new solid support chemistry version has been opened using PEG-derivatives in order to simplify purification of products and improving the facility to carry out biological activity tests on cell lines.



This work has resulted in three publications (among others) so far, which are included here:

- Peña, J.; Antón, A. B.; Moro, R. F.; Marcos, I. S.; Garrido, N. M. and Díez, D. *Tetrahedron* **2011**, *67*, 8331. (10.1016/j.tet.2011.08.068)
- Peña, J.; Moro, R. F.; Basabe, P.; Marcos, I. S. and Diez, D. *RSC Advances* **2012**, *2*, 8041. (10.1039/C2RA21306K)
- Peña, J.; Moro, R. F.; Marcos, I. S.; Sanz, F. and Díez D. *Tetrahedron* ***(2014)***, (10.1016/j.tet.2014.04.07)

Tetrahedron 67 (2011) 8331–8337

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Tandem catalysis for the synthesis of 2-alkylidene cyclohexenones

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Nazarov reagents

ABSTRACT

(5*R*,6*S*,*E*)-5-Alkyl-2-(2-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enones, have been obtained by a domino reaction using tandem catalysis with a Nazarov reagent **3**, and several unsaturated aldehydes.

1. Introduction

Organocatalysis is an area of organic chemistry in constant evolution.[1] One of the fields of research in this area that has inspired most interest to organic chemists is the development of tandem reactions due to their ability to provide complex compounds in a very simple manner, lowering the cost of the synthesis.[1c,2]

Of special interest to us is the excellent work of Prof. Ramachary et al. on the synthesis of functionalised push–pull olefins and phenols with Hagemmann's ester, using multicatalysis reactions.[3] Related works include the synthesis of cyclohexanones by a tandem Michael/Morita–Baylis–Hillman reaction using Nazarov reagents and prolinol derivatives as organocatalysts,[4] and the Michael–Knoevenagel condensation reaction using Nazarov reagents.[5]

The sulfone group is one of the latest groups to be incorporated into the panoply of organic functionalities used in organocatalysis[6] and has attracted very soon the attention of many researchers due to its versatility. In our group we were interested by the methodology of Prof. Jørgensen to obtain 2-alkylidene cyclohexanones[4,5] and that of Profs. Garcia Ruano and Alemán to obtain chiral cyclohexenones.[7]

2. Results and discussion

Previous work by Prof. Jørgensen described that the tandem reaction between compound **A**, Fig. 1, and the Nazarov reagent **B**,

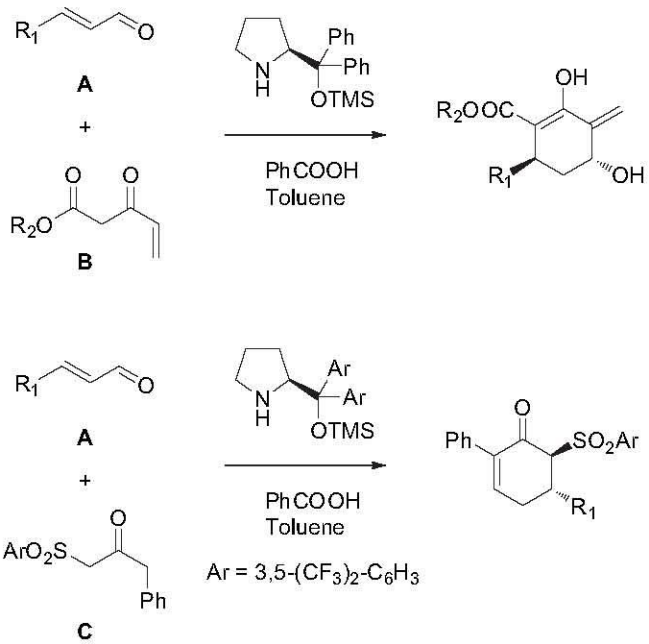

Fig. 1. Use of Nazarov reagents for the synthesis of cyclohexenones.

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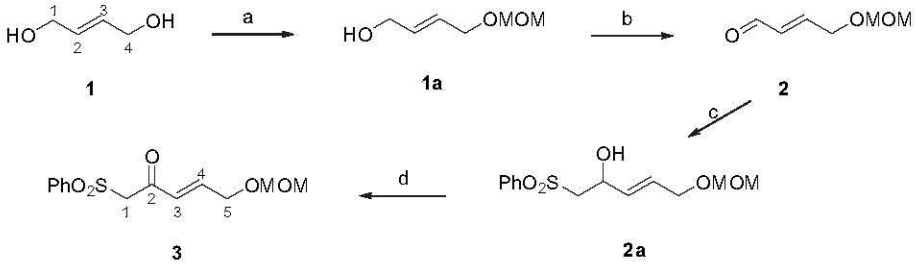
when substituted with a methyl group at the γ or δ positions of the alkene did not take place, and only a sluggish Michael addition is observed due to the steric hindrance associated with the Morita–Baylis–Hillman reaction.[4b] The groups of Profs. Garcia Ruano and Alemán, established an easy procedure for the synthesis of chiral cyclohexenones starting from α,β-unsaturated aldehydes, **A**, and α,β-keto sulfones, such as **C**[7a] Fig. 1.

2.1. Synthesis of Nazarov reagent 3

Our group has been interested in the reactivity of the sulfone group, and its application in organocatalysis,[8] so we initiated our research by preparing Nazarov reagent **3**, to obtain 2-alkylidene cyclohexenones via tandem catalysed reactions.

Compound **3** was easily synthesised in high yield from the commercially available diol **1** in four steps Scheme 1.



Scheme 1. Reagents and conditions for the synthesis of the Nazarov reagent **3**: (a) MOMCl, NaH, THF, 0 °C, 87%; (b) PDC (2 equiv), molecular sieves, DCM, rt, 72%; (c) Methylphenylsulfone (0.9 equiv), *n*-BuLi (0.9 equiv), THF, −78 °C, 63%; PDC (2 equiv), molecular sieves, rt, 50%.

(*E*)-1,4-Butanediol was protected under standard conditions to obtain the MOM protected derivative **1a**,[9] this was oxidised with PDC in DCM to give aldehyde **2**[10] in good yield over two steps. Addition of the lithium derivative of methylphenylsulfone to aldehyde **2** gave alcohol **2a**, this was oxidised to the corresponding ketone **3** as before, and allowed us to proceed with the organocatalysis study.

2.2. Reaction of 3 with different catalysts and conditions

We started our study with the reaction of compound **3** with (*E*)-2-pentenal **4**, following conditions proposed by Profs. Garcia Ruano and Alemán[7] with different organocatalysts and additives, already used in similar reactions,[7] for: table 1.

As shown in Table 1, the reaction does not take place without catalyst, entry 1, or even with additive, entry 2. When pyrrolidine is used as the catalyst, only decomposition is observed, entry 3. The use of *i*-PrOH as solvent accelerates the reaction when LiOAc is used as the additive, entries 4–6, in all cases giving the cyclisation product **7** in a diastereomeric ratio 2/1 of the olefins and no enantioselectivity. The anti relative stereochemistry for the sulfone and the ethyl group was established by NOE spectroscopy, as no NOE coupling was observed between H5 and H6, in both compounds. In the case of the olefin by the NOEs observed for both compounds, as shown in Fig. 2.

The use of benzoic acid as the additive stops the cyclisation and gives a mixture of diastereomeric aldehydes **6a** (*syn*) and **6b** (*anti*) in a 1/1 ratio in a good yield, but we were unable to establish the enantiomeric ratio, entry 7. In entries 8 and 9, without additive, the yield decreases slightly and the reaction is slower, but the same cyclisation products are obtained in the same diastereomeric ratio, with no enantioselectivity. Similar results have been obtained previously in similar processes.[11] Racemic proline was used to establish the conditions for the enantiomeric ratio determination by HPLC, giving the cyclisation product as the same mixture of diastereomeric olefins, entry 10. Catalysts **5a** and **5b**[12] gave good results in the Michael addition affording the mixture of diastereoisomeric aldehydes **6** *syn*/*anti* (1/1) at the carbon flanked by the carbonyl and sulfonyl group, but they did not give any cyclisation product, entries 11–15. MacMillan catalysts[13] **5c** gave no reaction, entries 16 and 17 and **5d** gave similar result as the catalyst **5b**, but in longer time.

2.3. Reaction of 3 with different unsaturated aldehydes using proline as catalyst

Although proline gave no enantioselectivity, the synthesis of the 2-alkylidene cyclohexenones **7** in a domino process in an easy and convenient manner is very significant. For this reason, and in order to check this reaction and extend its versatility, a variety of aldehydes **8**–**10** and **2** were chosen as starting materials.[14]

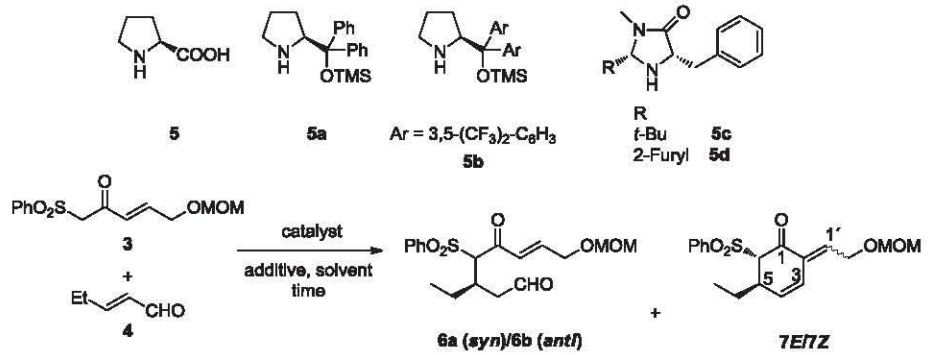
The results observed in Table 2, indicated that this domino reaction could be extended to several aldehydes, to provide different 2-alkylidene cyclohexenones. The reaction affords a 2/1 diastereomeric mixture of olefins in favour of the *E*-compound with no enantioselectivity. It is remarkable that bulkier alkyl chains led to better yields. In no case did this reaction proceed to the phenol structure under the reaction conditions. In order to obtain our goal, i.e., the synthesis of chiral 2-alkylidene cyclohexenones, we decided to carry out the domino reaction using two organocatalysts successively, in one pot.

2.4. Reaction of 3 with different unsaturated aldehydes using two catalysts in tandem

As Profs. Garcia Ruano and Alemán established, in a similar case, the reaction using catalyst **5b** proceed with high enantiomeric ratio to the Michael addition aldehydes.[7a] In order to obtain a better enantiomeric ratio, and increase the yield we chose to perform a tandem reaction, first obtaining the aldehydes **6** with enantiomeric excesses, using catalyst **5b**, and then adding proline to afford the cyclisation product. Although there is little difference between chloroform and isopropyl alcohol as solvents, entries 1 and 2 Table 3, $CDCl_3$ was the option selected in order to monitor the reaction by ^1H NMR, attending to the disappearance of the sulfone and the starting aldehyde employed. The reaction under the same conditions gives identical results using $CHCl_3$ as the solvent. The use of **5b** instead of **5d** is due to the reaction speed and better yields observed, entries 13, 14 and 18, 19, Table 1. When the reaction is completed, proline **5**, is added as the second catalyst. The reaction conditions were established using pentenal, hexenal and heptenal as aldehydes and extended to other alkyl aldehydes as **2** and **10**.

As shown in Table 3, entry 1, if isopropyl alcohol is used as solvent without any additive the reaction takes place in very good

Table 1
Screening of the reaction between Nazarov reagent **3** and (*E*)-2-pentenal **4**, using different catalysts and conditions



Entry	Catalyst	Additive	Solvent	Time[a] (h)	Yield[b] (%)		er[c]	dr[d]
					6a/6b	7*E*/7*Z*		
1			*i*-PrOH	6	S.M.		—	—
2		LiOAc	*i*-PrOH	6	S.M.		—	—
3	Pyrrolidine	LiOAc	*i*-PrOH	3	Decomposition		—	—
4	**5**	LiOAc	*i*-PrOH	3		40	1/1	2/1
5	**5**	LiOAc	EtOH	69		11	1/1	2/1
6	**5**	LiOAc	$CDCl_3$	13		60	1/1	2/1
7	**5**	B.A.	$CDCl_3$	120	60		n.d.	1/1
8	**5**	—	$CDCl_3$	63		33	1/1	2/1
9	**5**	—	*i*-PrOH	22		32	1/1	2/1
10	(±)**5**	LiOAc	*i*-PrOH	9		38	1/1	2/1
11	**5a**	LiOAc	$CDCl_3$	120	40		n.d.	1/1
12	**5a**	B. A.	$CDCl_3$	120	30		n.d.	1/1
13	**5b**	LiOAc	$CDCl_3$	42	38		n.d.	1/1
14	**5b**	B.A.	$CDCl_3$	23	32		n.d.	1/1
15	**5b**	LiOAc	*i*-PrOH	5	23		n.d.	1/1
16	**5c**	LiOAc	$CDCl_3$	120	S.M.		—	—
17	**5c**	B.A.	$CDCl_3$	120	S.M.		—	—
18	**5d**	LiOAc	$CDCl_3$	120	35		n.d.	1/1
19	**5d**	B.A.	$CDCl_3$	120	30		n.d.	1/1

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of catalyst and 20 mol % of additive. S.M.=starting materials. B.A.=benzoic acid.

[a] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored either by TLC or by ^1H NMR spectroscopy when $CDCl_3$ is used as the solvent).

[b] Yield referring to the mixtures of compounds **6a** (*syn*) and **6b** (*anti*) and to the mixtures of compounds 7*E* and 7*Z*, respectively (both with identical stereochemistry at C5 and C6).

[c] Enantiomeric ratio referred to the compounds 7*E* and 7*Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.

[d] Diastereomeric ratio referred to the *syn*/*anti* ratio in the case of compounds **6a**/**6b** or to the *E*/*Z* ratio in the case of 7*E*/7*Z*.

yield with good enantiomeric ratio. However using $CDCl_3$ as the solvent without an additive, although slightly lower yielding, leads to an excellent enantiomeric ratio. Optimal conditions to obtain the 2-alkylidene cyclohexenones were found to be $CDCl_3$, no additives, **5b** as the first catalyst, allowing to react until all starting materials have been consumed, followed by the addition of proline. This enables us to obtain the desired 2-alkylidene cyclohexenones in good yield and with good enantiomeric ratio.

The absolute configuration of the products is established tentatively according to the results obtained by Profs. Garcia Ruano and Alemán[7a] with similar sulfones and aldehydes and the Jørgensen group.[4b]

When bulkier alkyl aldehydes are employed, increased yields are obtained with excellent enantiomeric ratios. On the contrary, the use of aryl aldehydes does not produce any reaction. This

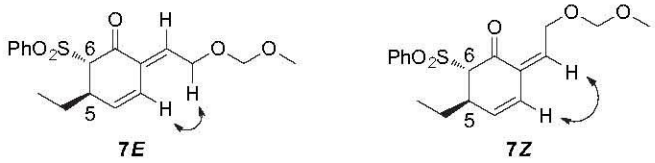
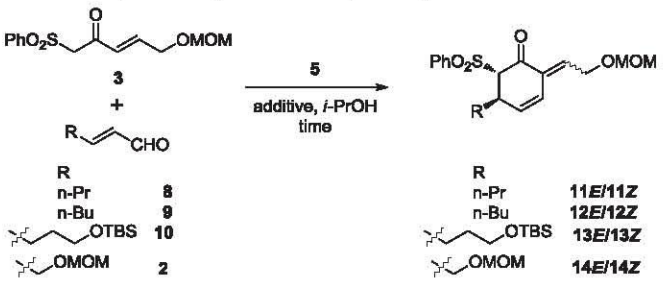


Fig. 2. NOEs that establish the configuration of the olefin for **7**.

Table 2
Proline as catalyst for the synthesis of 2-alkylidene cyclohexenones



Entry	Aldehyde	Additive	Time[a] (h)	Yield[b] (%)	Product	er[c]	dr[d]
1	**8**	LiOAc	8	69	**11**	1/1	2/1
2	**9**	LiOAc	8	80	**12**	1/1	2/1
3	**10**	LiOAc	6	51	**13**	1/1	2/1
4	**2**	LiOAc	16	31	**14**	1/1	2/1

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of **5**, and 20 mol % of additive. S.M.=starting materials.

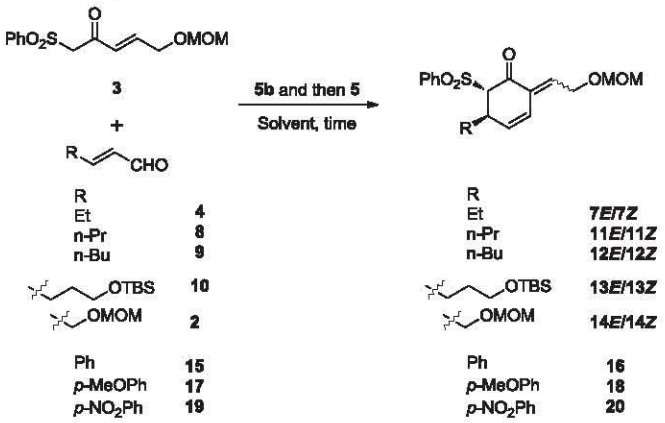
[a] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).

[b] Yield referring to the mixtures of isomers *E* and *Z*.

[c] Enantiomeric ratio referred to the compounds *E* and *Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.

[d] *E*/*Z* diastereomeric ratio.

Table 3
Synthesis of 2-alkylidene cyclohexenones via tandem catalysis



Entry	Aldehyde	Solvent[a]	Time[b] (h)	Time proline[c] (h)	Yield[d] (%)	Product	er[e]	dr[f]
1	**4**	*i*-PrOH	10	96	77	**7***E*/**7***Z*	10/1	2/1
2	**4**	$CDCl_3$	10	48	73	**7***E*/**7***Z*	20/1	2/1
3	**8**	$CDCl_3$	26	48	75	**11***E*/**11***Z*	98/2	2/1
4	**9**	$CDCl_3$	26	48	50	**12***E*/**12***Z*	98/2	2/1
5	**10**	$CDCl_3$	30	115	46	**13***E*/**13***Z*	n.d.	2/1
6	**2**	$CDCl_3$	2	42	41	**14***E*/**14***Z*	95/5	2/1
7	**15**	$CDCl_3$	63	—	S.M.	**16***E*/**16***Z*	—	—
8	**15a**	$CDCl_3$	73	—	S.M.	**16a***E*/**16a***Z*	—	—
9[g]	**15b**	$CDCl_3$	73	—	Michael (50%)	**16b***E*/**16b***Z*	—	—

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of **5b** and 20 mol % of **5**.
S.M.=starting materials.
[a] Identical results are obtained when $CHCl_3$ is used as the solvent.
[b] Time in which intermediate aldehyde is formed (monitored either by TLC or by ^1H NMR spectroscopy when $CDCl_3$ is used as the solvent).
[c] Extra time after the addition of proline.
[d] Yield referring to the mixtures of isomers *E* and *Z*.
[e] Enantiomeric ratio referred to the compounds *E* and *Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.
[f] *E*/*Z* diastereomeric ratio.
[g] This reaction does not proceed completely to the Michael addition product, being observed a 50% yield after 73 h; for this reason proline was not added.

behaviour has been reported by Profs. Garcia Ruano and Alemán[7a] in a similar case in which no reaction with cinnamaldehyde and other activated aldehydes was observed. In our case, oppositely only the Michael reaction with deactivated aryl aldehydes as **15b** is observed, although the addition step took more time.

The mechanism we postulate herein is a Michael reaction of the Nazarov reagent with the aldehyde through the standard catalytic cycle reported in the literature, A, Scheme 2.[4b,5] Once aldehydes **6** are formed, we understand that they enter in a new catalytic cycle B, in which a Morita–Baylis–Hillman reaction takes place with a concomitant Knoevenagel condensation[15] to obtain the cyclisation products.

3. Conclusions

Proline as the only organocatalyst is capable of producing 2-alkylidene cyclohexenones diastereoselectively, but with no enantiomeric excess, when using a Nazarov reagent as **3** and alkyl α,β-unsaturated aldehydes in a domino process. If two different catalysts are used successively, the domino reaction takes place in the same manner, but the 2-alkylidene cyclohexenones are produced with high enantioselectivity. The use of aryl aldehydes does not produce cyclisation products. All the compounds synthesised herein were stable and no transformation into phenols was detected.

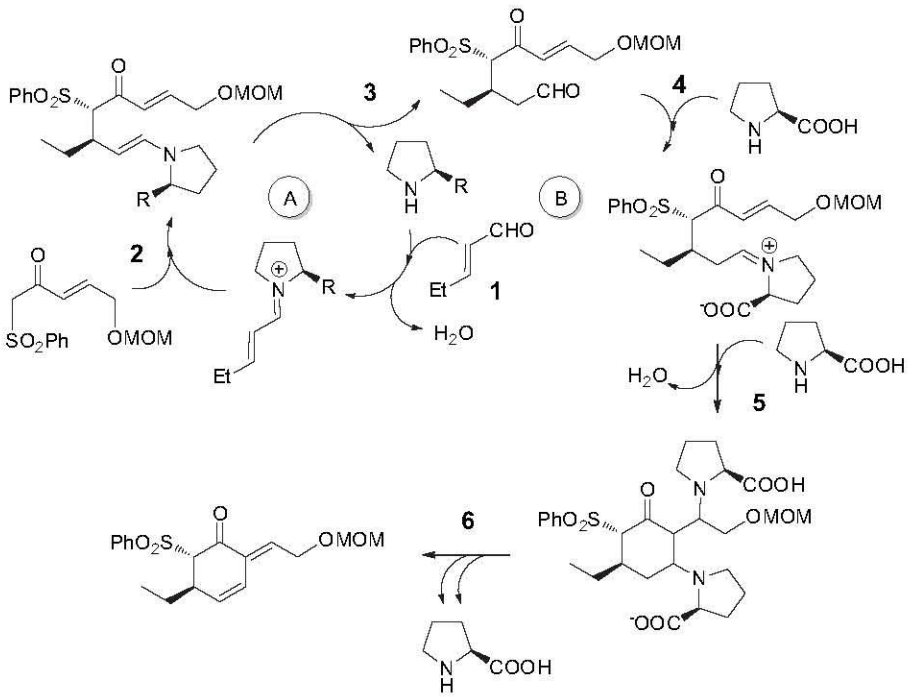
4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (*J*) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cell. HPLC analyses were carried out on a CHIRALCEL™ OD-H column [cellulose tris(3,5-dimethylphenycarbamate)] on silica gel. Column chromatography was performed using silica gel 60 (230–400 mesh), with solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under argon atmosphere prior to use. Hexane was distilled prior to use.

4.2. Synthesis of the Nazarov reagent, 3

4.2.1. Monoprotection of diol **1** *with MOMCl: (E)-4-methoxymethoxybut-2-en-1-ol,* **1a**[9]. (*E*)-1,4-Butanediol (4 ml, 48.66 mmol) was dissolved in 480 ml of THF under Ar at 0 °C. NaH (60%, 1.95 g, 48.66 mmol) was added and left to stir for 10 min. Then MOMCl (3.70 ml, 48.66 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with H_2O, and extracted with



Scheme 2. Proposed mechanism for the Michael/Morita–Baylis–Hillman/Knoevenagel tandem reaction.

EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to give a crude transparent oil of monoprotected diol, **1a** (5.6 g, 87%). ν_{max} (liquid film) 3408, 2936, 2888, 1151, 1104, 1044, 920; δ_H (200 MHz; $CDCl_3$) 5.60 (2H, m, H2 and H3), 4.50 (2H, s, O–CH_2–O), 4.04 (4H, m, H1 and H4), 3.24 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 132.9, 127.5, 95.5, 62.7, 58.3, 55.4.

*4.2.2. Oxidation of **1a** with PDC: (E)-4-methoxymethoxybut-2-enal: **2**[10].* A mixture of monoprotected diol **1a** (2.32 g, 17.60 mmol) and molecular sieves was dissolved in 88 ml of DCM under Ar and stirred at rt for 5 min. PDC (13.2 g, 35.20 mmol) was added and left to stir for 4 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil **2** (1.64 g, 72%). ν_{max} (liquid film) 2949, 2891, 1691, 1153, 1114, 1066, 1030, 968, 921; δ_H (200 MHz; $CDCl_3$) 9.48 (1H, d, J=7.9 Hz, CHO), 6.78 (1H, dt, J=15.7, 4.0 Hz, H3), 6.25 (1H, ddt, J=15.7, 7.9, 2.0 Hz, H2), 4.58 (2H, s, O–CH_2–O), 4.25 (2H, dd, J=4.0, 2.0 Hz, H4), 3.28 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 193.3, 153.0, 131.7, 96.3, 65.9, 55.6.

*4.2.3. Addition of methylphenylsulfone to **2**: (E)-5-(methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-ol, **2a**.* Methylphenylsulfone (3.27 g, 20.9 mmol) was dissolved in 190 ml of THF under Ar at −78 °C. *n*-BuLi (1.6 M in hexanes, 13 ml, 20.9 mmol) was added and the mixture was stirred 10 min. Separately, **2** (3.02 g, 23.23 mmol) was dissolved in 42 ml of THF under Ar at rt. This solution was added via cannula to the former one and the mixture was stirred at −78 °C under Ar for 1 h. Then the reaction was quenched with a NH_4Cl saturated solution and extracted with EtOAc. The combined organics were washed with H_2O, dried (Na_2SO_4), filtered and concentrated in vacuo to leave a crude yellow oil. Flash chromatography (hexane/EtOAc, 7/3) afforded **2a** (3.75 g, 63%). ν_{max} (liquid film) 3457, 2932, 2884, 1305, 1145, 1086, 1041; δ_H (200 MHz; $CDCl_3$) 7.92 (2H, dd, J=8.2, 1.4 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta}, ArH_{para}), 5.86 (1H, dt, J=14.0, 6.0 Hz, H4), 5.64 (1H, dd, J=14.0, 4.0 Hz, H3), 4.70 (1H, m, H2), 4.58 (2H, s, O–CH_2–O), 3.99 (2H, d, J=6.0 Hz, H5), 3.31 (3H, s, O–CH_3), 3.25 (2H, m, H1); δ_C (50 MHz; $CDCl_3$) 139.5, 134.3, 131.2, 129.7 (2C), 129.0, 128.2(2C), 96.0, 66.5, 62.1, 55.5; EIHRMS: calcd for $C_{13}H_{18}O_5S$(M+Na): 309.0773; found: 309.0767 (M+Na).

*4.2.4. Oxidation of **2a** with PDC: (E)-5-(methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-one, **3**.* A mixture of **2a** (1.08 g, 3.77 mmol) and molecular sieves was dissolved in 19 ml of DCM under Ar and stirred at rt for 5 min. PDC (2.84 g, 7.55 mmol) was added and left to stir for 3 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil. Flash chromatography (hexane/EtOAc, 6/4) afforded **3** (535 mg, 50%). ν_{max} (liquid film) 2938, 1671, 1324, 1152; δ_H (200 MHz; $CDCl_3$) 7.88 (2H, d, J=8.3 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta}, ArH_{para}), 6.96 (1H, dt, J=15.8, 3.9 Hz, H4), 6.55 (1H, d, J=15.8 Hz, H3), 4.66 (2H, s, O–CH_2–O), 4.31 (2H, s, H1), 4.27 (2H, d, J=3.9 Hz, H5), 3.37 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 187.1, 147.1, 138.8, 134.5, 129.5, 128.6, 128.0, 96.4, 66.0, 65.8, 55.8; EIHRMS: calcd for $C_{13}H_{16}O_5S$ (M+Na): 307.0616; found: 307.0610 (M+Na).

4.3. Typical procedure for reaction of 3 with pentenal and different catalysts and conditions (Table 1)

Compound **3** (50 mg, 17.6 mmol) and (*E*)-2-pentenal (18 μl, 17.6 mmol) were dissolved in 1 ml of the solvent used. Next, a solution of the catalyst (20 mol %), and additive (20 mol %) if needed, was added and left stirring for the appropriate time. Compounds **6a** and **6b** were isolated as a 1/1 mixture and compounds **7***E* and **7***Z* were isolated as a 2/1 mixture. From this mixture each compound **7***E* and **7***Z* was separated by flash chromatography and characterised.

4.3.1. (3R,4S*,E) and (3R*,4R*,E)-3-Ethyl-8-(methoxymethoxy)-5-oxo-4-(phenylsulfonyl)oct-6-enal, **6a** (syn)/**6b** (anti), (1/1) mixture.* Compound **6a** (*syn*)/**6b** (*anti*): ν_{max} (liquid film) 2959, 2936, 1718, 1670, 1448, 1309, 1282, 1022, 1062, 1033; δ_H (200 MHz; $CDCl_3$) 9.77 and 9.68 (1H, s, CHO), 7.88 (2H, m, Ar), 7.70–7.50 (3H, m, Ar), 6.97 (1H, dt, J=15.8, 3.9 Hz, H7), 6.57 (1H, dt, J=15.8, 2.0 Hz, H6), 4.67 (2H, s, O–CH_2–O), 4.62 (1H, m, H4), 4.31–4,16 (2H, m, H8), 3.37

(3H, s, O–CH_3), 3.20–2.40 (2H, m, H2), 1.68–1.40 (3H, m, H3 and H1′), 1.01–0.74 (3H, t, J=7.2 Hz, H2′); δ_C (50 MHz; $CDCl_3$) 200.9, 200.8, 191.5, 191.2, 145.8, 145.7, 138.5, 138.3, 134.5 (2C), 129.5 (4C), 129.2 (4C), 128.0126.7, 96.4, 96.3, 75.3, 74.1, 66.0, 65.9, 55.8(2C), 44.8, 43.3, 34.2, 33.9, 26.0, 24.4, 11.5, 11.1. EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 391.1191; found: 391.1189.

4.3.2. (5R,6S*,E)-5-Ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***7****E.* Compound **7***E*: ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; δ_H (400 MHz; $CDCl_3$, HMQC, HMBC) 7.80–7.75 (2H, m, Ar), 7.60–7.45 (3H, m, Ar), 6.60 (1H, t, J=6.0 Hz, H1′), 6.45 (1H, d, J=12.0 Hz, H3), 6.10 (1H, m, H4), 4.65 (2H, s, O–CH_2–O), 4.31 (2H, d, J=6.0 Hz, H2′), 3.91 (1H, s, H6), 3.38 (3H, m, O–CH_3), 3.35 (1H, m, H5), 1.45 (2H, m, H1″), 0.85 (3H, t, J=8.0 Hz, H2″); δ_C (100 MHz; $CDCl_3$) 189.3, 137.8, 134.7, 134.1, 131.2, 130.7, 128.9 (4C), 122.5, 96.3, 75.6, 63.3, 55.7, 37.9, 29.1, 10.7; EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; first peak t_R=22.4 min; second peak t_R=24.9 min.

4.3.3. (5R,6S*,Z)-5-Ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***7****Z.* Compound **7***Z*: ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; δ_H (200 MHz; $CDCl_3$) 7.85–7.75 (2H, m, Ar), 7.65 (1H, m, Ar), 7.60–7.40 (2H, m, Ar), 6.20 (1H, d, J=10.0 Hz, H3), 6.06 (1H, t, J=6.0 Hz, H1′), 5.86 (1H, dd, J=10.0, 6.0 Hz, H4), 4.65 (2H, s, O–CH_2–O), 4.51 (1H, dd, J=16.0, 6.0 Hz, $H2_A$′), 4.43 (1H, dd, J=16.0, 10.0 Hz, $H2_B$′), 3.88 (1H, s, H6), 3.38 (3H, s, O–CH_3), 3.35 (1H, m, H5), 1.75 (2H, m, H1″), 0.65 (3H, t, J=8.0 Hz, H2″); δ_C (50 MHz; $CDCl_3$) 190.8, 137.9, 134.9, 134.5, 130.9, 130.5, 129.2 (4C), 126.7, 96.5, 77.1, 67.0, 55.6, 38.6, 28.8, 9.8; EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; first peak t_R=18.3 min; second peak t_R=19.0 min, for the rest of spectral properties see Section 4.3.3.

4.4. Typical procedure for reaction of 3 with different aldehydes and L-proline (Table 2)

Compound **3** (50 mg, 17.6 mmol) and the corresponding aldehyde (17.6 mmol) were dissolved in 1 ml of isopropyl alcohol. Next, a solution of L-proline (20 mol %), and additive (20 mol %) if needed, was added and left stirring for the appropriate time. In this case, compounds **11**–**14** were isolated as a 2/1 mixture of diastereoisomers *E*/*Z*. When mixtures, the spectral data are indicated for the major compound.

4.4.1. (5R,6S*,E)-5-Propyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***11****E*/***11****Z.* Compound **11***E*/**11***Z*: ν_{max} (liquid film), 2940, 2931, 1676, 1384, 1310, 1150, 1084, 1038; δ_H (200 MHz; $CDCl_3$) 7.97–7.69 (2H, m, Ar), 7.67–7.42 (3H, m, Ar), 6.61 (1H, t, J=6.2 Hz, H1′), 6.42 (1H, d, J=10.2 Hz, H3), 6.05 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.32 (2H, d, J=6.2 Hz, H2′), 3.91 (1H, s, H6), 3.52–3.30 (1H, m, H5), 3.38 (3H, s, O–CH_3), 1.48–1.18 (4H, m, H1″, H2″), 0.87 (3H, t, J=8.0 Hz, H-2″); δ_C (50 MHz; $CDCl_3$) 189.0, 142.8, 138.0, 135.0, 134.4, 131.3, 129.5 (2C), 129.3(2C), 122.6, 96.5, 76.0, 63.7, 55.6, 38.4, 20.2, 19.8, 13.9. EIHRMS: calcd for $C_{19}H_{24}O_5S$ (M+Na): 387.1242; found: 387.1247 (M+Na).

4.4.2. (5R,6S*,E)-5-Butyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***12****E*/***12****Z.* Compound **12***E*/**12***Z*: ν_{max} (liquid film) 2957, 2932, 2872, 1281, 1138, 1124, 1097, 1043; δ_H (200 MHz; $CDCl_3$) 7.80–7.75 (2H, m, Ar), 7.60–7.49 (3H, m, Ar), 6.61 (1H, t, J=6.2 Hz, H1′), 6.42 (1H, d, J=10.3 Hz, H3), 6.03 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.32 (2H, d, J=6.2 Hz, H-2′), 3.91 (1H, s, H6), 3.42 (1H, m, H5), 3.38 (1H, s, O–CH_3) 1.26 (4H, m, H1″, H2″), 0.85 (3H, t, J=6.6 Hz, H2″); δ_C (50 MHz; $CDCl_3$) 189.6, 144.0, 138.0, 135.0, 134.4, 131.4, 131.4, 129.3 (3C), 122.5, 96.4, 76.1, 63.6, 55.7, 36.7, 36.1, 28.7, 22.6, 14.0. EIHRMS: calcd for $C_{13}H_{18}O_5S$ (M+Na): 401.1399; found: 401.1402 (M+Na).

4.4.3. (5R,6S*,E)-5-(3-tert-Butyldimethylsilyloxy)-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***13****E*/***13****Z.* Compound **13***E*/**13***Z*: ν_{max} (liquid film) 2955, 2932, 2887, 2858, 1375, 1281, 1174, 1140, 837; δ_H (200 MHz; $CDCl_3$) 7.80–7.75 (2H, m, Ar), 7.6–7.39 (3H, m, Ar), 6.62 (1H, t, J=6.2 Hz, H1′), 6.43 (1H, d, J=10.3 Hz, H3), 5.95–5.83 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.31 (2H, d, J=6.2 Hz, H2′), 3.91 (1H, s, H6), 3.55 (2H, m, H2″) 3.38 (O–CH_3), 3.35 (1H, m, H5), 1.49 (2H, m, H1″), 0.86 (9H, O–Si–*t*-Bu), −0.08 (6H, O–Si–Me_2); δ_C (50 MHz; $CDCl_3$) 189.5, 138.0, 135.1, 134.5, 131.2, 131.1, 129.3 (3C), 122.7, 96.4, 76.0, 63.6, 62.5, 55.7, 36.4, 32.9, 30.0, 26.2 (3C), 18.5, −5.1 (2C). EIHRMS: calcd for $C_{25}H_{38}O_6SSi$ (M+Na): 517.2056; found: 517.2059 (M+Na).

4.4.4. Using aldehyde ***2*** *we were able to separate the cyclisation products: (5R,6S,E)-5-(1-methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***14****E.* Compound **14***E*: ν_{max} (liquid film) 2938, 2889, 1699, 1448, 1321, 1281, 1151, 1039; δ_H (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.61 (1H, t, J=8.4 Hz, H3), 6.55 (1H, d, J=10.0 Hz, H1′), 5.93 (1H, m, H4), 4.63 (2H, s, O–CH_2–O), 4.46 (O–CH_2–O), 4.30 (2H, m, H2′), 4.13 (1H, s, H6), 3.61 (2H, m, H1″), 3.39 (1H, m, H5), 3.35 (3H, s, O–CH_3), 3.22 (3H, s, O–CH_3); δ_C (100 MHz; $CDCl_3$) 188.6, 137.9, 135.3, 134.5, 131.3, 128.6 (4C), 127.0, 125.0, 96.5, 96,3, 73.7, 69.1, 63.5, 55.7 (2C), 37.9. EIHRMS: calcd for $C_{20}H_{26}O_7S$ (M+Na): 433.1297; found: 433.1294 (M+Na).

4.4.5. (5R,6S,Z)-5-(1-Methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***14****Z.* Compound **14***Z*: ν_{max} (liquid film) 2937, 2889, 1448, 1375, 1309, 1281, 1149, 1109, 1037, 918; δ_H (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.30 (1H, d, J=10.0 Hz, H3), 6.10 (1H, t, J=5.2 Hz, H1′), 5.80 (1H, m, H4), 4.65 (2H, s, O–CH_2–O), 4.60 (O–CH_2–O), 4.60 (2H, m, H2′), 4.10 (1H, s, H6), 3.65 (2H, m, H1″), 3.41 (3H, s, O–CH_3), 3.40 (1H, m, H5), 3.25 (3H, s, O–CH_3); δ_C (100 MHz; $CDCl_3$) 189.8, 144.5, 137.9, 134.5, 130.7, 130.4, 129.3 (2C), 129.2 (2C) 124.7, 96.5(2C), 74.9, 69.1, 67,1, 55.8, 55.6, 38.4. EIHRMS: calcd for $C_{20}H_{26}O_7S$ (M+Na): 433.1297; found: 433.1292 (M+Na).

4.5. Typical procedure for reaction of 3 with catalysts 5b and L-proline in a tandem way (Table 3)

Compound **3** (50 mg, 17.6 mmol) and aldehyde (17.6 mmol) were dissolved in 1 ml of $CDCl_3$ or $CHCl_3$. Next, catalyst **5b** (20 mol %) was added and the mixture was stirred for the specified time. When the disappearance of the starting materials is observed by ^1H NMR, L-proline (20 mol %), is added and the reaction continues until the cyclic compounds are formed.

Compounds **7**–**14** were isolated as a 2/1 mixture of diastereoisomers *E*/*Z*.

Compounds **7***E* and **7***Z*, and **14***E* and **14***Z* were separated by flash chromatography.

4.5.1. We were able to separate compounds **7***E and* **7***Z from the mixture: (5R,6S,E)-5-ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* **7***E.* $[\alpha]_D^{22}$ −6.8 (c 0.3, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; t_R (major)=22.4 min; t_R (minor)=24.9 min, for the rest

of spectral properties see Section 4.3.2. (5*R*,6*S*,*Z*)-5-*Ethyl*-2-(2′-(*methoxymethoxy*)*ethylidene*)-6-(*phenylsulfonyl*)*cyclohex*-3-*enone*, **7***Z*. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; t_R (major)=18.3 min; t_R (minor)=19.0 min, for the rest of spectral properties see Section 4.3.3.

4.5.2. (5R,6S,E/Z)-5-Propyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***11****E*/***11****Z*. For a mixture 2/1 of compounds $[\alpha]_D^{22}$ −17.2 (*c* 1.1, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **11***E*: t_R (major)=15.5 min; t_R (minor)=19.6 min; compound **11***Z*: t_R (major)=17.4 min; t_R (minor)=21.5 min; for the rest of spectral properties see Section 4.4.1.

4.5.3. (5R,6S,E/Z)-5-Butyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***12****E*/***12****Z*. For a mixture 2/1, $[\alpha]_D^{22}$ −14.5 (*c* 1.1, $CHCl_3$); we were able to separate a small amount of compound **12***E*. $[\alpha]_D^{22}$ −13.0 (*c* 0.2, $CHCl_3$). Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **12***E* t_R (major)=16.9 min; t_R (minor)=14.2 min; compound **12***Z* t_R (major)=14.8 min; t_R (minor)=13.6 min. For the rest of spectral properties see Section 4.4.2.

4.5.4. (5R,6S,E/Z)-5-(3-tert-Butyldimethylsilyloxy)-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***13****E*/***13****Z*. For a mixture 2/1, $[\alpha]_D^{22}$ −27.5 (*c* 0.6, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **13***E* t_R (major)=10.2 min; t_R (minor)=11.8 min; compound **13***Z* t_R (major)=9.1 min; t_R (minor)=10.5 min. For the rest of spectral properties see Section 4.4.3.

4.5.5. Using the aldehyde ***2*** *we were able to separate the cyclisation products: (5R,6S,E)-5-(1-methoxymethoxymethyl)-2-(2′-methoxy methoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***14****E*. $[\alpha]_D^{25}$ +0.97 (*c*1.9, $CHCl_3$). For the rest of spectral properties see Section 4.4.4.

4.5.6. (5R,6S,Z)-5-(1-Methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***14****Z*. $[\alpha]_D^{25}$ −7.57 (*c* 0.8, $CHCl_3$). For the rest of spectral properties see Section 4.4.5.

In this case we were unable to determine the enantiomeric ratio of the compounds.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.068. These data include MOL files and InChiKeys of the most important compounds described in this article.

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PAPER

Solvent free L-proline-catalysed domino Knoevenagel/6π-electrocyclization for the synthesis of highly functionalised 2*H*-pyrans†

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An environmentally benign synthesis of 2*H*-pyrans has been achieved in high yield using β-oxosulfones and 3,3-dialkylsubstituted α,β-unsaturated aldehydes. The key reaction is a solvent free L-proline catalysed domino Knoevenagel/6π-electrocyclization. As 3,3-dialkylsubstituted α,β-unsaturated aldehydes are a very common feature in many natural products, the transformation into highly functionalised 2*H*-pyrans makes this procedure a green and excellent method for a diversity oriented synthesis of biologically active compounds.

Introduction

Molecules with a pyran heterocycle in their structure are very interesting due to their biological activities and applications in medicine.[1] Benzopyrans, such as daurichromenic acid, an anti-HIV agent,[2] seselin, an antinociceptive along with other activities,[3] or privileged structures, such as 2-pyrones, an essential pharmacophore in many naturally occurring and biologically active compounds,[4] led our attention to the 2*H*-pyran ring. Although these compounds are very interesting, there is not a great variety of starting materials to synthesise them, being usually made by iminium activation of a carbonyl group and a 1,3-dicarbonyl compound.[5] As an example, Profs. Chang and Marsella *et al.* described the reaction of the *E*/*Z* mixture of citral with 1,3-cyclohexanodione to yield *perhydro*-CBC (cannabichromene), which was later transformed into a Δ^1-tetrahydrocannabinol analogue[6] (Fig. 1). Prof. Jørgensen *et al.* have reported other very interesting uses of β-ketoesters in organocatalytic conditions.[6b,c]

In our group we have been interested in the reactivity of β-oxosulfones, which are known substrates in organocatalysis,[7] for the synthesis of 2-alkylidene cyclohexenones by a Michael addition[8] using organocatalyst **5** followed by a Morita–Baylis–Hillman reaction after addition of L-proline (Scheme 1). The use of β-oxosulfones over 1,3-dicarbonyl compounds will add the extra versatility of the sulfone moiety, mainly due to easy elimination and reactivity.

Prof. Inokuchi *et al.* established that 2-alkylsubstituted enals favour the formation of (*E*)-Knoevenagel adducts for the ensuing electrocyclization.[4] We became interested in carrying out the reaction with our β-oxosulfones and 3,3-dialkylsubstituted enals, because of its profusion in nature,[9] as in the case of Chang and Marsella,[6] using organocatalysts in order to develop environmentally benign processes for the synthesis of 2*H*-pyrans. We were also wondering if it would be possible to obtain the corresponding pyrans by changing the mechanism of the reaction between Nazarov reagents such as **1a** and 3,3-dialkylsubstituted α,β-unsaturated aldehydes.

L-Proline has been, since the leading paper of List, Lerner and Barbas,[10] one of the most widely employed organocatalysts, not only for simple reactions such as the aldol,[11] Mannich,[12] Michael,[13] Biginelli,[14] Diels–Alder/Knoevenagel,[15] Baylis–Hillman,[16] aza-Morita–Baylis–Hillman,[17] α-selenylation,[18] α-halogenation[19] and

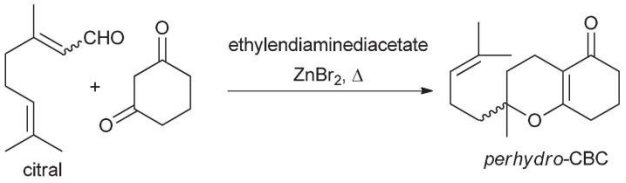
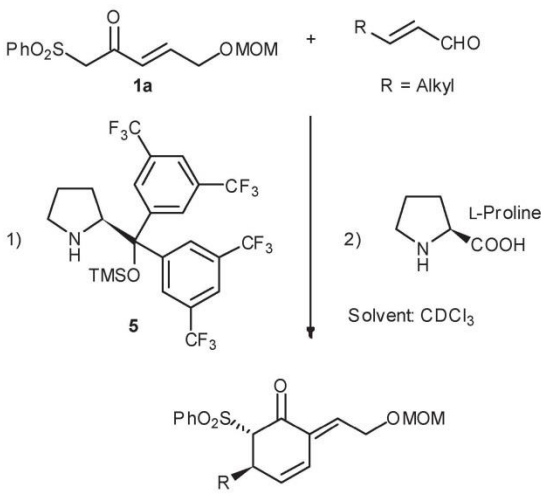


Fig. 1 Synthesis of *perhydro*-CBC by Profs. Chang and Marsella.



Scheme 1 Synthesis of 2-alkylidene cyclohexenones.

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oxidation[20] reactions, among others, but also in tandem or multicomponent reactions.[21] Proline is a very cheap, nontoxic amino acid available in both enantiomeric forms, from which many derivatives have been developed for its use in organocatalysis,[22] and ideal for green chemistry.[21a,b] This is an area of growing interest in recent years, as better procedures with less toxic solvents and no hazardous chemicals should be the aim of any chemist.[23]

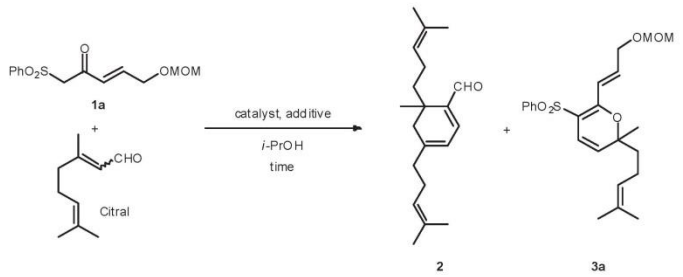
Herein we report, to the best of our knowledge, the first synthesis of highly substituted 2*H*-pyrans using an efficient, practical and environmentally friendly methodology under solvent-free conditions, using L-proline as a catalyst.

Results and discussions

The key strategy is the reaction of a β-oxosulfone with 3,3-disubstituted enals.[24] First of all we decided to screen different catalysts and additives (Table 1 and Fig. 2) in the reaction between β-oxosulfone **1a** and the *E*/*Z* mixture of citral in isopropyl alcohol, as it was the best solvent used in our previous studies for the synthesis of 2-alkylidene cyclohexenones.[8]

We first used the usual bases to see if the Knoevenagel reaction proceeded as the first step, but these led to low yields, decomposition or simply no reaction after several days (Table 1, entries 1–6). Benzoic acid or even chiral acids, *i.e.* **12** and **13**,[25] were tested, as they can be used as additives, and thioureas, *i.e.* **11**, were also tested, but the reaction either did not proceed at all or did not proceed in a reasonable time (entries 7–10). Only the citral dimer **2** was formed in very low yield after 45 days with benzoic acid, previously obtained by Watanabe *et al.* in the reaction of citral with proline[26] (entry 7). Then several organocatalysts (Fig. 2) were tested, with and without additives. When L-proline was used, the yield of 2*H*-pyran **3a** increased dramatically, especially when acid **13** was used as an additive (entries 11–15). Other organocatalysts did not give any good results with or without additives (entries 16–25).

Table 1 Screening of catalysts and additives for the reaction between β-oxosulfone **1a** and *E*/*Z*-citral in isopropyl alcohol[a,b]



Entry	Catalyst	Additive	Time[c]	Yield[d] (%) 2	3a
1	DABCO	—	21 h	S.M.	
2	DBU	—	3 d	S.M.	
3	Et_3N	—	3 d	S.M.	
4	Piperidine	—	3 d	Decomposition	
5	Pyrrolidine	—	2 h	Decomposition	
6	Pyridine	—	3 d	—	16
7	—	B.A.	45 d	<5	—
8	—	**12**	10 h	S.M.	
9	—	**13**	12 h	S.M.	
10	**11**	B.A.	8 d	S.M.	
11	L-Proline	—	6 h	11	63
12	L-Proline	LiOAc	13 h	29	44
13	L-Proline	B.A.	17 h	9	62
14	L-Proline	**12**	24 h	4	96
15	**L-Proline**	**13**	**17 h**	**1**	**99**
16[e]	**4**	B.A.	8 d	S.M.	
17[f]	**5**	B.A.	8 d	S.M.	
18[g]	**5**	**12**	60 d	—	15
19[f,h]	**5** + L-Proline	LiOAc	39 h	10	—
20[f,h]	**5** + L-Proline	B.A.	39 h	7	33
21	**6**	—	6 d	—	60
22	**7**	—	13 h	—	33
23	**8**	—	25 d	S.M.	
24	**9**	—	10 d	—	11
25[i]	**10**	B.A.	8 d	S.M.	

[a] All the reactions were carried out at r.t., in *i*PrOH at 0.18 M, with a 2 : 1 ratio of sulfone to *E*/*Z*-citral, 20 mol% catalyst and 20 mol% additive. [b] S.M. = starting materials; B.A. = benzoic acid; **12** = BinapPOH = (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate; **13** = CF_3-BinapPOH = (*R*)-3,3′-bis[3,5-bis(trifluoromethyl)phenyl]-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate. [c] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [d] Isolated yield after chromatography on silica gel. [e] Benzoic acid was added 6 days after catalyst **4**. [f] Benzoic acid was added 6 days after catalyst **5**. [g] Catalyst **5** was added 10 h after BinapPOH. [h] L-Proline was added 26 h after catalyst **5**. [i] Benzoic acid was added 6 days after catalyst **10**.

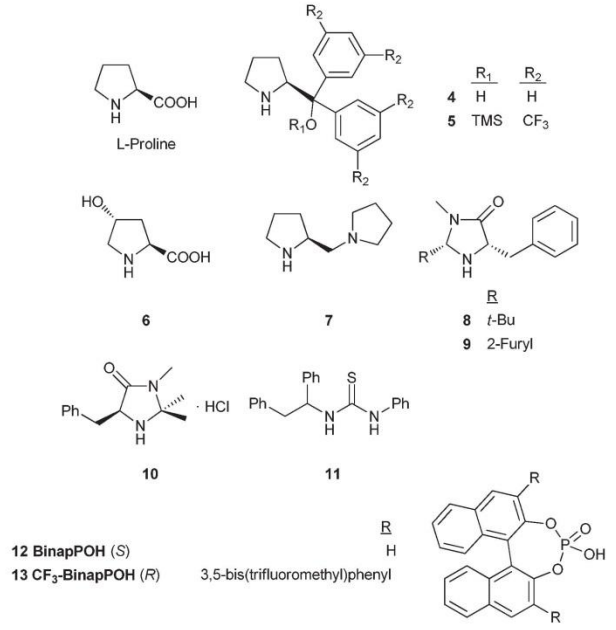


Fig. 2 Catalysts and additives for use in the synthesis of 2*H*-pyrans.

As L-proline was found to be the best organocatalyst, we then screened different solvents (Table 2). From this study, solvent free conditions with no additive turned out to be the best conditions (entry 10). Surprisingly, using additive **13** did not lead to any increase in the yield, but suppressed the production of the citral dimer in no solvent conditions (Table 2, entries 11 and 12). In all cases racemic mixtures were obtained, ascertained by HPLC and optical rotatory power, even when additives **12** or **13** were used in order to induce chirality. Although the yield was excellent when isopropyl alcohol and additive **13** were used (Table 1, entry 15) the use of no solvent and no expensive additives makes this procedure to obtain 2*H*-pyrans easier and more environmentally efficient than the previous ones. In the case of reagent solubility problems, the use of isopropyl alcohol is a green alternative too. These conditions are not exclusive to β-oxosulfones and can be applied to 1,3-diketones, β-ketoesters or β-ketoamides.

Table 2 Screening of solvents for the synthesis of 2*H*-pyrans with L-proline and additives[a]

Entry	Solvent	Time[b] (h)	Yield[c] (%)	
			2	**3a**
1	Hexane	54	12	72
2	Toluene	29	—	32
3	$CHCl_2$	29	13	34
4	$CHCl_3$	29	—	42
5	Diethyl ether	29	—	37
6	THF	29	—	20
7	MeOH	8	—	28
8	EtOH	8	—	39
9	H_2O	56	S.M.[d]	
10[e]	**NO SOLVENT**	**22**	**13**	**87**
11	NO SOLVENT	24	—	58
12[f]	NO SOLVENT	21	—	49

[a] All the reactions were carried out at r.t., at 0.18 M, with a 2 : 1 ratio of sulfone to *E*/*Z*-citral, 20 mol% L-proline and 20 mol% **12**. [b] Time in which the highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] S.M. = starting materials. [e] No additives used. [f] 20 mol % **13** added to the reaction as additive instead of **12**.

Having established the best conditions, we decided to evaluate our method with different aldehydes, using firstly the same starting material, the β-oxosulfone **1a**, as shown in Table 3. In all cases where the unsaturated aldehyde was 3,3-dialkylsubstituted, the 2*H*-pyran was obtained in a very good yield but as a racemic mixture, ascertained by HPLC and optical rotatory power, entries 1–6, or even in the case of entry 7. In the case of compounds **18** and **20**, entries 5 and 6, the corresponding diastereoisomeric mixtures were obtained due to the presence of epimers at the tetrasubstituted carbon of the pyran ring. These results can be explained by the proposed mechanism (Fig. 3): initial Knoevenagel condensation leads to intermediate **A**, which after 6π-electrocyclization produces the corresponding 2*H*-pyran.[27] Other aldehydes, with a different substitution pattern, only gave the corresponding Knoevenagel products (entries 8–10), whose stereochemistry was established by bidimensional NMR and NOE experiments. A similar result was obtained by Profs. Mischne and Riveira in polycyclization reactions of 1,3-dicarbonyl compounds and α,β,γ,δ-unsaturated aldehydes, where the unsubstituted one gives only condensation and no cyclization.[28] Of special interest are the compounds obtained in entries 5 and 6, analogues of marine natural products, such as the pyranocoumarin ferprenin.[29] As there are many natural products with a 3,3-dialkylsubstituted α,β-unsaturated aldehyde functionality,[9] this procedure opens up an environmentally acceptable method for the synthesis of 2*H*-pyrans for diversity oriented synthesis.[30]

Once the procedure for the synthesis of 2*H*-pyrans had been carried out consistently with different aldehydes, it was subjected to a study with other β-oxosulfones in order to define the scope and consistency of the reaction (Table 4).

The synthesis of these β-oxosulfones is shown in Scheme 2. After monoprotection under standard conditions of the commercially available *E*-1,4-butenediol with 3,4-dihydro-2*H*-pyran (DHP) gave **26**,[31] which was oxidised with pyridinium dichromate (PDC) and condensed with the lithium derivative of methylphenylsulfone, leading to the corresponding alcohol **28**, whose oxidation gave the corresponding mixture of β-oxosulfones **1b** and **1c** in a 99 : 1 ratio. Use of other oxidising conditions, including the use of catalytic tetrapropylammonium perruthenate (TPAP), led to a decrease in the yield of the oxidation steps. These sulfones were separated by flash chromatography on silica gel and deprotection of the major compound gave the β-oxosulfone **1d**. As shown in Table 4, the three sulfones **1b**, **1c**, and **1d** behave exactly as before, yielding the corresponding 2*H*-pyrans when reacted with *E*/*Z*-citral, making this procedure ideal for the synthesis of highly functionalised 2*H*-pyrans in environmentally safe conditions. The presence of the sulfone group in these compounds adds an extra functionality and so more versatility for further research.

Conclusions

We have established a new and simple procedure for the synthesis of 2*H*-pyrans. This method shows once again the versatility of L-proline as a catalyst, since it is the only one that gives the reaction. The reaction proceeds under solvent free conditions, becoming a green way to obtain compounds of high

Table 3 Screening of α,β-unsaturated aldehydes[a]

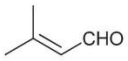
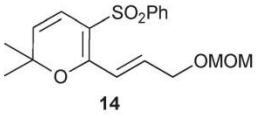
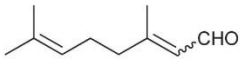
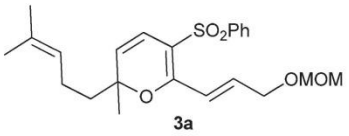
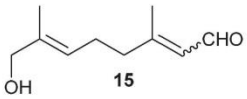
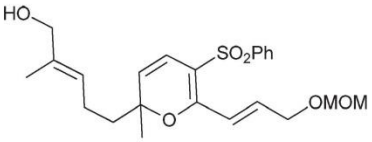
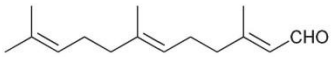
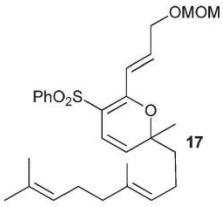
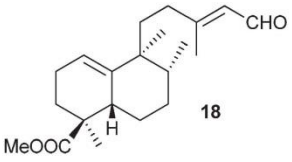
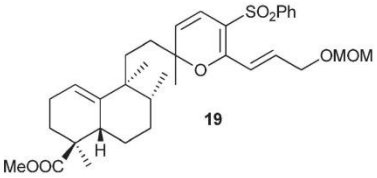
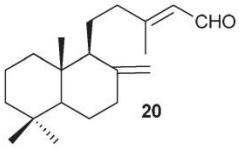
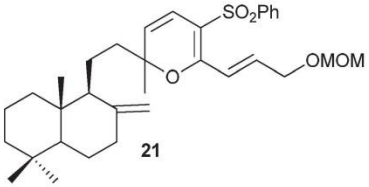
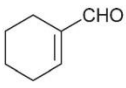
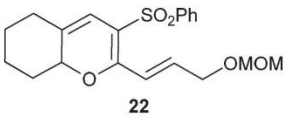
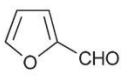
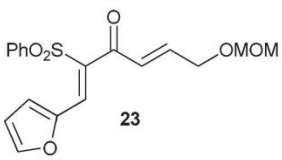
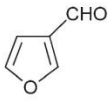
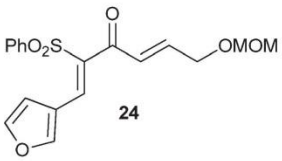
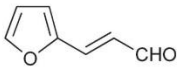
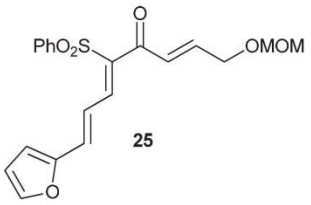
Entry	α,β-Unsaturated aldehyde	Time[b]	Product	Yield[c] (%)
1		4.5 h	 **14**	82
2		6 h	 **3a**	63
3	 **15**	15 h	 **16**	58
4[d]		15 h	 **17**	58
5	 **18**	7 h	 **19**	38
6	 **20**	3 d	 **21**	63
7		5 d	 **22**	43
8		21 h	 **23**	87
9		1 d	 **24**	99

Table 3 (*Continued*)

10		15 h	 **25**	56

[a] All the reactions were carried out at r.t., in *i*PrOH at 0.18 M, with a 2 : 1 ratio of sulfone **1a** to aldehyde and 20 mol% L-proline or under solvent free conditions. In all cases the yields were similar. [b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel. [d] 20 mol% of BinapPOH, **12**, added to the reaction.

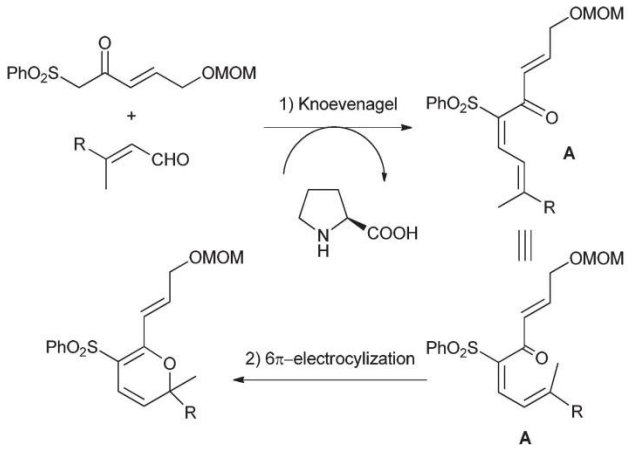


Fig. 3 Proposed mechanism for the formation of 2*H*-pyrans.

impact for the synthesis of natural compound analogues with biological activity in diversity oriented synthesis.

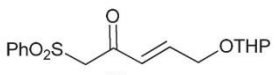
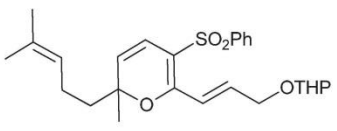
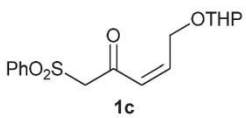
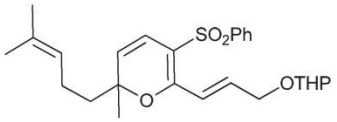
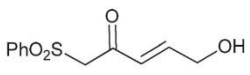
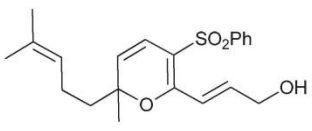
Experimental section

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification, except for **1a**,[8] 10-hydroxycitral **15**,[32] farnesal,[33] **18**[9c] and **20**,[9d,f] which were synthesised according to the literature procedures. For more details see the ESI.†

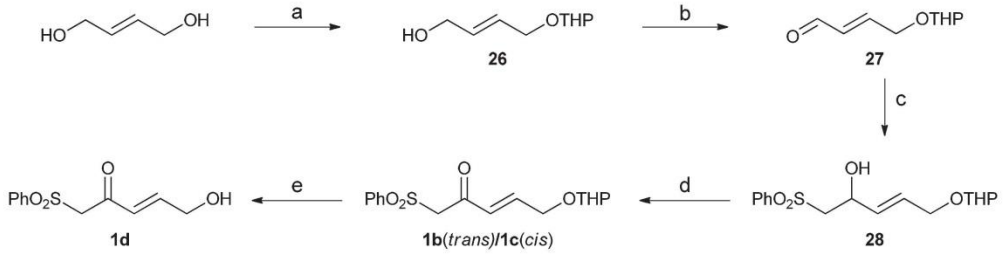
1. Synthesis of the Nazarov reagents (1b–1d)

1.1 Monoprotection of (*E*)-1,4-butanediol with DHP: (*E*)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-en-1-ol (26). (*E*)-1,4-Butanediol (4 ml, 48.66 mmol) was dissolved in 194 ml DCM under Ar at r.t. 3,4-Dihydro-2*H*-pyran (97%, 4.22 g, 48.66 mmol) and *p*-toluenesulfonic acid monohydrate (93 mg, 0.486 mmol) were added and left to stir for 3 h. The reaction was quenched with

Table 4 2*H*-pyrans using different β-oxosulfones and *E*/*Z*-citral[a]

Entry	β-oxosulfone	Product	Time[b] (h)	Yield[c] (%)	
				2	**3(b,c)**
1	 **1b**	 **3b**	7	3	97
2	 **1c**	 **3b**	5	12	88
3	 **1d**	 **3c**	15	36	64

[a] All the reactions were carried out at r.t., in *i*PrOH at 0.18 M, or under free solvent conditions with a 2 : 1 ratio of sulfone to *E*/*Z*-citral, and 20 mol% L-proline. In all cases the yield was similar, except for compound **1c** which, being a solid, was reacted in *i*PrOH only. [b] Time in which the highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC). [c] Isolated yield after chromatography on silica gel.



Scheme 2 Reagents and conditions for the synthesis of β-oxosulfones **1b**, **1c** and **1d**: (a) DHP, *p*TsOH (1%), DCM, r.t., 96%; (b) PDC (2 equiv.), molecular sieves, DCM, r.t., 91%; (c) methylphenylsulfone (0.9 equiv.), *n*-BuLi (0.9 equiv.), THF, −78 °C, 61%; (d) PDC (2 equiv.), molecular sieves, r.t., 58%, (ratio **1b** : **1c** = 99 : 1); and (e) *p*TsOH (10%), THF–H_2O (1 : 1), r.t., 88%.

a $NaHCO_3$ saturated solution, and extracted with DCM. The combined organics were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **26** (8.01 g, 96%). υ_{max} (liquid film) 3417, 2943, 2870, 1454, 1352, 1261, 1134; δ_H (200 MHz; $CDCl_3$) 5.88–5.33 (2H, m, H2 and H3), 4.67–4.60 (1H, m, H6), 4.32–3.99 (4H, m, H1 and H4), 3.92–3.71 (1H, m, $H8_a$), 3.57–3.40 (1H, m, $H8_b$), 1.91–1.36 (6H, m, H9, H10, and H11); δ_C (50 MHz; $CDCl_3$) 132.6, 127.3, 97.6, 62.6, 62.0, 57.9, 30.5, 25.4, 19.3; EIHRMS: Calcd for $C_9H_{16}O_3$ (M + Na): 195.0592; found: 195.0991 (M + Na).

1.2 Oxidation of 26 with PDC: (*E*)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-enal (27). A mixture of monoprotected diol **26** (8.01 g, 46.5 mmol) and molecular sieves was dissolved in 232 ml DCM under Ar and stirred at room temperature for 5 min. PDC (34.9 g, 93.02 mmol) was added and left to stir for 5 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford **27** (7.19 g, 91%). υ_{max} (liquid film) 2945, 2870, 2853, 2727, 1693, 1454, 1352, 1261, 1201, 1120; δ_H (200 MHz; $CDCl_3$) 9.54 (1H, d, J = 8.0 Hz, CHO), 6.85 (1H, dt, J = 15.7, 4.0 Hz, H3), 6.34 (1H, ddt, J = 15.7, 8.0, 2.0, Hz, H2), 4.68–4.61 (1H, m, H6), 4.49 (1H, ddd, J = 17.3, 4.0, 2.0 Hz, $H4_a$), 4.21 (1H, ddd, J = 17.3, 4.0, 2.0 Hz, $H4_b$), 3.86–3.72 (1H, m, $H8_a$), 3.56–3.42 (1H, m, $H8_b$), 1.86–1.43 (6H, m, H9, H10, and H11); δ_C (50 MHz; $CDCl_3$) 193.5, 153.7, 131.5, 98.4, 65.6, 62.2, 30.4, 25.4, 19.2; EIHRMS: Calcd for $C_9H_{14}O_3$ (M + Na): 193.0835; found: 193.0835 (M + Na).

1.3 Addition of methylphenylsulfone to 27: (*E*)-1-(phenylsulfonyl)-5-((tetrahydro2*H*-pyran-2-yl)oxy)pent-3-em-2-ol (28). Methylphenylsulfone (3.64 g, 23.29 mmol) was dissolved in 100 ml THF under Ar at −78 °C. *n*-BuLi (1.6 M in hexanes, 14.9 ml, 23.29 mmol) was added and the mixture was stirred for 15 min. Separately, **27** (4.40 g, 25.88 mmol) was dissolved in 30 ml THF under Ar at r.t. This solution was added *via cannula* to the former, and the mixture was stirred at −78 °C under Ar for 2 h. Then the reaction was quenched with a NH_4Cl saturated solution and left to warm at room temperature. Then it was extracted with EtOAc and the combined organics were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to leave a crude yellow oil. Flash chromatography (hexane–EtOAc, 6 : 4) afforded **28** (4.63 g, 61%). υ_{max} (liquid film) 3444, 2953, 2872, 2250, 1732, 1446, 1288, 1138 δ_H (200 MHz; $CDCl_3$) 7.97–7.83 (2H, m, ArH_{ortho}), 7.71–7.46 (3H, m, ArH_{meta}, ArH_{para}), 5.83 (1H, dt, J = 15.5, 5.2 Hz, H4), 5.62 (1H, dd, J = 15.5, 5.2 Hz, H3), 4.76–4.59 (1H, m, H7), 4.59–4.49 (1H, m, H2), 4.15 (1H, dd, J = 13.3, 4.6 Hz, $H5_a$), 3.95–3.69 (2H, m, $H1_a$ and $H5_a$), 3.55–3.41 (2H, m, H9), 3.30–3.19 (2H, m, $H1_b$ and 5_b), 1.84–1.37 (6H, m, H10, H11, and H12); δ_C (50 MHz; $CDCl_3$) 139.7, 134.1, 131.4, 129.5 (2C), 128.8, 128.1 (2C), 98.1, 66.6, 66.5, 62.2, 62.1, 30.6, 25.5, 19.5; EIHRMS: Calcd for $C_{16}H_{22}O_5S$ (M + Na): 349.1080; found: 349.1080 (M + Na).

1.4 Oxidation of 28 with PDC: (*E*)-1-(phenylsulfonyl)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-en-2-one(1b and 1c). A mixture of **28** (537 g, 1.65 mmol) and molecular sieves was dissolved in 8 ml DCM under Ar and stirred at r.t. for 5 min. PDC (1.24 g, 3.30 mmol) was added and left to stir for 4 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil. Flash chromatography (hexane–EtOAc, 6 : 4) afforded **1b** (304 mg, 57%) and **1c** (5 mg, 1%). **1b**: υ_{max} (liquid film) 2943, 2870, 2852, 1693, 1666, 1633, 1446, 1384, 1325, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, J = 7.0 Hz, ArH_{ortho}), 7.74–7.50 (3H, m, ArH_{meta} and ArH_{para}), 6.98 (1H, dt, J = 15.8, 3.9 Hz, H4), 6.54 (1H, dt, J = 15.8, 1.9 Hz, H3), 4.65 (1H, t, J = 3.1 Hz, H7), 4.46 (1H, ddd, J = 17.6, 3.9, 1.9 Hz, $H5_a$), 4.32 (2H, s, H1), 4.18 (1H, ddd, J = 17.6, 3.9, 2.0 Hz, $H5_b$), 3.89–3.74 (1H, m, $H9_a$), 3.59–3.42 (1H, m, $H9_b$), 1.90–1.40 (6H, m, H10, H11, and H12); δ_C (50 MHz; $CDCl_3$) 187.3, 147.7, 138.9, 134.4, 129.4 (2C), 128.6 (2C), 128.0, 98.4, 65.6, 65.3, 62.2, 30.5, 25.5, 19.3; EIHRMS: Calcd for $C_{16}H_{20}O_5S$ (M + Na): 347.0924; found: 347.0924 (M + Na). **1c**: υ_{max} (liquid film) 2943, 2872, 2852, 1693, 1666, 1614, 1448, 1377, 1323, 1155; δ_H (200 MHz; $CDCl_3$) 8.01–7.80 (2H, m, ArH_{ortho}), 7.79–7.50 (3H, m, ArH_{meta} and ArH_{para}), 6.65–6.37 (2H, m, H3 and H4), 4.75–4.39 (3H, m, H5 and H7), 4.21 (2H, s, H1), 3.92–3.71 (1H, m, $H9_a$), 3.58–3.38 (1H, m, $H9_b$), 1.95–1.36 (6H, m, H10, H11, and H12); δ_C (50 MHz; $CDCl_3$) 187.4, 152.4, 138.8, 134.5, 129.6 (2C), 128.5 (2C), 124.7, 99.2, 68.1, 67.2, 62.8, 30.8, 25.6, 19.8; EIHRMS: Calcd for $C_{16}H_{20}O_5S$ (M + Na): 347.0924; found: 347.0924 (M + Na).

1.5 Deprotection of 1b with *p*TsOH: (*E*)-5-hydroxy-1-(phenylsulfonyl)pent-3-en-2-one (1d). 1b (203 mg, 0.62 mmol) and *p*-toluenesulfonic acid monohydrate (12 mg, 0.06 mmol) were dissolved in 6 ml of a 1 : 1 mixture of THF–H_2O, and the whole mixture was stirred for 5 days. The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **1d** (130.2 mg, 88%). υ_{max} (liquid film) 3504, 2931, 1691, 1664, 1627, 1448, 1309, 1151; δ_H (200 MHz; $CDCl_3$) 7.93–7.82 (2H, m, ArH_{ortho}), 7.72–7.50

(3H, m, ArH_{meta} and ArH_{para}), 7.04 (1H, dt, J = 15.8, 3.6 Hz, H4), 6.58 (1H, dt, J = 15.8, 2.0 Hz, H3), 4.38 (2H, m, H5), 4.33 (2H, s, H1); δ_C (50 MHz; $CDCl_3$) 187.2, 150.4, 138.8, 134.6, 129.6 (2C), 128.6 (2C), 127.1, 65.8, 62.0; EIHRMS: Calcd for $C_{11}H_{12}O_4S$ (M + Na): 263.0349; found: 263.0349 (M + Na).

2. General procedure for the synthesis of 2*H*-pyrans (3a–3c)

β-Oxosulfone **(1a–1d)** (17.6 mmol) and *E*/*Z*-citral (8.7 mmol) were dissolved in 1 ml isopropyl alcohol. Next, L-proline (20 mol%), and an additive (20 mol%) if needed, were added and left stirring for the appropriate time. All products were purified by flash chromatography on silica gel using different mixtures of hexane–EtOAc.

2.1 (*E*)-6-(3-(Methoxymethoxy)prop-1-en-1-yl)-2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2*H*-pyran, 3a. υ_{max} (liquid film) 2926, 1674, 1539, 1446, 1377, 1321, 1151; δ_H (400 MHz; $CDCl_3$) 7.84 (2H, d, J = 8.3 Hz, ArH_{ortho}), 7.59–7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.42 (1H, dt, J = 15.4, 1.8 Hz, H1′), 6.56 (1H, dt, J = 15.4, 5.2 Hz, H2′), 6.36 (1H, d, J = 10.0 Hz, H4), 5.34 (1H, d, J = 10.0 Hz, H3), 5.05–4.93 (1H, m, H3′′), 4.67 (2H, s, O–CH_2–O), 4.25 (2H, dd, J = 5.2, 1.8 Hz, H3′), 3.39 (3H, s, O–CH_3), 2.06–1.86 (2H, m, H2′′), 1.63 (6H, s, $(CH_3)_2$–C4′′), 1,40 (2H, m, H1′′), 1.27 (3H, s, CH_3–C2); δ_C (101 MHz; $CDCl_3$) 156.0, 143.0, 136.1, 132.6, 132.0, 129.0 (2C), 126.4 (2C), 124.2, 123.4, 121.5, 119.1, 114.3, 96.0, 80.6, 66.9, 55.4, 40.8, 25.7, 22.2, 17.7 (2C); EIHRMS: Calcd for $C_{23}H_{30}O_5S$ (M + Na): 441.1712; found: 441.1706 (M + Na).

2.2 (*E*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-6-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-en-1-yl)-2*H*-pyran (3b). υ_{max} (liquid film) 2926, 1647, 1537, 1446, 1377, 1321, 1153; δ_H (200 MHz; $CDCl_3$) 7.94–7.77 (2H, m, ArH_{ortho}), 7.60–7.45 (3H, m, ArH_{meta}, ArH_{para}), 7.45–7.32 (1H, m, H1′), 6.58 (1H, dt, J = 15.3, 5.0 Hz, H2′), 6.38 (1H, d, J = 10.0 Hz, H4), 5.33 (1H, d, J = 10.0 Hz, H3), 5.05–4.92 (1H, m, H3′′), 4.67 (1H, t, J = 3.2 Hz, O–CH–O), 4.50–4.33 (1H, m, $H3'_a$), 4.27–4.07 (1H, m, $H3'_b$), 3.94–3.76 (1H, m, $H7'_a$), 3.60–3.45 (1H, m, $H7'_b$), 2.06–1.86 (2H, m, H2′′), 1.64 (6H, s, $(CH_3)_2$–C4′′), 1.60–1.53 (4H, m, H10′ and H1′′), 1.53–1.44 (4H, m, H8′ and H9′), 1.27 (3H, s, CH_3–C2); δ_C (50 MHz; $CDCl_3$) 156.5, 143.4, 136.8, 132.8, 132.3, 129.2 (2C), 126.7 (2C), 124.3, 123.7, 121.3, 119.5, 114.3, 98.4, 80.8, 66.8, 62.3, 40.8, 30.7, 25.9, 25.8, 25.7, 22.5, 19.5, 17.8; EIHRMS: Calcd for $C_{26}H_{34}O_5S$ (M + Na): 481.2025; found: 481.2019 (M + Na).

2.3 (*E*)-3-(2-Methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2*H*-pyran-6-yl)prop-2-en-1-ol (3c). υ_{max}(liquid film) 3493, 2968, 2916, 2850, 1645, 1621, 1537, 1446, 1317, 1155; δ_H (200 MHz; $CDCl_3$) 7.91–7.78 (2H, m, ArH_{ortho}), 7.60–7.47 (3H, m, ArH_{meta}, ArH_{para}), 7.41 (1H, dt, J = 15.3, 1.8 Hz, H1′), 6.64 (1H, dt, J = 15.3, 4.9 Hz, H2′), 6.36 (1H, d, J = 10.0 Hz, H4), 5.34 (1H, d, J = 10.0 Hz, H3), 5.07–4.94 (1H, m, H3′′), 4.43–4.30 (2H, m, H3′), 2.02–1.88 (2H, m, H2′′), 1.76–1.51 (8H, m, H1′′ and $(CH_3)_2$–C4′′), 1.27 (3H, s, CH_3–C2); δ_C (50 MHz; $CDCl_3$) 156.3, 143.2, 139.2, 132.9, 132.3, 129.3 (2C), 126.7 (2C), 124.4, 123.6, 120.6, 119.4, 114.5, 80.9, 63.2, 40.8, 25.9, 25.8, 22.5, 17.8; EIHRMS: Calcd for $C_{21}H_{26}O_4S$ (M + Na): 397.1444; found: 397.1444 (M + Na).

3. General procedure for the synthesis of 2*H*-pyrans and Knoevenagel adducts

β-Oxosulfone **1a** (50 mg, 17.6 mmol) and the corresponding aldehyde (8.7 mmol) were dissolved in 1 ml isopropyl alcohol. Next, L-proline (20 mol%), and an additive (20 mol%) if needed were added and left stirring for the appropriate time. All products were purified by flash chromatography on silica gel using different mixtures of hexane–EtOAc.

3.1 (*E*)-6-(3-(Methoxymethoxy)prop-1-en-1-yl)-2,2-dimethyl-5-(phenylsulfonyl)-2*H*-pyran (14). υ_{max} (liquid film) 2935, 1647, 1537, 1446, 1379, 1319, 1153; δ_H (200 MHz; $CDCl_3$) 7.85 (2H, dd, J = 7.9, 1.7 Hz, ArH_{ortho}), 7.59–7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.39 (1H, dt, J = 15.4, 1.7 Hz, H1′), 6.57 (1H, dt, J = 15.4, 5.2 Hz, H2′), 6.33 (1H, d, J = 9.9 Hz, H4), 5.38 (1H, d, J = 9.9 Hz, H3), 4.68 (2H, s, O–CH_2–O), 4.25 (2H, dd, J = 5.2, 1.7 Hz, H3′), 3.39 (3H, s, O–CH_3), 1.31 (6H, s, $(CH_3)_2$–C2); δ_C (50 MHz; $CDCl_3$) 156.2, 143.3, 137.1, 132.9, 129.3 (2C), 126.7 (2C), 125.5, 121.9, 119.1, 114.9, 96.3, 78.3, 67.2, 55.6, 27.4 (2C); EIHRMS: Calcd for $C_{18}H_{22}O_5S$ (M + Na): 373.1086; found: 373.1080 (M + Na).

3.2 (*E*)-5-(6-((*E*)-3-(Methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2*H*-pyran-2-yl)-2-methylpent-2-en-1-ol (16). υ_{max} (liquid film) 3469, 2934, 2889, 1649, 1537, 1446, 1307, 1213, 1151; δ_H (200 MHz; $CDCl_3$) 7.84 (2H, d, J = 7.9 Hz, ArH_{ortho}), 7.62–7.35 (4H, m, ArH_{meta}, ArH_{para} and H1′), 6.56 (1H, dt, J = 15.3, 5.4 Hz, H2′), 6.37 (1H, d, J = 10.1 Hz, H4), 5.39–5.22 (2H, m, H3 and H3′′), 4.67 (2H, s, O–CH_2–O), 4.25 (2H, d, J = 4.7 Hz, H3′), 3.94 (2H, s, CH_2–OH), 3.39 (3H, s, O–CH_3), 2.12–1.95 (2H, m, H2′′), 1.80–1.58 (2H, m, H1′′), 1.55 (3H, s, CH_3–C4′′), 1.25 (3H, s, CH_3C2); δ_C (50 MHz; $CDCl_3$) 156.2, 143.2, 136.4, 135.5, 132.9, 129.3 (2C), 126.7 (2C), 125.0, 124.3, 121.8, 119.6, 114.5, 96.3, 80.9, 68.8, 67.2, 55.6, 40.5, 26.1, 22.2, 13.8; EIHRMS: Calcd for $C_{23}H_{30}O_6S$ (M + Na): 457.1655; found: 457.1655 (M + Na).

3.3 2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-6-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2*H*-pyran (17). υ_{max} (liquid film) 2926, 1649, 1539, 1446, 1379, 1321, 1151; δ_H (200 MHz; $CDCl_3$) 7.85 (2H, dd, J = 7.9, 1.7 Hz, ArH_{ortho}), 7.59–7.44 (3H, m, ArH_{meta}, ArH_{para}), 7.40 (1H, dt, J = 15.3, 1.7 Hz, H1′), 6.57 (1H, dt, J = 15.3, 5.2 Hz, H2′), 6.36 (1H, d, J = 10.0 Hz, H4), 5.35 (1H, d, J = 10.0 Hz, H3), 5.13–4.91 (2H, m, H3′′ and H7′′), 4.68 (2H, s, O–CH_2–O), 4.25 (2H, dd, J = 5.2, 1.7 Hz, H3′), 3.40 (3H, s, O–CH_3), 2.11–1.85 (8H, m, H1′′, H2′′, H5′′ and H6′′), 1.67 (3H, s, CH_3–C4′′), 1.59 (3H, s, CH_{3a}–C8′′), 1.50 (3H, s, CH_{3b}–C8′′), 1.28 (3H, s, CH_3–C2); δ_C (50 MHz; $CDCl_3$) 156.3, 143.3, 136.4, 136.0, 132.8, 131.6, 129.5 (2C), 126.7 (2C), 124.5, 124.4, 123.5, 121.9, 119.4, 114.6, 96.3, 80.9, 67.2, 55.6, 40.8, 39.8,26.8, 26.0 (2C), 22.4, 17.9, 16.1; EIHRMS: Calcd for $C_{28}H_{38}O_5S$ (M + Na): 509.2338; found: 509.2332 (M + Na).

3.4 (1*S*,5*S*,6*R*,8a*S*)-Methyl 5-(3-(6-((*E*)-3-(methoxymethoxy)-prop-1-en-1-yl)-2-methyl-5-phenylsulfonyl)-2*H*-pyran-2-yl)propyl)-1,5,6-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (19). Caution: the name does not correspond to the numeration used.

$[\alpha]^{D}$ = +35.4 (*c* 1.07, $CHCl_3$); υ_{max} (liquid film) 2932, 2874, 1726, 1539, 1446, 1321, 1157; δ_H (400 MHz; $CDCl_3$) 7.86 (2H, d, *J* = 7.3 Hz, ArH_{ortho}), 7.59–7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.41 (1H, m, H1′), 6.59 (1H, m, H2′), 6.37 (1H, dd, *J* = 9.8, 3.0 Hz, H4), 5.33 (1H, d, *J* = 9.8 Hz, H3), 5.29–5.17 (1H, m, H9′′), 4.68 (2H, s, O–CH_2–O), 4.26 (2H, d, *J* = 5.2, Hz, H3′), 3.61 (3H, s, COO–CH_3), 3.40 (3H, s, O–CH_3), 2.65–2.50 (1H, m, H5′′), 1.97–0.65 (25H, m, H1′′, H2′′, H6′′, H7′′, H8′′, H10′′, H11′′, H13′′, H14′′, H16′′, H1′′′); δ_C (101 MHz; $CDCl_3$) 178.3, 156.3, 143.1, 141.1, 135.9, 132.5, 129.0 (2C), 126.4 (2C), 124.8, 121.5, 119.8, 119.1, 114.3, 96.0, 80.9, 67.1, 55.3, 51.6, 44.8, 42.7, 38.3(2C), 34.6, 31.4, 30.6, 28.6, 26.2, 22.9, 22.8, 22.3, 19.9, 15.4; EIHRMS: Calcd for $C_{34}H_{46}O_7S$ (M + Na): 621.2856; found: 621.2856 (M + Na).

3.5 6-((*E*)-3-(Methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)ethyl)-2*H*-pyran (21). Caution: the name does not correspond to the numeration used.

$[\alpha]^{D}$ = +4.58 (*c* 0.3, $CHCl_3$); υ_{max} (liquid film) 2918, 2848, 1539, 1446, 1321, 1153; δ_H (200 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 7.6, 1.6 Hz, ArH_{ortho}), 7.60–7.47 (3H, m, ArH_{meta}, ArH_{para}), 7.40 (1H, m, H1′), 6.56 (1H, dt, *J* = 10.1, 5.4 Hz, H2′), 6.36 (1H, dd, *J* = 10.1, 1.3 Hz, H4), 5.34 (1H, d, *J* = 10.1, H3), 4.74 (1H, s, $H29''_a$), 4.68 (2H, s, O–CH_2–O), 4.38 (1H, s, $H29''_b$), 4.25 (2H, d, *J* = 5.4, Hz, H3′), 3.40 (3H, s, O–CH_3), 2.44–0.87 (28H, m, H1′′, H2′′, H3′′, H5′′, H6′′, H7′′, H9′′, H10′′, H11′′, H13′′, H15′′, H16′′, H1′′′); δ_C (50 MHz; $CDCl_3$) 156.3, 148.5, 143.4, 136.4, 132.8, 129.3 (2C), 126.7 (2C), 124.6, 121.8, 119.5, 114.5, 106.6, 96.2, 81.3, 67.2, 57.3, 55.7, 55.6, 42.4, 40.1, 40.0, 39.1, 38.5, 33.8, 33.5, 26.2, 24.6, 21.9, 19.6, 19.2, 14.6; EIHRMS: Calcd for $C_{33}H_{46}O_5S$ (M + Na): 577.2958; found: 577.2958 (M + Na).

3.6 (*E*)-2-(3-(Methoxymethoxy)prop-1-en-1-yl)-3-(phenylsulfonyl)-6,7,8,8a-tetrahydro-5*H*-chromene (22). υ_{max} (liquid film) 2933, 1722, 1446, 1321, 1151; δ_H (200 MHz; $CDCl_3$) 7.86 (2H, dd, *J* = 7.8, 1.7 Hz, ArH_{ortho}), 7.64–7.44 (3H, m, ArH_{meta} and ArH_{para}), 7.36 (1H, dd, *J* = 14.9, 1.7 Hz, H1′), 6.48 (1H, dt, *J* = 14.9, 5.4 Hz, H2′), 5.98 (1H, s, H4), 4.91–4.73 (1H, m, H2), 4.66 (2H, s, O–CH_2–O), 4.23 (2H, d, *J* = 5.4 Hz, H3′), 3.39 (3H, s, O–CH_3), 2.45–1.18 (8H, m, H7, H8, H9, and H10); δ_C (50 MHz; $CDCl_3$) 155.0, 145.3, 134.7, 133.5, 132.8, 129.3 (2C), 126.8 (2C), 121.5, 116.9, 112.2, 96.2, 77.4, 67.2, 55.6, 34.5, 32.5, 26.3, 24.1; EIHRMS: Calcd for $C_{20}H_{24}O_5S$ (M + Na): 399.1237; found: 399.1237 (M + Na).

3.7 (1*Z*,4*E*)-1-(Furan-2-yl)-6-(methoxymethoxy)-2-(phenylsulfonyl)hexa-1,4-dien-3-one (23). υ_{max} (liquid film) 2947, 2889, 1659, 1622, 1446, 1319, 1197, 1149; δ_H (400 MHz; $CDCl_3$) 7.86 (2H, dd, *J* = 8.4, 1.3 Hz, ArH_{ortho}), 7.64–7.57 (2H, m, H1 and ArH_{para}), 7.57–7.49 (2H, m, ArH_{meta}), 7.49–7,43 (1H, m, H5′), 6.84 (1H, dt, *J* = 16.0, 4.1 Hz, H5), 6.78 (1H, d, *J* = 3.5 Hz, H3′), 6.54 (1H, dt, *J* = 16.0, 2.0 Hz, H4), 6.46 (1H, dd, *J* = 3.5, 1.8 Hz, H4′), 4.60 (2H, s, O–CH_2–O), 4.21 (2H, dd, *J* = 4.1, 2.0 Hz, H6), 3.33 (3H, s, O–CH_3); δ_C (101 MHz; $CDCl_3$) 190.1, 147.9, 147.5, 146.9, 139.8, 135.7, 133.6), 129.8, 129.1 (2C), 128.3 (2C), 126.9, 119.3, 112.8, 96.0, 65.7, 55.4; EIHRMS: Calcd for $C_{18}H_{18}O_6S$ (M + Na): 385.0716; found: 385.0716 (M + Na).

3.8 (1*Z*,4*E*)-1-(Furan-3-yl)-6-(methoxymethoxy)-2-(phenylsulfonyl)hexa-1,4-dien-3-one (24). υ_{max} (liquid film) 2949, 2889, 1654, 1622, 1446, 1309, 1205, 1149; δ_H (400 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 8.5, 1.3 Hz, ArH_{ortho}), 7.74 (1H, dd, *J* = 1.1, 0.5 Hz, H1), 7.72–7.71 (1H, m, H2′), 7.63–7.58 (1H, m, ArH_{para}), 7.55–7.49 (2H, m, ArH_{meta}), 7.40–7.35 (1H, m, H5′), 6.92 (1H, dt, *J* = 15.9, 4.0 Hz, H5), 6.55 (1H, dt, *J* = 15.9, 2.1 Hz, H4), 6.29 (1H, dtd, *J* = 1.4, 0.9, 0.4 Hz, H4′), 4.60 (2H, s, O–CH_2–O), 4.22 (2H, dd, *J* = 4.0, 2.1 Hz, H6), 3.33 (3H, s, O–CH_3); δ_C (101 MHz; $CDCl_3$) 191.2, 149.5, 147.3, 144.7, 139.7, 138.1, 136.6, 131.6, 129.1 (2C), 129.0, 128.3 (2C), 119.0, 109.3, 96.0, 65.7, 55.4; EIHRMS: Calcd for $C_{18}H_{18}O_6S$ (M + Na): 385.0716; found: 385.0716 (M + Na).

3.9 (2*E*,5*Z*,7*E*)-8-(Furan-2-yl)-1-(methoxymethoxy)-5-(phenylsulfonyl)octa-2,5,7-trien-4-one (25). υ_{max} (liquid film) 2933, 2889, 1647, 1616, 1583, 1463, 1446, 1307, 1147; δ_H (400 MHz; $CDCl_3$) 7.88 (2H, d, *J* = 7.9 Hz, ArH_{ortho}), 7.72–7.43 (5H, m, H6, ArH_{meta}, ArH_{para} and H5′), 7.00–6.80 (3H, m, H2, H7 and H8), 6.71 (1H, d, *J* = 15.7 Hz, H3), 6.60 (1H, m, H3′), 6.48 (1H, m, H4′), 4.65 (2H, s, O–CH_2–O), 4.33–4.22 (2H, m, H1), 3.37 (3H, s, O–CH_3); δ_C (101 MHz; $CDCl_3$) 188.5, 151.5, 148.0, 145.1, 143.5, 140.5, 138.6, 133.4, 132.2, 129.0 (3C), 128.1 (2C), 119.9, 114.9, 112.6, 96.1, 65.9, 55.4; EIHRMS: Calcd for $C_{20}H_{20}O_6S$ (M + Na): 411.0873; found: 411.0873 (M + Na).

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Highly functionalised cyclohexa-1,3-dienes by sulfonyl Nazarov reagents

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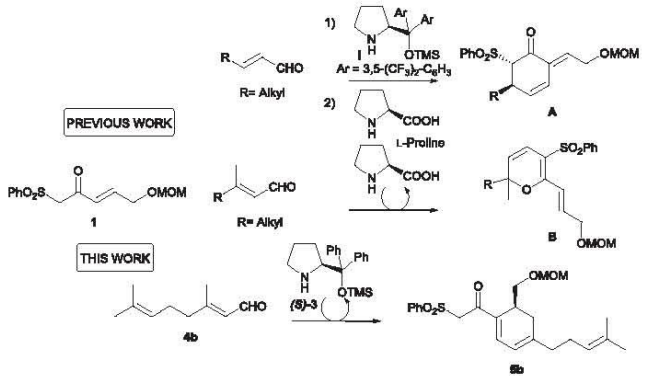
ABSTRACT

The Hayashi–Jørgensen organocatalyst has made possible a sulfonyl Nazarov analogue reagent to give a Diels–Alder reaction at the double bond, without involving the activated methylene affording chiral highly functionalised cyclohexa-1,3-dienes.

1. Introduction

The chemistry of Nazarov reagents has increased in the last years due to their versatility and possibility to be excellent starting materials for the synthesis of biologically active compounds.[1] The sulfone group, both as a powerful electron withdrawing group and as an easily removable substituent,[2] is ideal for the substitution of the carboethoxymethyl group in the Nazarov reagent. Sulfone and sulfoxide analogues of Nazarov reagents have been used as dienophiles in asymmetric Diels–Alder reactions with dienes and employing a chiral metallic Lewis acid as catalyst or in anionic polycyclisations.[3] In our group, the reactivity of Nazarov reagent **1** has been developed in a divergent manner for diversity oriented syntheses (Scheme 1).[4,5] The interest of a compound like **1** is, besides the fact that it can act as a Nazarov reagent, the extra functionality provided by the hydroxyl group, which can be further employed for the synthesis of diversity oriented compounds or as a linker in solid support chemistry.[6] It was observed that employing organocatalyst **I** and L-Proline in a tandem reaction different cyclohexenones **A** were obtained diastereoselectively.[4] On the other hand, using L-Proline or derivatives, MacMillan catalysts, thioureas or even chiral phosphoric acids in the reaction of **1** with



Scheme 1. Reactivity of Nazarov reagent **1** with unsaturated aldehydes and prenal derivatives.

β,β-disubstituted aldehydes, racemic pyrans **B** were obtained instead of the cyclohexenone ring (Scheme 1).[5]

Monosubstituted unsaturated aldehydes have been widely used in organocatalysis for the synthesis of very interesting compounds.[7] However, β-methyl-β-disubstituted unsaturated aldehydes have been much less used in organocatalysis. Prof. Serebryakov et al. have developed the asymmetric synthesis of cyclohexa-1,3-dienes from prenal and unsaturated esters or derivatives,[8] Watanabe et al., using Proline as organocatalyst, made citral to dimerise through a Diels–Alder reaction[9] and Christmann

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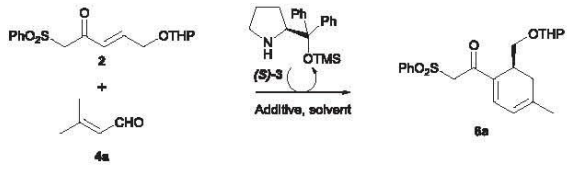
et al. reported an intramolecular Rauhut–Curier-type reaction via dienamine activation.[10] We realised that neither us, nor Prof. Serebryakov had employed the Hayashi–Jørgensen organocatalyst.[11] Thus, we decided to test the reactivity of sulfone **1** with citral **4b** using organocatalyst (*S*)-**3**. To our delight the reaction worked and surprisingly led to a new structure, namely cyclohexa-1,3-dienes, instead of cyclohexenones or pyran rings, constituting the first time that a Nazarov reagent acts as dienophile using organocatalysis (Scheme 1). This fact gives an idea that organocatalysis is still an undeveloped area and that a reaction can be diversely directed just by tuning the organocatalyst used.

2. Results and discussion

Cyclohexa-1,3-dienes and their derivatives are structurally important since they are versatile intermediates for the synthesis of natural products and biologically active compounds.[12] We started our study (Table 1) using commercially available 3-methyl-butenal **4a** and sulfone **2** since, as we previously demonstrated,[4,5] it behaves exactly the same as **1** but the tetrahydropyranyl (THP) protecting group is much more easily removable.

Table 1
Reaction of Nazarov reagent **2** with **4a**[a]



Entry	**2**/**4a** Ratio	Additive (20 mol %)	Solvent	Time[b]	Yield[c] (%)
1	2/1	—	2-Propanol	47 h	42
2	1/2	—	2-Propanol	44 h	49
3	2/1	B.A.	2-Propanol	47 h	50
4	2/1	BinapOH	2-Propanol	46 h	27
5	2/1	*p*-TsOH	2-Propanol	40 h	13
6	2/1	Na_2CO_3	2-Propanol	7 days	17
7	2/1	K_2CO_3	2-Propanol	6 days	31
8	2/1	$CsCO_3$	2-Propanol	2 days	60
9	2/1	LiOAc· H_2O	2-Propanol	3 days	65
10	2/1	NaOAc	2-Propanol	6 days	63
11	2/1	$FeCl_3 \cdot 6H_2O$	2-Propanol	42 h	S.M.
12	2/1	$ZnCl_2$	2-Propanol	47 h	S.M.
13	2/1	—	Hexane	80 h	23
14	2/1	—	Toluene	79 h	66
15	2/1	—	CH_2Cl_2	74 h	67
16	2/1	—	$CHCl_3$	71 h	73
17	2/1	—	Et_2O	30 h	26
18	2/1	—	THF	46 h	32
19	2/1	—	MeOH	56 h	DEC
20	2/1	—	EtOH	49 h	75[d]
21	1/2	—	EtOH	24 h	40
22	1/1	—	EtOH	45 h	7
23	**2/1**	**B.A.**	**EtOH**	**48 h**	**79**[e]

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in the corresponding solvent at 0.18 M and 50 mol % (*S*)-**3**.
[b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).
[c] Isolated yield after chromatography on silica gel.
[d] 89% ee determined by HPLC.
[e] 92% ee determined by HPLC. B.A.=benzoic acid. BinapOH=(*S*)-(+)-1,19-binaphthyl-2,29-diyl hydrogen phosphate. S.M.=Starting Material. DEC=decomposition.

A screening of different sulfone/aldehyde ratios, solvents and additives was carried out in order to test the importance of the β-substituent.

As shown in Table 1, the sulfone/aldehyde ratio did not change the reaction yield substantially, (entries 1 and 2). Use of acid additives (entries 3–5) decreased yields comparing to initial conditions except for benzoic acid (entry 3). Brønsted bases had similar effect, and although lithium or sodium acetate made a good improvement, the reaction time increased (entries 6–10). Lewis acids did not produce any reaction (entries 11 and 12). Solvent screening (entries 13–20) proved EtOH to be the best solvent. After testing the sulfone/aldehyde ratio (entries 21 and 22) and the use of benzoic acid (entry 23) we found the best conditions were a sulfone/aldehyde ratio of 2/1 and 20% of benzoic acid in EtOH. The ee was measured for the best conditions (entries 20 and 23) observing that the use of benzoic acid slightly increased the yield and the enantiomeric excess (ee) as before. Finally we carried out a study of catalyst loading (Table 2), finding that a 50 mol % catalyst was the optimum amount needed for the best yield and ee. The absolute stereochemistry was determined by X-ray analysis of an analogue as shown later on.

Table 2
Catalyst load screening[a]

Entry	Catalyst (*S*)-**3** (mol %)	Yield[b] (%)	ee[c] (%)
1	5	S.M.	—
2	10	S.M.	—
3	20	39	89
4	**50**	**79**	**92**
5	100	75	90

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of **2**/**4a** and 20 mol % benzoic acid.
[b] Isolated yield of **6a** after chromatography on silica gel.
[c] ee determined by HPLC analysis, carried out on a CHIRALCEL IC column; *n*-hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min.

Once the best conditions were established for this reaction, several β,β-alkylsubstituted aldehydes **4a–f**, were tested with differently protected sulfones **1** and **2** (Table 3).

When sulfone **1** was used, yields were from moderate to good except for compounds **5c** and **5e** (entries 3 and 5) due to a possible oxo-Michael reaction.[13] The enantiomeric excess in all cases vary from good to excellent. Similar behaviour was observed when using sulfone **2**. In this case and in order to corroborate the obtained results, enantiomeric catalyst (*R*)-**3** was used (entries 7, 9 and 13) obtaining the corresponding enantiomers with similar ee, adding more versatility to this procedure.

It can be concluded that when both β-substituents are alkyl groups, cyclohexa-1,3-diene derivatives **5**/**6** are obtained from low to good yields (16–79%) and in good to excellent ee (75–92%).

Compounds **5**/**6** obtention can be understood through a Diels–Alder mechanism between dienamine **II** formed between the catalyst and the α,β-unsaturated aldehyde,[14] and the Nazarov reagent acting as dienophile similarly as in the cases of Prof. Serebryakov et al.[8] It is noteworthy that in this reaction the diene is established with the methyl group and not with the methylene group as in the case of the Rauhut–Curier-type reaction of Christmann et al. (Fig. 1).[10a] Intermediate **III** is demonstrated by NMR and HRMS experiments and observed its slowly transformation into the final products.

With these results in hand we decided to test the behaviour when one of the alkyl groups is changed to an aromatic ring. Using Nazarov reagent **2** with different aromatic aldehydes under the same conditions, cyclohexa-1,3-dienes **7** were formed instead of cyclohexa-1,3-dienes **6** (Table 4). The stereochemistry at the new chiral centre in **7** is proposed to come from a 1,5-*H* sigmatropic rearrangement, since the formation of the same intermediate **III** is observed with both aliphatic and aromatic substituents. As shown in Table 4, yields and enantiomeric excesses are good in all cases.

In order to see the value of this reaction, different compounds in a diversity oriented strategy were obtained. Compound **5a** was submitted to oxygen atmosphere and direct sunlight using Rose

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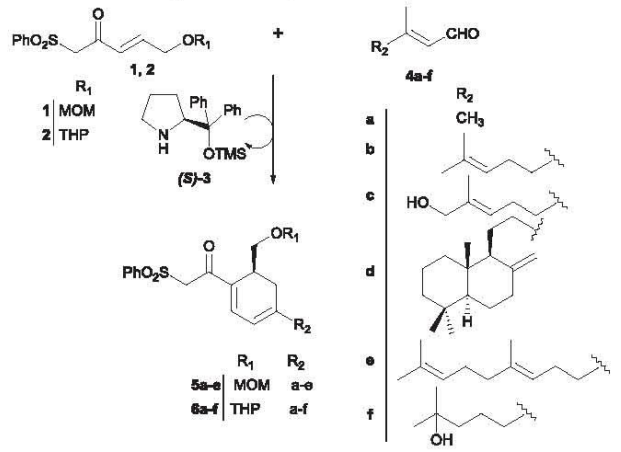
Table 3
Reaction of Nazarov reagents **1,2** with prenals **4a–f**[a]



Entry	Sulfone	Aldehyde	Product	Yield[b] (%)	ee[c] (%)
1	**1**	**4a**	**5a**	62	79
2	**1**	**4b**	**5b**	69	82
3	**1**	**4c**	**5c**	20	80
4	**1**	**4d**	**5d**	58	75
5	**1**	**4e**	**5e**	24	39
6	**2**	**4a**	**6a**	**79**	**92**
7[d]	**2**	**4a**	*ent*-**6a**	75	−92
8	**2**	**4b**	**6b**	62	90
9[d]	**2**	**4b**	*ent*-**6b**	65	−91
10	**2**	**4c**	**6c**	49	80
11	**2**	**4d**	**6d**	16	88
12	**2**	**4d**	**6e**	33	89
13[d]	**2**	**4e**	*ent*-**6e**	36	−89
14	**2**	**4f**	**6f**	32	91

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of sulfone/aldehyde, 50 mol % (*S*)-**3** and 20 mol % benzoic acid.
[b] Isolated yield after chromatography on silica gel.
[c] ee determined by HPLC analysis, carried out on a CHIRALCEL IC column; *n*-hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min.
[d] Using catalyst (*R*)-**3**.

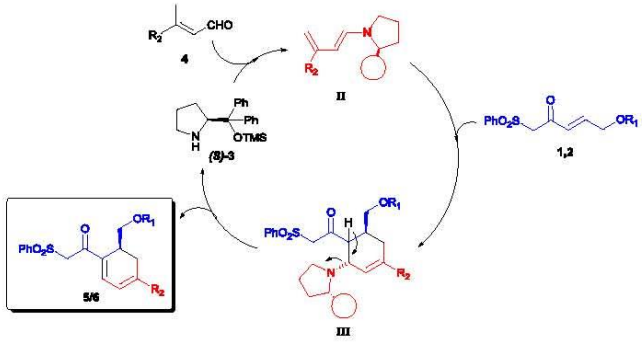
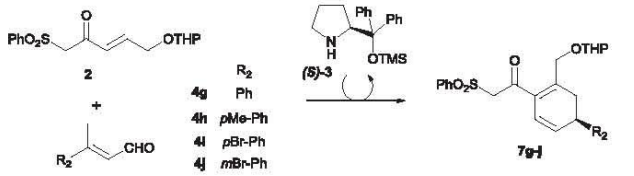


Fig. 1. Proposed Diels–Alder mechanism for the synthesis of **5**/**6**.

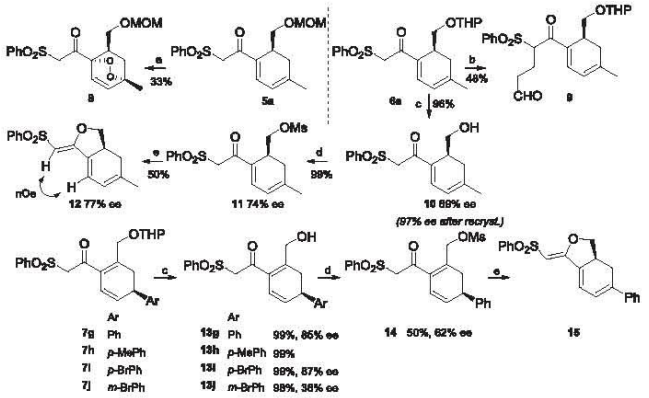
Bengal as catalyst to provide **8** in moderate yield (Scheme 2). Diene **6a** was made to react with acrolein affording **9** in good yield. Unfortunately compound **9** was much less reactive than expected and did not react when submitted to intramolecular hetero-Diels–Alder conditions, and when compound **6a** was submitted to a variety of dienophiles (dihydropyran, maleimide and *N*-phenylmaleimide, maleic anhydride, 2-pentenal or diphenylmethanimine) only starting materials or degradation products were obtained. Thus compound **6a** was deprotected affording **10**, although with some racemisation, but we were able to crystallise it and allowing us to establish the absolute configuration of

Table 4
Reaction of Nazarov reagent **2** with aromatic-β-substituted unsaturated aldehydes[a]



Entry	Aldehyde	Product	Yield[b] (%)	ee[c] (%)
1	**4g**	**7g**	59	91
2	**4h**	**7h**	69	90
3	**4i**	**7i**	59	91
4	**4j**	**7j**	**81**	**93**

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of **2**/**4g–j**, 50 mol % (*S*)-**3** and 20 mol % benzoic acid.
[b] Isolated yield after chromatography on silica gel.
[c] ee determined by HPLC analysis, carried out on a CHIRALCEL AD-H column; *n*-hexane/isopropyl alcohol [80/20–70/30 (v/v)]; flow rate: 1.0 mL/min.



Scheme 2. (a) O_2 atmosphere, Rose Bengal (25 mol %), sunlight, MeOH, rt, 4 h; (b) acrolein (2 equiv), K_2CO_3 (8 equiv), THF, rt, 4 h; (c) *p*-TsOH·H_2O (50 mol %), THF/H_2O (1/1), rt; (d) MsCl, Et_3N, DMAP, DCM, rt; (e) DBU, DCM, rt.

cyclohexadienes **6** and **7** formed in the organocatalytic reaction (Fig. 2).[15] Mesylation of **10** afforded **11**, which by treatment in basic conditions led to triene **12**. The double bond stereochemistry of this enolether was established by NOE's experiments (Scheme 2). Aromatic derivatives **7g–j** were submitted to the same conditions, i.e., deprotection and mesylation, but the resulting compounds were more unstable than aliphatics and only mesylated phenyl derivative **14** obtained from **13g** could be isolated. Aromatic triene **15** was observed by NMR, after basic treatment of **14**, but was not stable enough to be fully characterised. Compounds as **13g** are precursors of carbonyliron complexes and further studies will be conducted in this way.[16]

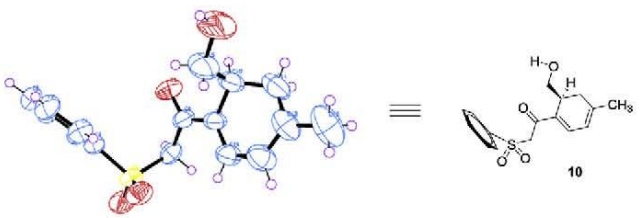
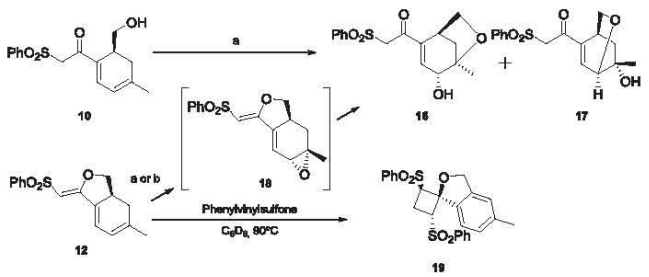


Fig. 2. ORTEP diagram for compound **10**.

More diversity oriented structures were obtained from reactivity studies of diene **10** and triene **12** (Scheme 3, Table 5). When **10** was treated with *m*-CPBA a 1/1 mixture of tetrahydrofuran and tetrahydropyran **16**/**17** was obtained in moderate yield. However, if



Scheme 3. (a) *m*-CPBA, $CDCl_3$, 0 °C – rt; (b) $CHCl_3$, heat (37 °C).

Table 5
Reactivity of compounds **9** and **10**[a]

Entry	S.M.	Conditions	Time (h)	Product	Yield[b] (%)
1	**10**	*m*-CPBA	15	**16+17 (1/1)**	38
2	**12**	*m*-CPBA	6	**16**	62
3	**12**	Heat[c] (37 °C)	72	**16**	53
4	**12**	PVS,[d] 90 °C	2.5	**19**	42

[a] For more details see ESI.
[b] Isolated yield after chromatography on silica gel.
[c] Under air atmosphere.
[d] Phenylvinylsulfone.

compound **12** was submitted to the same conditions, or just heating, only **16** was obtained in better yields in a chemo, regio- and stereocontrolled way. This substructure is present in quinocycline and isoquinocycline compounds with antibiotic and cytotoxic activities.[17] In this case it was possible to isolate intermediate epoxide **18**, corroborating the mechanism of the reaction. Analogues of these compounds have been used for the synthesis of natural products.[18] This kind of compounds is related to Bruceantin, an antitumour agent isolated from *Bruceas* species.[19] When compound **12** was heated in benzene in the presence of phenylvinylsulfone (PVS) cyclobutane **19** was obtained by a [2+2] cycloaddition in moderate yield, adding even more versatility to these compounds.

3. Conclusions

In conclusion, it has been made a sulfone Nazarov reagent to react in organocatalytic conditions in a Diels–Alder manner for the first time. This reaction has made possible to obtain diverse chiral highly functionalised cyclohexa-1,3-dienes, depending on whether the aldehyde substitution is an alkyl or aryl group. These kinds of cyclohexadienes have been used in Diels–Alder bioconjugation of diene modified oligonucleotides.[20] Herein, we report their application for the synthesis of different bicyclic or tricyclic compounds in a diversity oriented synthesis, opening the way for the use of these compounds in bioconjugation chemistry.

4. Experimental section

4.1. General experimental methods

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification, except for **1**,[4] **2**,[5] 10-hydroxycitral **4c**,[21] **4d**, farnesal **4e**[22] and **4f**,[23] which were synthesised according to the literature procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured on 200, 400 and 600 MHz spectrometers and performed in $CDCl_3$ or C_6D_6, and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm or to the residual peak of C_6H_6 at δ 7.15 ppm and δ 128.6 ppm, for ^1H and ^{13}C, respectively. Chemical shifts are reported in δ parts per million and coupling constants (J) are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer, using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, electrospray ionisation (ESI) was employed. Optical rotations were determined in 1 dm cell. HPLC analysis were carried out on a chiral column [amylose tris(3,5-dimethylphenycarbamate)] or [cellulose tris(3,5-dichlorophenycarbamate)] on silica gel using *n*-hexane/2-propanol. Column chromatography was performed using silica gel 60 (230–400 mesh), with solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under argon atmosphere prior to use. Hexane was distilled prior to use.

4.2. General procedure for the synthesis of cyclohexadienes, 5a–e, 6a–f and 7g–j

β-Ketosulfone (**1**,**2**) (0.18 mmol) and the corresponding aldehyde (0.08 mmol) were dissolved in 1 ml of EtOH. Next, catalyst (*S*)-**3** (50 mol %), and benzoic acid (20 mol %) were added successively and left stirring at room temperature for 48 h. All products were purified by flash chromatography on silica gel using different mixtures of *n*-hexane/ethyl acetate.

*4.2.1. (S)-1-(6-((Methoxymethoxy)methyl)-4-(methyl)-cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**5a**).* Yellow oil (17.4 mg, 62%): ν_{max} (liquid film) 2929, 1718, 1629, 1570, 1448, 1383, 1309, 1290, 1151; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, J=6.9 Hz), 7.81–7.24 (3H, m), 7.03 (1H, d, J=5.9 Hz), 6.02–5.78 (1H, m), 4.54 (2H, s), 4.45 (2H, d, J=8.1 Hz), 3.31 (3H, s), 3.21–3.16 (3H, m), 2.55–2.28 (1H, m), 1.92 (3H, s), 1.65–1.58 (1H, m); δ_C (50 MHz; $CDCl_3$) 186.6, 148.4, 140.7, 139.0, 134.3, 133.1, 129.4 (2CH), 128.8 (2CH), 119.2, 96.6, 66.0, 62.8, 55.4, 31.1, 30.8, 24.4; EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)= 37.5 min; t_R (major)=41.6 min; $[\alpha]_D^{25}$ −9.57 (*c* 1.42, $CHCl_3$).

*4.2.2. (S)-1-(6-((Methoxymethoxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**5b**).* Yellow oil (23.1 mg, 69%): ν_{max} (liquid film) 2956, 2929, 2873, 1715, 1651, 1566, 1446, 1323, 1288, 1153; δ_H (400 MHz; $CDCl_3$) 7.89 (2H, d, J=7.0 Hz), 7.72–7.47 (3H, m), 7.06 (1H, d, J=6.0 Hz), 6.02–5.80 (1H, m), 5.12–4.76 (1H, m), 4.54 (2H, s), 4.54–4.51 (1H, m), 4.49–4.41 (1H, m), 3.31 (3H, s), 3.19–3.14 (3H, m), 2.53 (1H, d, J=17.8 Hz), 2.23–2.11 (4H, m), 1.69 (3H, s), 1.61 (3H, s), 1.40–1.35 (1H, m); δ_C (100 MHz; $CDCl_3$) 186.6, 152.0, 140.7, 139.0, 134.3, 133.4, 132.7, 129.4 (2CH), 128.8 (2CH), 123.3, 118.6, 96.6, 65.9, 62.8, 55.4, 38.2, 30.7, 29.7, 26.0, 25.9, 17.9; EIHRMS: calcd for $C_{23}H_{30}O_5S$ (M+Na): 441.1712; found: 441.1706 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=31.6 min; t_R (major)=34.5 min; $[\alpha]_D^{25}$ −4.56 (*c* 0.57, $CHCl_3$).

*4.2.3. (S,E)-1-(6-((Methoxymethoxy)methyl)-4-(4-methyl-5-hydroxy-pent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl) ethan-1-one (**5c**).* Yellow oil (6.9 mg, 20%): ν_{max} (liquid film) 3452, 2935, 2885, 1716, 1637, 1564, 1446, 1379, 1309, 1292, 1151; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, J=7.0 Hz), 7.75–7.48 (3H, m), 7.06 (1H, d, J=5.8 Hz), 5.94 (1H, d, J=4.9 Hz), 5.43–5.32 (1H, m), 4.54 (2H, s), 4.54–4.35 (2H, d, J=9.1 Hz), 4.00 (2H, s), 3.31 (3H, s), 3.22–3.19 (3H, m), 2.53 (1H, d, J=18.2 Hz), 2.35–2.19 (4H, m), 1.69 (3H, s), 1.33–1.08 (1H, m); δ_C (50 MHz; $CDCl_3$) 186.6, 151.5, 140.5, 139.0, 136.1, 134.3, 133.5, 129.4 (2CH), 128.7 (2CH), 124.4, 118.9, 96.6, 68.8, 65.9, 62.8, 55.5, 37.6, 30.6, 29.7, 25.6, 13.9; EIHRMS: calcd for $C_{23}H_{30}O_6S$ (M+Na): 457.1661; found: 457.1655 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl

alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=58.8 min; t_R (major)=67.9 min; $[\alpha]_D^{25}$ −1.02 (*c* 1.08, $CHCl_3$).

*4.2.4. 1-((6S)-(6-((Methoxymethoxy)methyl)-4-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-2-(phenylsulfonyl))ethan-1-one (**5d**).* Yellow oil (25.7 mg, 58%): ν_{max} (liquid film) 2937, 2848, 1718, 1649, 1566, 1446, 1321, 1309, 1151; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=7.9), 7.71–7.40 (3H, m), 7.06 (1H, d, *J*=5.7 Hz), 5.97–5.79 (1H, m), 4.84 (1H, s), 4.54 (2H, s), 4.54–4.42 (4H, m), 4.27 (1H, s), 3.31 (3H, s), 3.21–3.16 (3H, m), 2.59–2.40 (1H, m), 2.44–0.74 (24H, m); δ_C (50 MHz; $CDCl_3$) 186.6, 153.2, 148.6, 140.9, 138.9, 134.3, 133.7, 129.4 (2CH), 128.8 (2CH), 118.2, 106.6, 96.6, 65.9, 62.8, 56.7, 55.7, 55.4, 42.3, 40.0, 39.9, 39.3, 38.5, 33.8, 33.5, 30.7, 28.6, 24.7, 21.9, 19.6, 19.2, 14.7; EIHRMS: calcd for $C_{33}H_{46}O_5S$ (M+Na): 577.2964; found: 577.2958 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=31.4 min; t_R (major)=33.3 min; $[\alpha]_D^{25}$ +13.98 (*c* 2.21, $CHCl_3$).

*4.2.5. (S,E)-1-(6-((Methoxymethoxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**5e**).* Yellow oil (9.3 mg, 24%): ν_{max} (liquid film) 2926, 2856, 1716, 1651, 1566, 1448, 1379, 1309, 1288, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=8.2 Hz), 7.68–7.42 (3H, m), 7.06 (1H, d, *J*=5.8 Hz), 6.02–5.83 (1H, m), 5.28–4.93 (2H, m), 4.54 (2H, s), 4.50–4.40 (2H, m), 3.31 (3H, s), 3.22–3.11 (3H, m), 2.54 (1H, d, *J*=18.2 Hz), 2.31–2.14 (8H, m), 1.68 (3H, s), 1.61 (6H, s), 1.35–1.10 (1H, m); δ_C (50 MHz; $CDCl_3$) 186.9, 152.1, 140.8, 136.3, 134.3, 133.4, 133.3, 130.4, 129.4 (2CH), 128.8 (2CH), 124.4, 123.3, 118.6, 96.6, 66.0, 62.8, 55.4, 39.9, 38.3, 30.7, 29.7, 26.9, 25.9 ($2CH_2$), 17.9, 16.3; EIHRMS: calcd for $C_{28}H_{38}O_5S$ (M+Na): 509.2338; found: 509.2332 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (major)=29.1 min; t_R (minor)=34.8 min; $[\alpha]_D^{25}$ −12.07 (*c* 1.42, $CHCl_3$).

*4.2.6. (S)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**6a**). Note*: The presence of THP protecting group makes many of NMR signals, both ^1H and ^{13}C, to appear twice. Hence, for compounds with THP group only NMR shift values for one isomer are given here.

Yellow oil (24.6 mg, 79%): ν_{max} (liquid film) 2941, 2868, 1718, 1637, 1570, 1446, 1383, 1323, 1309, 1288, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=8.3 Hz), 7.71–7.50 (3H, m), 7.02 (1H, d, *J*=5.9 Hz), 6.02–5.73 (1H, m), 4.57–4.33 (3H, m), 3.83–3.69 (1H, m), 3.50–3.35 (2H, m), 3.21–3.10 (1H, m), 3.09–2.98 (1H, m), 2.67–2.48 (1H, m), 1.92 (3H, s), 1.84–1.39 (7H, m); δ_C (50 MHz; $CDCl_3$) 186.6, 148.6, 140.7, 139.0, 134.3, 133.1, 129.4 (2CH), 128.8 (2CH), 119.2, 99.2, 65.5, 62.8, 62.4, 31.4, 31.1, 30.8, 25.6, 24.4, 19.7; EIHRMS: calcd for $C_{21}H_{26}O_5S$ (M+Na): 413.1399; found: 413.1393 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=41.5 min; t_R (major)=49.9, 66.5 min; $[\alpha]_D^{25}$ −15.0 (*c* 0.16, $CHCl_3$).

*4.2.7. (R)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**ent-6a**).* Yellow oil (23.4 mg, 75%); $[\alpha]_D^{25}$ +8.9 (*c* 0.9, $CHCl_3$).

*4.2.8. (S)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**6b**).* Yellow oil (22.7 mg, 62%): ν_{max} (liquid film) 2941, 2870, 1716, 1651, 1566, 1446, 1381, 1321, 1309, 1288, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=8.1 Hz), 7.68–7.40 (3H, m), 7.04 (1H, d, *J*=5.9 Hz), 5.98–5.83 (1H, m), 5.11–5.01 (1H, m), 4.62–4.33 (3H, m), 3.88–3.60 (1H, m), 3.59–3.27 (2H, m), 3.26–2.92 (2H, m), 2.57–2.39 (1H, m), 2.25–2.13 (4H, m), 1.72–1.39 (13H, m); δ_C (50 MHz; $CDCl_3$) 186.7, 152.1, 140.6, 139.1, 134.3, 133.4, 132.6, 129.3 (2CH), 128.8 (2CH), 123.3, 118.7, 99.1, 65.5, 62.9, 62.4, 38.2, 30.8, 30.7, 29.8, 25.9, 25.8, 25.7, 19.5, 17.9; EIHRMS: calcd for $C_{26}H_{34}O_5S$ (M+Na): 481.2025; found: 481.2019 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=36.6 min; t_R (major)=43.4 min, 56.8 min; $[\alpha]_D^{25}$ −15.1 (*c* 2.63, $CHCl_3$).

*4.2.9. (R)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (ent-**6b**).* Yellow oil (23.8 mg, 65%): $[\alpha]_D^{25}$ +7.81 (*c* 0.71, $CHCl_3$).

*4.2.10. (S)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4-methyl-5-hydroxy-pent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**6c**).* Yellow oil (18.6 mg, 49%): ν_{max} (liquid film) 3449, 2943, 2870, 1718, 1651, 1564, 1446, 1383, 1321, 1309, 1290, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=7.6 Hz), 7.68–7.49 (3H, m), 7.04 (1H, d, *J*=5.7 Hz), 6.01–5.85 (1H, m), 5.49–5.31 (1H, m), 4.66–4.40 (3H, m), 3.99 (2H, s), 3.84–3.64 (1H, m), 3.57–3.31 (2H, m), 3.26–3.00 (2H, m), 2.71–2.50 (1H, m), 2.37–2.20 (4H, m), 1.67 (3H, s), 1.59–1.35 (7H, m); δ_C (50 MHz; $CDCl_3$) 186.7, 151.3, 140.5, 139.1, 136.1, 134.3, 133.4, 129.4 (2CH), 128.8 (2CH), 124.4, 118.9, 99.0, 68.7, 65.6, 62.8, 62.1, 37.6, 30.8, 30.6, 29.7, 25.6, 25.0, 19.5, 13.9; EIHRMS: calcd for $C_{26}H_{34}O_6S$ (M+Na): 497.1974; found: 497.1947 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=360 nm; t_R (minor)=60.4, 64.0 min; t_R (major)=89.7, 124.6 min; $[\alpha]_D^{25}$ −5.78 (*c* 2.49, $CHCl_3$).

*4.2.11. 1-((6S)-6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-2-(phenylsulfonyl)ethan-1-one (**6d**).* Yellow oil (7.6 mg, 16%): ν_{max} (liquid film) 2941, 2868, 1718, 1649, 1564, 1448, 1321, 1309, 1155; δ_H (200 MHz; $CDCl_3$) 7.97–7.83 (2H, m), 7.73–7.40 (3H, m), 7.05 (1H, d, *J*=5.8 Hz), 6.03–5.84 (1H, m), 4.85 (1H, s), 4.61–4.31 (4H, m), 3.93–3.68 (1H, m), 3.57–3.28 (2H, m), 3.22–2.94 (2H, m), 2.63–2.43 (1H, m), 2.40–0.69 (32H, m); δ_C (50 MHz; $CDCl_3$) 186.7, 153.4, 148.6, 140.8, 139.0, 134.3, 133.6, 129.3 (2CH), 128.8 (2CH), 118.3, 106.6, 98.7, 65.4, 62.9, 62.1, 57.9, 55.8, 42.4, 40.0, 39.9, 39.3, 38.6, 37.1, 33.8, 33.5, 30.6, 29.9, 25.6, 24.7, 21.9, 19.6 ($2CH_2$), 19.2, 14.7; EIHRMS: calcd for $C_{36}H_{50}O_5S$ (M+Na): 617.3277; found: 617.3271 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=360 nm; t_R (minor)=35.4 min; t_R (major)=40.0, 49.0 min; $[\alpha]_D^{25}$ +22.90 (*c* 1.43, $CHCl_3$).

*4.2.12. (S,E)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**6e**).* Yellow oil (14.1 mg, 33%): ν_{max} (liquid film) 2937, 2868, 1716, 1651, 1566, 1448, 1381, 1321, 1309, 1288, 1155; δ_H (200 MHz; $CDCl_3$) 7.95–7.82 (2H, m), 7.73–7.40 (3H, m), 7.04 (1H, d, *J*=6.0 Hz), 5.98–5.82 (1H, m), 5.21–4.98 (2H, m), 4.60–4.32 (3H, m), 3.87–3.66 (1H, m), 3.57–3.28 (2H, m), 3.25–2.98 (2H, m), 2.66–2.42 (1H, m), 2.35–2.12 (4H, m), 2.11–1.83 (4H, m), 1.78–1.45 (16H, m); δ_C (50 MHz; $CDCl_3$) 186.7, 152.0, 140.6, 139.1, 134.3, 133.8, 133.5, 130.3, 129.3 (2CH), 128.8 (2CH), 124.4, 123.3, 118.5, 98.7, 66.1, 62.9, 62.4, 39.9, 38.3, 30.8, 30.7, 29.8, 26.9, 25.9, 25.7, 25.6, 23.6, 19.5, 17.9; EIHRMS: calcd for $C_{31}H_{42}O_5S$ (M+Na): 549.2641; found: 549.2645 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=360 nm; t_R (minor)=29.3 min; t_R (major)=33.6, 40.8 min; $[\alpha]_D^{25}$ −3.87 (*c* 1.60, $CHCl_3$).

4.2.13. (R)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-

*(phenylsulfonyl)ethan-1-one (ent-**6e**).* Yellow oil (15.1 mg, 36%): $[\alpha]_D^{25}$ +18.57 (*c* 0.56, $CHCl_3$).

*4.2.14. (S)-1-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4-methyl-4-hydroxy-pentan-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**6f**).* Yellow oil (12.2 mg, 32%): ν_{max} (liquid film) 3460, 2943, 2870, 1716, 16,457, 1566, 1448, 1379, 1323, 1309, 1290, 1153; δ_H (200 MHz; $CDCl_3$) 7.89 (2H, d, *J*=8.5 Hz), 7.75–7.46 (3H, m), 7.02 (1H, d, *J*=5.8 Hz), 5.97–5.79 (1H, m), 4.57–4.29 (3H, m), 3.93–3.63 (1H, m), 3.51–3.24 (2H, m), 3.21–2.92 (2H, m), 2.74–2.41 (1H, m), 2.30–2.01 (4H, m), 1.76–1.33 (9H, m), 1.32–1.14 (6H, m); δ_C (50 MHz; $CDCl_3$) 186.6, 152.4, 140.7, 139.1, 134.3, 133.3, 129.4 (2CH), 128.8 (2CH), 119.1, 99.3, 70.6, 65.6, 62.8, 62.3, 43.5, 38.3, 38.0, 31.1, 30.8, 29.7, 29.6, 28.9, 25.6, 19.6; EIHRMS: calcd for $C_{26}H_{36}O_6S$ (M+Na): 499.2130; found: 499.2125 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (minor)=44.6; t_R (major)=51.4, 61.9 min; $[\alpha]_D^{25}$ +13.91 (*c* 1.86, $CHCl_3$).

*4.2.15. (R)-2-(1-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(phenyl) cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**7g**).* Yellow oil (21.3 mg, 59%): ν_{max} (liquid film) 2941, 2870, 1718, 1647, 1545, 1447, 1323, 1309, 1292, 1153; δ_H (400 MHz; $CDCl_3$) 7.91 (2H, d, *J*=7.3 Hz), 7.73–7.48 (3H, m), 7.47–7.34 (5H, m), 7.22 (1H, d, *J*=6.3 Hz), 6.53 (1H, dd, *J*=6.1, 2.6 Hz), 4.65–4.38 (3H, m), 3.89–3.69 (1H, m), 3.49–3.35 (2H, m), 3.35–3.27 (1H, m), 3.15–3.00 (2H, m), 2.84–2.53 (1H, m), 1.89–1.30 (6H, m); δ_C (100 MHz; $CDCl_3$) 186.5, 146.2, 140.0, 138.7, 134.6, 134.5, 134.1, 129.3, 129.1 (2CH), 128.6 (4CH), 126.0 (2CH), 119.2, 98.9, 64.9, 62.8, 61.9, 30.5, 30.9, 30.3, 25.3, 19.3; EIHRMS: calcd for $C_{26}H_{28}O_5S$ (M+Na): 475.1555; found: 475.1549 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ=340 nm; t_R (major)=25.4, 27.0 min; t_R (minor)=36.1 min; $[\alpha]_D^{25}$ +18.42 (*c* 1.33, $CHCl_3$).

*4.2.16. (R)-2-(1-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(4-methylphenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**7h**).* Yellow oil (25.7 mg, 69%): ν_{max} (liquid film) 2941, 2870, 1720, 1645, 1539, 1448, 1383, 1323, 1309, 1292, 1155; δ_H (400 MHz; $CDCl_3$) 7.96–7.83 (2H, m), 7.74–7.37 (3H, m), 7.22–7.16 (5H, m), 6.50 (1H, ddd, *J*=6.1, 2.7, 1.3 Hz), 4.60–4.49 (3H, m), 3.81–3.70 (1H, m), 3.49–3.35 (2H, m), 3.35–3.27 (1H, m), 3.15–3.00 (2H, m), 2.72–2.57 (1H, m), 2.37 (3H, s), 1.80–1.26 (6H, m); δ_C (100 MHz; $CDCl_3$) 186.4, 146.5, 140.2, 139.5, 139.0, 138.7, 136.7, 134.6, 128.8 (2CH), 128.6 (2CH), 129.6 (2CH), 126.2 (2CH), 118.4, 98.8, 64.9, 62.7, 61.8, 30.9, 30.8, 27.8, 25.3, 21.2, 19.3; EIHRMS: calcd for $C_{27}H_{30}O_5S$ (M+Na): 489.1712; found: 489.1706 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ=420 nm; t_R (minor) 13.6, 15.6 min; t_R (major)=18.7, 20.8 min; $[\alpha]_D^{25}$ +44.70 (*c* 0.97, $CHCl_3$).

*4.2.17. (R)-2-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**7i**).* Yellow oil (25.0 mg, 59%): ν_{max} (liquid film) 2947, 2870, 1718, 1647, 1544, 1448, 1383, 1323, 1309, 1290, 1155; δ_H (200 MHz; $CDCl_3$) 7.98–7.85 (2H, m), 7.75–7.33 (3H, m), 7.27–7.16 (5H, m), 6.60–6.42 (1H, m), 4.67–4.34 (3H, m), 3.86–3.67 (1H, m), 3.57–3.38 (2H, m), 3.35–3.23 (1H, m), 3.19–3.03 (2H, m), 2.78–2.58 (1H, m), 1.84–1.29 (6H, m); δ_C (50 MHz; $CDCl_3$) 186.7, 144.7, 139.9, 139.5, 139.0, 135.0, 134.4, 129.4 (2CH), 128.7 (2CH), 127.8 (2CH), 127.6 (2CH), 123.4, 119.9, 98.6, 65.2, 63.1, 62.2, 27.9, 31.1, 30.6, 25.6, 19.7; EIHRMS: calcd for $C_{26}H_{27}BrO_5S$ (M+Na): 553.0660; found: 553.0655 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [80/20 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (major) 30.3, 31.8 min; t_R (minor)=34.6 min; $[\alpha]_D^{25}$ +46.80 (*c* 1.02, $CHCl_3$).

*4.2.18. (R)-2-(6-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(3-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**7j**).* Yellow oil (34.3 mg, 81%): ν_{max} (liquid film) 2943, 2870, 1717, 1651, 1547, 1448, 1408, 1323, 1309, 1290, 1155; δ_H (200 MHz; $CDCl_3$) 7.91 (2H, d, *J*=7.8 Hz), 7.74–7.39 (3H, m), 7.33–7.13 (5H, m), 6.50 (1H, dd, *J*=6.0, 2.6 Hz), 4.64–4.39 (3H, m), 3.83–3.65 (1H, m), 3.63–3.26 (3H, m), 3.23–2.94 (2H, m), 2.78–2.55 (1H, m), 1.88–1.34 (6H, m); δ_C (50 MHz; $CDCl_3$) 186.8, 144.7, 141.9, 141.7, 139.7, 138.9, 134.4 (2CH), 132.0, 130.4, 129.4 (2CH), 128.7 (2CH), 124.7, 123.1, 120.6, 98.7, 65.1, 63.0, 62.2, 31.2, 30.8, 28.2, 25.6, 19.7; EIHRMS: calcd for $C_{26}H_{27}BrO_5S$ (M+Na): 553.0660; found: 553.0655 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (major)=23.6 min; t_R (minor)=26.9 min; $[\alpha]_D^{25}$ +30.09 (*c* 1.29, $CHCl_3$).

4.3. Synthesis of 1-((1*S*,4*S*,7*R*)-7-((methoxymethoxy)methyl)-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-en-1-yl)-2-(phenylsulfonyl)ethan-1-one (8)

Compound **5a** (22 mg, 0.06 mmol) and Rose Bengal (15 mg, 0.015 mmol) were dissolved in 1 ml of MeOH and left to stir under O_2 atmosphere and solar light for 4 h. After the solvent was evaporated in vacuo, flash chromatography (*n*-hexane/EtOAc, 6:4) afforded **8** as a yellow oil (7 mg, 33%). ν_{max} (liquid film) 2957, 2929, 2873, 1728, 1448, 1323, 1311, 1290, 1149; δ_H (200 MHz; $CDCl_3$) 8.01 (2H, d, *J*=8.2 Hz), 7.75–7.52 (3H, m), 6.80 (1H, d, *J*=8.5 Hz), 6.46 (1H, d, *J*=8.5 Hz), 4.74–4.36 (2H, m), 4.22 (2H, s), 3.45–3.26 (2H, m), 3.19 (3H, s), 3.18–3.06 (1H, m), 2.41–2.15 (2H, m), 1.48 (3H, s); δ_C (50 MHz; $CDCl_3$) 191.3, 139.9, 137.4, 134.2, 129.3 (2CH), 129.0 (2CH), 128.0, 96.5, 83.6, 76.3, 68.9, 62.4, 55.8, 39.0, 33.1, 21.1; EIHRMS: calcd for $C_{18}H_{22}O_7S$ (M+Na): 405.0984; found: 405.0978 (M+Na). $[\alpha]_D^{25}$ +8.15 (*c* 0.92, $CHCl_3$).

4.4. Synthesis of 5-((6*S*)-4-methyl-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)cyclohexa-1,3-dien-1-yl)-5-oxo-4-(phenylsulfonyl)pentanal (9)

A mixture of compound **6a** (26 mg, 0.067 mmol) and potassium carbonate (74 mg, 0.536 mmol) was suspended in THF (0.7 ml) under an Argon atmosphere. The suspension was stirred at room temperature for 10 min, and acrolein (9 μL, 0.133 mmol) was then added. The reaction mixture was stirred for 17 h and then filtered through Celite®, which was washed with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and all the volatiles evaporated. Flash chromatography (*n*-hexane/EtOAc, 7:3) afforded **9** as a yellow oil (15 mg, 48%). ν_{max} (liquid film) 2941, 2870, 1722, 1651, 1637, 1566, 1446, 1386, 1321, 1309, 1288, 1149; δ_H (200 MHz; $CDCl_3$) 9.68 (1H, s), 7.91–7.29 (5H, m), 6.97 (1H, dd, *J*=11.7, 5.8 Hz), 5.99–5.79 (1H, m), 4.93 (1H, dd, *J*=9.3H, 4.8 Hz), 4.61–4.40 (1H, m), 3.97–3.62 (1H, m), 3.62–3.24 (2H, m), 3.24–2.89 (2H, m), 2.75–2.10 (3H, m), 1.92 (3H, s), 1.77–1.39 (9H, m); δ_C (50 MHz; $CDCl_3$) 200.5, 190.3, 148.8, 140.0, 136.9, 133.9, 133.8, 129.9 (2CH), 129.1 (2CH), 119.2, 98.7, 67.0, 62.6, 62.4, 40.6, 31.1, 30.9, 30.7, 25.7 ($2CH_2$), 24.4, 19.7; EIHRMS: calcd for $C_{24}H_{30}O_6S$ (M+Na+MeOH): 501.1923; found: 501.1917 (M+Na+MeOH). $[\alpha]_D^{25}$ −2.34 (*c* 1.45, $CHCl_3$).

4.5. General procedure for the deprotection with pTsOH: synthesis of compounds 10, 13g–j

Tetrahydropyranyl derivative (1 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 mmol) were dissolved in 10 ml of a 1:1

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mixture of THF/H_2O, and the whole mixture was stirred until no starting material was observed (typically 3–7 days). The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the desired product.

*4.5.1. (S)-1-(6-(Hydroxymethyl)-4-(4-methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**10**).* Pale yellow solid (293.8 mg, 96%): mp 116–118 °C; ν_{max} (liquid film) 3446, 2932, 2872, 1718, 1635, 1566, 1446, 1321, 1309, 1288, 1152; δ_H (200 MHz; $CDCl_3$) 7.95–7.82 (2H, m), 7.76–7.49 (3H, m), 7.05 (1H, d, *J*=5.8 Hz), 6.01–5.81 (1H, m), 4.55 (1H, d, *J*=13.5 Hz), 4.38 (1H, d, *J*=13.5 Hz), 3.51–3.27 (2H, m), 3.15–2.90 (1H, m), 2.46–2.37 (2H, m), 1.93 (3H, s); δ_C (50 MHz; $CDCl_3$) 187.6, 149.0, 141.0, 139.0, 134.4, 133.4, 129.4 (2CH), 128.7 (2CH), 119.1, 62.7, 62.6, 33.5, 31.2, 24.3; EIHRMS: calcd for $C_{16}H_{18}O_4S$ (M+Na): 329.0823; found: 329.0818 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=28.5 min; t_R (major)=53.6 min; $[\alpha]_D^{25}$ −27.40 (*c* 0.16, $CHCl_3$).

*4.5.2. (R)-2-(6-(Hydroxymethyl)-5-(phenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**13g**).* Yellow oil (364.3 mg, 99%): ν_{max} (liquid film) 3487, 3061, 2931, 2872, 1718, 1645, 1544, 1446, 1314, 1309, 1153; δ_H (200 MHz; $CDCl_3$) 7.92 (2H, d, *J*=7.0 Hz), 7.74–7.48 (3H, m), 7.47–7.32 (5H, m), 7.24 (1H, d, *J*=6.2 Hz), 6.53 (1H, dd, *J*=6.2, 2.7), 4.52 (1H, d, *J*=13.5 Hz), 4.28–4.10 (1H, m), 3.61–3.32 (2H, m), 3.29–3.09 (1H, m), 3.04 (1H, d, *J*=1.6 Hz), 2.76 (1H, dd, *J*=17.9, 8.6 Hz); δ_C (50 MHz; $CDCl_3$) 187.5, 146.4, 140.3, 139.2, 134.8 (2C), 134.2, 129.2 (2CH), 128.7 (2CH), 128.5, 125.9 (4CH), 119.2, 62.5, 62.7, 33.6, 28.1; EIHRMS: calcd for $C_{21}H_{20}O_4S$ (M+H): 369.1161; found: 369.1155 (M+H). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=430 nm; t_R (minor)=35.9 min; t_R (major)=39.3 min; $[\alpha]_D^{25}$ +13.62 (*c* 0.94, $CHCl_3$).

*4.5.3. (R)-2-(6-(Hydroxymethyl)-5-(4-methylphenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**13h**).* Yellow oil (378.2 mg, 99%): ν_{max} (liquid film) 3442, 2923, 2873, 1714, 1643, 1514, 1446, 1354, 1309, 1153; δ_H (200 MHz; $CDCl_3$) 7.96–7.81 (2H, m), 7.73–7.41 (3H, m), 7.28–7.13 (5H, m), 6.50 (1H, dd, *J*=6.2, 2.6), 4.60 (1H, d, *J*=13.5 Hz), 4.43 (1H, d, *J*=13.5 Hz), 3.57–3.30 (2H, m), 3.26–3.08 (1H, m), 3.02 (1H, d, *J*=4.7 Hz), 2.73 (1H, dd, *J*=20.5, 8.6 Hz), 2.37 (3H, s); δ_C (50 MHz; $CDCl_3$) 187.6, 146.7, 140.8, 139.8, 138.9 (2C), 136.4, 134.4, 130.0 (2CH), 128.9 (2CH), 128.8 (2CH), 126.1 (2CH), 118.5, 62.9, 62.8, 33.8, 28.3, 21.5; EIHRMS: calcd for $C_{22}H_{22}O_4S$ (M+Na): 405.1136; found: 405.1141 (M+Na).

*4.5.4. (R)-2-(6-(Hydroxymethyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**13i**).* Yellow oil (441.5 mg, 99%): ν_{max} (liquid film) 3477, 2941, 2872, 1718, 1643, 1543, 1489, 1446, 1312, 1309, 1153; δ_H (200 MHz; $CDCl_3$) 7.91 (2H, d, *J*=8.3 Hz), 7.73–7.48 (3H, m), 7.47–7.36 (4H, m), 7.23 (1H, d, *J*=6.1 Hz), 6.52 (1H, dd, *J*=6.2, 2.7 Hz), 4.60 (1H, d, *J*=13.4 Hz), 4.43 (1H, d, *J*=13.5 Hz), 3.62–3.26 (1H, m), 3.26–3.05 (2H, m), 3.00 (1H, d, *J*=1.7 Hz), 2.87–2.64 (1H, m); δ_C (50 MHz; $CDCl_3$) 187.4, 144.9, 139.9, 138.7, 138.0, 135.1, 134.3, 129.3 (2CH), 128.5 (2CH), 127.5 (2CH), 127.4 (2CH), 123.4, 119.5, 62.7, 62.3, 33.5, 27.8; EIHRMS: calcd for $C_{21}H_{19}O_4SBr$ (M+Na): 469.0085; found: 469.0079 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (major)=30.6 min; t_R (minor)=38.8 min; $[\alpha]_D^{25}$ +5.88 (*c* 1.75, $CHCl_3$).

*4.5.5. (R)-2-(6-(Hydroxymethyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**13j**).* Yellow oil (437.1 mg, 98%): ν_{max} (liquid film) 3502, 3062, 2929, 2872, 1718, 1645, 1545, 1473, 1446, 1312, 1309, 1153; δ_H (200 MHz; $CDCl_3$) 8.00–7.82 (2H, m), 7.77–7.41 (6H, m), 7.30 (1H, s), 7.25–7.19 (1H, m), 6.52 (1H, dd, *J*=6.2, 2.7 Hz), 4.61 (1H, d, *J*=13.5 Hz), 4.43 (1H, d, *J*=13.5 Hz), 3.42 (1H, d, *J*=12.3 Hz), 3.29–3.11 (2H, m), 2.99 (1H, d, *J*=1.7 Hz), 2.86–2.60 (1H, m); δ_C (50 MHz; $CDCl_3$) 187.5, 144.5, 141.3, 139.6, 138.7, 138.7, 134.3, 132.1, 131.9, 130.2, 129.3 (2CH), 128.9 (2CH), 124.5, 122.9, 120.1, 62.7, 62.3, 33.5, 27.9; EIHRMS: calcd for $C_{21}H_{19}O_4SBr$ (M+Na): 469.0085; found: 469.0079 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=360 nm; t_R (minor)=31.2 min; t_R (major)=35.1 min; $[\alpha]_D^{25}$ +23.29 (*c* 0.97, $CHCl_3$).

4.6. General procedure for mesylation reaction: synthesis of compounds 11 and 14

Hydroxyl derivative (1 mmol), 4-(dimethylamino)pyridine (0.2 mmol) and triethylamine (1.3 mmol) were dissolved in 10 ml of DCM, and then methanesulfonyl chloride (1.2 mmol) was added. The mixture was stirred at room temperature for 40 min. The reaction was quenched with H_2O and extracted with ethyl acetate after 10 min. The organic layers were washed with HCl (2 M), $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the desired product.

*4.6.1. (S)-1-(6-(Methanesulfonyl)oxymethyl)-4-(4-methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**11**).* Yellow oil (380.2 mg, 99%): ν_{max} (liquid film) 2939, 1718, 1651, 1637, 1568, 1446, 1323, 1309, 1292, 1153; δ_H (200 MHz; $CDCl_3$) 7.95–7.84 (2H, m), 7.72–7.50 (3H, m), 7.10 (1H, d, *J*=5.9 Hz), 5.94 (1H, d, *J*=5.9 Hz), 4.51 (1H, d, *J*=13.5 Hz), 4.38 (1H, d, *J*=13.5 Hz), 3.91 (1H, dd, *J*=10.7, 8.3 Hz), 3.79 (1H, dd, *J*=10.7, 5.0 Hz), 3.31–3.16 (1H, m), 2.95 (3H, s), 2.50–2.35 (2H, m), 1.94 (3H, s); δ_C (50 MHz; $CDCl_3$) 186.6, 148.9, 142.2, 139.0, 134.5, 130.7, 129.5 (2CH), 128.6 (2CH), 119.4, 67.8, 62.7, 37.5, 30.8, 30.4, 24.3; EIHRMS: calcd for $C_{17}H_{20}O_6S_2$ (M+Na): 407.0599; found: 407.0593 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-hexane/isopropyl alcohol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (minor)=69.0 min; t_R (major)=79.0 min; $[\alpha]_D^{25}$ −9.00 (*c* 1.1, $CHCl_3$).

*4.6.2. (R)-1-(6-(Methanesulfonyl)oxymethyl)-4-(4-phenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one (**14**).* Yellow oil (223.0 mg, 50%): ν_{max} (liquid film) 2963, 2932, 1718, 1650, 1541, 1446, 1354, 1323, 1309, 1292, 1174, 1153; δ_H (200 MHz; $CDCl_3$) 7.92 (2H, d, *J*=7.9 Hz), 7.76–7.49 (3H, m), 7.49–7.37 (5H, m), 7.34 (1H, d, *J*=6.2 Hz), 6.58 (1H, dd, *J*=6.3, 2.7 Hz), 4.58 (1H, d, *J*=13.4 Hz), 4.44 (1H, d, *J*=13.4 Hz), 4.22 (1H, d, *J*=5.7 Hz), 3.96 (1H, t, *J*=6.7 Hz), 3.49–3.38 (1H, m), 2.93 (3H, s), 2.78 (2H, ddd, *J*=11.3, 9.0, 2.8 Hz); δ_C (50 MHz; $CDCl_3$) 186.3, 146.4, 141.5, 138.6, 134.4, 132.1, 130.9, 129.6, 129.4 (2CH), 128.5 (4CH), 126.1 (2CH), 119.2, 67.6, 62.7, 37.2, 30.4, 27.8; EIHRMS: calcd for $C_{22}H_{22}O_6S_2$ (M+Na): 469.0755; found: 469.0750 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ=325 nm; t_R (minor)=17.9 min; t_R (major)=23.2 min; $[\alpha]_D^{25}$ +7.22 (*c* 0.36, $CHCl_3$).

4.7. Synthesis of (*Z*)-5-methyl-1-((phenylsulfonyl)methylene)-1,3,3a,4-tetrahydroisobenzofuran (12)

Compound **11** (162 mg, 0.38 mmol) was dissolved in 4 ml of DCM, and then 1,8-diazabicyclo[5.4.0]undec-7-ene (85 μl, 0.57 mmol) was added. The mixture was stirred at room temperature for 35 min. The reaction was quenched with H_2O and extracted with ethyl acetate after 10 min. The organic layers were washed with H_2O, dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography

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(*n*-hexane/EtOAc, 6:4) afforded **12** as a yellow oil (56.1 mg, 50%). ν_{max} (liquid film) 3066, 2929, 2900, 1610, 1579, 1446, 1304, 1140; δ_H (200 MHz; benzene-d_6) 8.32–8.21 (2H, m), 7.14–6.97 (3H, m), 5.92 (1H, s), 5.84–5.73 (1H, m), 5.43–5.35 (1H, m), 4.01 (1H, t, *J*=8.6 Hz), 3.19–3.02 (1H, m), 2.26–2.01 (1H, m), 1.37 (3H, s), 1.32–1.08 (2H, m); δ_C (50 MHz; benzene-d_6) 162.1, 145.4, 140.2, 131.9, 130.4, 128.6 (2CH), 127.9 (2CH), 122.8, 120.2, 97.0, 77.9, 35.3, 31.2, 22.9; EIHRMS: calcd for $C_{16}H_{16}O_3S$ (M+H): 289.0898; found: 289.0893 (M+H). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-hexane/isopropyl alcohol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ=350 nm; t_R (minor)= 16.9 min; t_R (major)=19.4 min; $[\alpha]_D^{25}$ −86.50 (*c* 1.57, MeOH).

4.8. Synthesis of compounds 16, 17 (and 18)

Procedure a: To a solution of 1 mmol of starting material (**10**, 45.9 mg, 0.15 mmol or **12**, 46.1 mg, 0.16 mmol) in $CDCl_3$ (10 ml) was added *m*-CPBA (70% pure, 1 equiv) and the reaction was left to stir for the specified time (15 h for compound **10** and 6 h for compound **12**). Flash chromatography (EtOAc/MeOH, 95:5) afforded the corresponding product (1/1 mixture of **16**/**17**, 18.4 mg, 38% starting from **10**; only **16**, 31.9 mg, 62% starting from **12**).

Procedure b: A solution of **12** (38.4 mg, 0.13 mmol) in $CHCl_3$ (1 ml) was heated at 37 °C under normal air atmosphere for 72 h. Flash chromatography (EtOAc/MeOH, 95:5) afforded **16** (22.1 mg, 53%).

*4.8.1. 1-((1S,4R,5R)-4-Hydroxy-5-methyl-6-oxabicyclo[3.2.1]oct-2-en-2-yl)-2-(phenylsulfonyl)ethan-1-one (**16**).* Yellow oil: ν_{max} (liquid film) 3471, 2970, 2932, 2873, 1712, 1666, 1625, 1448, 1379, 1321, 1309, 1259, 1150; δ_H (600 MHz; $CDCl_3$) 7.95–7.80 (2H, m), 7.75–7.47 (3H, m), 6.72 (1H, d, *J*=3.9 Hz), 4.49 (2H, s), 3.91–3.85 (1H, m), 3.85–3.79 (1H, m), 3.48–3.38 (1H, m), 3.34 (1H, d, *J*=7.5 Hz), 1.63 (1H, d, *J*=8.0 Hz), 1.56 (1H, dd, *J*=8.0 Hz, 4.0 Hz), 1.45 (3H, s); δ_C (150 MHz; $CDCl_3$) 187.3, 144.2, 141.9, 138.7, 134.4, 129.4 (2CH), 128.5 (2CH), 81.4, 73.7, 72.4, 62.4, 35.7, 35.3, 21.8; EIHRMS: calcd for $C_{16}H_{18}O_5S$ (M+Na): 345.0773; found: 345.0767 (M+Na). $[\alpha]_D^{25}$ −13.05 (*c* 0.95, $CHCl_3$).

*4.8.2. 1-((4S,7S)-7-Hydroxy-7-methyl-2-oxabicyclo[2.2.2]oct-5-en-5-yl)-2-(phenylsulfonyl)ethan-1-one (**17**).* Yellow oil: ν_{max} (liquid film) 3464, 2929, 1710, 1664, 1626, 1448, 1321, 1309, 1153; δ_H (600 MHz; $CDCl_3$) 7.98–7.80 (2H, m), 7.74–7.50 (3H, m), 7.32 (1H, d, *J*=4.6 Hz), 4.59 (1H, d, *J*=13.6 Hz), 4.38 (1H, d, *J*=13.6 Hz), 3.59–3.30 (3H, m), 2.21 (1H, d, *J*=15.4 Hz), 2.09–1.83 (2H, m), 1.51 (3H, s); δ_C (150 MHz; $CDCl_3$) 187.6, 141.9, 141.1, 138.5, 134.4, 129.3 (2CH), 128.5 (2CH), 82.0, 66.3, 63.0, 53.8, 35.2, 30.9, 21.8; EIHRMS: calcd for $C_{16}H_{18}O_5S$ (M+Na): 345.0773; found: 345.0771 (M+Na). $[\alpha]_D^{25}$ −99.95 (*c* 0.19, $CHCl_3$).

*4.8.3. (1aS,2aS,6aR,Z)-1a-Methyl-5-((phenylsulfonyl)methylene)-1a,2,2a,3,5,6a-hexahydrooxireno[2,3-f]isobenzofuran (**18**).* Yellow oil: ν_{max} (liquid film) 2961, 2928, 1614, 1446, 1304, 1142; δ_H (600 MHz; benzene-d_6) 8.22 (2H, dd, *J*=7.8, 1.8 Hz), 7.06–6.92 (3H, m), 5.84 (1H, s), 5.51 (1H, t, *J*=3.7 Hz), 3.71 (1H, t, *J*=8.7 Hz), 3.00–2.80 (1H, m), 2.47 (1H, d, *J*=3.7 Hz), 2.19–2.03 (1H, m), 1.18 (1H, dd, *J*=13.9, 7.5 Hz), 0.91 (3H, s), 0.14 (1H, dd, *J*=13.9, 11.5 Hz); δ_C (150 MHz; benzene-d_6) 161.5, 144.7, 137.8, 131.9, 128.4 (2CH), 127.5 (2CH), 122.7, 98.2, 76.6, 59.9, 53.1, 34.6, 29.0, 20.5; EIHRMS: calcd for $C_{16}H_{16}O_4S$ (M+H): 305.0848; found: 305.0843 (M+H). $[\alpha]_D^{25}$ +101.61 (*c* 0.31, $CHCl_3$).

4.9. Synthesis of (2*R*,4*R*)-5′-methyl-2,4-bis(phenylsulfonyl)-3′*H*-spiro[cyclobutane-1,1′-isobenzofuran] (19)

Compound **12** (56 mg, 0.19 mmol) and phenyl vinyl sulfone (66 mg, 0.39 mmol) were dissolved in 1 ml of benzene-d_6. The mixture was stirred at reflux for 2.5 h. Flash chromatography (*n*-Hexane/EtOAc, 6:4) afforded **19** as a yellow oil (36.2 mg, 42%). ν_{max} (liquid film) 3062, 2970, 2926, 1714, 1381, 1146, 1319, 1148; δ_H (600 MHz; benzene-d_6) 8.01–7.83 (4H, m), 7.08–6.70 (9H, m), 5.26 (1H, dd, *J*=9.8, 4.3 Hz), 5.04 (1H, d, *J*=15.0 Hz, 4.70 (1H, d, *J*=4.8 Hz), 3.90 (1H, d, *J*=15.0 Hz), 2.04 (3H, s), 1.90–1.75 (2H, m); δ_C (150 MHz; benzene-d_6) 145.3, 143.7, 142.0 (2C), 138.0, 129.1 (2CH), 128.7 (2CH), 128.2 (2CH), 127.9 (2CH), 127.8 (2CH), 121.4, 119.9, 119.4, 85.5, 78.9, 62.7, 56.2, 33.2, 19.6; EIHRMS: calcd for $C_{24}H_{22}O_5S_2$ (M+NH_4): 472.1247; found: 472.1247 (M+NH_4). $[\alpha]_D^{25}$ −6.67 (*c* 0.81, MeOH).

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.076.

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15. Crystal data for **10**: CCDC 975368. See http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx for crystallographic data in cif or other electronic format.
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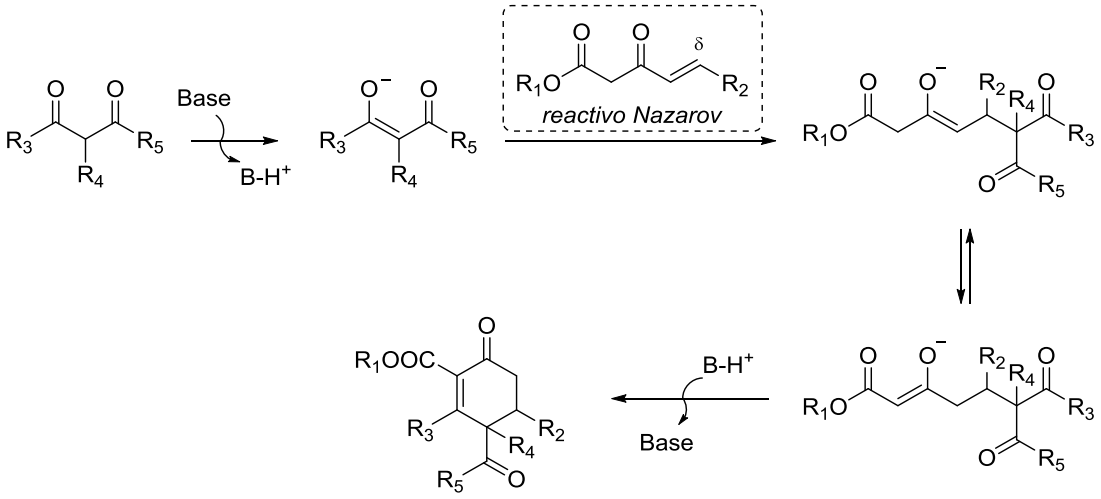
RESUMEN EN CASTELLANO Y CONCLUSIONES

RESUMEN EN CASTELLANO. TABLA DE CONTENIDOS.

1. Introducción.

En 1953 Nazarov[296] propuso un nuevo reactivo, una vinil cetona que se había activado como β-cetoester, conocido desde entonces como reactivo de Nazarov. El 3-oxo-3-pentenoato de etilo y de metilo se han utilizado en diferentes síntesis desde el trabajo de Nazarov y Zav'yalov, quienes fueron los primeros en demostrar su utilidad en la ciclación de β-dicetonas cíclicas.

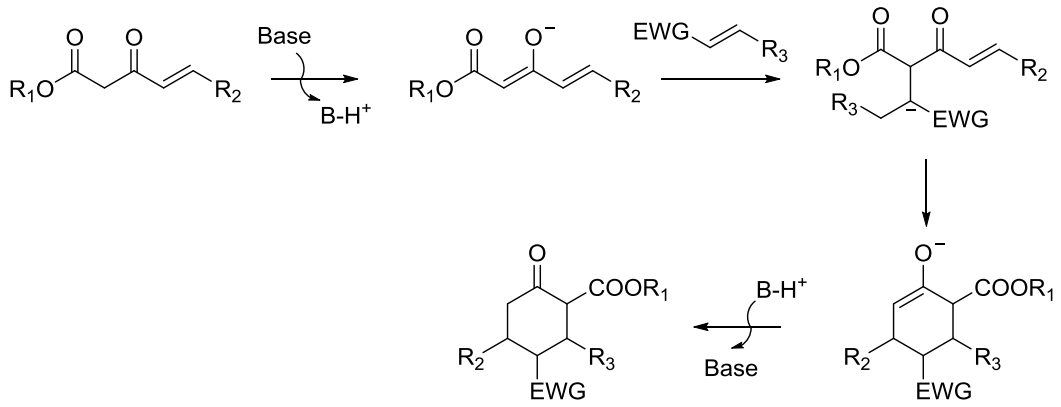
Los reactivos de Nazarov dan lugar a ciclos según dos procesos. En el primero, descrito por el propio Nazarov, un carbanión estabilizado induce una adición de Michael a la parte vinil cetona del reactivo. A continuación termina la ciclación a través de una aldolización intramolecular. De esta forma el reactivo Nazarov aparece, en el primer paso, como un electrófilo y la reacción global se asemeja a la anelación de Robinson[297] (Esquema 1). Su reactividad como electrófilo dependerá de la sustitución en el carbono δ, y cuando se dé una disustitución, el paso de adición de Michael estará más desfavorecido.



Esquema 1

En el segundo proceso, la enolización de la parte β-cetoester conduce a un carbanión estabilizado que puede reaccionar con un aceptor de Michael electrófilo. En este caso, primero reaccionará como nucleófilo (Esquema 2).

[296] Bergelson, L. D. *Tetrahedron* **1959**, *6*, 161. (10.1016/0040-4020(59)85010-9)
[297] Gawley, R. E. *Synthesis* **1976**, 777. (10.1055/s-1976-24200)

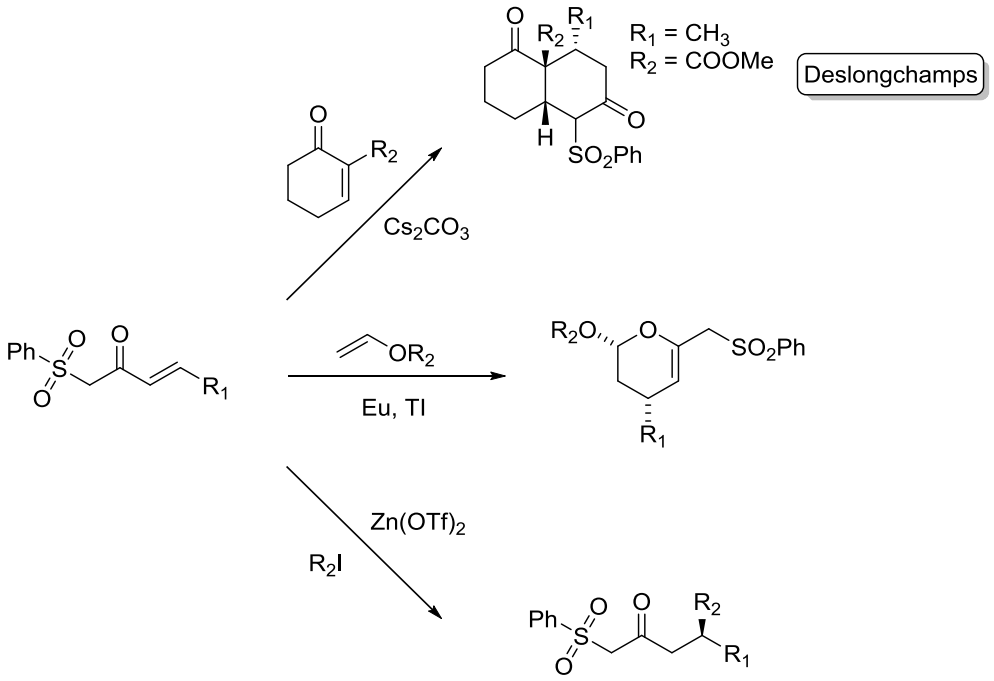


Esquema 2

Ocurren dos reacciones de Michael consecutivas y en algunas publicaciones se nombra una adición de Michael tándem o una adición Michael-Michael. Pero en ciertos casos, la estereoquímica de los productos obtenidos así sugiere una reacción de Diels-Alder concertada. Las síntesis de *cis*-decalinas más recientes basadas en la denominada anelación de Deslongchamps involucran este mecanismo.

Aunque existen muchos ejemplos en bibliografía de reacciones de esteres α,β-insaturados utilizados como reactivos de Nazarov, la presencia del grupo funcional ester no siempre es posible o no se desea dentro de una determinada ruta sintética. Por ello también se han desarrollado ciertos análogos de reactivos Nazarov (principalmente sulfóxidos, sulfonas o fosfonatos).[298] Sin embargo la reactividad de los sulfonil análogos de Nazarov no se han explorado demasiado aún y la mayoría de las publicaciones sólo describen reacciones de adición nucleofílica al doble enlace o reacciones de Diels-Alder. Solamente Deslongchamps *et al*. publicó una ciclación *via* doble adición de Michael de una β-cetosulfona utilizando Cs_2CO_3 pero sin ningún tipo de enantiocontrol (Esquema 3).

[298] Audran, G.; Brémond, P.; Feuerstein, M.; Marque, S. R. A. and Santelli, M. *Tetrahedron* **2013**, *69*, 8325. (10.1016/j.tet.2013.06.065) y las referencias aquí citadas.



Esquema 3

Con la entrada de este siglo, el campo de la organocatálisis asimétrica ha sido foco de inmensa investigación y desarrollo,[299] evolucionando y emergiendo como una poderosa herramienta para la síntesis asimétrica, la cual se ha vuelto cada vez más útil dentro del rango de las disciplinas sintéticas como la síntesis orientada a la diversidad (DOS).[300] Varios grupos funcionales han sido importantes para este desarrollo, entre ellos la aplicación de sulfonas,[301] las cuales han contribuido en gran medida a la aplicación sintética de la organocatálisis asimétrica. La fuerte capacidad inductiva del grupo sulfona lo hace ideal para intervenir en varios tipos de reacciones organocatalizadas, y las diferentes transformaciones que pueden sufrir hace de los subsecuentes intermedios apropiados para la generación de varios productos importantes que de otra forma serían más difíciles de obtener. Considerando las muchas y nuevas transformaciones desarrolladas, la organocatálisis asimétrica con sulfonas debe verse como una buena contribución a este área emergente de síntesis organocatalítica estereoselectiva orientada a la diversidad.

[299] Bertelsen, S. and Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (10.1039/B903816G)
[300] Trabocchi, A. *Diversity-oriented synthesis : basics and applications in organic synthesis, drug discovery, and chemical biology*; Hoboken, New Jersey : Wiley, **2013**.
[301] Alba, A.-N. R.; Companyo, X. and Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018. (10.1039/B911852G)

En este trabajo planeamos desarrollar una nueva síntesis de sulfonil análogos de Nazarov y emplearlos como material de partida para el estudio de nuevas reacciones organocatalizadas, empleando para ello diferentes organocatalizadores comerciales (Figura 1),[302] y estudiando el comportamiento con diferentes aldehídos α,β-insaturados.

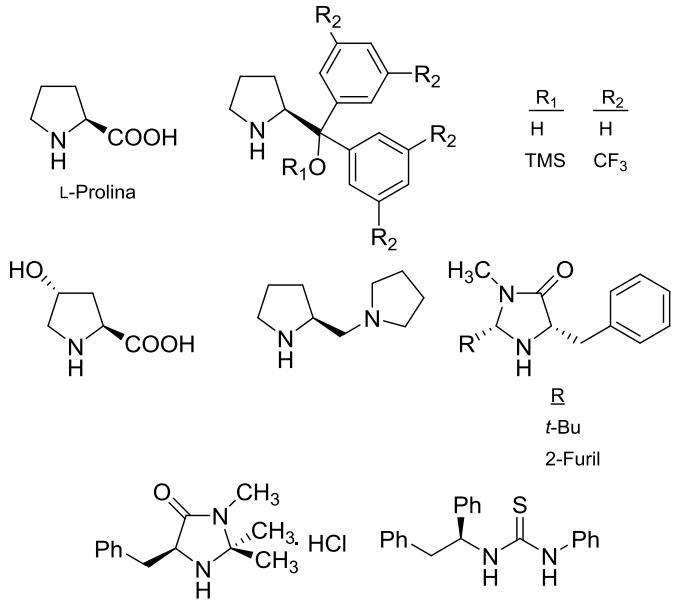


Figura 1

Así, se irá incrementando la complejidad de los aldehídos α,β-insaturados empleados con el fin de estudiar la reactividad de las β-cetosulfonas en condiciones organocatalíticas (Figura 2).

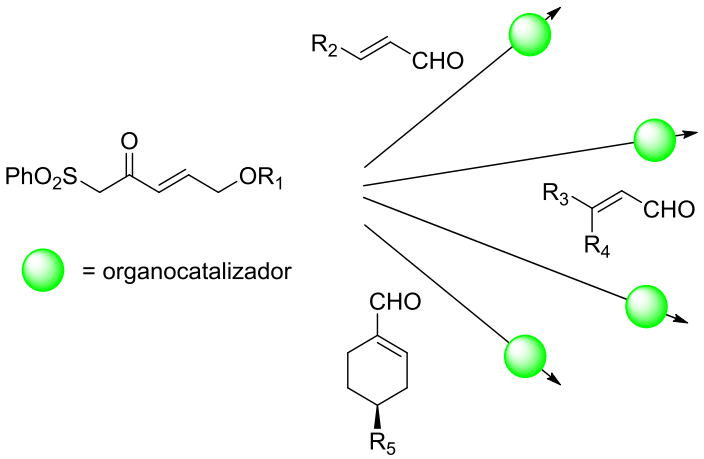


Figura 2

[302] Díez, D.; Antón, A. B.; Peña, J.; García, P.; Garrido, N. M.; Marcos, I. S.; Sanz, F.; Basabe, P. and Urones, J. G. *Tetrahedron: Asymmetry* **2010**, *21*, 786. (10.1016/j.tetasy.2010.05.005)

2. Síntesis de reactivos sulfonil Nazarov I-A, I-B, I-C y I-D.

La mayoría de las reacciones con β-cetosulfonas γ,δ-insaturadas que se encuentran en bibliografía sólo emplean la reactividad del metileno activo, el grupo carbonilo o el doble enlace por separado. En nuestro grupo queríamos explirar la reactividad de dichas sulfonas como reactivos de Nazarov, donde al menos dos de las tres funcionalidades participasen la reacción. Además decidimos introducir una funcionalidad extra en el extremo de estas sulfonas donde colocamos un grupo hidroxilo (protegido o libre) que pudiese ser empleado más adelante para la síntesis de compuestos orientados a la diversidad o como nexo de unión en química de soporte sólido.[303] De esta forma desarrollamos la síntesis de cuatro nuevos sulfonil análogos de Nazarov **I-A**, **I-B**, **I-C** y **I-D** (Figura 3).

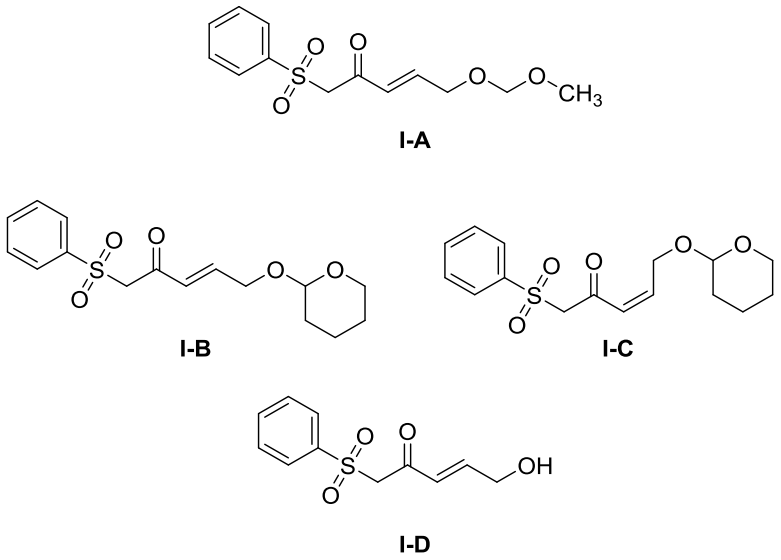
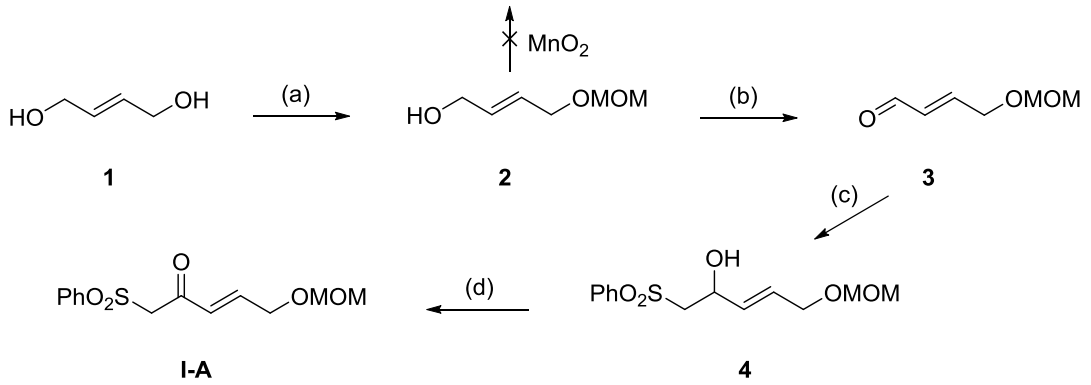


Figura 3

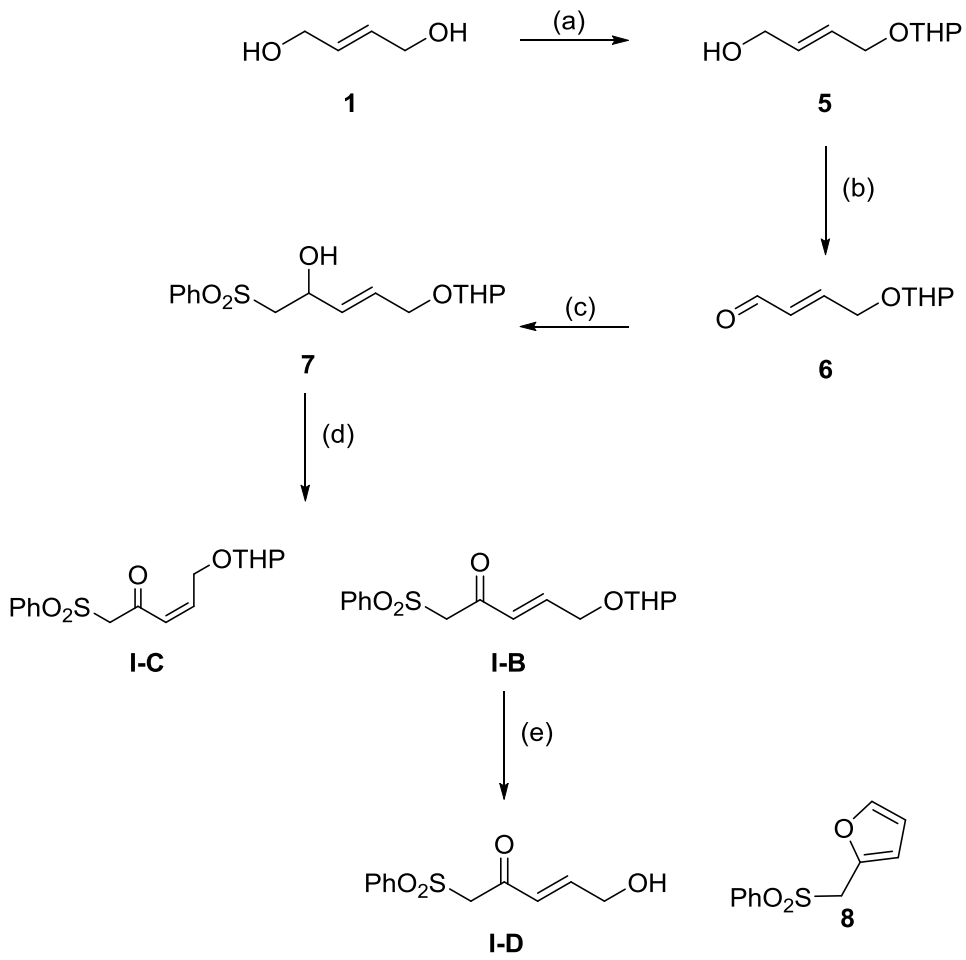
[303] Arboré, A.; Dujardin, G. and Maignan, C. *Eur. J. Org. Chem.* **2003**, 4118. (10.1002/ejoc.200300417)

En primer lugar desarrollamos la síntesis del reactivo de Nazarov **I-A** como se muestra en el Esquema 4.



Esquema 4 (a) MOMCl, NaH, THF, 0 ºC, 87%; (b) PDC (2 equivs.), MS, DCM, ta, 72%; (c) Metilfenilsulfona (0.9 equivs.), *n*-BuLi (0.9 equivs.), THF, -78 ºC, 63%; (d) PDC (2 equivs.), MS, ta, 50 %.

La síntesis de las β-cetosulfonas **I-B, I-C** y **I-D** se muestra en el Esquema 5. Las sulfonas **I-B** y **I-C** pudieron separarse fácilmente por cromatografía en columna. Tras estudiar las condiciones de desprotección del grupo THP, se encontró que el mejor disolvente era una mezcla de THF/H_2O ya que al hacerlo en 2-propanol sólo se obtenía un 28% del producto deseado y un 27% del producto de ciclación intramolecular **8**.



Esquema 5 (a) DHP, *p*-TsOH·H_2O (1 mol%), DCM, ta, 96%; (b) PDC (2 equivs.), MS, DCM, ta, 91%; (c) Metilfenilsulfona (0.9 equivs.), *n*-BuLi (0.9 equivs.), THF, -78 ºC, 61%; (d) PDC (2 equivs.), MS, ta, 58%, (ratio **I-B**/**I-C**: 99/1); (e) *p*-TsOH·H_2O (10%), THF/H_2O (1/1), ta, 88%.

3. Estudio de la reactividad de los reactivos sulfonil Nazarov I-A, I-B, I-C y I-D en reacciones organocatalíticas.

Dado que las β-cetosulfonas γ,δ-insaturadas se han empleado principalmente en reacciones de Diels-Alder, en nuestro grupo quisimos estudiar su comportamiento como análogos de Nazarov y utilizarlas en la síntesis de diversas estructuras cíclicas. Con este propósito probamos diferentes condiciones organocatalíticas con el fin de obtener los compuestos deseados con buenos rendimientos controlando la regio- y la estereoselectividad de los productos obtenidos.

Así, en este trabajo se describen las diferentes condiciones organocatalíticas y reacciones estudiadas con las β-cetosulfonas **I-A, I-B, I-C** y/o **I-D** y aldehídos α,β-insaturados de distinto grado de sustitución en la posición β. Esto nos ha permitido poder sintetizar diversas estructuras cíclicas (Figura 4), a saber: (1) ciclohexenonas quirales;[304] (2) ciclohexa-1,3-dienos quirales;[305] (3) 2*H*-piranos;[306] (4) y *cis*-decalinas quirales.[307]

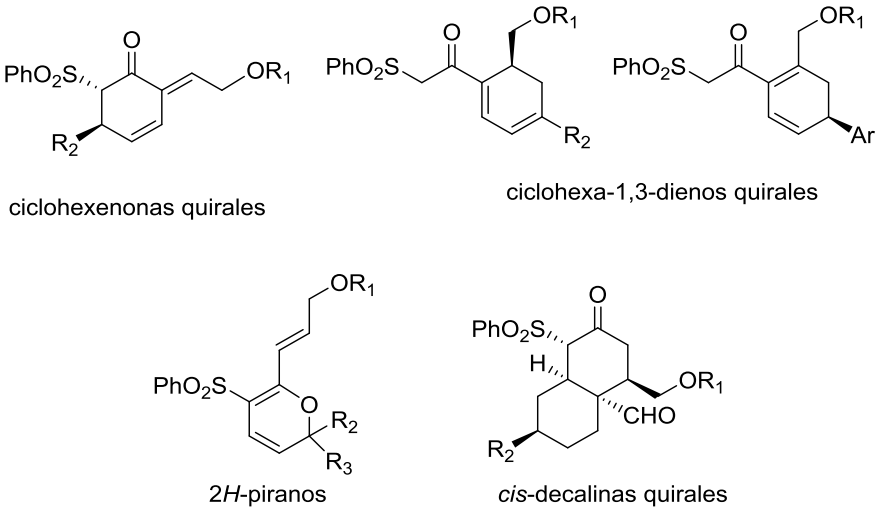


Figura 4

Por último se desea implementar esta metodología mediante la unión de las β-cetosulfonas a un sistema polimérico y aplicar las condiciones organocatalíticas encontradas para realizar la síntesis de las nuevas estructuras obtenidas en un soporte sólido.

[304] García Ruano, J. L.; Alvarado, C.; Díaz-Tendero, S. and Alemán, J. *Chem. Eur. J.* **2011**, *17*, 4030. (10.1002/chem.201003267)
[305] Bench, B. J.; Liu, C.; Evett, C. R. and Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458. (10.1021/jo061763t)
[306] Garcia, A.; Borchardt, D.; Chang, C.-E. A. and Marsella, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 16640. (10.1021/ja907062v)
[307] Singh, V.; Iyer, S. R. and Pal, S. *Tetrahedron* **2005**, *61*, 9197. (10.1016/j.tet.2005.06.102)

3.1. Reactividad con aldehídos α,β-insaturados β-monosustituidos.

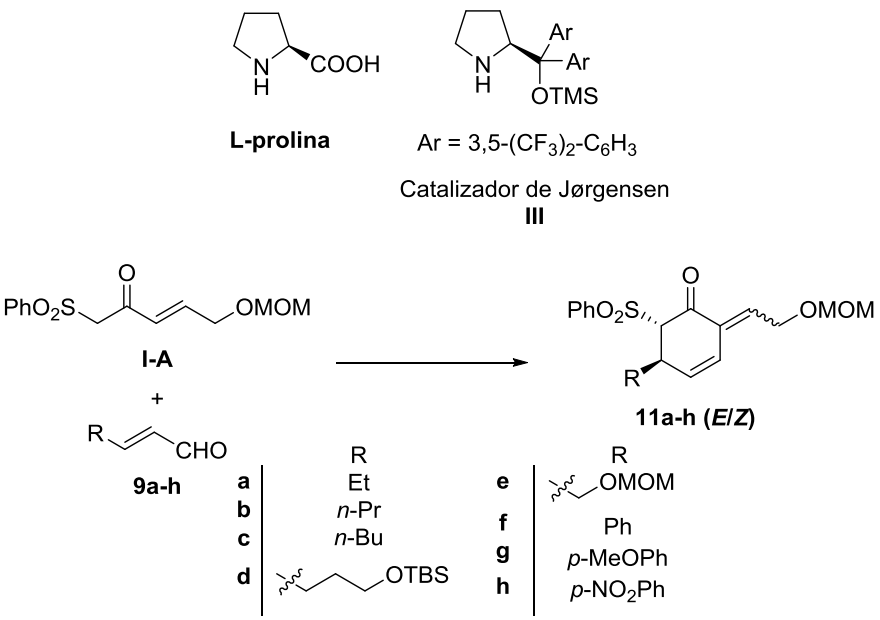
Los ejemplos del uso de reactivos Nazarov en síntesis de ciclohexenonas quirales son escasos. Jørgensen *et al.* emplearon un reactivo de Nazarov en la reacción con aldehídos α,β-insaturados, sin embargo lo que obtuvieron fueron 2-alkiliden-ciclohexanonas.[308,309] Ruano y Alemán *et al.* sintetizaron ciclohexenonas quirales pero empleando simples β-cetosulfonas y no análogos de Nazarov.[310] En 2006 Takemoto *et al.* publicaron una adición de Michael de β-cetoesteres γ,δ-insaturados a nitroalcanos catalizada por una tiourea bifuncional.[311]

La investigación se ha centrado recientemente en el desarrollo de reacciones cascada y multicomponente, particularmente de reacciones organocatalizadas. La Naturaleza emplea este principio para construir múltiples enlaces de manera eficiente en sistemas biológicos de muchos productos naturales con la ayuda de enzimas. Así, las reacciones cascada organocatalíticas recuerdan a los procesos biosintéticos que son altamente quimio-, regio- y estereoselectivos.[312] Estas transformaciones son "atomo-económicas" y evitan reacciones de protección/desprotección y aislar los intermedios. Además generan un mínimo de residuos.

Las reacciones organocatalíticas tándem han demostrado ser una gran herramienta para la síntesis de ciclohexenonas quirales. Sin embargo han de resolverse muchos problemas cruciales para conseguir una buena síntesis asimétrica.

Tras un importante estudio de diversos catalizadores, disolventes, aditivos, etc., encontramos las mejores condiciones para sintetizar ciclohexenonas quirales. Así, empleando el catalizador de Jørgensen y prolina en tándem en $CDCl_3$ (Esquema 6) se obtuvieron ciclohexenonas quirales con buenos rendimientos (41 – 77%) y enantioselectividades (hasta un 96% ee). La configuración absoluta de los productos se estableció de acuerdo a los resultados obtenidos por Ruano y Alemán *et al.*[313] con sulfonas y aldehídos similares.

[308] Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S. and Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 121. (10.1002/anie.200704076)
[309] Albrecht, Ł.; Richter, B.; Vila, C.; Krawczyk, H. and Jørgensen, K. A. *Chem. Eur. J.* **2009**, *15*, 3093. (10.1002/chem.200802285)
[310] García Ruano, J. L.; Alvarado, C.; Díaz-Tendero, S. and Alemán, J. *Chem. Eur. J.* **2011**, *17*, 4030. (10.1002/chem.201003267)
[311] Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H. and Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (10.1016/j.tet.2005.08.109)
[312] Clardy, J. and Walsh, C. *Nature* **2004**, *432*, 829.
[313] Alemán, J.; Marcos, V.; Marzo, L. and García Ruano, J. L. *Eur. J. Org. Chem.* **2010**, 4482. (10.1002/ejoc.201000502)


COOH
N
H
L-prolina
Ar
Ar
OTMS
Ar = 3,5-(CF3)2-C6H3
Catalizador de Jørgensen
III
O
PhO2S
OMOM
I-A
+
R
CHO
9a-h
a Et
b n-Pr
c n-Bu
d OTBS
e OMOM
f Ph
g p-MeOPh
h p-NO2Ph
11a-h (E/Z)

Esquema 6

3.2. Reactividad con aldehídos α,β-insaturados β-metil-β-disustituidos.

Los aldehídos α,β-insaturados monosustituidos se han empleado ampliamente en organocatálisis en la síntesis de compuestos muy interesantes.[314] Sin embargo, los aldehídos α,β-insaturados β-metil-β-disustituidos se han utilizado mucho menos. Por este motivo y dados los buenos resultados obtenidos previamente, decidimos estudiar otros aldehídos más complejos así que, en lugar de emplear los aldehídos α,β-insaturados monosustituidos anteriores, esta vez usamos aldehídos α,β-insaturados β-metil-β-disustituidos. Así llevamos a cabo la reacción entre nuestra sulfona **I-A** y citral en presencia del catalizador de Hayashi-Jørgensen **XXV** ya que éste daba el mismo resultado que el catalizador **III** en la síntesis de cyclohexenonas quirales y era más fácil de manejar. Además, se trata de un catalizador no fluorado y es más soluble en 2-propanol, lo que lo hace más adecuado para trabajar en "química verde". Nuestro plan era añadir la prolina justo después del catalizador **XXV**, sin embargo y sorprendentemente, éste catalizador no dio lugar únicamente al producto de adición de Michael sino que se obtuvo una nueva estructura, a saber, un ciclohexa-1,3-dieno quiral.

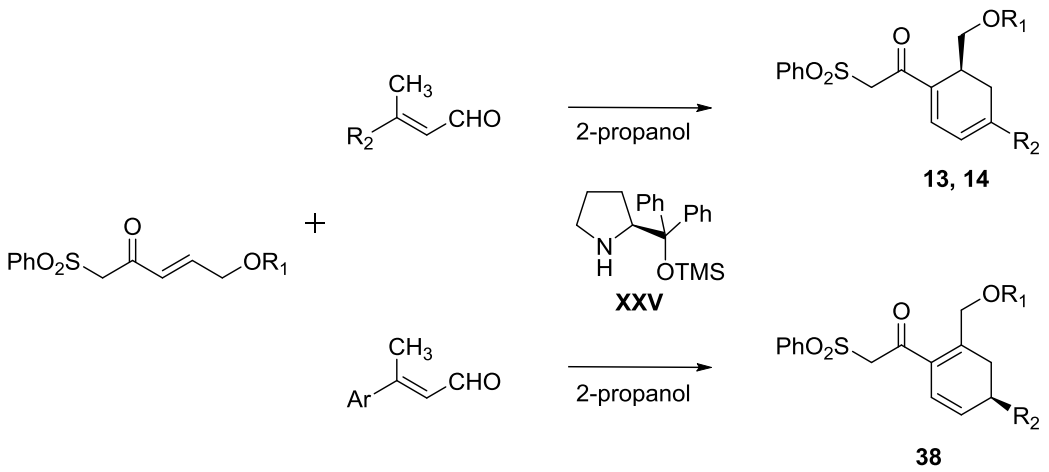
Los ciclohexa-1,3-dienos y sus derivados son estructuras importantes dada su versatilidad como intermedios en la síntesis de productos naturales y compuestos biológicamente activos,[315] incluyendo terpenos, carotenoides y esteroides. El compuesto ciclohexa-1,3-dieno por sí mismo se ha empleado como material de partida en la síntesis estereoselectiva de 11-desoxiprostaglandinas.[316] Tanto el dieno en sí mismo como la amplia mayoría de sus derivados únicamente se obtienen por síntesis. A pesar de la importancia de esta clase de compuestos, los principales métodos para su síntesis tienen como material de partida el anillo de ciclohexano y muchos de los métodos sintéticos empleados dan lugar a la formación de productos secundarios, incluyendo dienos isomerizados. La alta reactividad de los ciclohexadienos, particularmente su tendencia a dimerizar, polimerizar, aromatizar y oxidarse también puede ser la causa del reducido rendimeiento de los productos obtenidos y de la apairción de impurezas.[317]

Serebryakov *et al.* desarrollaron la síntesis asimétrica de ciclohexa-1,3-dienos a partir de prenal y esteres insaturados o derivados,[318] Watanabe *et al.*, empleando prolina como organocatalizador consiguieron dimerizar el citral a través de una reacción de Diels-Alder[319] y Christmann *et al.* publicaron una reacción intramolecular tipo Rauhut-Curier *via* activación dienamina.[320] En

[314] Giacalone, F.; Gruttadauria, M.; Agrigento, P. and Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406. (10.1039/C1CS15206H)
[315] Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F. and Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459. (10.1021/jo701477v)
[316] Corey, E. J. and Ravindranathan, T. *Tetrahedron Lett.* **1971**, *12*, 4753. (10.1016/S0040-4039(01)87545-6)
[317] Mironov, V. A.; Fedorovich, A. D. and Akhrem, A. A. Russ. Chem. Rev. **1983**, *52*, 61. (10.1070/RC1983v052n01ABEH002797)
[318] Serebryakov, E. P.; Shcherbakov, M. A.; Gamalevich, G. D. and Struchkova, M. I. *Russ. Chem. Bull.* **2003**, *52*, 734. (10.1023/A:1023987613185)
[319] Bench, B. J.; Liu, C.; Evett, C. R. and Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458. (10.1021/jo061763t)
[320] Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M. and Christmann, M. *Org. Lett.* **2009**, *11*, 4116. (10.1021/ol901614t)

bibliografía no existen ejemplos de síntesis de ciclohexa-1,3-dienos a partir de β-cetosulfonas o de sulfonil análogos de Nazarov. Sólo Perumal *et al.* emplearon β-cetosulfonas en una reacción de Michael con aldehídos utilizando NH_4OAc pero lo que obtuvieron fueron ciclohexa-1,4-dienos.

Tras un amplio estudio de condiciones de reacción, se comprobó que las mejores condiciones era emplear un 50 mol% de catalizador en EtOH como disolvente. Esta reacción fue extendida a más aldehídos similares así como a aldehídos con sustituyentes aromáticos en lugar de alquílicos. En este caso, la disposición de los dobles enlaces endocíclicos cambiaba (Esquema 7). La estereoquímica absoluta fue determinada mediante estudios de difracción de rayos-X de un derivado tras desproteger el grupo THP. Así mismo, la estereoquímica absoluta de los derivados aromáticos se explica a través de un reordenamiento *1,5*-sigmatrópico de hidrógeno.



Esquema 7

Con este estudio encontramos las condiciones con las que por primera vez se ha hecho reaccionar un sulfonil análogo de Nazarov en una reacción de Diels-Alder en condiciones de organocatálisis, obteniendo distintos ciclohexa-1,3-dienos quirales dependiendo de si el sustituyente en el aldehído α,β-insaturado es alquilo o arilo.

3.3. Reactividad con aldehídos α,β-insaturados β,β-disustituidos más complejos.

Dado la distinta reactividad observada de los aldehídos β-metil-β-disustituidos con el catalizador de Hayashi-Jørgensen **XXV**, decidimos probar con una metodología tándem. Nuestro plan era estudiar distintas bases como DABCO, DBU, Et_3N y diferentes organocatalizadores que emplearíamos en un primer paso de adición de Michael y a continuación añadiríamos el catalizador **XXV** para dar lugar a la ciclación. De esta manera esperábamos poder mejorar tanto el rendimiento como la enantioselectividad de la reacción.

Tras estudiar varias bases y organocatalizadores observamos como ninguno era capaz de dar lugar a un buen resultado, obteniendo sólo materiales de partida o productos de descomposición. Sin embargo, la L-prolina produjo un resultado sorprendente, pues dio lugar a una nueva estructura, a saber, piranos.

Las moléculas que contienen un heterociclo de pirano en su estructura son muy interesantes debido a su actividad biológica y sus aplicaciones en Medicina. Sin embargo no existe una gran variedad de materiales de partida para sintetizarlas, y normalmente se forman por activación *via* imínio de un carbonilo y un compuesto 1,3-dicarbonílico.[321] Como ejemplo, Chang y Marsella *et al*. describieron la reacción de la mezcla *E*/*Z* de citral con 1,3-ciclohexanodiona para formar perhidro-CBC (cannabicromeno) que posteriormente se transformó en un análogo de Δ^1-tetrahidrocannabinol.[322]

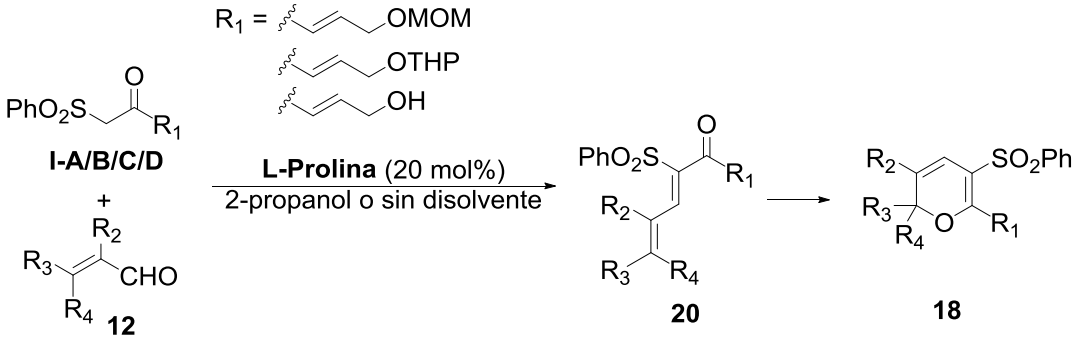
El uso de β-cetosulfonas con respecto a compuestos 1,3-dicarbonílicos añade la versatilidad extra del grupo sulfona, fundamentalmente por su facilidad de eliminación y su reactividad. Aunque las β-cetosulfonas se han utilizado en la síntesis de derivados de pirano, los sulfonil análogos de Nazarov, es decir, las β-cetosulfonas γ,δ-insaturadas sólo las emplearon Wada *et al.* para producir piranos *via* reacción de hetero-Diels-Alder con vinil éteres. Así, las mejores condiciones de reacción según este procedimiento requerían de (i) un catalizador organometálico complejo, (ii) un disolvente clorado (DCM), (iii) un enol éter activado y que (iv) el sulfonil análogo de Nazarov estuviese desactivado y no muy impedido. Además, este procedimiento siempre da lugar a 2-alkoxi-3,4-dihidro-2*H*-piranos, que ciertas condiciones de reacción durante una determinada ruta síntetica podrían romper el enlace acetal. Por estas razones en nuestro grupo quisimos desarrollar un nuevo método para sintetizar estructuras piránicas empleando nuestros sulfonil análogos de Nazarov en condiciones organocatalíticas y empleando disolventes más respetuosos con el medioambiente (o sin disolvente). También nos planteamos si sería posible obtener dichos piranos cambiando el mecanismo de reacción entre los reactivos Nazarov como **I-A** y aldehídos α,β-insaturados 3,3-disustituídos. Ya Inokuchi *et al.*

[321] Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y.; You, L.-F. and Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105. (10.1016/j.tet.2011.09.111)
[322] Garcia, A.; Borchardt, D.; Chang, C.-E. A. and Marsella, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 16640. (10.1021/ja907062v)

establecieron que los enales 2-alkilsustituídos favorecían la formación de aductos de Knoevenagel *trans* para su posterior electrociclación.[323]

Nuestro grupo se interesó en llevar a cabo la reacción con nuestras β-cetosulfonas y enales 3,3-dialquilsustituídos dada su profusión en la Naturaleza[324] como en el caso de Chan y Marsella *et al.*, empleando organocatalizadores con el fin de desarrollar procesos para sintetizar 2*H*-piranos beneficiosos con el medioambiente.

Tras un extenso estudio de catalizadores, disolventes y aditivos se encontró que sólo la prolina era capaz de producir la transformación mostrada en el Esquema 8.



Esquema 8

De esta forma encontramos por primera vez las condiciones para obtener 2*H*-piranos a partir de sulfonil análogos de Nazarov a través de una reacción de Diels-Alder en condiciones de organocatálisis y sin disolvente, haciendo de este un procedimiento seguro para el medioambiente.

[323] Peng, W.; Hirabaru, T.; Kawafuchi, H. and Inokuchi, T. *Eur. J. Org. Chem.* **2011**, 5469. (10.1002/ejoc.201100780)
[324] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G. and Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144. (10.1039/C2NP00090C)

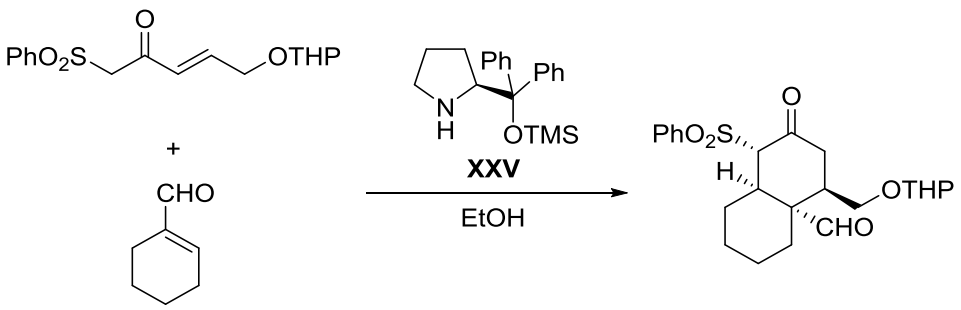
3.4. Reacción con aldehídos α,β-insaturados cíclicos.

Tras observar el resultado obtenido previamente con el 1-ciclohexen-1-carboxaldehído durante el estudio de la síntesis de piranos en presencia de prolina, decidimos extender el estudio con este y otros aldehídos α,β-insaturados cíclicos pero en presencia del catalizador de Jørgensen **III**, con el fin de obtener sistemas bicíclicos. Tras evaluar la reactividad de nuestra sulfona **I-B** con 1-ciclohexen-1-carboxaldehído en 2-propanol empleando el catalizador **III** observamos como en lugar de las estructuras previamente ya descritas se formó una nueva, a saber, una *cis*-decalina, como quedó demostrado por diversos análisis y finalmente por rayos-X.

El esqueleto de *cis*-decalina se encuentra en la estructura de varias clases de productos naturales como *cis*-clerodanos,[325] kalihinenos,[326] thelepoganos,[327] cadinanos,[328] eremofilanos,[329] y valeranonas.[330] Típicamente estos productos se obtienen a partir de productos naturales. Muchos de estos compuestos basados en la *cis*-decalina poseen amplias e interesantes actividades biológicas. Es evidente que muchos de ellos poseen diferentes grados de sustitución y hasta cuatro o más centros estereogénicos contínuos dentro del esqueleto de decalina, haciendo de su síntesis un considerable reto sintético. La complejidad estructural de estos productos naturales junto con sus interesantes propiedades biológicas ha conducido a cierto interés en el desarrollo de nuevos eficaces métodos con los que sintetizar *cis*-decalinas y los ya mencionados productos naturales.[331]

Los reactivos de Nazarov se han empleado para la síntesis de *cis*-decalinas mediante la denominada anelación de Deslongchamps[332] pero los productos se obtenían sin ningún tipo de control sobre la estereoquímica absoluta.[229] Además no existen ejemplos en bibliografía donde los sulfonil análogos de Nazarov se hayan empleado para sintetizar *cis*-decalinas. Por estos motivos nuestro grupo decidimos utilizar nuestra metodología con β-ceto sulfonas γ,δ-insaturadas en condiciones organocatalíticas para sintetizar *cis*-decalinas empleando aldehídos α,β-insaturados cíclicos como materiales de partida junto con nuestras sulfonas.

[325] Merritt, A. T. and Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243. (10.1039/NP9920900243)
[326] Okino, T.; Yoshimura, E.; Hirota, H. and Fusetani, N. *Tetrahedron Lett.* **1995**, *36*, 8637. (10.1016/0040-4039(95)01861-B)
[327] Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M. and van Soest, R. W. M. *J. Nat. Prod.* **1998**, *61*, 1310. (10.1021/np980173q)
[328] Ohta, Y. and Hirose, Y. *Tetrahedron Lett.* **1969**, *10*, 1601. (10.1016/S0040-4039(01)87956-9)
[329] Tada, M.; Moriyama, Y.; Tanahashi, Y. and Takahashi, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1999. (10.1246/bcsj.47.1999)
[330] Kulkarni, K. S.; Paknikar, S. K. and Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 1289. (10.1016/S0040-4020(01)98993-8)
[331] Singh, V.; Iyer, S. R. and Pal, S. *Tetrahedron* **2005**, *61*, 9197. (10.1016/j.tet.2005.06.102)
[332] Lavallée, J.-F. and Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117. (10.1016/S0040-4039(00)80694-2)



Esquema 9

Así tras estudiar diversas condiciones de reacción y distintos aldehídos cíclicos conseguimos sintetizar por primera vez *cis*-decalinas a partir de sulfonil análogos de Nazarov. Gracias al catalizador de Hayashi-Jørgensen se consiguieron muy buenos resultados enantioméricos (hasta un 96% ee) y en moderados rendimientos (50 – 85%, Esquema 9). Esta metodología abre una nueva vía para sintetizar *cis*-decalinas con un gran control enantiomérico y que además cuenta con los grupos sulfona e hidroxilo (protegido o libre), lo cual añade una mayor versatilidad a la hora de llevar a cabo más transformaciones o realizar esta química en estado sólido unido a soportes poliméricos.

4. Transformación de los productos obtenidos para síntesis orientada a la diversidad.

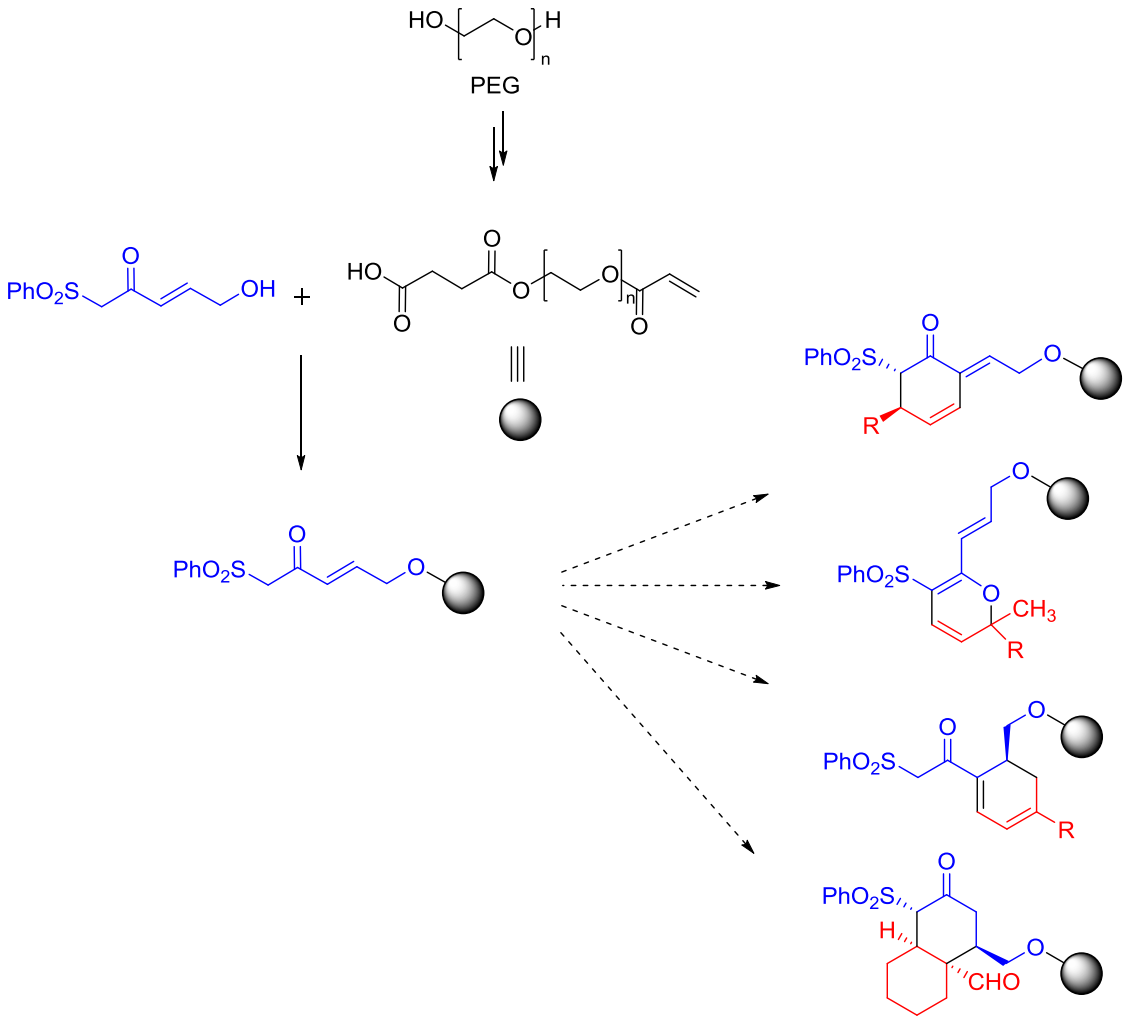
El término síntesis orientada a la diversidad (sus siglas en inglés, DOS) apareció por primera vez en la bibliografía química en el año 200 en un artículo escrito por Stuart Schreiber.[333] Más tarde, Spring *et al.* han redefinido este concepto diciendo que " la síntesis orientada a la diversidad se trata de una síntesis deliberada, simultánea y eficiente de más de un compuesto objetivo en una aproximación dirigida a la diversidad con el fin de responder a un problema complejo".[334] La llegada de la DOS está suministrando un poderoso incentivo para inventar nuevas reacciones. Las nuevas metodologías de reacción que llevan a la síntesis rápida de nuevos quimiotipos son la fuente más efectiva de librerías de "screening" biológico estructural y estereoquímicamente diversas. El uso de reacciones dominó puede ofrecer varios beneficios comparados con las síntesis de varios pasos, "workups", etc…[335]

Además, como ya se ha mostrado, la simple modificación de los organocatalizadores empleados en una reacción puede dar lugar a distintas estructuras. Con estas nuevas moléculas en nuestra mano (dienos, piranos, decalinas…) llevamos a cabo diferentes reacciones con el fin de demostrar la gran diversidad de estructuras que se pueden alcanzar gracias a las nuevas rutas sintéticas que hemos abierto durante este trabajo.

Cabe destacar como el uso de metodologías con polímeros para llevar a cabo reacciones asimétricas de formación de enlaces carbono-carbono se ha convertido en una estrategia cada vez más atractiva.[336] Así, reactivos quirales o catalizadores inmovilizados sobre polímeros ofrecen oportunidades específicas para recuperar fácilmente las caras fuentes de quiralidad y poder volver a emplearlas. Una aproximación complementaria, que evita el prerrequisito de unir el polímero a un auxiliar o ligando quiral, consiste en unir un sustrato proquiral. Se han publicado algunos ejemplos de reacciones de Diels-Alder y hetero-Diels-Alder realizadas en estas condiciones heterogéneas.[235] Mientras que la síntesis de péptidos y oligonucleótidos en estado sólido ya está bien establecida, la preparación de pequeñas moléculas orgánicas sigue siendo un área de investigación relativamente nueva y de rápido crecimiento.[337]

En nuestro grupo nos hemos interesado recientemente en esta química en estado sólido empleando derivados de polietilenglicol (PEG). Así se podrá abrir un nuevo campo para la síntesis de todos aquellos compuestos que hemos sintetizado hasta la fecha (Esquema 10).

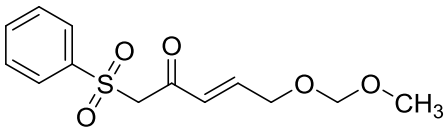
[333] Schreiber, S. L. *Science* **2000**, *287*, 1964. (10.1126/science.287.5460.1964)
[334] Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (10.1039/B310752N)
[335] Tietze, L.-F.; Brasche, G. and Gericke, K. M. *Domino reactions in organic synthesis*; Wiley-VCH: Weinheim [Germany], **2006**.
[336] Sammelson, R. E. and Kurth, M. J. *Chem. Rev.* **2000**, *101*, 137. (10.1021/cr000086e)
[337] Boll, E.; Drobecq, H.; Ollivier, N.; Raibaut, L.; Desmet, R.; Vicogne, J. and Melnyk, O. *Chem. Sci.* **2014**. (10.1039/C3SC53509F)



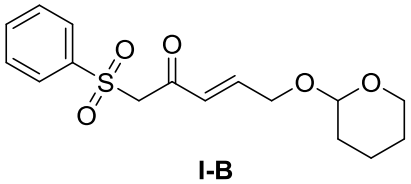
Esquema 10

Este se trata de nuestro más reciente trabajo de investigación en el laboratorio y actualmente nos encontramos en el desarrollo de nuevas metodologías incluyendo este tipo de polímeros. Satisfactoriamente, hemos logrado unir nuestra sulfona a un derivado de PEG mediante una unión ester entre el grupo hidroxilo de nuestro reactivo Nazarov y un extremo carboxílico en la cadena polimérica. La novedad y complejidad de los nuevos sistemas obtenidos hace más difícil determinar la estructura de los compuestos sintetizados, por lo que actualmente nos encontramos analizando los últimos datos obtenidos con el fin de saber el tamaño del polímero y cómo se encuentra realmente unida nuestra sulfona a dicho polímero. Una vez optimizada la síntesis de este material de partida comenzaremos con los estudios de reactividad en condiciones de organocatálisis.

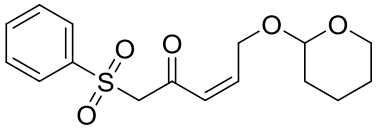
1. Empleando materiales de partida fácilmente disponibles, se han desarrollado y optimizado las síntesis de cuatro reactivos sulfonil Nazarov nuevos:



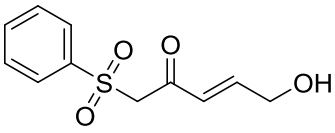
I-A



I-B



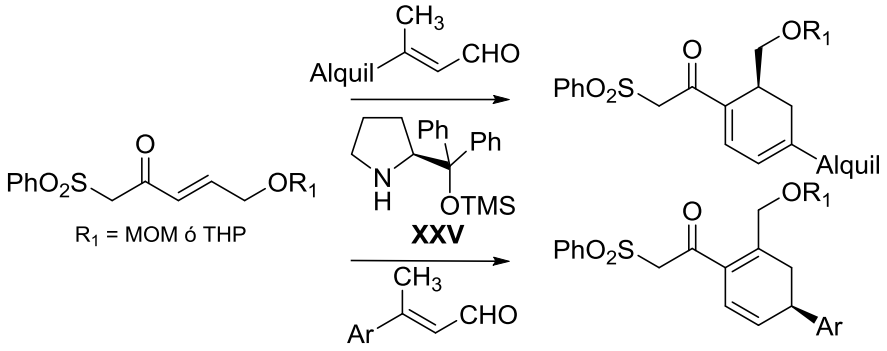
I-C



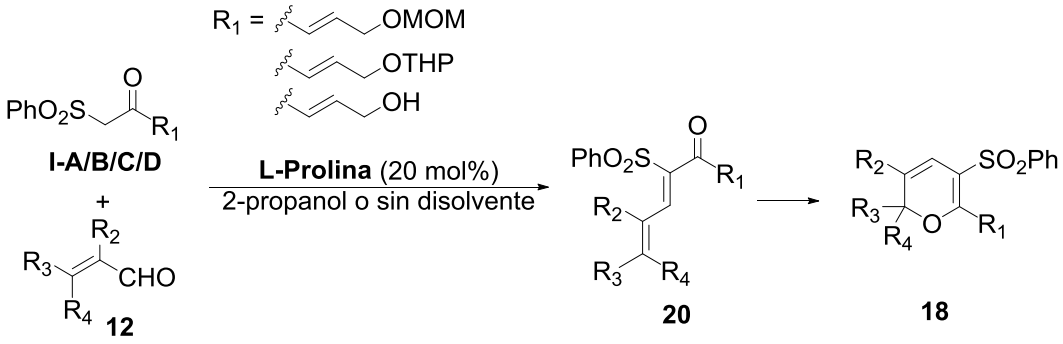
I-D

2. De entre los diferentes catalizadores estudiados, se encontró que la **prolina** y el catalizador de Jørgensen **III** eran los mejores para la síntesis de 2-alquiliden ciclohexenonas quirales, de forma diastereoselectiva y con alta enantioselectividad, empleando para ello el reactivo Nazarov **I-A** y aldehídos β-alquilmonosustituidos α,β-insaturados. Todos los compuestos sintetizados eran estables y no se detectó ninguna transformación en fenoles.

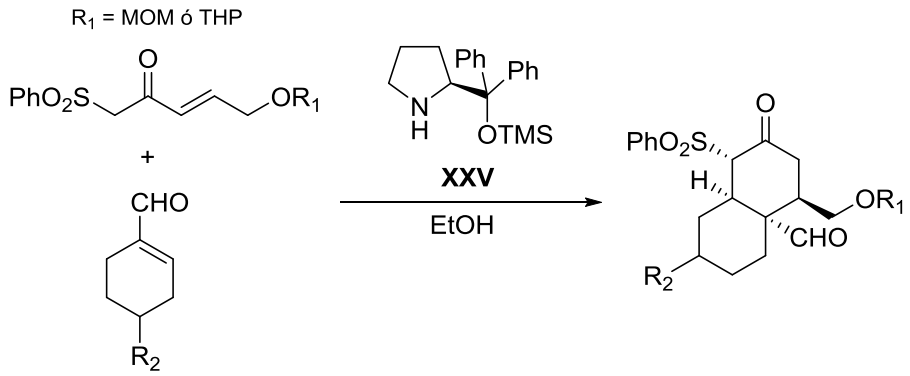
3. De entre los diferentes organocatalizadores estudiados, el catalizador de Hayashi-Jørgensen **XXV** demostró ser el único capaz de producir ciclohexa-1,3-dioenos quirales. De esta forma hemos demostrado por primera vez como un reactivo sulfonil Nazarov puede dar lugar a una reacción de Diels-Alder en condiciones organocatalíticas. Esta reacción ha hecho posible obtener diversos ciclohexa-1,3-dienos quirales altamente funcionalizados, dependiendo de si el aldehído tiene un sustituyente alifático o aromático.



4. De entre todos los catalizadores estudiados para la síntesis de 2*H*-piranos, partiendo de nuestros reactivos Nazarov y aldehídos β,β-disustituidos α,β-insaturados, la prolina demostró ser el mejor y el único catalizador capaz de dar esta reacción, demostrando una vez más su versatilidad como organocatalizador. La reacción procede sin disolvente, haciéndola un método "verde" para la obtención de compuestos de alto impacto para la síntesis de análogos de compuestos naturales con actividad biológica. Además se ha podido sintetizar distintos aductos de Knoevenagel con buenos rendimientos.

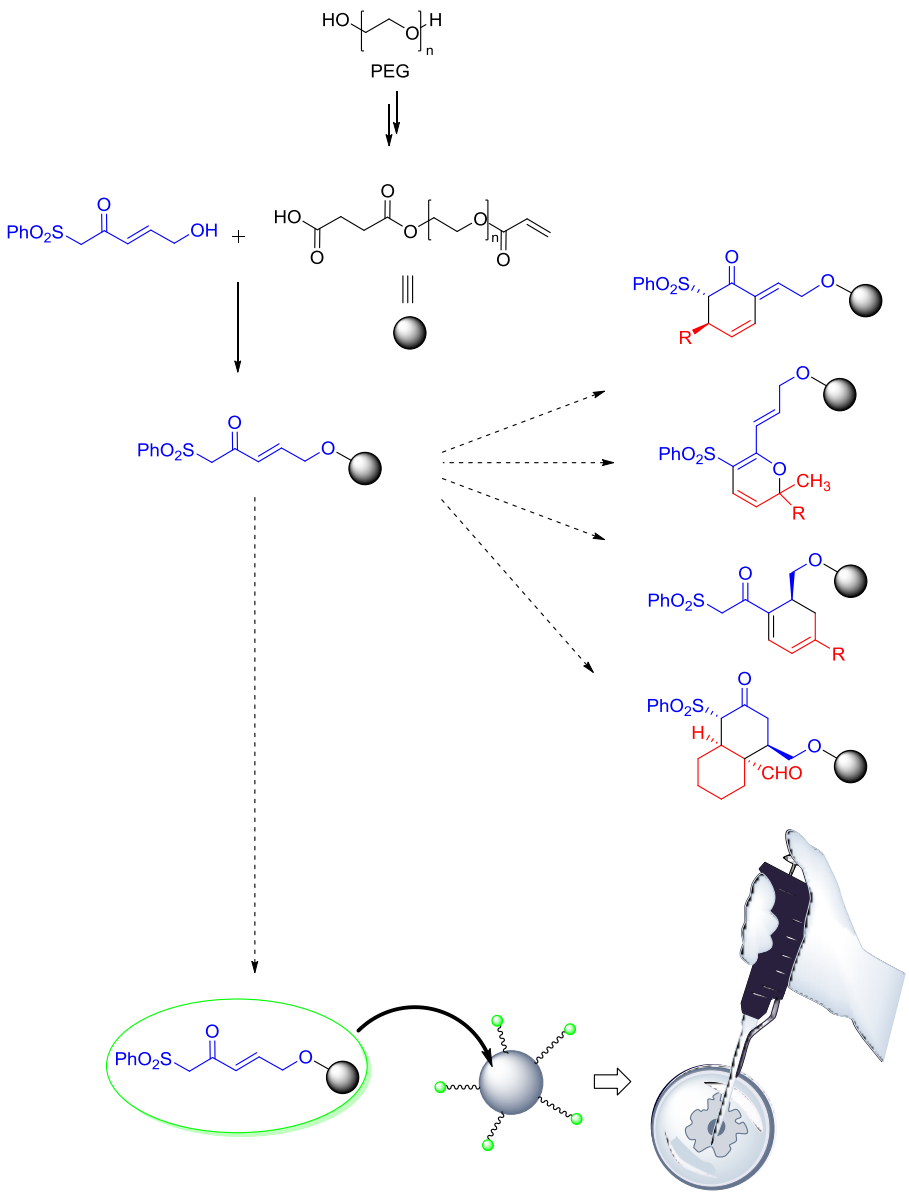


5. Tras una re-exploración del catalizador de Hayashi-Jørgensen **XXV** con la reacción de nuestros reactivos Nazarov y enales cíclicos se obtuvieron *cis*-decalinas de forma estereoespecífica y con buena enantioselectividad.



6. Se han obtenido compuestos de alto valor que puedan emplearse como materiales de partida en la síntesis de diversas estructuras químicas. Además se ha explorado la reactividad aplicada a la síntesis orientada a la diversidad con el fin de obtener diversas esqueletos.

7. Se ha abierto una nueva versión de esta química en soporte sólido empleando derivados de PEG con el fin de simplificar la purificación de los productos y mejorar la facilidad de realizar los ensayos de actividad biológica en líneas celulares.



Este trabajo ha dado lugar a tres publicaciones (entre otras) hasta la fecha, que se incluyen a contonuación:

- Peña, J.; Antón, A. B.; Moro, R. F.; Marcos, I. S.; Garrido, N. M. and Díez, D. *Tetrahedron* **2011**, *67*, 8331. (10.1016/j.tet.2011.08.068)
- Peña, J.; Moro, R. F.; Basabe, P.; Marcos, I. S. and Diez, D. *RSC Advances* **2012**, *2*, 8041. (10.1039/C2RA21306K)
- Peña, J.; Moro, R. F.; Marcos, I. S.; Sanz, F. and Díez D. *Tetrahedron* ***(2014)***, (10.1016/j.tet.2014.04.076)

GENERAL TECHNIQUES

1. EQUIPMENT

1.1. Specific optical rotation.

Recorded on a Perkin-Elmer 241 polarimeter using a 1 dm path lenght sample cell and chloroform as solvent. Concentration for each measure is given as g/100 mL and is specified for each compound.

1.2. Melting points

Recorded on a Kofler hot-stage microscope. Values are uncorrected.

1.3. FT-IR spectra

Recorded on an AVATAR 370 FT-IR Thermo Nicolet and Shimadzu IRAffinity-1 spectrometers using a thin liquid layer on a NaCl plate.

AVATAR 370 FT-IR THERMO NICOLET

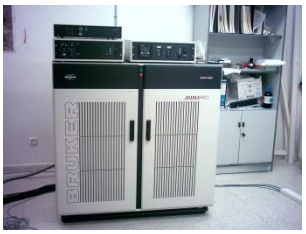
SHIMADZU IRAffinity-1

1.4. NMR spectra

^{1}H and ^{13}C

Recorded on a VARIAN 200 (200 MHz ^{1}H and 50 MHz ^{13}C) and a BRUKER AVANCE 400 MHz DRX (400 MHz ^{1}H and 100 MHz ^{13}C, equipped with an inverse probe with gradient coil and a $^{1}H/^{13}C$ probe) spectrometres. The spectra were performed in $CDCl_3$ as usual solvent. Chemical shifts (δ) are given in ppm and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm for ^{1}H and ^{13}C, respectively and coupling constants (*J*) are given in Hz.


VARIAN 200

BRUKER 400

Carbon multiplicity is determined by Distorsionless Enhancement by Polarization Transfer (DEPT) sequence. This sequence distinguish protonated carbon atoms CH, CH_2 y CH_3 using proton pulses through decoupling at 90º and 135º.

nOe (nuclear Overhauser effect)

When a proton chemical signal is irradiated, this produces variations on one or several protons. This variation is reated to the inverse of the sixth power of the distance between the nuclei. The signal is normally irradiated with low power and continuously. Moreover, an irradiated spectrum out of the resonance area is obtained. One is subtracted from the other and it is observed if there is any variation in the signal intensity. The sequence used allows the irradiation of each component in a multiplet with a much lower power than that one used to irradiate the centre.

Bidimensional experiments:

HMQC (Heteronuclear Multiple Quantum Coherence)

The $^{1}H/^{13}C$ HMQC experiments are adquired using Bruker inv4gs sequence with zero quantum and double quantum coherence with a series of three sinusoidal gradient pulses. The gradient pulse length is 1.5 ms and pulses are related in 50:30:40 respect to the total pulse length. The gradient recover interval is a 100 ms.

A typical experiment adquieres 256 series of one or two transients each. The recycle interval is three seconds and modulation is tuned at $^{1}J_{H,C}$ = 145 Hz, corresponding to a 3.45 ns interval and decoupling with a garp sequence at ^{13}C at the acquisition time.

Fourier transform (FT) of both dimensions is realised after applying an exponential function of 0.3 Hz in F2 (^{1}H) and a sinusoidal function in F1 (^{13}C). The spectrum obtained are correlated in magnitude with 1024 pints in F2 and 512 in F1, corresponding with a resolution of 4.68 Hz/pt in F2 and 45.2 Hz/pt in F1.

HMBC (Heteronuclear Multiple Bond Conectivity)

For correlations at 2 or 3 bond-length, inv4gslplrnd sequence is used, using a long path filter for elimination of direct correlation depending on the coupling constant $^{1}J_{H,C}$ = 145 Hz. Gradient pulse sequence for coherence selection is the same as before and a new evolution interval is applied [$^{1}J_{H,C}$ function which values can be 50 ms (10 Hz), 83 ms (6 Hz) y 110 ms (4.5 Hz)] before coherence selection and it is no decoupled during the acquisition. A typical coupling is acquired with 256 series of 4 transients each.

Fourier transform (FT) of both dimensions is realised with the same functions as before. The spectrum obtained are correlated in magnitude with 1024 pints in F2 and 512 in F1, corresponding with a resolution of 4.68 Hz/pt in ^{1}H and 45.2 Hz/pt in ^{13}C.

COSY (COrrelation SpectroscopY)

Basic COSY sequence has two 90º pulses and an evolution time. Sinusoidal functions in both directions are used for processing, obtaining a symmetrical matrix of 512 points in both directions. A sequence with double quantum filter is typically used, eliminating or diminishing intense signals, due to solvent or singlets in the diagonal and their corresponding artifacts.

ROESY (Rotation frame Overhauser Effect SpectroscopY).

A ROESY experiment determinates the transversal cross relaxation values instead of longitudinal as in NOESY experiment. The main advantage is that these values are always positive.

To observe these values a "spin-lock" experiment is needed: a non-selective 90º pulse followed by an evolution time, which places magnetisations at the starting point of the mixing period; the "spin-lock" pulse is applied along the X axis during the first part of the phases cyclisation. All the components in X evolve due to the relaxation.

A typical experiment is obtained with 1024 points in F2 and 256 in F1 from 256 series of 8 transients. The recycle interval is 3 μs. The "spin-lock" time may vary from 250 ms to 650 ms, depending on the molecule.

Fourier transform (FT) of both dimensions is realised after applying an exponential function in F2 and a π/2 displaced sinusoidal function in F1 for Time Proportional Phase Increment mode.

1.5. Mass spectra

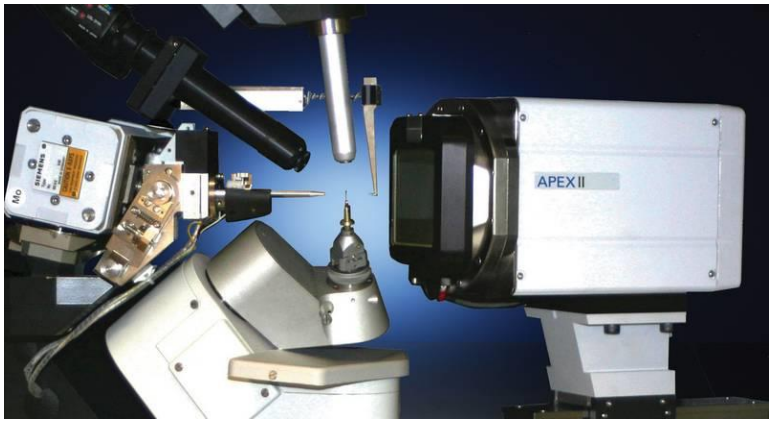
Recorded on a VG TS-250 high resolution spectrometer which can realise electronic impact, chemical ionisation and fast atom bombardment experiments. It has direct inyection system and it can determinate an exact mass with a 15 ppm precision in high resolution experiments. Applied Biosystems QSTAR XL quadrupole-time of flight spectrometer has also been used. It has electrospray, atmospheric pressure chemical ionization and photospray probes, allowing to work in positive or negative mode. It can determinate the exact mass of a single compound or one of its fragments by bidimensional mass spectrometry, with an 0.0005% error.

VG TS-250

QSTAR XL

1.6. X-Ray diffraction

Crystalline structures determination was realised using a Bruker Kappa Apex II 4-cyrcle automatic difractometer with kappa geometry and a high sensibility CCD area detector. Single-crystal is measured at room temperature using CuK_α (λ =1,54178 Å) radiation with a X-ray generator operating at 40 kV and 30 mA. We can consider that the difractometer is constituted by a parallel monochromatic radiation source, a goniometer to orientate the crystal in almost every space direaction, a diffracted radiation detector and a computer to control the goniometer, the detector and to process the data.



2. GENERAL CHROMATOGRAPHIC TECHNIQUES

2.1. CHIRAL-HPLC

Recorded on a SHIMADZU LC-20AD using different CHIRALCEL® and CHIRALPACK® columns. Detection was performed with a Diode Array Detector SPD-M20A (UV and Visible) and the temperature was controlled in an oven CTO-10AS.

2.2. THIN LAYER CHROMATOGRAPHY

Performed on 0.2 mm thick plates of Merck Silica-gel (60 F254) using UV light (254 nm and 306 nm) as visualizing agent and/or iodine, ammonium molibdate or potassium permanganate as developing agents.

2.3. Column chromatography

Performed in a glass column packed with Merck-60 Silica-gel, (0.200-0.063 mm or flash 0.063-0.040 mm). Samples are eluted using different solvent mixtures and it is specified for each compound.

3. REAGENTS AND SOLVENTS PURIFICATION

- Acetone (Me_2CO): boiled over $KMnO_4$ and distilled.
- Acetonitrile (MeCN): boiled over CaH_2 under argon and distilled.
- Benzene (C_6H_6): distilled over Na and benzofenone under argon.
- Chloroform ($CHCl_3$): distilled over P_2O_5.
- Dichlorometane (CH_2Cl_2): distilled over CaH_2 under argon.
- Diisopropilamine (iPr_2NH): distilled over KOH.
- *N*,*N*-Dimetilformamide ($HCONMe_2$): distilled over CaH_2 under argon at low pressure.
- Ether (Et_2O): boiled over Na and distilled over Na and benzofenone.
- *n*-Hexane (C_6H_{12}): distilled over $CaCl_2$.
- Methanol (MeOH): distilled.
- Pyridine (C_5H_5N): distilled over BaO.
- Tetrahydrofurane (C_4H_8O): boiled over Na and distilled over Na and benzofenone.
- Toluene (MeC_6H_5): distilled over Na.
- Triethylamine (Et_3N): boiled over CaH_2 and distilled over KOH.

All the liquid reagents and solvents were distilled prior to use.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION. TABLE OF CONTENTS.

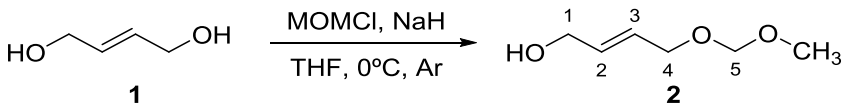
General.

All reactions and manipulations were performed under an inert atmosphere of argon unless otherwise stated. Melting points are uncorrected. Optical rotations concentrations are given as g / 100 mL. Infrared spectra values are given in cm^{-1}. NMR spectra were recorded at room temperature in $CDCl_3$, unless otherwise stated. *J* values are reported in Hertz and chemical shifts in ppm. For more specific information see "General techniques section".

1. Synthesis of β-ketosulfones I-A, I-B, I-C, I-D and I-E.

1.1. Synthesis of β-ketosulfone I-A.

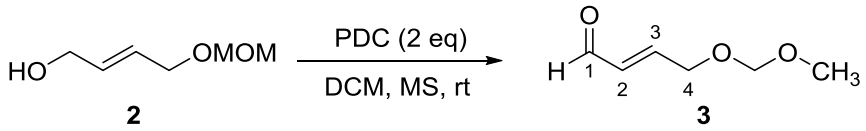
1.1.i **Monoprotection of diol 1 with MOMCl: (E)-4-Methoxymethoxybut-2-en-1-ol, 2.**



1 **2**

(*E*)-But-2-ene-1,4-diol **1** (4 mL, 48.66 mmol) was dissolved in 480 mL of THF under Ar at 0 ºC. NaH (60%, 1.95 g, 48.66 mmol) was added and left to stir for 10 minutes. Then MOMCl (3.70 mL, 48.66 mmol) was added and the mixture was stirred for 1 hour. The reaction was quenched with H_2O, and extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude transparent oil of monoprotected diol, **2** (5.6 g, 87%). ν_{max} (liquid film) 3408, 2936, 2888, 1151, 1104, 1044, 920; δH (200 MHz; $CDCl_3$) 5.80 – 5.36 (2H, m, H2 and H3), 4.50 (2H, s, O-CH_2-O), 4.08 – 3.97 (4H, m, H1 and H4), 3.24 (3H, s, O-CH_3); δC (50 MHz; $CDCl_3$) 132.9 (CH, C2), 127.5 (CH, C3), 95.5 (CH_2, O-CH_2-O), 62.7 (CH_2, C4), 58.3 (CH_2, C1), 55.4 (CH_3, CH_3-O). **MS**: EI: Calcd. for $C_6H_{12}O_3$ (M–H_2O) 114; found: 114 (M–H_2O).

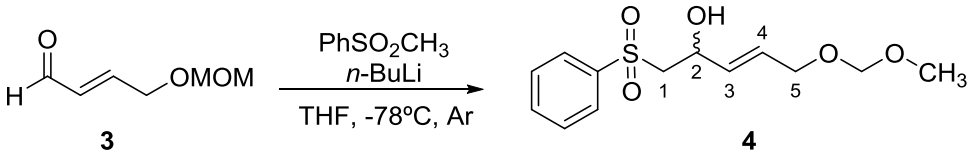
1.1.ii Oxidation of 2 with PDC: (E)-4-Methoxymethoxybut-2-enal, 3.



2 **3**

A mixture of monoprotected diol **2** (2.32 g, 17.60 mmol) and molecular sieves were dissolved in 88 mL of DCM under Ar and stirred at room temperature for 5 minutes. PDC (13.2 g, 35.20 mmol) was added and left to stir for 4 hours. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil **3** (1.64 g, 72%). ν_{max} (liquid film) 2949, 2891, 1691, 1153, 1114, 1066, 1030, 968, 921; δH (200 MHz; $CDCl_3$) 9.48 (1H, d, *J* = 7.9 Hz, CHO), 6.78 (1H, dt, *J* = 15.7, 4.0 Hz, H3), 6.25 (1H, ddt, *J* = 15.7, 7.9, 2.0 Hz, H2), 4.58 (2H, s, O-CH_2-O), 4.25 (2H, dd, *J* = 4.0, 2.0 Hz, H4), 3.28 (3H, s, O-CH_3); δC (50 MHz; $CDCl_3$) 193.3 (CH, CHO), 153.0 (CH, C3), 131.7 (CH, C2), 96.3 (CH_2, O-CH_2-O), 65.9 (CH_2, C4), 55.6 (CH_3, CH_3-O); MS: EI: Calcd. for $C_6H_{10}O_3$ ($M–H^+$) 129; found: 129 ($M–H^+$).

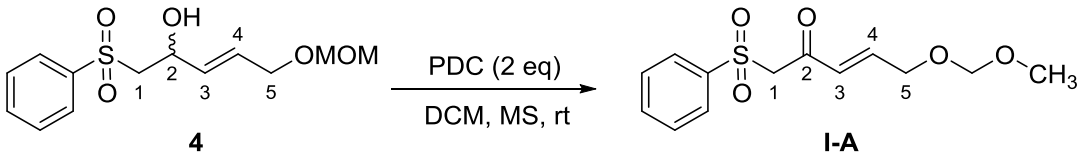
1.1.iii Addition of methylphenylsulfone to 3: (E)-5-(Methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-ol, 4.



3 **4**

Methylphenylsulfone (3.27 g, 20.9 mmol) was dissolved in 190 mL of THF under Ar at -78 ºC. *n*-BuLi (1.6 M in hexanes, 13 mL, 20.9 mmol) was added and the mixture was stirred 10 minutes. Separately, **3** (3.02 g, 23.23 mmol) was dissolved in 42 mL of THF under Ar at room temperature. This solution was added *via cannula* to the former one and the mixture was stirred at -78 ºC under Ar for 1 hour. Then the reaction was quenched with a NH_4Cl saturated solution and extracted with EtOAc. The combined organics were washed with H_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo* to leave a crude yellow oil. Flash chromatography (*n*-Hexane/EtOAc, 7/3) afforded **4** (3.75 g, 63%). ν_{max} (liquid film) 3457, 2932, 2884, 1305, 1145, 1086, 1041; δH (200 MHz; $CDCl_3$) 7.92 (2H, dd, *J* = 8.2, 1.4 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta}, ArH_{para}), 5.86 (1H, dt, *J* = 14.0, 6.0 Hz, H4), 5.64 (1H, dd, *J* = 14.0, 4.0 Hz, H3), 4.77 – 4.62 (1H, m, H2), 4.58 (2H, s, O-CH_2-O), 3.99 (2H, d, *J* = 6.0 Hz, H5), 3.31 (3H, s, O-CH_3), 3.28 – 3.24 (2H, m, H1); δC (50 MHz; $CDCl_3$) 139.5 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 131.2 (CH, C4), 129.7 (2CH, ArC_{meta}), 129.0 (CH, C3), 128.2 (2CH, ArC_{ortho}), 96.0 (CH_2, O-CH_2-O), 66.9 (CH, C2), 66.5 (CH_2, C5), 62.1 (CH_2, C1), 55.5 (CH_3, CH_3-O); EIHRMS: Calcd. for $C_{13}H_{18}O_5S$ (M+Na): 309.0773; found: 309.0767 (M+Na).

1.1.iv Oxidation of 4 with PDC: (*E*)-5-(Methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-one, I-A.

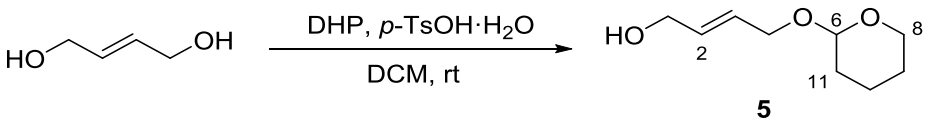


4 **I-A**

A mixture of **4** (1.08 g, 3.77 mmol) and molecular sieves were dissolved in 19 mL of DCM under Ar and stirred at room temperature for 5 minutes PDC (2.84 g, 7.55 mmol) were added and left to stir for 3 hours. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **I-A** (535 mg, 50%). ν_{max} (liquid film) 2938, 1671, 1324, 1152; δH (200 MHz; $CDCl_3$) 7.88 (2H, d, *J* = 8.3 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta} and ArH_{para}), 6.96 (1H, dt, *J* = 15.8, 3.9 Hz, H4), 6.55 (1H, d, *J* = 15.8 Hz, H3), 4.66 (2H, s, O-CH_2-O), 4.31 (2H, s, H1), 4.27 (2H, d, *J* = 3.9 Hz, H5), 3.37 (3H, s, O-CH_3); δC(50 MHz; $CDCl_3$) 187.1 (C, C2), 147.1 (CH, C4), 138.8 (C, ArC_{ipso}), 134.5 (CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 128.0 (CH, C3), 96.4 (CH_2, O-CH_2-O), 66.0 (CH_2 C5), 65.8 (CH_2, C1), 55.8 (CH_3, CH_3-O); EIHRMS: Calcd. for $C_{13}H_{16}O_5S$ (M+Na): 307.0616; found: 307.0610 (M+Na).

1.2. Synthesis of β-ketosulfones I-B and I-C.

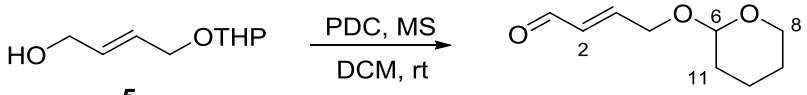
1.2.i Monoprotection of diol 1 with DHP: (*E*)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-en-1-ol, 5.



5

(*E*)-But-2-ene-1,4-diol **1** (4 mL, 48.66 mmol) was dissolved in 194 mL of DCM under Ar at room temperature 3,4-dihydro-2*H*-pyran (97%, 4.22g, 48.66 mmol) and *p*-toluenesulfonic acid monohydrate (93 mg, 0.486 mmol) were added and left to stir for 3 hours. The reaction was quenched with a $NaHCO_3$ saturated solution, and extracted with DCM. The combined organics were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **5** (8.01 g, 96%). ν_{max} (liquid film) 3417, 2943, 2870, 1454, 1352, 1261, 1134; δH (200 MHz; $CDCl_3$) 5.88-5.33 (2H, m, H2 and H3), 4.67-4.60 (1H, m, H6), 4.32-3.99 (4H, m, H1 and H4), 3.92-3.71 (1H, m, $H8_A$), 3.57-3.40 (1H, m, $H8_B$), 1.91-1.36 (6H, m, H9, H10, and H11); δC (50 MHz; CDCl3) 132.6 (CH, C2), 127.3 (CH, C3), 97.6 (CH, C6), 62.6 (CH_2, C4), 62.0 (CH_2, C8), 57.9 (CH_2, C1), 30.5 (CH_2, C11), 25.4 (CH_2, C9), 19.3 (CH_2, C10); EIHRMS: Calcd. for $C_9H_{16}O_3$ (M+Na): 195.0997; found: 195.0991 (M+Na).

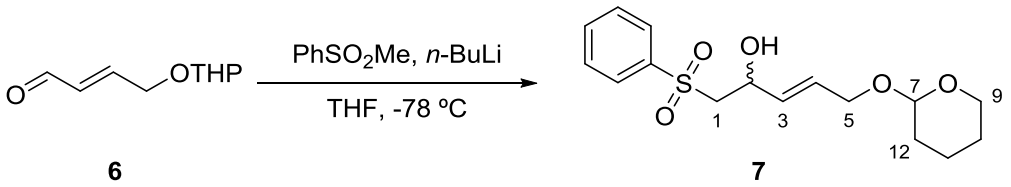
1.2.ii Oxidation of 5 with PDC: (*E*)-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-enal, 6.



5 **6**

A mixture of monoprotected diol **5** (8.01 g, 46.5 mmol) and molecular sieves were dissolved in 232 mL of DCM under Ar and stirred at room temperature for 5 minutes. PDC (34.9 g, 93.02 mmol) was added and left to stir for 5 hours. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford **6** (7.19 g, 91%). ν_{max} (liquid film) 2945, 2870, 2853, 2727, 1693, 1454, 1352, 1261, 1201, 1120; δH (200 MHz; $CDCl_3$) 9.54 (1H, d, *J* = 8.0 Hz, CHO), 6.85 (1H, dt, *J* = 15.7, 4.0 Hz, H3), 6.34 (1H, ddt, *J* = 15.7, 8.0, 2.0, Hz, H2), 4.68-4.61 (1H, m, H6), 4.49 (1H, ddd, *J* = 17.3, 4.0, 2.0 Hz, $H4_A$), 4.21 (1H, ddd, *J* = 17.3, 4.0, 2.0 Hz, $H4_B$), 3.86 – 3.72 (1H, m, $H8_A$), 3.56 – 3.42 (1H, m, $H8_B$), 1.86 – 1.43 (6H, m, H9, H10, and H11); δC (50 MHz; CDCl3) 193.5 (CH, CHO), 153.7 (CH, C3), 131.5 (CH, C2), 98.4(CH, C6), 65.6 (CH_2, C4), 62.2 (CH_2, C8), 30.4 (CH_2, C11), 25.4 (CH_2, C9), 19.2 (CH_2, C10); EIHRMS: Calcd. for $C_9H_{14}O_3$ (M+Na): 193.0835; found: 193.0835 (M+Na).

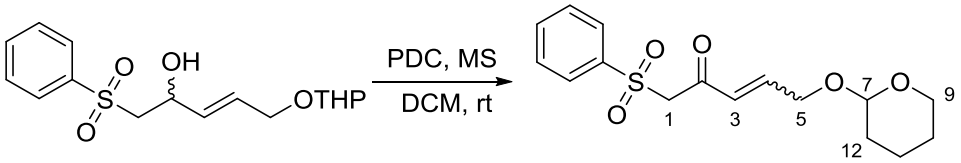
1.2.iii Addition of methylphenylsulfone to 6: (*E*)-1-(phenylsulfonyl)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-em-2-ol, 7.



6 **7**

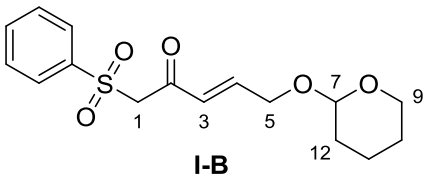
Methylphenylsulfone (3.64 g, 23.29 mmol) was dissolved in 100 mL of THF under Ar at -78 ºC. *n*-BuLi (1.6 M in hexanes, 14.9 mL, 23.29 mmol) was added and the mixture was stirred 15 minutes. Separately, **6** (4.40 g, 25.88 mmol) was dissolved in 30 mL of THF under Ar at room temperature This solution was added *via cannula* to the former one and the mixture was stirred at -78 ºC under Ar for 2 hours. Then the reaction was quenched with a NH_4Cl saturated solution and left to warm at room temperature. Then it was extracted with EtOAc and the combined organics were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to leave a crude yellow oil. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **7** (4.63 g, 61%). ν_{max} (liquid film) 3444, 2953, 2872, 2250, 1732, 1446, 1288, 1138 δH (200 MHz; $CDCl_3$) 7.78 (2H, d, *J* = 7.9 Hz, ArH_{ortho}), 7.57 – 7.34 (3H, m, ArH_{meta}, ArH_{para}), 5.69 (1H, dt, *J* = 15.5, 5.2 Hz, H4), 5.53 (1H, dd, *J* = 15.5, 5.2 Hz, H3), 4.63 – 4.49 (1H, m, H7), 4.48 – 4.38 (1H, m, H2), 4.02 (1H, dd, *J* = 13.3, 4.6 Hz, $H5_A$), 3.86 – 3.55 (2H, m, $H1_A$ and $H5_B$), 3.40 – 3.02 (3H, m, H9 and $H1_B$), 1.74 – 1.24 (6H, m, H10, H11 and H12); δC (50 MHz; $CDCl_3$) 139.7 (C, ArC_{ipso}), 134.1 (CH, C4), 131.4 (CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 128.8 (CH, C3), 128.1 (2CH, ArC_{ortho}), 98.1 (CH, C7), 66.6 (CH_2, C5), 66.5 (CH, C2), 62.2 (CH_2, C9), 62.1 (CH_2, C1), 30.6 (CH_2, C12), 25.5 (CH_2, C10), 19.5 (CH_2, C11); EIHRMS: Calcd. for $C_{16}H_{22}O_5S$ (M+Na): 349.1080; found: 349.1080 (M+Na).

1.2.iv Oxidation of 7 with PDC: (*E*)-1-(phenylsulfonyl)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-en-2-one, I-B and I-C.



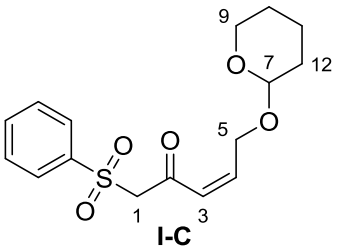
7 **I-B**(*trans*)/**I-C**(*cis*)

A mixture of **7** (537 g, 1.65 mmol) and molecular sieves were dissolved in 8 mL of DCM under Ar and stirred at room temperature for 5 minutes PDC (1.24 g, 3.30 mmol) was added and left to stir for 4 hours. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **I-B** (304 mg, 57%) and **I-C** (5 mg, 1%).



I-B

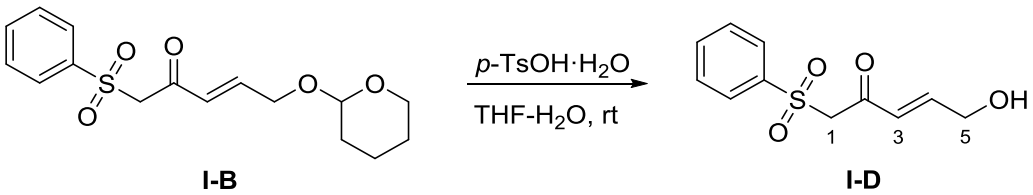
I-B: ν_{max} (liquid film) 2943, 2870, 2852, 1693, 1666, 1633, 1446, 1384, 1325, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 7.0 Hz, ArH_{ortho}), 7.74 – 7.50 (3H, m, ArH_{meta} and ArH_{para}), 6.98 (1H, dt, *J* = 15.8, 3.9 Hz, H4), 6.54 (1H, dt, *J* = 15.8, 1.9 Hz, H3), 4.65 (1H, t, *J* = 3.1 Hz, H7), 4.46 (1H, ddd, *J* = 17.6, 3.9, 1.9 Hz, $H5_A$), 4.32 (2H, s, H1), 4.18 (1H, ddd, *J* = 17.6, 3.9, 2.0 Hz, $H5_B$), 3.89 – 3.74 (1H, m, $H9_A$), 3.59 – 3.42 (1H, m, $H9_B$), 1.90 – 1.40 (6H, m, H10, H11 and H12); δC (50 MHz; CDCl3) 187.3 (C, C2), 147.7 (CH, C4), 138.9 (C, ArC_{ipso}), 134.4 (CH, ArC_{para}), 129.4 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 128.0 (CH, C3), 98.4 (CH, C7), 65.6 (CH_2, C5), 65.3 (CH_2, C1), 62.2 (CH_2, C9), 30.5 (CH_2, C12), 25.5 (CH_2, C10), 19.3 (CH_2, C11); EIHRMS: Calcd. for $C_{16}H_{20}O_5S$ (M+Na): 347.0924; found: 347.0924 (M+Na).



I-C

I-C: ν_{max} (liquid film) 2943, 2872, 2852, 1693, 1666, 1614, 1448, 1377, 1323, 1155; δH (200 MHz; $CDCl_3$) 8.01 – 7.80 (2H, m, ArH_{ortho}), 7.79 – 7.50 (3H, m, ArH_{meta} and ArH_{para}), 6.65-6.37 (2H, m, H3 and H4), 4.75 – 4.39 (3H, m, H5 and H7), 4.21 (2H, s, H1), 3.92 – 3.71 (1H, m, $H9_A$), 3.58 – 3.38 (1H, m, $H9_B$), 1.95 – 1.36 (6H, m, H10, H11 and H12); δC (50 MHz; CDCl3) 187.4 (C, C2), 152.4 (CH, C4), 138.8 (C, ArC_{ipso}), 134.5 (CH, ArC_{para}), 129.6 (2CH, ArC_{meta}), 128.5 (2CH, ArC_{ortho}), 124.7 (CH, C3), 99.2 (CH, C7), 68.1 (CH_2, C5), 67.2 (CH_2, C1), 62.8 (CH_2, C9), 30.8 (CH_2, C12), 25.6 (CH_2, C10), 19.8 (CH_2, C11); EIHRMS: Calcd. for $C_{16}H_{20}O_5S$ (M+Na): 347.0924; found: 347.0924 (M+Na).

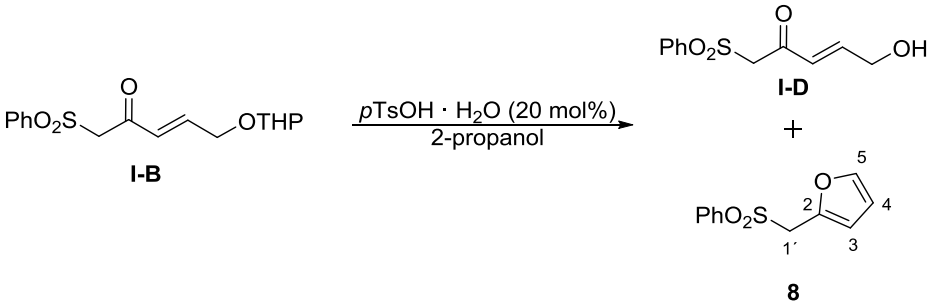
1.3. Synthesis of β-ketosulfone I-D by deprotection of I-B.



I-B **I-D**

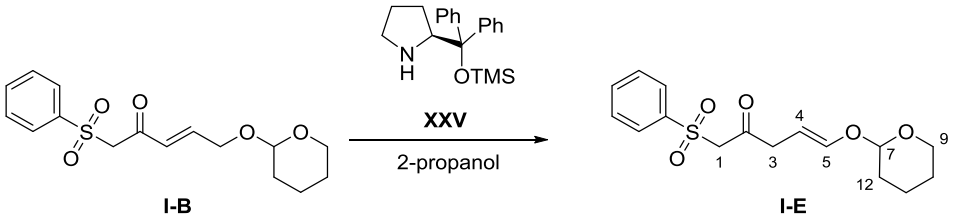
I-B (203 mg, 0.62 mmol) and *p*-toluenesulfonic acid monohydrate (12 mg, 0.06 mmol) were dissolved in 6 mL of a 1/1 mixture of THF/H_2O, and the hole mixture was stirred for 5 days. The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **I-D** (130.2 mg, 88%). ν_{max} (liquid film) 3504, 2931, 1691, 1664, 1627, 1448, 1309, 1151; δH (200 MHz; $CDCl_3$) 7.93 – 7.82 (2H, m, ArH_{ortho}), 7.72 – 7.50 (3H, m, ArH_{meta} and ArH_{para}), 7.04 (1H, dt, *J* = 15.8, 3.6 Hz, H4), 6.58 (1H, dt, *J* = 15.8, 2.0 Hz, H3), 4.44 – 4.35 (2H, m, H5), 4.33 (2H, s, H1); δC (50 MHz; CDCl3) 187.2 (C, C2), 150.4 (CH, C4), 138.8 (C, ArC_{ipso}), 134.6 (CH, ArC_{para}), 129.6 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 127.1 (CH, C3), 65.8 (CH_2, C5), 62.0 (CH_2, C1); EIHRMS: Calcd. for $C_{11}H_{12}O_4S$ (M+Na): 263.0349; found: 263.0349 (M+Na).

1.4. Ciclisation of I-D. Synthesis of 2-((phenylsulfonyl)methyl)furan, 8.



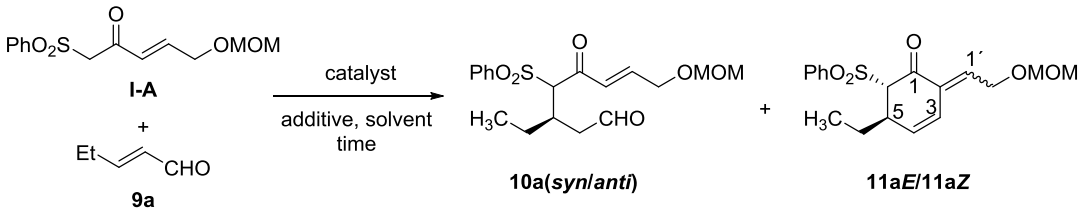
I-B (20 mg, 0.06 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.012 mmol) were dissolved in 1 mL of a 1/1 mixture of 2-propanol, and the hole mixture was stirred for 44 hours. The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a mixture of **8** (4.1 mg, 31%) and **I-D** (8.2 mg, 57%) separated by flash chromatography (*n*-Hexane/EtOAc, 6/4). **8**: ν_{max} (liquid film) 3122, 2933, 2870, 1722, 1588, 1496, 1446, 1309, 1155; δH (200 MHz; $CDCl_3$) 7.69 (2H, t, *J* = 4.4 Hz, ArH_{ortho}), 7.67 – 7.56 (1H, m, ArH_{para}), 7.53 – 7.43 (2H, m, ArH_{meta}), 7.29 (1H, dd, *J* = 1.8, 0.7 Hz, H5), 6.28 (2H, dt, *J* = 11.3, 2.6 Hz, H3 and H4), 4.40 (2H, s, H1´); δC (50 MHz; CDCl3) 143.9 (CH, C5), 142.5 (C, C2), 138.3 (C, ArC_{ipso}), 134.2 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 112.4 (CH, C3), 111.4 (CH, C4), 56.1 (CH_2, C1´). EIHRMS: Calcd. for $C_{11}H_{10}O_3S$ (M+Na): 245.0248; found: 245.0243 (M+Na).

1.5. Synthesis of β-ketosulfone I-E by deconjugation of I-B.



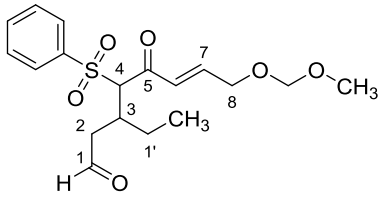
I-B (16.6 mg, 0.05 mmol), **XXV** (3.2 mg, 0.01 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.012 mmol) were dissolved in 0.3 mL of 2-propanol, and the whole mixture was stirred for 37 hours. The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **I-E** (3.4 mg, 24%). v_{max} (liquid film) 2943, 1741, 1446, 1323, 1153; δH (200 MHz; $CDCl_3$) 7.97 – 7.82 (2H, m, ArH_{ortho}), 7.70 – 7.52 (3H, m, ArH_{meta} and ArH_{para}), 6.40 (1H, dt, *J* = 6.1, 1.4 Hz, H5), 5.00 – 4.91 (1H, m, H7), 4.58 (1H, dd, *J* = 13.4, 6.1 Hz, H4), 4.25 (2H, s, H1), 3.89 – 3.69 (1H, m, $H9_A$), 3.65 – 3.52 (1H, m, $H9_B$), 3.46 (2H, dt, *J* = 7.3, 1.4 Hz, H3), 1.94 – 1.46 (6H, m, H10, H11 and H12); δC (50 MHz; CDCl3) 196.6 (C, C2), 145.5 (CH, C5), 139.0 (C, Ar_{ipso}), 134.4 (CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 99.0 (CH, C7), 97.6 (CH, C4), 65.8 (CH_2, C1), 62.4 (CH_2, C9), 40.5 (CH_2, C3), 29.8 (CH_2, C12), 25.2 (CH_2, 10), 18.8 (CH_2, C11). EIHRMS: Calcd. for $C_{16}H_{20}O_5S$ (M+Na): 347.0929; found: 347.0924 (M+Na).

2. Typical procedure for reaction of I-A with pentenal and different catalysts and conditions. Synthesis of 10a(*syn*/*anti*) and 11a*E* and 11a*Z*.



Compound **I-A** (50 mg, 0.18 mmol) and (*E*)-2-pentenal **9a** (18 µl, 0.18 mmol) were dissolved in 1 mL of the solvent used. Next, a solution of the catalyst (20 mol%), and additive (20 mol%) if needed, was added and left stirring for the appropriate time. Compounds **11a*E*** and **11a*Z*** were separated by flash chromatography and characterised.

2.1. **(*E*)-3-ethyl-8-(methoxymethoxy)-5-oxo-4-(phenylsulfonyl)oct-6-enal, 10a(*syn*/*anti*).**



10a (*syn*/*anti*)

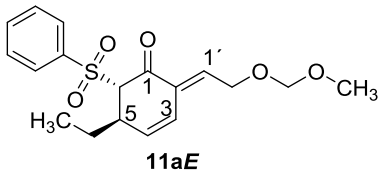
(3*R**,4*S**,*E*) and (*3R**,*4R**,*E*)-3-ethyl-8-(methoxymethoxy)-5-oxo-4-(phenylsulfonyl)oct-6-enal, **10a(*syn*)/10a(*anti*)**, (1/1) mixture: ν_{max} (liquid film) 2959, 2936, 1718, 1670, 1448, 1309, 1282, 1022, 1062, 1033;

ANTI δH (200 MHz; $CDCl_3$): 9.79 (1H, s, CHO), 7.88 (2H, m, ArH_{ortho}), 7.70 – 7.50 (3H, m, ArH_{meta} and ArH_{para}), 6.97 (1H, dt, *J* = 15.8, 3.9 Hz, H7), 6.57 (1H, dt, *J* = 15.8, 2.0 Hz, H6), 4.70 – 4.56 (3H, m, H4 and O-CH_2-O), 4.36 – 4.26 (2H, m, H8), 3.37 (3H, s, CH_3-O), 3.20 – 2.40 (3H, m, H2 and H3), 1.68 – 1.40 (2H, m, H1´), 1.01 – 0.74 (3H, m, H2´).

SYN δH (200 MHz; $CDCl_3$): 9.69 (1H, s, CHO), 7.88 (2H, m, ArH_{ortho}), 7.70 – 7.50 (3H, m, Ar_{meta} and ArH_{para}), 6.77 (1H, dt, *J* = 15.8, 3.9 Hz, H7), 6.45 (1H, dt, *J* = 15.8, 2.0 Hz, H6), 4.52 (3H, m, H4 and O-CH_2-O), 4.18 (2H, m, H8), 3.37 (3H, s, CH_3-O), 3.20 – 2.40 (3H, m, H2 and H3), 1.68 – 1.40 (2H, m, H1´), 1.01 – 0.74 (3H, t, *J*= 7.2 Hz, H2´).

10a(*syn*)/10a(*anti*), (1/1) mixture: δC (50 MHz; $CDCl_3$) 200.9, 200.8 (CH, CHO), 191.5, 191.2 (C, C5), 145.8, 145.7 (CH, C7), 138.5, 138.3 (C, ArC_{ipso}), 134.5 (2CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 129.2 (2CH, ArC_{ortho}), 128.0, 126.7 (CH, C6), 96.4, 96.3 (CH_2, O-CH_2-O), 75.3, 74.1 (CH, C4), 66.0, 65.9 (CH_2, C8), 55.8 (CH_3, CH_3-O), 44.8, 43.3 (CH_2, C2), 34.2, 33.9 (CH, C3), 26.0, 24.4 (CH_2, C1´), 11.5, 11.1 (CH_3, C2). EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+Na): 391.1191; found: 391.1189.

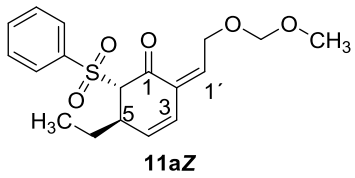
2.2. (5*R,6*S**,*E*)-5-ethyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11a*E*.**



11a*E*

ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; δH (400 MHz; $CDCl_3$) 7.80–7.75 (2H, m, ArH-*ortho*), 7.60–7.45 (3H, m, ArH_{meta} and ArH_{para}), 6.60 (1H, t, *J* = 6.0 Hz, H1´), 6.45 (1H, d, *J* = 12.0 Hz, H3), 6.15 – 5.94 (1H, m, H4), 4.65 (2H, s, O-CH_2-O), 4.31 (2H, d, *J* = 6.0 Hz, H2´), 3.91 (1H, s, H6), 3.47 – 3.31 (4H, m, H5 and CH_3-O), 1.56 – 1.37 (2H, m, H1´´), 0.85 (3H, t, *J* = 8.0 Hz, H2´´); δC (100 MHz; $CDCl_3$) 189.3 (C, C1), 143.9 (CH, C1´), 137.7 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 131.2 (C, C2), 129.1 (CH, C4), 128.9 (2CH, ArC_{meta}), 128.7 (2CH, Ar C_{ortho}), 122.5 (CH, C3), 96.1 (CH_2, O-CH_2-O), 75.6 (CH, C6), 63.3 (CH_2, C2´), 55.4 (CH_3, CH_3-O), 37.9 (CH, C5), 29.1 (CH_2, C1´´), 10.7 (CH_3, C2´´); EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. E.R. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; t_R (1) = 22.4 min; t_R (2) = 24.9 min.

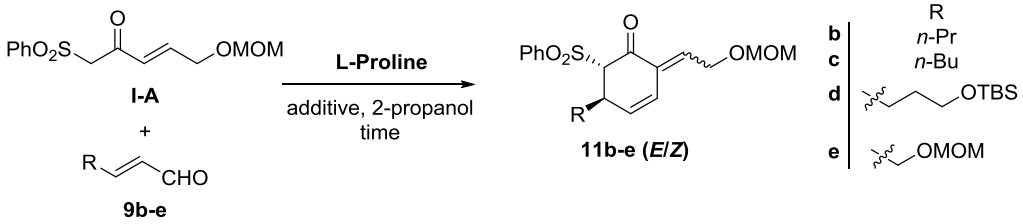
2.3. (5*R,6*S**,*Z*)-5-ethyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11a*Z*.**



11a*Z*

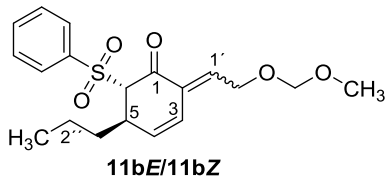
ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; d_H (200 MHz; $CDCl_3$) 7.85–7.75 (2H, m, Ar), 7.65 (1H, m, Ar), 7.60 – 7.40 (2H, m, Ar), 6.20 (1H, d, *J* = 10.0 Hz, H3), 6.06 (1H, t, *J* = 6.0 Hz, H1´), 5.86 (1H, dd, *J* = 10.0, 6.0 Hz, H4), 4.65 (2H, s, O-CH_2-O), 4.51 (1H, dd, *J* = 16.0, 6.0 Hz, $H2_A$´), 4.43 (1H, dd, *J* = 16.0, 10.0 Hz, $H2_B$´), 3.88 (1H, s, H6), 3.40 – 3.29 (4H, m, H5 and CH_3-O), 1.75 (2H, m, H1´´), 0.65 (3H, t, *J* = 8.0 Hz, H2´´); δC (50 MHz; $CDCl_3$) 190.8 (C, C1), 137.9 (C, ArC_{ipso}), 143.9 (CH, C1´), 134.5 (CH, ArC_{para}), 130.9 (C, C2), 129.2 (CH, C4), 128.9 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 122.5 (CH, C3), 96.1 (CH_2, O-CH_2-O), 77.1 (CH, C6), 67.0 (CH_2, C2´), 55.6 (CH_3, CH_3-O), 38.6 (CH, C5), 28.8 (CH_2, C1´´), 9.8 (CH_3, C2´´); EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. E.R. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; t_R (1) = 18.3 min; t_R (2) = 19.0 min.

3. Reaction of I-A with different β-monosubstituted α,β-unsaturated aldehydes using proline as catalyst.



Compound **I-A** (50 mg, 0.18 mmol) and and the corresponding aldehyde (0.18 mmol) were dissolved in 1 mL of 2-propanol. Next, a solution of *L*-Proline (20 mol%), and additive (20 mol%) if needed, was added and left stirring for the appropriate time. In this case, compounds **11b-e** were isolated as a 2/1 mixture of diastereoisomers *E/Z. When mixtures, the spectral data are indicated for the major compound.*

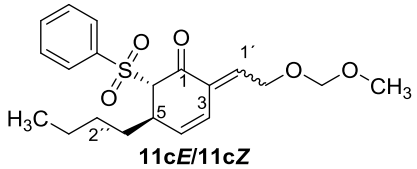
3.1. (5*R**,6*S**,*E*)-5-Propyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11b*E*/11b*Z*.



11b*E*/11b*Z*

Yellow oil (45.2 mg, 69%): ν_{max} (liquid film), 2940, 2931, 1676, 1384, 1310, 1150, 1084, 1038; δH (200 MHz; $CDCl_3$) 7.97–7.69 (2H, m, Ar), 7.67–7.42 (3H, m, Ar), 6.61 (1H, t, *J* = 6.2 Hz, H1´), 6.42 (1H, d, *J* = 10.2 Hz, H3), 6.22 – 6.00 (1H, m, H4), 4.64 (2H, s, O-CH_2-O), 4.32 (2H, d, *J* = 6.2 Hz, H2´), 3.91 (1H, s, H6), 3.52 – 3.30 (1H, m, H5), 3.38 (3H, s, O-CH_3), 1.48 – 1.18 (4H, m, H1´´, H2´´), 0.87 (3H, t, *J* = 8.0 Hz, H-2´´); δC (50 MHz; $CDCl_3$) 189.1 (C, C1), 142.8 (CH, C1´) , 137.9 (C, ArC_{ipso}), 134.9 (CH, ArC_{para}), 134.4 (CH, C4), 131.3 (C, C2), 129.5 (2CH, ArC_{meta}), 129.3 (2CH, ArC_{ortho}), 122.6 (CH, C3), 96.5 (CH_2, O-CH_2-O), 76.0 (CH, C6), 63.7 (CH_2, C2´), 55.6 (CH_3, CH_3-O), 38.4 (CH, C5), 20.2 (CH_2, C1´´), 19.8 (CH_2, C2´´), 13.9 (CH_3, C3´´). EIHRMS: Calcd. for $C_{19}H_{24}O_5S$ (M+Na): 387.1242; found: 387.1247 (M+Na).

3.2. (5*R**,6*S**,*E*)-5-Butyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11c*E*/11c*Z*.

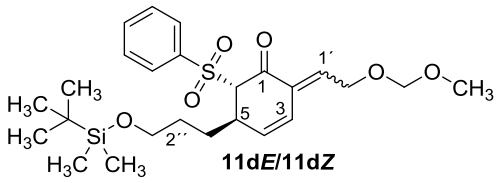


11c*E*/11c*Z*

Yellow oil (54.4 mg, 80%): ν_{max} (liquid film) 2957, 2932, 2872, 1281, 1138, 1124, 1097, 1043; δH (200 MHz; $CDCl_3$) 7.80–7.75 (2H, m, Ar), 7.60 – 7.49 (3H, m, Ar), 6.61 (1H, t, *J* = 6.2 Hz, H1´), 6.42 (1H, d, *J* = 10.3 Hz, H3), 6.22 – 5.96 (1H, m, H4), 4.64 (2H, s, O-CH_2-O), 4.32 (2H, d, *J* = 6.2 Hz, H-2´), 3.91 (1H, s, H6), 3.48 – 3.34 (4H, m, H5 and CH_3-O), 1.36 – 1.19 (4H, m, H1´´and H2´´), 0.97 – 0.78 (5H, m, H3´´ and H4´´); δC (50 MHz; $CDCl_3$) 189.6 (C,

C1), 144.0 (CH, C1´) , 138.0 (C, ArC_{ipso}), 135.0 (CH, ArC_{para}), 134.4 (CH, C4), 131.4 (C, C2), 129.5 (2CH, ArC_{meta}), 129.3 (2CH, ArC_{ortho}), 122.5 (CH, C3), 96.5 (CH_2, O-CH_2-O), 76.1 (CH, C6), 63.6 (CH_2, C2´), 55.7 (CH_3, CH_3-O), 36.7 (CH, C5), 36.1 (CH_2, C1´´), 28.7 (CH_2, C2´´), 22.6 (CH_2, C3´´), 14.0 (CH_2, C4´´), 13.9 (CH_3, C3´´); EIHRMS: Calcd. for $C_{13}H_{18}O_5S$(M+Na): 401.1399; found: 401.1402 (M+Na).

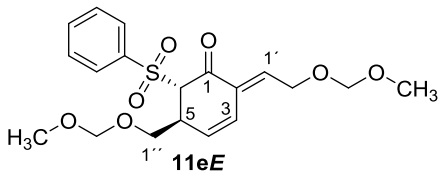
3.3. (5*R**,6*S**,*E*)-5-(3-t-Butyldimethylsilyloxy)-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11d*E*/11d*Z*.



Yellow oil (45.3 mg, 51%):ν_{max} (liquid film) 2955, 2932, 2887, 2858, 1375, 1281, 1174, 1140, 837; δH (200 MHz; $CDCl_3$) 7.80 –7.75 (2H, m, ArH_{ortho}), 7.69 – 7.39 (3H, m, ArH_{meta} and ArH_{para}), 6.62 (1H, t, *J* = 6.2 Hz, H1´), 6.43 (1H, d, *J* = 10.3 Hz, H3), 5.95 – 5.83 (1H, m, H4), 4.64 (2H, s, O-CH_2-O), 4.31 (2H, d, *J* = 6.2 Hz, H2´), 3.91 (1H, s, H6), 3.60 – 3.49 (2H, m, H2´´), 3.48 – 3.33 (4H, s, H5 and CH_3-O), 1.69 – 1.41 (2H, m, H1´´), 0.86 (9H, O-Si-*t*-Bu), -0.08 (6H, O-Si-Me_2); δC (50 MHz; $CDCl_3$) 189.5 (C, C1), 142.6 (CH, C1´), 138.0 (C, ArC_{ipso}), 135.1 (CH, ArC_{para}), 134.5 (CH, C4), 131.2 (C, C2), 129.6 (2CH, ArC_{meta}), 129.3 (2CH, ArC_{ortho}), 122.7 (CH, C3), 96.4 (CH_2, O-CH_2-O), 76.0 (CH, C6), 63.6 (CH_2, C2´), 62.5 (CH_2, C3´´), 55.7 (CH_3, CH_3-O), 36.4 (CH, C5), 32.9 (CH_2, C2´´), 29.9 (CH_2, C1´´), 26.2 ($3CH_3$, *t*-Bu-Si), 18.5 (C, *t*-BuSi), -5.1 ($2CH_3$, $(CH_3)_2$-Si); EIHRMS: Calcd. for $C_{25}H_{38}O_6SSi$ (M+Na): 517.2056; found: 517.2059 (M+Na).

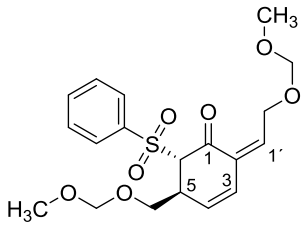
Using aldehyde **9e (3)** we were able to separate the cyclisation products. Yield in *E* isomer is referred to mixture of both isomers.

3.4. (5*R*,6*S*,*E*)-5-(1-Methoxymethoxymethyl)-2-(2´-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11e*E*.



Yellow oil (22.9 mg, 31%): ν_{max} (liquid film) 2938, 2889, 1699, 1448, 1321, 1281, 1151, 1039; δH (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.61 (1H, t, *J* = 8.4 Hz, H3), 6.55 (1H, d, *J* = 10.0 Hz, H1´), 6.05 – 5.86 (1H, m, H4), 4.63 (2H, s, O-CH_2-O), 4.46 (2H, O-CH_2-O), 4.34 – 4.26 (2H, m, H2´), 4.13 (1H, s, H6), 3.72 – 3.55 (2H, m, H1´´), 3.38 – 3.34 (4H, m, H5 and O-CH_3), 3.22 (3H, s, O-CH_3); δC (100 MHz; $CDCl_3$) 188.6 (C, C1), 137.9 (C, ArC_{ipso}), 135.3 (2CH, C1´ and ArC_{para}), 134.5 (CH, C4), 131.3 (C, C2), 128.6 (4CH, ArC_{ortho} and ArC_{meta}), 125.0 (CH, C3), 96.5 (CH_2, O-CH_2-O), 96.3 (CH_2, O-CH_2-O), 73.7 (CH, C6), 69.1 (CH_2, C2´), 63.5 (CH_2, C1´´), 55.7 ($2CH_3$, CH_3-O), 37.9 (CH, C5); EIHRMS: Calcd. for $C_{20}H_{26}O_7S$ (M+Na): 433.1297; found: 433.1294 (M+Na); $[\alpha]_D^{25}$ = + 0.97 (c=1.95, $CHCl_3$).

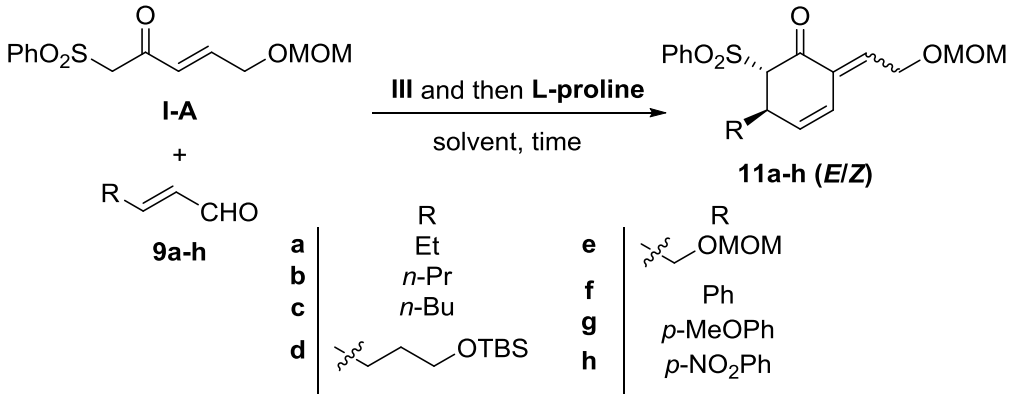
3.5. (5*R*,6*S*,*Z*)-5-(1-Methoxymethoxymethyl)-2-(2´-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11e*Z*.



11e*Z*

ν_{max} (liquid film) 2937, 2889, 1448, 1375, 1309, 1281, 1149, 1109, 1037, 918; δH (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.30 (1H, d, *J* = 10.0 Hz, H3), 6.10 (1H, t, *J* = 5.2 Hz, H1´), 5.91 – 5.72 (1H, m, H4), 4.65 (2H, s, O-CH_2-O), 4.60 (2H, s, O-CH_2-O), 4.55 – 4.45 (2H, m, H2´), 4.10 (1H, s, H6), 3.72 – 3.54 (2H, m, H1´´), 3.42 – 3.36 (1H, m, H5 and CH_3-O), 3.25 (3H, s, CH_3-O); δC (100 MHz; $CDCl_3$) 189.8 (C, C1), 144.5 (CH, C1´), 137.9 (C, ArC_{ipso}), 134.5 (CH, ArC_{para}), 130.7 (C, C2), 130.4 (CH, C4), 129.3 (2CH, ArC_{meta}), 129.2 (2CH, ArC_{ortho}), 124.7 (CH, C3), 96.5 (2CH_2, O-CH_2-O), 74.9 (CH, C6), 69.1 (CH_2, C2´), 67.1 (CH_2, C1´´), 55.8 (CH_3, CH_3-O), 55.6 (CH_3, CH_3-O), 38.4 (CH, C5); EIHRMS: Calcd. for $C_{20}H_{26}O_7S$(M+Na): 433.1297; found: 433.1292 (M+Na); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -7.57 (c=0.81, $CHCl_3$).

4. Typical procedure for reaction of I-A and β-monosubstituted α,β-unsaturated aldehydes with catalysts III and *L*-proline in a tandem way.



Compound **I-A** (50 mg, 17.6 mmol) and aldehyde (17.6 mmol) were dissolved in 1 mL of $CDCl_3$. Next, catalyst **III (**20 mol%) was added and the mixture was stirred for the specified time. When the disappearance of the starting materials is observed by ^{1}H-NMR, *L*-proline (20 mol%), is added and the reaction continues until the cyclic compounds are formed. In this case the compounds **11a-e** were isolated as a 2/1 mixture of diastereoisomers *E/Z*. Compounds **11e*E*** and **11e*Z*** were separated by flash chromatography. We were able to separate a small amount of compounds **11a*E*** and **11a*Z***.

4.1. (5*R*,6*S*,*E*)-5-Ethyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11a*E*.

$[\alpha]_D^{25}$ = -6.8 (*c* 0.3, $CHCl_3$); e.r. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; t_R (major) = 22.4 min; t_R (minor)= 24.9 min, for the rest of spectral properties see section 2.2.

4.2. (5*R*,6*S*,*Z*)-5-Ethyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11a*Z*.

e.r. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; t_R (major) = 18.3 min; t_R (minor)= 19.0 min, for the rest of spectral properties see section 2.3.

4.3. (5*R*,6*S*,*E*/*Z*)-5-Propyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11b*E*/11b*Z*.

For a mixture 2/1 of compounds: Yellow oil (49.1 mg, 75%), $[\alpha]_D^{25}$ = -17.2 (*c* 1.1, $CHCl_3$); e.r. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; **11b*E***: t_R (major) = 15.5 min; t_R (minor) = 19.6 min; **11b*Z***: t_R (major) = 17.4 min; t_R (minor) = 21.5 min; for the rest of spectral properties see section 3.1.

4.4. (5*R*,6*S*,*E*/*Z*)-5-Butyl-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11c*E*/11c*Z*.

For a mixture 2/1 of compounds: Yellow oil (34.0 mg, 50%), $[\alpha]_D^{25}$ = -14.5 (*c* 1.1, $CHCl_3$); We were able to separate a small amount of compound **11c*E***. $[\alpha]_D^{25}$ = -13.0 (*c* 0.2, $CHCl_3$). e.r. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; **11c*E*** t_R (major) = 16.9 min; t_R (minor) = 14.2 min; **11c*Z*** t_R (major) = 14.8 min; t_R (minor) = 13.6 min. For the rest of spectral properties see section 3.2.

4.5. (5*R*,6*S*,*E*/*Z*)-5-(3-t-Butyldimethylsilyloxy)-2-(2´-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11d*E*/11d*Z*.

For a mixture 2/1 of compounds: Yellow oil (40.9 mg, 46%), $[\alpha]_D^{25}$ = -27.5 (*c* 0.6, $CHCl_3$); e.r. determined by HPLC: CHIRALCEL OD-H column; *n*-Hexane/2-propanol [90:10 (v/v)]; flow rate: 1.0 mL/min; λ = 218 nm; **11d*E*** t_R (major) = 10.2 min; t_R (minor) = 11.8 min; **11d*Z*** t_R (major) = 9.1 min; t_R (minor) = 10.5 min. For the rest of spectral properties see section 3.3.

Using aldehyde **9e (3)** we were able to separate the cyclisation products. Yield in isomer *E* is referred to mixture of both isomers.

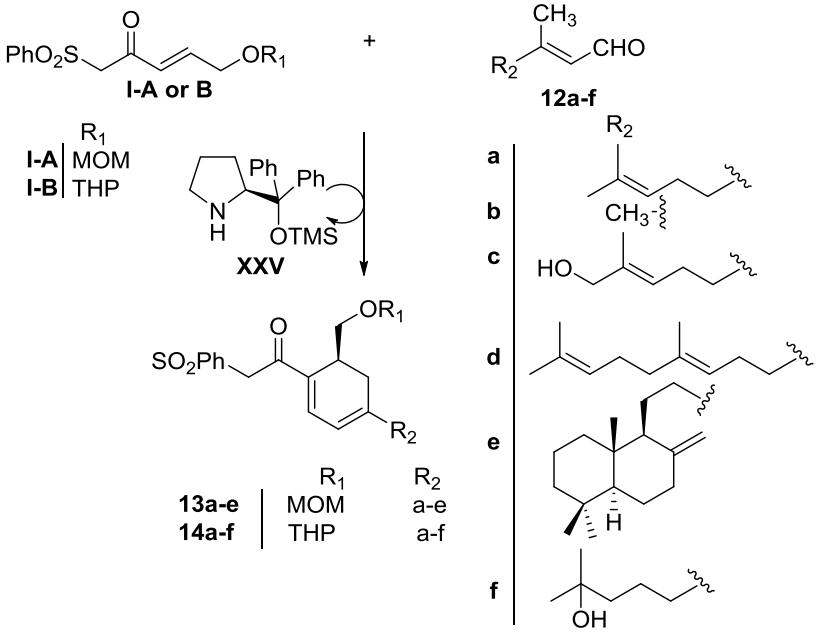
4.6. (5*R*,6*S*,*E*)-5-(1-Methoxymethoxymethyl)-2-(2´-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11e*E*.

Yellow oil (30.2 mg, 41%): $[\alpha]_D^{25}$ = +0.97 (*c*1.9, $CHCl_3$); For the rest of spectral properties see section 3.4.

4.7. (5*R*,6*S*,*Z*)-5-(1-Methoxymethoxymethyl)-2-(2´-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, 11e*Z*.

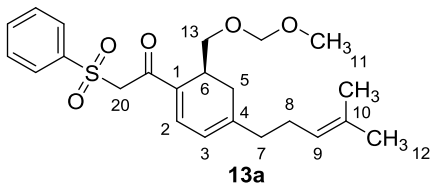
$[\alpha]_D^{25}$ = -7.57 (*c* 0.8, $CHCl_3$); For the rest of spectral properties see section 3.5.
In this case we were unable to determine the enantiomeric ratio of the compounds.

5. Typical procedure for reaction of I-A or I-B and β-methyl-β-disubstituted α,β-unsaturated aldehydes with catalyst XXV. Synthesis of chiral cyclohexadienes 13a-e and 14a-f.



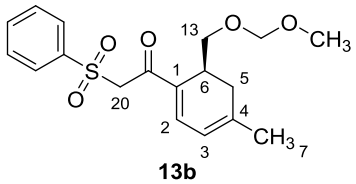
β-ketosulfone (**I-A** or **I-B**) (0.18 mmol) and the corresponding aldehyde **12** (0.08 mmol) were dissolved in 1 mL of EtOH. Next, catalyst **XXV** (50 mol%), and benzoic acid (20 mol%) were added successively and left stirring at room temperature for 48 hours. All products were purified by flash chromatography on silica gel using different mixtures of *n*-Hexane/EtOAc.

5.1. (*S*)-1-(6-((methoxymethoxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 13a.



Yellow oil (23.1 mg, 69%): ν_{max} (liquid film) 2956, 2929, 2873, 1715, 1651, 1566, 1446, 1323, 1288, 1153; δH (400 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 7.0 Hz, ArH_{ortho}), 7.72 – 7.47 (3H, m, ArH_{meta}, ArH_{para}), 7.06 (1H, d, *J* = 6.0 Hz, H2), 6.02 – 5.80 (1H, m, H3), 5.12 – 4.76 (1H, m, H9), 4.54 (2H, s, O-CH_2-O), 4.54 – 4.51 (1H, m, $H20_A$), 4.49 – 4.41 (1H, m, $H20_B$), 3.31 (3H, s, O-CH_3), 3.19 – 3.14 (3H, m, H6 and H13), 2.53 (1H, d, *J* = 17.8 Hz, $H5_A$), 2.23 – 2.11 (4H, m, H7 and H8), 1.69 (3H, s, H12), 1.61 (3H, s, H11), 1.40 – 1.23 (1H, m, $H5_B$); δC (101 MHz; $CDCl_3$) 186.6 (C, C=O), 152.0 (C, C1), 140.7 (CH, C2), 139.0 (C, C_{ipso}), 134.3 (CH, C_{para}), 133.4 (C, C10), 132.7 (C, C4), 129.4 (2CH, C_{meta}), 128.8 (2CH, C_{ortho}), 123.3 (CH, C9), 118.6 (CH, C3), 96.6 (CH_2, O-CH_2-O), 65.9 (CH_2, C13), 62.8 (CH_2, C20), 55.4 (CH_3, O-CH_3), 38.2 (CH_2, C7), 30.7 (CH, C6), 29.7 (CH_2, C5), 26.0 (CH_2, C8), 25.9 (CH_3, C12), 17.9 (CH_3, C11); EIHRMS: Calcd. for $C_{23}H_{30}O_5S$ (M+Na): 441.1712; found: 441.1706 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 31.6 min; t_R (major) = 34.5 min; $[\alpha]_D^{25}$ = -4.56 (c=0.57, $CHCl_3$).

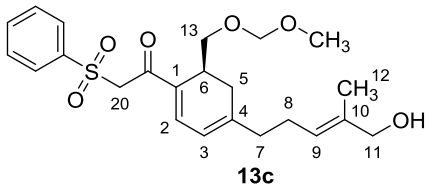
5.2. (*S*)-1-(6-((methoxymethoxy)methyl)-4-(methyl)-cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 13b.



13b

Yellow oil (17.4 mg, 62%): ν_{max} (liquid film) 2929, 1718, 1629, 1570, 1448, 1383, 1309, 1290, 1151; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 6.9 Hz, ArH_{ortho}), 7.81 – 7.24 (3H, m, ArH_{meta}, ArH_{para}), 7.03 (1H, d, *J* = 5.9 Hz, H2), 6.02 – 5.78 (1H, m, H3), 4.54 (2H, s, O-CH_2-O), 4.45 (2H, d, *J* = 8.1 Hz, H20), 3.31 (3H, s, CH_3-O), 3.21 – 3.16 (2H, m, H6 and H13), 2.55 – 2.28 (1H, m, $H5_A$), 1.92 (3H, s, H7), 1.65 – 1.58 (1H, m, $H5_B$); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 148.4 (C, C1), 140.7 (CH, C2), 139.0 (C, C_{ipso}), 134.3 (CH, C_{para}), 133.1 (C, C4), 129.4 (2CH, C_{meta}), 128.8 (2CH, C_{ortho}), 119.2 (CH, C3), 96.6 (CH_2, O-CH_2-O), 66.0 (CH_2, C13), 62.8 (CH_2, C20), 55.4 (CH_3, O-CH_3), 31.1 (CH_2, C5), 30.8 (CH, C6), 24.4 (CH_3, C7); EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 37.5 min; t_R (major) = 41.6 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -9.57 (c=1.42, $CHCl_3$).

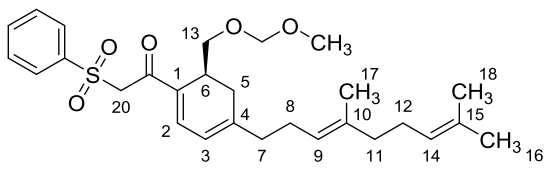
5.3. (*S*,*E*)-1-(6-((methoxymethoxy)methyl)-4-(4-methyl-5-hydroxy-pent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 13c.



13c

Yellow oil (6.9 mg, 20%): ν_{max} (liquid film) 3452, 2935, 2885, 1716, 1637, 1564, 1446, 1379, 1309, 1292, 1151; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 7.0 Hz, ArH_{ortho}), 7.75 – 7.48 (3H, m, ArH_{meta}, ArH_{para}), 7.06 (1H, d, *J* = 5.8 Hz, H2), 5.94 (1H, d, *J* = 4.9 Hz, H3), 5.43 – 5.32 (1H, m, H9), 4.54 (2H, s, O-CH_2-O), 4.54 – 4.35 (2H, m, H20), 4.00 (2H, s, H11), 3.31 (3H, s, CH_3-O), 3.22 – 3.19 (3H, m, H6 and H13), 2.53 (1H, d, *J* = 18.2 Hz, $H5_A$), 2.35 – 2.19 (4H, m, H7 and H8), 1.69 (3H, s, H12), 1.33 – 1.08 (1H, m, $H5_B$); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 151.5 (C, C1), 140.5 (CH, C2), 139.0 (C, ArC_{ipso}), 136.1 (C, C10), 134.3 (CH, ArC_{para}), 133.5 (C, C4), 129.4 (2CH, ArC_{meta}), 128.7 (2CH, ArC_{ortho}), 124.4 (CH, C9), 118.9 (CH, C3), 96.6 (CH_2, O-CH_2-O), 68.8 (CH_2, C11), 65.9 (CH_2, C13), 62.8 (CH_2, C20), 55.5 (CH_3, O-CH_3), 37.6 (CH_2, C7), 30.6 (CH, C6), 29.7 (CH_2, C5), 25.6 (CH_2, C8), 13.9 (CH_3, C12); EIHRMS: Calcd. for $C_{23}H_{30}O_6S$ (M+Na): 457.1661; found: 457.1655 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 58.8 min; t_R (major) = 67.9 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -1.02 (c=1.08, $CHCl_3$).

5.4. (*S*,*E*)-1-(6-((methoxymethoxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 13d.

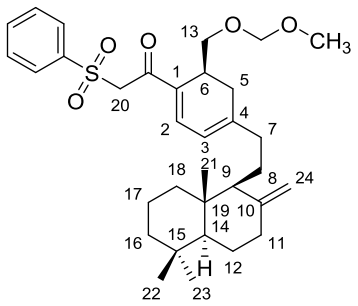


13d

Yellow oil (9.3 mg, 24%): ν_{max} (liquid film) 2926, 2856, 1716, 1651, 1566, 1448, 1379, 1309, 1288, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 8.2 Hz, ArH_{ortho}), 7.68 – 7.42 (3H, m, ArH_{meta}, ArH_{para}), 7.06 (1H, d, *J* = 5.8 Hz,

H2), 6.02 – 5.83 (1H, m, H3), 5.28 – 4.93 (2H, m, H9 and H14), 4.54 (2H, s, O-CH_2-O), 4.50 – 4.40 (2H, m, H20), 3.31 (3H, s, CH_3-O), 3.22 – 3.11 (3H, m, H6 and H13), 2.54 (1H, d, *J* = 18.2 Hz, $H5_A$), 2.31 – 2.14 (8H, m, H7, H8, H11, and H12), 1.68 (3H, s, H17), 1.61 (6H, s, H16 and H18), 1.35 – 1.10 (1H, m, $H5_B$); δC (50 MHz; $CDCl_3$) 186.9 (C, C=O), 152.1 (C, C1), 140.8 (CH, C2), 138.9 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.4 (C, 10), 133.3 (C, C15), 130.4 (C, C4), 129.4 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 124.4 (CH, C9), 123.3 (CH, C14), 118.6 (CH, C3), 96.6 (CH_2, O-CH_2-O), 66.0 (CH_2, C13), 62.8 (CH_2, C20), 55.4 (CH_3, O-CH_3), 39.9 (CH_2, C7), 38.3 (CH_2, C11), 30.7 (CH, C6), 29.7 (CH_2, C5), 26.9 (CH_2, C8), 25.9 (CH_2, C12), 23.6 (CH_3, C17), 17.9 (CH_3, C18), 16.3 (CH_3, C16); EIHRMS: Calcd. for $C_{28}H_{38}O_5S$ (M+Na): 509.2338; found: 509.2332 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (major) = 29.1 min; t_R (minor) = 34.8 min; $[\alpha]_D^{25}$ = -12.07 (c=1.42, $CHCl_3$).

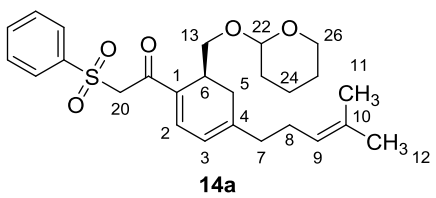
5.5. 1-((6*S*)-(6-((methoxymethoxy)methyl)-4-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-2-(phenylsulfonyl))ethan-1-one, 13e.



13e

Yellow oil (25.7 mg, 58%): ν_{max} (liquid film) 2937, 2848, 1718, 1649, 1566, 1446, 1321, 1309, 1151; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 7.9, ArH_{ortho}), 7.71 – 7.40 (3H, m, ArH_{meta}, ArH_{para}), 7.06 (1H, d, *J* = 5.7 Hz, H2), 5.97 – 5.79 (1H, m, H3), 4.84 (1H, s, $H24_A$), 4.54 (2H, s, O-CH_2-O), 4.54 – 4.42 (4H, m, H20), 4.27 (1H, s, $H24_B$), 3.31 (3H, s, CH_3-O), 3.21 – 3.16 (3H, m, H6 and H13), 2.59 – 2.40 (1H, m, $H5_A$), 2.44 – 0.74 (24H, m, $H5_B$, H7, H8, H9, H11, H12, H14, H16, H17, H18, H21, H22 and H23); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 153.2 (C, C1), 148.6 (C, C10), 140.9 (CH, C2), 138.9 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.7(C, C4), 129.4 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 118.2 (CH, C3), 106.6 (CH_2, C24), 96.6 (CH_2, O-CH_2-O), 65.9 (CH_2, C13), 62.8 (CH_2, C20), 56.7 (CH, C9), 55.7 (CH, C14), 55.4 (CH_3, O-CH_3), 42.3 (CH_2, C16), 40.0 (C, C19), 39.9 (CH_2, C7), 39.3 (CH_2, C11), 38.5 (CH_2, C18), 33.8 (CH_3, C23), 33.5 (C, C15), 30.7 (CH, C6), 28.6 (CH_2, C5), 24.7 (CH_2, C8), 21.9 (CH_3, C22), 19.6 (CH_2, C12), 19.2 (CH_2, C17), 14.7 (CH_3, C21); EIHRMS: Calcd. for $C_{33}H_{46}O_5S$ (M+Na): 577.2964; found: 577.2958 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 31.4 min; t_R (major) = 33.3 min; $[\alpha]_D^{25}$ = +13.98 (c=2.21, $CHCl_3$).

5.6. (*S*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 14a.

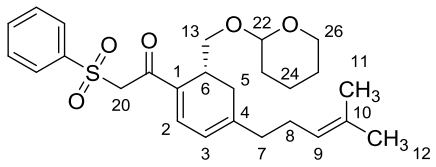


14a

Yellow oil (22.7 mg, 62%): ν_{max} (liquid film) 2941, 2870, 1716, 1651, 1566, 1446, 1381, 1321, 1309, 1288, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 8.1 Hz, ArH_{ortho}), 7.68 – 7.40 (3H, m, ArH_{meta}, ArH_{para}), 7.04 (1H, d, *J* = 5.9 Hz, H2), 5.98 – 5.83 (1H, m, H3), 5.11 – 5.01 (1H, m, H9), 4.62 – 4.33 (3H, m, H20 and H22), 3.88 – 3.60

(1H, m, $H26_A$), 3.59 – 3.27 (2H, m, $H13_A$ and $H26_B$), 3.26 – 2.92 (2H, m, H6 and $H13_A$), 2.57 – 2.39 (1H, m, $H5_A$), 2.25 – 2.13 (4H, m, H7 and H8), 1.72 – 1.39 (13H, m, $H5_B$, H11, H12, H23, H24 and H25); δC (50 MHz; $CDCl_3$) 186.7 (C, C=O), 152.1 (C, C1), 140.6 (CH, C2), 139.1 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.4 (C, C10), 132.6 (C, C4), 129.3 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 123.3 (CH, C9), 118.7 (CH, C3), 99.1 (CH, O-CH-O), 65.5 (CH_2, C13), 62.9 (CH_2, C20), 62.4 (CH_2, C26), 38.2 (CH_2, C7), 30.8 (CH_2, C5), 30.7 (CH, C6), 29.8 (CH_2, C23), 25.9 (CH_3, C12), 25.8 (CH_2, C8), 25.7 (CH_2, C25), 19.5 (CH_2, C24), 17.9 (CH_3, C11); EIHRMS: Calcd. for $C_{26}H_{34}O_5S$ (M+Na): 481.2025; found: 481.2019 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 36.6, 43.4 min; t_R (major) = 56.8 min; $[\alpha]_D^{25}$ = -15.1 (c=2.63, $CHCl_3$).

5.7. (*R*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, *ent*-14a.

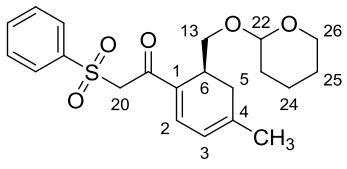


***ent*-14a**

Yellow oil (23.8 mg, 65%): $[\alpha]_D^{25}$ = +7.81 (c=0.71, $CHCl_3$).

5.8. (*S*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 14b.

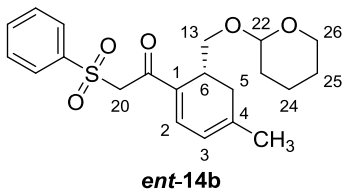
Note: the presence of THP protecting group makes many of NMR signals, both ^1H and ^{13}C, to appear twice. Hence, for compounds with THP group only NMR shift values for one isomer are given here.



14b

Yellow oil (24.6 mg, 79%): ν_{max} (liquid film) 2941, 2868, 1718, 1637, 1570, 1446, 1383, 1323, 1309, 1288, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 8.3 Hz, ArH_{ortho}), 7.71 – 7.50 (3H, m, ArH_{meta}, ArH_{para}), 7.02 (1H, d, *J* = 5.9 Hz, H2), 6.02 – 5.73 (1H, m, H3), 4.57 – 4.33 (3H, m, H20 and H22), 3.83 – 3.69 (1H, m, $H26_A$), 3.50 – 3.35 (2H, m, $H13_A$ and $H26_B$), 3.21 – 3.10 (1H, m, H6), 3.09 – 2.98 (1H, m, $H13_B$), 2.67 – 2.48 (1H, m, $H5_A$), 1.92 (3H, s, H7), 1.84 – 1.39 (7H, m, $H5_B$ H23, H24 and H25); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 148.6 (C, C1), 140.7 (CH, C2), 139.0 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.1 (C, C4), 129.4 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 119.2 (CH, C3), 99.2 (CH, O-CH-O), 65.5 (CH_2, C13), 62.8 (CH_2, C20), 62.4 (CH_2, C26), 31.4 (CH_2, C5), 31.1 (CH_2, C23), 30.8 (CH, C6), 25.6 (CH_2, C25), 24.4 (CH_3, C7), 19.7 (CH_2, C24); EIHRMS: Calcd. for $C_{21}H_{26}O_5S$ (M+Na): 413.1399; found: 413.1393 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 41.5, 49.9 min; t_R (major) = 66.5 min; $[\alpha]_D^{25}$ = -15.0 (c=0.16, $CHCl_3$).

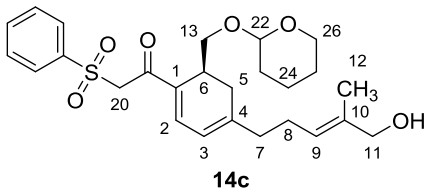
5.9. (*R*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, *ent*-14b.



***ent*-14b**

Yellow oil (23.4 mg, 75%); $[\alpha]_D^{25}$ = + 8.9 (c=0.9, $CHCl_3$).

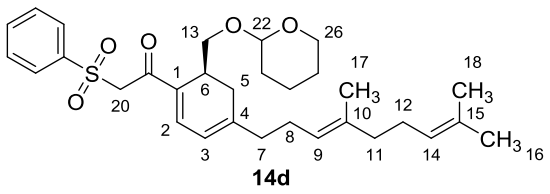
5.10. (*S*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4-methyl-5-hydroxy-pent-3-en-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 14c.



14c

Yellow oil (18.6 mg, 49%): ν_{max} (liquid film) 3449, 2943, 2870, 1718, 1651, 1564, 1446, 1383, 1321, 1309, 1290, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 7.6 Hz, ArH_{ortho}), 7.68 – 7.49 (3H, m, ArH_{meta}, ArH_{para}), 7.04 (1H, d, *J* = 5.7 Hz, H2), 6.01 – 5.85 (1H, m, H3), 5.49 – 5.31 (1H, m, H9), 4.66 – 4.40 (3H, m, H20 and H22), 3.99 (2H, s, H11), 3.84 – 3.64 (1H, m, $H26_A$), 3.57 – 3.31 (2H, m, $H13_A$ and $H26_B$), 3.26 – 3.00 (2H, m, H6 and $H13_B$), 2.71 – 2.50 (1H, m, $H5_A$), 2.37 – 2.20 (4H, m, H7 and H8), 1.67 (3H, s, H12), 1.59 – 1.35 (7H, m, $H5_B$, H23, H24 and H25); δC (50 MHz; $CDCl_3$) 186.7 (C, C=O), 151.3 (C, C1), 140.5 (CH, C2), 139.1 (C, ArC_{ipso}), 136.1 (C, C10), 134.3 (CH, ArC_{para}), 133.4 (C, C4), 129.4 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 124.4 (CH, C9), 118.9 (CH, C3), 99.0 (CH, O-CH-O), 68.7 (CH_2, C11), 65.6 (CH_2, C13), 62.8 (CH_2, C20), 62.1 (CH_2, C26), 37.6 (CH_2, C7), 30.8 (CH_2, C5), 30.6 (CH, C6), 29.7 (CH_2, C23), 25.6 (CH_2, C8), 25.0 (CH_2, C25), 19.5 (CH_2, C24), 13.9 (CH_3, C12); EIHRMS: Calcd. for $C_{26}H_{34}O_6S$ (M+Na): 497.1974; found: 497.1947 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 360 nm t_R (minor) = 60.4, 64.0 min; t_R (major) = 89.7, 124.6 min; $[\alpha]_D^{25}$ = -5.78 (c=2.49, $CHCl_3$).

5.11. (*S*,*E*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 14d.

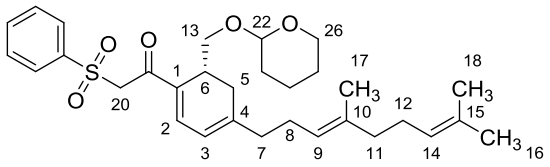


14d

Yellow oil (14.1 mg, 33%): ν_{max} (liquid film) 2937, 2868, 1716, 1651, 1566, 1448, 1381, 1321, 1309, 1288, 1155; δH (200 MHz; $CDCl_3$) 7.95 – 7.82 (2H, m, ArH_{ortho}), 7.73 – 7.40 (3H, m, ArH_{meta}, ArH_{para}), 7.04 (1H, d, *J* = 6.0 Hz, H2), 5.98 – 5.82 (1H, m, H3), 5.21 – 4.98 (2H, m, H9 and H14), 4.60 – 4.32 (3H, m, H20 and H22), 3.87 – 3.66 (1H, m, $H26_a$), 3.57 – 3.28 (2H, m, $H13_A$ and $H26_B$), 3.25 – 2.98 (2H, m, H6 and $H13_B$), 2.66 – 2.42 (1H, m, $H5_A$), 2.35 – 2.12 (4H, m, H7 and H8), 2.11 – 1.83 (4H, m, H11 and H12), 1.78 – 1.45 (16H, m, $H5_B$, H16, H17, H18, H23, H24 and H25); δC (50 MHz; $CDCl_3$) 186.7 (C, C=O), 152.0 (C, C1), 140.6 (CH, C2), 139.1 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.8 (C, C10), 133.5 (C, C15), 130.3 (C, C4), 129.3 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 124.4 (CH, C9), 123.3 (CH, C14), 118.5 (CH, C3), 98.7 (CH, O-CH-O), 66.1 (CH_2, C13), 62.9 (CH_2, C20), 62.4 (CH_2, C26), 39.9 (CH_2,

C7), 38.3 (CH_2, C11), 30.8 (CH_2, C5), 30.7 (CH, C6), 29.8 (CH_2, C23), 26.9 (CH_2, C8), 25.9 (CH_3, C16), 25.7 (CH_2, C12), 25.6 (CH_2, C25), 23.6 (CH_3, C17), 19.5 (CH_2, C24), 17.9 (CH_3, C18); EIHRMS: Calcd. for $C_{31}H_{42}O_5S$ (M+Na): 549.2641; found: 549.2645 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 360 nm t_R (minor) = 29.3 min; t_R (major) = 33.6, 40.8 min; $[\alpha]_D^{25}$ = -3.87 (c=1.60, $CHCl_3$).

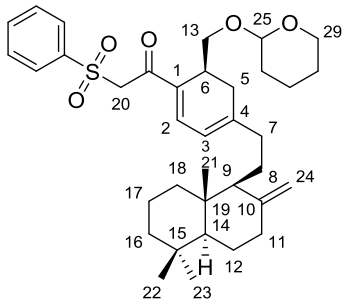
5.12. (*R*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4,8-dimethylnon-3,7-dien-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, *ent*-14d.



***ent*-14d**

Yellow oil (15.1 mg, 36%): $[\alpha]_D^{25}$ = +18.57 (c=0.56, $CHCl_3$).

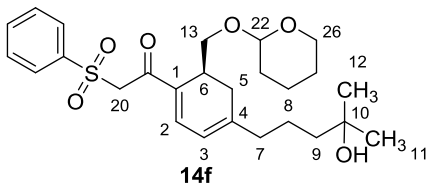
5.13. 1-((6*S*)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-2-(phenylsulfonyl)ethan-1-one, 14e.



14e

Yellow oil (7.6 mg, 16%): ν_{max} (liquid film) 2941, 2868, 1718, 1649, 1564, 1448, 1321, 1309, 1155; δH (200 MHz; $CDCl_3$) 7.97 – 7.83 (2H, m, ArH_{ortho}), 7.73 – 7.40 (3H, m, ArH_{meta}, ArH_{para}), 7.05 (1H, d, *J* = 5.8 Hz, H2), 6.03 – 5.84 (1H, m, H3), 4.85 (1H, s, $H24_A$), 4.61 – 4.31 (4H, m, H20, $H24_B$, and H25), 3.93 – 3.68 (1H, m, $H29_A$), 3.57 – 3.28 (2H, m, $H13_A$ and $H29_B$), 3.22 – 2.94 (2H, m, H6 and $H13_A$), 2.63 – 2.43 (1H, m, $H5_A$), 2.40 – 0.69 (32H, m, $H5_B$, H7, H8, H9, H11, H12, H14, H16, H17, H18, H21, H22, H23, H26, H27 and H28); δC (50 MHz; $CDCl_3$) 186.7 (C, C=O), 153.4 (C, C1), 148.6 (C, C10), 140.8 (CH, C2), 139.0 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.6 (C, C4), 129.3 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 118.3 (CH, C3), 106.6 (CH_2, C24), 98.7 (CH, O-CH-O), 65.4 (CH_2, C13), 62.9 (CH_2, C20), 62.1 (CH_2, C29), 57.9 (CH, C9), 55.8 (CH, C14), 42.4 (CH_2, C16), 40.0 (C, C19), 39.9 (CH_2, C7), 39.3 (CH_2, C11), 38.6 (CH_2, C18), 37.1 (CH_2, C26), 33.8 (CH_3, C23), 33.5 (C, C15), 30.6 (CH, C6), 29.9 (CH_2, C5), 25.6 (CH_2, C28), 24.7 (CH_2, C8), 21.8 (CH_3, C22), 19.6 ($2CH_2$, C12 and C27), 19.2 (CH_2, C17), 14.7 (CH_3, C21); EIHRMS: Calcd. for $C_{36}H_{50}O_5S$ (M+Na): 617.3277; found: 617.3271 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 360 nm t_R (minor) = 35.4 min; t_R (major) = 40.0, 49.0 min; $[\alpha]_D^{25}$ = +22.90 (c=1.43, $CHCl_3$).

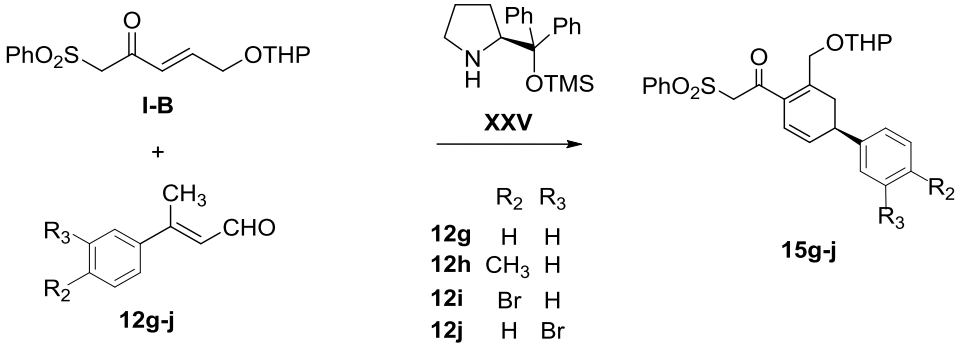
5.14. (*S*)-1-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(4-methyl-4-hydroxy-pentan-1-yl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 14f.



14f

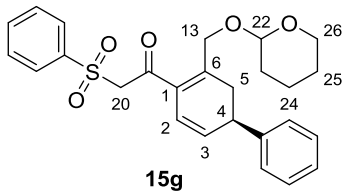
Yellow oil (12.2 mg, 32%): v_{max} (liquid film) 3460, 2943, 2870, 1716, 1645, 1566, 1448, 1379, 1323, 1309, 1290, 1153; δH (200 MHz; $CDCl_3$) 7.89 (2H, d, *J* = 8.5 Hz, ArH_{ortho}), 7.75 – 7.46 (3H, m, ArH_{meta}, ArH_{para}), 7.02 (1H, d, *J* = 5.8 Hz, H2), 5.97 – 5.79 (1H, m, H3), 4.57 – 4.29 (3H, m, H20 and H22), 3.93 – 3.63 (1H, m, $H26_a$), 3.51 – 3.24 (2H, m, $H13_A$ and $H26_B$), 3.21 – 2.92 (2H, m, H6 and $H13_B$), 2.74 – 2.41 (1H, m, $H5_A$), 2.30 – 2.01 (4H, m, H7 and H9), 1.76 – 1.33 (9H, m, $H5_B$, H8, H23, H24 and H25), 1.32 – 1.14 (6H, m, H11 and H12); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 152.4 (C, C1), 140.7 (CH, C2), 139.1 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 133.3 (C, C4), 129.4 (2CH, ArC_{meta}), 128.8 (2CH, ArC_{ortho}), 119.1 (CH, C3), 99.3 (CH, O-CH-O), 70.6 (C, C10), 65.6 (CH_2, C13), 62.8 (CH_2, C20), 62.3 (CH_2, C26), 43.5 (CH_2, C9), 38.3 (CH_2, C7), 38.0 (CH_2, C5), 31.1 (CH_2, C23), 30.8 (CH, C6), 29.7 (CH_3, C11), 29.6 (CH_2, C8), 28.9 (CH_3, C12), 25.6 (CH_2, C25), 19.6 (CH_2, C24); EIHRMS: Calcd. for $C_{26}H_{36}O_6S$ (M+Na): 499.2130; found: 499.2125 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (minor) = 44.6; t_R (major) = 51.4, 61.9 min; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +13.91 (c=1.86, $CHCl_3$).

6. Typical procedure for reaction of I-B and β-methyl-β-aryldisubstituted α,β-unsaturated aldehydes with catalyst XXV. Synthesis of chiral cyclohexadienes 15g-j.



β-ketosulfone (**I-B)** (0.18 mmol) and the corresponding aldehyde **12g-j** (0.08 mmol) were dissolved in 1 mL of EtOH. Next, catalyst **XXV** (50 mol%), and benzoic acid (20 mol%) were added successively and left stirring at room temperature for 48 hours. All products were purified by flash chromatography on silica gel using different mixtures of *n*-Hexane/EtOAc.

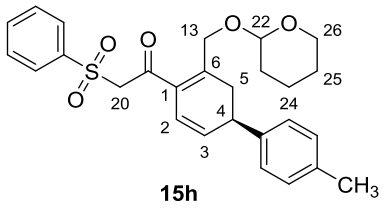
6.1. (*R*)-2-(1-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-5-(phenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 15g.



15g

Yellow oil (21.3 mg, 59%): ν_{max} (liquid film) 2941, 2870, 1718, 1647, 1545, 1447, 1323, 1309, 1292, 1153; δH (400 MHz; $CDCl_3$) 7.91 (2H, d, *J* = 7.3 Hz, SO_2-ArH_{ortho}), 7.73 – 7.48 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.47 – 7.34 (5H, m, ArH_{ortho}, ArH_{meta} and ArH_{para}), 7.22 (1H, d, *J* = 6.3 Hz, H2), 6.53 (1H, dd, *J* = 6.1, 2.6 Hz, H3), 4.65 – 4.38 (3H, m, H20 and H22), 3.89 – 3.69 (1H, m, $H26_a$), 3.49 – 3.35 (2H, m, $H13_A$ and $H26_B$), 3.35 – 3.27 (1H, m, H4), 3.15 – 3.00 (2H, m, $H5_A$ and $H13_B$), 2.84 – 2.53 (1H, m, $H5_B$), 1.89 – 1.30 (6H, m, H23, H24 and H25); δC (101 MHz; $CDCl_3$) 186.5 (C, C=O), 146.2 (C, C6), 140.0 (CH, C2), 138.7 (C, SO_2-ArC_{ipso}), 134.6 (C, ArC_{ipso}), 134.5 (C, C1), 134.1 (CH, SO_2-ArC_{para}), 129.3 (CH, ArC_{para}), 129.1 (2CH, SO_2-ArC_{meta}), 128.6 (4CH, SO_2-ArC_{ortho}, ArC_{meta}), 126.0 (2CH, ArC_{ortho}), 119.2 (CH, C3), 98.9 (CH, O-CH-O), 64.9 (CH_2, C13), 62.8 (CH_2, C20), 61.9 (CH_2, C26), 30.5 (CH_2, C23), 30.9 (CH, C4), 30.3 (CH_2, C5), 25.3 (CH_2, C25), 19.3 (CH_2, C24); EIHRMS: Calcd. for $C_{26}H_{28}O_5S$ (M+Na): 475.1555; found: 475.1549 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ = 420 nm; t_R (major) = 25.4, 27.0 min; t_R (minor) = 36.1 min; $[\alpha]_D^{25}$ = +18.42 (c=1.33, $CHCl_3$).

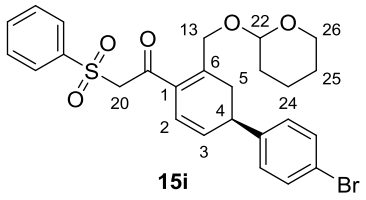
6.2. (*R*)-2-(1-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-5-(4-methylphenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 15h.



15h

Yellow oil (25.7 mg, 69%): ν_{max} (liquid film) 2941, 2870, 1720, 1645, 1539, 1448, 1383, 1323, 1309, 1292, 1155; δH (400 MHz; $CDCl_3$) 7.96 – 7.83 (2H, m, SO_2-ArH_{ortho}), 7.74 – 7.37 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.22 – 7.16 (5H, m, H2, ArH_{ortho} and ArH_{meta}), 6.50 (1H, ddd, J = 6.1, 2.7, 1.3 Hz, H3), 4.60 – 4.49 (3H, m, H20 and H22), 3.81 – 3.70 (1H, m, $H26_a$), 3.49 – 3.35 (2H, m, $H13_A$ and $H26_B$), 3.35 – 3.27 (1H, m, H4), 3.15 – 3.00 (2H, m, $H5_A$ and $H13_B$), 2.72 – 2.57 (1H, m, $H5_B$), 2.37 (3H, s, CH_3-Ar), 1.80 – 1.26 (6H, m, H23, H24 and H25); δC (101 MHz; $CDCl_3$) 186.4 (C, C=O), 146.5 (C, C6), 140.2 (CH, C2), 139.5 (C, ArC_{ipso}), 139.0 (C, ArC-CH_3), 138.7 (C, SO_2-ArC_{ipso}), 136.7 (C, C1), 134.6 (CH, SO_2-ArC_{para}), 129.6 (2CH, ArC_{meta}), 128.8 (2CH, SO_2-ArC_{meta}), 128.6 (2CH, SO_2-ArC_{ortho}), 126.2 (2CH, ArC_{ortho}), 118.4 (CH, C3), 98.8 (CH, O-CH-O), 64.9 (CH_2, C13), 62.7 (CH_2, C20), 61.8 (CH_2, C26), 30.9 (CH_2, C23), 30.8 (CH, C4), 27.8 (CH_2, C5), 25.3 (CH_2, C25), 21.2 (CH_3, Ar-CH_3), 19.3 (CH_2, C24); EIHRMS: Calcd. for $C_{27}H_{30}O_5S$ (M+Na): 489.1712; found: 489.1706 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ = 420 nm t_R (minor) 13.6, 15.6 min; t_R (major) = 18.7, 20.8 min; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +44.70 (c=0.97, $CHCl_3$).

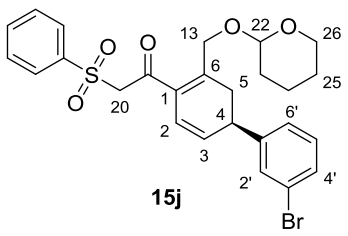
6.3. (*R*)-2-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 15i.



15i

Yellow oil (25.0 mg, 59%): ν_{max} (liquid film) 2947, 2870, 1718, 1647, 1544, 1448, 1383, 1323, 1309, 1290, 1155; δH (200 MHz; $CDCl_3$) 7.98 – 7.85 (2H, m, SO_2-ArH_{ortho}), 7.75 – 7.33 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.27 – 7.16 (5H, m, H2, ArH_{ortho} and ArH_{meta}), 6.60 – 6.42 (1H, m, H3), 4.67 – 4.34 (3H, m, H20 and H22), 3.86 – 3.67 (1H, m, $H26_A$), 3.57 – 3.38 (2H, m, $H13_A$ and $H26_B$), 3.35 – 3.23 (1H, m, H4), 3.19 – 3.03 (2H, m, $H5_A$ and $H13_B$), 2.78 – 2.58 (1H, m, $H5_B$), 1.84 – 1.29 (6H, m, H23, H24 and H25);δC (50 MHz; $CDCl_3$) 186.7 (C, C=O), 144.7 (C, C6), 139.9 (CH, C2), 139.5 (C, SO_2-ArC_{ipso}), 139.0 (C, ArC_{ipso}), 135.0 (C, C1), 134.4 (CH, SO_2-ArC_{para}), 129.4 (2CH, ArC_{meta}), 128.7 (2CH, ArC_{ortho}), 127.8 (2CH, SO_2-ArC_{meta}), 127.6 (2CH, SO_2-ArC_{ortho}), 123.4 (C, ArC-Br), 119.9 (CH, C3), 98.6 (CH, O-CH-O), 65.2 (CH_2, C13), 63.1 (CH_2, C20), 62.2 (CH_2, C26), 27.9 (CH_2, C23), 31.1 (CH, C4), 30.6 (CH_2, C5), 25.6 (CH_2, C25), 19.7 (CH_2, C24); EIHRMS: Calcd. for $C_{26}H_{27}BrO_5S$ (M+Na): 553.0660; found: 553.0655 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [80/20 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (major) 30.3, 31.8 min; t_R (minor) 3 = 34.6 min; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +46.80 (c=1.02, $CHCl_3$).

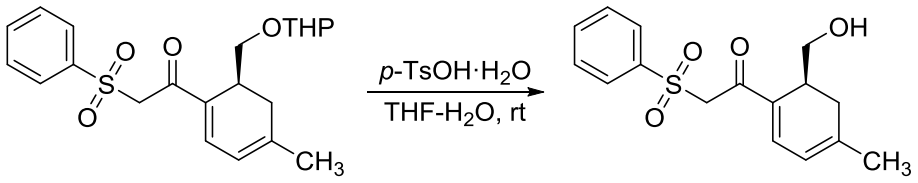
6.4. (*R*)-2-(6-((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-5-(3-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 15j.



15j

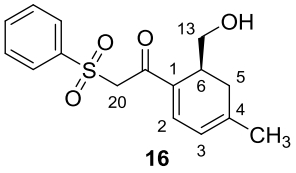
Yellow oil (34.3 mg, 81%): ν_{max} (liquid film) 2943, 2870, 1717, 1651, 1547, 1448, 1408, 1323, 1309, 1290, 1155; δH (200 MHz; $CDCl_3$) 7.91(2H, d, *J* = 7.8 Hz, SO_2-ArH_{ortho}), 7.74 – 7.39 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.33 – 7.13 (5H, m, H2, ArH_{ortho}, ArH_{meta} and ArH_{para}), 6.50 (1H, dd, *J* = 6.0, 2.6 Hz, H3), 4.64 – 4.39 (3H, m, H20 and H22), 3.83 – 3.65 (1H, m, $H26_a$), 3.63 – 3.26 (3H, m, H4, $H13_A$ and $H26_B$), 3.23 – 2.94 (2H, m, $H5_A$ and $H13_B$), 2.78 – 2.55 (1H, m, $H5_A$), 1.88 – 1.34 (6H, m, H23, H24 and H25); δC (50 MHz; $CDCl_3$) 186.8 (C, C=O), 144.7 (C, C1), 141.9 (C, C6), 141.7 (C, ArC_{ipso}), 139.7 (CH, C2), 138.9 (C, SO_2-ArC_{ipso}), 134.4 (2CH, SO_2-C_{para} and ArC_{para}), 132.0 (CH, ArC_{ortho}), 130.4 (CH, ArC_{meta}), 129.4 (2CH, SO_2-ArC_{meta}), 128.7 (2CH, SO_2-ArC_{ortho}), 124.7 (CH, ArC_{ortho}), 123.1 (C, ArC-Br), 120.6 (CH, C3), 98.7 (CH, O-CH-O), 65.1 (CH_2, C13), 63.0 (CH_2, C20), 62.2 (CH_2, C26), 31.2 (CH, C4), 30.8 (CH_2, C5), 28.2 (CH_2, C23), 25.6 (CH_2, C25), 19.7 (CH_2, C24); EIHRMS: Calcd. for $C_{26}H_{27}BrO_5S$ (M+Na): 553.0660; found: 553.0655 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (major) = 23.6 min; t_R (minor) = 26.9 min; $[\alpha]_D^{25}$ = +30.09 (c=1.29, $CHCl_3$).

7. Synthesis of (*S*)-1-(6-(hydroxymethyl)-4-(4-methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 16, by deprotection of 14b with *p*TsOH.



14b **16**

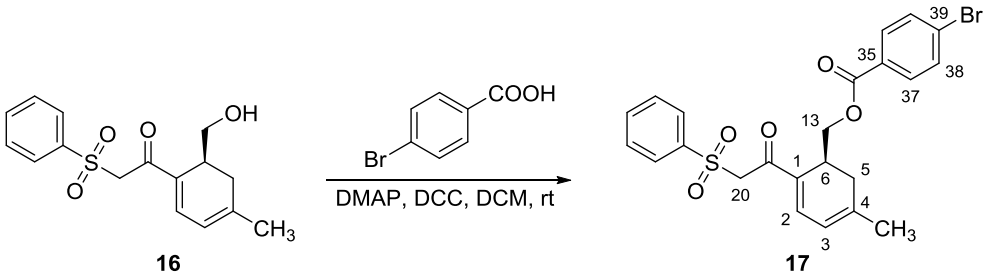
Tetrahydropyanyl derivative **14b** (1 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 mmol) were dissolved in 10 mL of a 1 : 1 mixture of THF–H_2O, and the whole mixture was stirred until no starting material was observed (typically 48 hours). The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **16**.



16

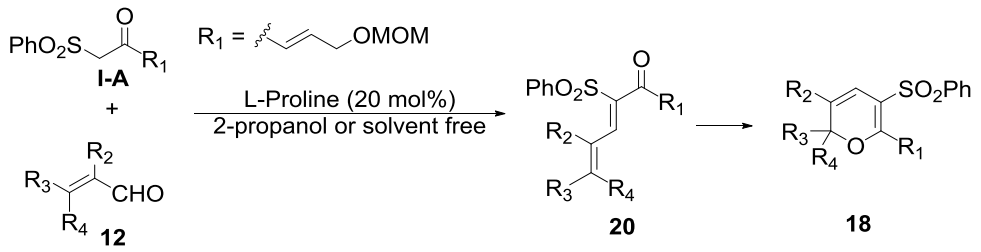
Pale yellow solid (293.8 mg, 96%): mp 116−118 °C; ν_{max} (liquid film) 3446, 2932, 2872, 1718, 1635, 1566, 1446, 1321, 1309, 1288, 1152; δH (200 MHz; $CDCl_3$) 7.95 – 7.82 (2H, m, ArH_{ortho}), 7.76 – 7.49 (3H, m, ArH_{meta}, ArH_{para}), 7.05 (1H, d, J = 5.8 Hz, H2), 6.01 – 5.81 (1H, m, H3), 4.55 (1H, d, J = 13.5 Hz, $H20_A$), 4.38 (1H, d, J = 13.5 Hz, $H20_B$), 3.51 – 3.27 (2H, m, H13), 3.15 – 2.90 (1H, m, H6), 2.46 – 2.37 (2H, m, H5), 1.93 (3H, s, H7); δC (50 MHz; $CDCl_3$) 187.6 (C, C=O), 149.0 (C, C1), 141.0 (CH, C2), 139.0 (C, ArC_{ipso}), 134.4 (CH, ArC_{para}), 133.4 (C, C4), 129.4 (2CH, ArC_{meta}), 128.7 (2CH, ArC_{ortho}), 119.1 (CH, C3), 62.7 (CH_2, C20), 62.6 (CH_2, C13), 33.5 (CH, C6), 31.2 (CH_2, C5), 24.3 (CH_3, CH_3-C4); EIHRMS: Calcd. for $C_{16}H_{18}O_4S$ (M+Na): 329.0823; found: 329.0818 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 33.5 min; t_R (major) = 68.4 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -27.40 (c=0.16, $CHCl_3$).

8. Synthesis of (*S*)-(4-methyl-1-(2-(phenylsulfonyl)acetyl)cyclohexa-1,3-dien-6-yl)methyl *para*-bromobenzoate, 17.



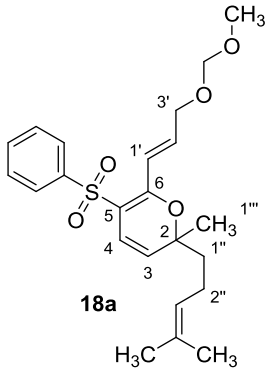
16 (191 mg, 0.62 mmol), *p*-bromobenzoic acid (249 mg, 1.24 mmol) and 4-(dimethylamino)pyridine (76 mg, 0.62 mmol) were dissolved in 3 mL of DCM, and then dicyclohexylcarbodiimide (256 mg, 1.24 mmol) was slowly added. The mixture was stirred at room temperature for 15 hours. The solid residues were filtered off and the solvent evaporated *in vacuo*. Flash chromatography (*n*-Hexane/EtOAc, 7/3) afforded **17**: White solid, (151 mg, 60%); mp: 118 – 120 ºC; ν_{max} (liquid film) 2956, 2937, 1718, 1678, 1637, 1589, 1568, 1446, 1321, 1309, 1271, 1153; δH (200 MHz; $CDCl_3$) 7.93 – 7.79 (4H, m, ArH_{ortho}), 7.69 – 7.47 (5H, m, ArH_{meta}, ArH_{para}), 7.12 (1H, d, *J* = 5.9 Hz, H2), 6.01 – 5.87 (1H, m, H3), 4.51 (1H, d, *J* = 13.6 Hz, $H20_A$), 4.43 (1H, d, *J* = 13.6 Hz, $H20_B$), 4.12 (1H, dd, *J* = 10.7, 8.3 Hz, $H13_A$), 3.94 (1H, dd, *J* = 10.7, 5.0 Hz, $H13_B$), 3.31 (1H, ddd, *J* = 13.2 Hz, 8.3, 1.6 Hz, H6), 2.53 – 2.31 (2H, m, H5), 1.89 (3H, s, H7); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 166.1 (C, O-C=O), 148.5 (C, C1), 141.6 (CH, C2), 139.0 (C, ArC_{ipso}), 134.4 (CH, ArC_{para}), 132.2 (C, C4), 131.9 (2CH, C38), 129.4 (2CH, ArC_{meta}), 129.2 (2CH, C37), 129.0 (C, C35), 128.7 (2CH, ArC_{ortho}), 128.6 (C, C39), 119.4 (CH, C3), 64.6 (CH_2, C13), 62.8 (CH_2, C20), 31.8 (CH_2, C5), 30.0 (CH, C6), 24.3 (CH_3, C7); EIHRMS: Calcd. for $C_{23}H_{21}BrO_5S$ (M+Na): 511.0191; found: 511.0185 (M+Na); ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (major) = 59.0 min; t_R (minor) = 62.7 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -6.61 (c=1.28, $CHCl_3$).

9. General procedure for the synthesis of 2*H*-pyrans 18a-m and Knoevenagel adducts 20n-q.



β-ketosulfone **I-A** (50 mg, 0.18 mmol) and the corresponding aldehyde **12** (0.09 mmol) were dissolved in 1 mL of 2-propanol. Next, *L*-Proline (20 mol%), and additive (20 mol%) if needed was added and left stirring for the appropriate time. All products were purified by flash chromatography on silica gel using different mixtures of *n*-Hexane/EtOAc.

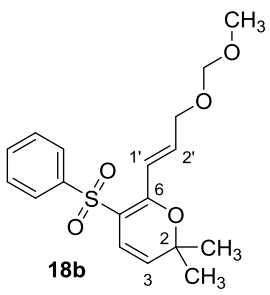
9.1. (*E*)-6-(3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2*H*-pyran, 18a.



18a

Yellow oil (23.7 mg, 63%):ν_{max} (liquid film) 2926, 1674, 1539, 1446, 1377, 1321, 1151; δH (400 MHz; $CDCl_3$) 7.84 (2H, d, *J* = 8.3 Hz, ArH_{ortho}), 7.59 – 7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.42 (1H, dt, *J* = 15.4, 1.8 Hz, H1´), 6.56 (1H, dt, *J* = 15.4, 5.2 Hz, H2´), 6.36 (1H, d, *J* = 10.0 Hz, H4), 5.34 (1H, d, *J* = 10.0 Hz, H3), 5.05 – 4.93 (1H, m, H3´´), 4.67 (2H, s, O-CH_2-O), 4.25 (2H, dd, *J* = 5.2, 1.8 Hz, H3´), 3.39 (3H, s, O-CH_3), 2.06 – 1.86 (2H, m, H2´´), 1.68 – 1.45 (8H, m, $(CH_3)_2$-C4´´ and H1´´), 1.27 (3H, s, CH_3-C2); δC (101 MHz; CDCl3) 156.0 (C, C6), 143.0 (C, ArC_{ipso}), 136.1 (CH, C2´), 132.6 (CH, ArC_{para}), 132.0 (C, C4´´), 129.0 (2CH, ArC_{meta}), 126.4 (2CH, ArC_{ortho}), 124.2 (CH, C3), 123.4 (CH, C3´´), 121.5 (CH, C1´), 119.1 (CH, C4), 114.3 (C, C5), 96.0 (CH_2, O-CH_2-O), 80.6 (C, C2), 66.9 (CH_2, C3´), 55.4 (CH_3, O-CH_3), 40.8 (CH_2, C1´´), 25.7 (CH_3, C1´´´), 22.2 (CH_2, C2´´), 17.7 ($2CH_3$, $(CH_3)_2$-C4´´); EIHRMS: Calcd. for $C_{23}H_{30}O_5S$ (M+Na): 441.1712; found: 441.1706 (M+Na).

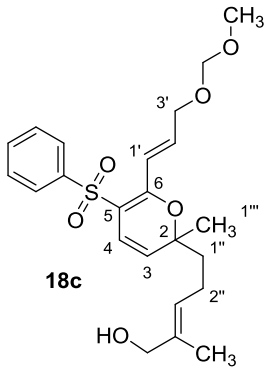
9.2. (*E*)-6-(3-(methoxymethoxy)prop-1-en-1-yl)-2,2-dimethyl-5-(phenylsulfonyl)-2*H*-pyran, 18b.



18b

Yellow oil (25.8 mg, 82%):ν_{max} (liquid film) 2935, 1647, 1537, 1446, 1379, 1319, 1153; δH (200 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 7.9, 1.7 Hz, ArH_{ortho}), 7.59 – 7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.39 (1H, dt, *J* = 15.4, 1.7 Hz, H1´), 6.57 (1H, dt, *J* = 15.4, 5.2 Hz, H2´), 6.33 (1H, d, *J* = 9.9 Hz, H4), 5.38 (1H, d, *J* = 9.9 Hz, H3), 4.68 (2H, s, O-CH_2-O), 4.25 (2H, dd, *J* = 5.2, 1.7 Hz, H3´), 3.39 (3H, s, O-CH_3), 1.31 (6H, s, $(CH_3)_2$-C2); δC (50 MHz; $CDCl_3$) 156.2 (C, C6), 143.3 (C, ArC_{ipso}), 137.1 (CH, C2´), 132.9 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 125.5 (CH, C3), 121.9 (CH, C1´), 119.1 (CH, C4), 114.9 (C, C5), 96.3 (CH_2, O-CH_2-O), 78.3 (C, C2), 67.2 (CH_2, C3´), 55.6 (CH_3, O-CH_3), 27.4 (2CH_3, $(CH_3)_2$-C2); EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080 (M+Na).

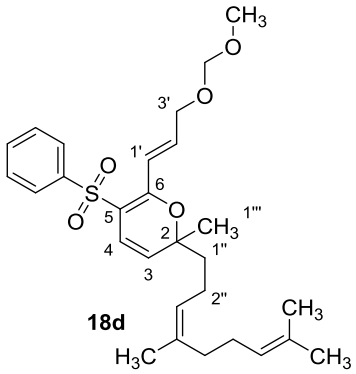
9.3. (*E*)-5-(6-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2*H*-pyran-2-yl)-2-methylpent-2-en-1-ol, 18c.



18c

Yellow oil (22.6 mg, 58%):ν_{max} (liquid film) 3469, 2934, 2889, 1649, 1537, 1446, 1307, 1213, 1151; δH (200 MHz; $CDCl_3$) 7.84 (2H, d, *J* = 7.9 Hz, ArH_{ortho}), 7.62 – 7.35 (4H, m, ArH_{meta}, ArH_{para} and H1´), 6.56 (1H, dt, *J* = 15.3, 5.4 Hz, H2´), 6.37 (1H, d, *J* = 10.1 Hz, H4), 5.39 – 5.22 (2H, m, H3 and H3´´), 4.67 (2H, s, O-CH_2-O), 4.25 (2H, d, J = 4.7 Hz, H3´), 3.94 (2H, s, CH_2-OH), 3.39 (3H, s, O-CH_3), 2.12 – 1.95 (2H, m, H2´´), 1.80 – 1.58 (2H, m, H1´´), 1.55 (3H, s, CH_3-C4´´), 1.25 (3H, s, CH_3-C2); δC (50 MHz; $CDCl_3$) 156.2 (C, C6), 143.2 (C, ArC_{ipso}), 136.4 (CH, C2´), 135.5 (C, C4´´), 132.9 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 125.0 (CH, C3´´), 124.3 (CH, C3), 121.8 (CH, C1´), 119.6 (CH, C4), 114.5 (C, C5), 96.3 (CH_2, O-CH_2-O), 80.9 (C, C2), 68.8 (CH_2, CH_2-OH), 67.2 (CH_2, C3´), 55.6 (CH_3, O-CH_3), 40.5 (CH_2, C1´´), 26.1 (CH_3, CH_3-C2), 22.2 (CH_2, C2´´), 13.8 (CH_3, CH_3-C4´´); EIHRMS: Calcd. for $C_{23}H_{30}O_6S$ (M+Na): 457.1655; found: 457.1655 (M+Na).

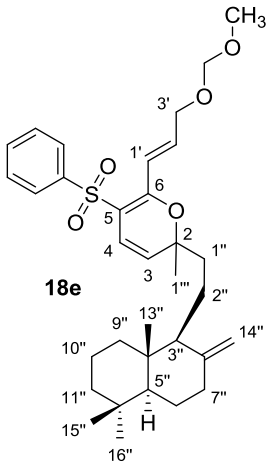
9.4. 2-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-6-((E)-3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2*H*-pyran, 18d.



Yellow oil (25.3 mg, 58%):ν_{max} (liquid film) 2926, 1649, 1539, 1446, 1379, 1321, 1151; δH (200 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 7.9, 1.7 Hz, ArH_{ortho}), 7.59 – 7.44 (3H, m, ArH_{meta}, ArH_{para}), 7.40 (1H, dt, *J* = 15.3, 1.7 Hz, H1´), 6.57 (1H, dt, *J* = 15.3, 5.2 Hz, H2´), 6.36 (1H, d, *J* = 10.0 Hz, H4), 5.35 (1H, d, *J* = 10.0 Hz, H3), 5.13 – 4.91 (2H, m, H3´´ and H7´´), 4.68 (2H, s, O-CH_2-O), 4.25 (2H, dd, *J* = 5.2, 1.7 Hz, H3´), 3.40 (3H, s, O-CH_3), 2.11 – 1.85 (8H, m, H1´´, H2´´, H5´´ and H6´´), 1.67 (3H, s, CH_3-C4´´), 1.59 (3H, s, CH_{3A}-C8´´), 1.50 (3H, s, CH_{3B}-C8´´), 1.28 (3H, s, CH_3-C2); δC (50 MHz; $CDCl_3$) 156.3 (C, C6), 143.3 (C, ArC_{ipso}), 136.4 (CH, C2´), 136.0 (C, C4´´), 132.8 (C, C8´´) , 131.6 (CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 124.5 (CH, C3), 124.4 (CH, C3´´), 123.5 (CH, C7´´), 121.9 (CH, C1´), 119.4 (CH, C4), 114.6 (C, C5), 96.3 (CH_2, O-CH_2-O), 80.9 (C, C2), 67.2 (CH_2, C3´), 55.6 (CH_3, O-CH_3), 40.8 (CH_2, C1´´), 39.8 (CH_2, C5´´), 26.8 (CH_2, C6´´), 26.0 ($2CH_3$, CH_3-C2 and $(CH_3)_b$-C8´´), 22.4 (CH_2, C2´´), 17.9 (CH_3, CH_3-C4´´), 16.1 $(CH_3)_a$-C8´´); EIHRMS: Calcd. for $C_{28}H_{38}O_5S$ (M+Na): 509.2338; found: 509.2332 (M+Na).

9.5. 6-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)-2*H*-pyran, 18e.

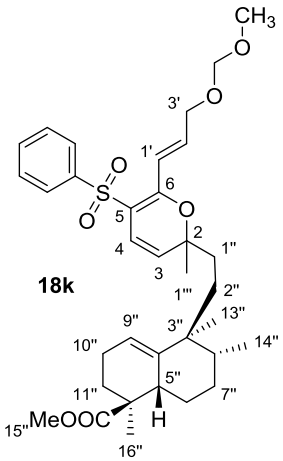
Caution: the name does not correspond to the numeration used.



Yellow oil (31.4 mg, 63%):ν_{max} (liquid film) 2918, 2848, 1539, 1446, 1321, 1153; δH (200 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 7.6, 1.6 Hz, ArH_{ortho}), 7.60 – 7.47 (3H, m, ArH_{meta}, ArH_{para}), 7.40 (1H, m, H1´), 6.56 (1H, dt, *J* = 10.1, 5.4 Hz, H2´), 6.36 (1H, dd, *J* = 10.1, 1.3 Hz, H4), 5.34 (1H, d, *J* = 10.1, H3), 4.74 (1H, s, $H29''_A$), 4.68 (2H, s, O-CH_2-O), 4.38 (1H, s, $H29''_B$), 4.25 (2H, d, *J* = 5.4, Hz, H3´), 3.40 (3H, s, O-CH_3), 2.44 – 0.87 (28H, m, H1´´, H2´´, H3´´, H5´´, H6´´, H7´´, H9´´, H10´´, H11´´, H13´´, H15´´, H16´´and H1´´´); δC (50 MHz; $CDCl_3$) 156.3 (C, C6), 148.5 (C, C23´´), 143.4 (C, ArC_{ipso}), 136.4 (CH, C2´), 132.8 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 124.6 (CH, C3), 121.8 (CH, C1´), 119.5 (CH, C4), 114.5 (C, C5), 106.6 (CH_2, C29´´), 96.2 (CH_2, O-CH_2-O), 81.3 (C, C2), 67.2 (CH_2, C3´), 57.3 (CH, C18´´), 55.7 (CH, C20´´), 55.6 (CH_3, O-CH_3), 42.4 (CH_2, C26´´), 40.1 (C, C19´´), 40.0 (CH_2, C1´´), 39.1 (CH_2, C22´´), 38.5 (CH_2, C24´´), 33.8 (CH_3, C31´´), 33.5 (C, C27´´), 26.2 (CH_3, C1´´´), 24.6 (CH_2, C2´´), 21.9 (CH_3, C30´´), 19.6 (CH_2, C21´´), 19.2 (CH_2, C25´´), 14.6 (CH_3, C32´´);EIHRMS: Calcd. for $C_{33}H_{46}O_5S$ (M+Na): 577.2958; found: 577.2958 (M+Na); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +4.58 (*c* 0.3, $CHCl_3$);

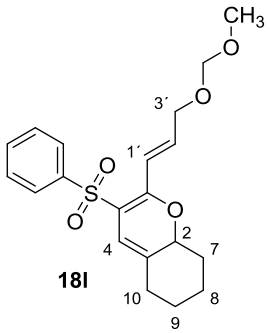
9.6. (1*S*,5*S*,6*R*,8a*S*)-methyl-5-(3-(6-((E)-3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-phenylsulfonyl)-2H-pyran-2-yl)propyl)-1,5,6-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboxylate, 18k.

Caution: the name does not correspond to the numeration used.



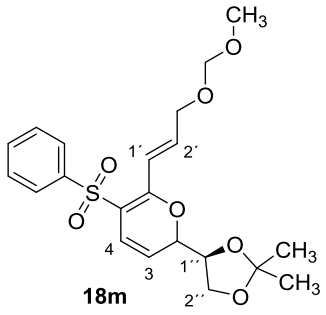
Yellow oil (20.4 mg, 38%):ν_{max} (liquid film) 2932, 2874, 1726, 1539, 1446, 1321, 1157; δH (400 MHz; $CDCl_3$) 7.86 (2H, d, *J* = 7.3 Hz, ArH_{ortho}), 7.59 – 7.41 (3H, m, ArH_{meta}, ArH_{para}), 7.41 (1H, m, H1´), 6.59 (1H, m, H2´), 6.37 (1H, dd, *J* = 9.8, 3.0 Hz, H4), 5.33 (1H, d, *J* = 9.8 Hz, H3), 5.29 – 5.17 (1H, m, H9´´), 4.68 (2H, s, O-CH_2-O), 4.26 (2H, d, *J* = 5.2, Hz, H3´), 3.61 (3H, s, COO-CH_3), 3.40 (3H, s, O-CH_3), 2.65 – 2.50 (1H, m, H5´´), 1.97 – 0.65 (25H, m, H1´´, H2´´, H6´´, H7´´, H8´´, H10´´, H11´´, H13´´, H14´´, H16´´ and H1´´´); δC (101 MHz; $CDCl_3$) 178.3 (C, $COOCH_3$), 156.3 (C, C6), 143.1 (C, ArC_{ipso}), 141.1 (C, C19´´), 135.9 (CH, C2´), 132.5 (CH, ArC_{para}), 129.0 (2CH, ArC_{meta}), 126.4 (2CH, ArC_{ortho}), 124.8 (CH, C3), 121.5 (CH, C1´), 119.8 (CH, C24´´), 119.1 (CH, C4), 114.3 (C, C5), 96.0 (CH_2, O-CH_2-O), 80.9 (C, C2), 67.1 (CH_2, C3´), 55.3 (CH_3, O-CH_3), 51.6 (CH_3, COO-CH_3), 44.8 (C, C27´´), 42.7 (C, C18´´), 38.3 (2CH, C20´´ and C23´´), 34.6 (CH_2, C2´´), 31.4 (CH_2, C1´´), 30.6 (CH_2, C26´´), 28.6 (CH_2, C22´´), 26.2 (CH_3, C1´´´), 22.9 (CH_2, C21´´), 22.8 (CH_2, C25´´), 22.3 (CH_3, C28´´), 19.9 (CH_3, C31´´), 15.4 (CH_3, C29´´); EIHRMS: Calcd. for $C_{34}H_{46}O_7S$ (M+Na): 621.2856; found: 621.2856 (M+Na); $[\alpha]_D^{25}$ = +35.4 (*c* 1.07, $CHCl_3$);

9.7. (*E*)-2-(3-(methoxymethoxy)prop-1-en-1-yl)-3-(phenylsulfonyl)-6,7,8,8a-tetrahydro-5*H*-chromene, 18l.



Yellow oil (14.6 mg, 43%):ν_{max} (liquid film) 2939, 1722, 1446, 1321, 1151; δH (200 MHz; $CDCl_3$) 7.86 (2H, dd, *J* = 7.8, 1.7 Hz, ArH_{ortho}), 7.64 – 7.44 (3H, m, ArH_{meta} and ArH_{para}), 7.36 (1H, dd, *J* = 14.9, 1.7 Hz, H1´), 6.48 (1H, dt, *J* = 14.9, 5.4 Hz, H2´), 5.98 (1H, s, H4), 4.91 – 4.73 (1H, m, H2), 4.66 (2H, s, O-CH_2-O), 4.23 (2H, d, *J* = 5.4 Hz, H3´), 3.39 (3H, s, O-CH_3), 2.45 – 1.18 (8H, m, H7, H8, H9, and H10); δC (50 MHz; $CDCl_3$) 155.0 (C, C6), 145.3 (C, ArC_{ipso}), 134.7 (CH, C2´), 133.5 (C, C3), 132.8 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 126.8 (2CH, ArC_{ortho}), 121.5 (CH, C1´), 116.9 (C, C5), 112.2 (CH, C4), 96.2 (CH_2, O-CH_2-O), 77.4 (CH, C2), 67.2 (CH_2, C3´), 55.6 (CH_3, O-CH_3), 34.5 (CH_2, C7), 32.5 (CH_2, C10), 26.3 (CH_2, C9), 24.1 (CH_2, C8); EIHRMS: Calcd. for $C_{20}H_{24}O_5S$ (M+Na): 399.1237; found: 399.1237 (M+Na).

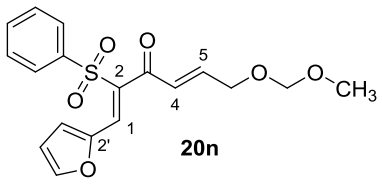
9.8. (*E*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-(3-(methoxymethoxy)prop-1-en-1-yl)-5-(phenylsulfonyl)-2*H*-pyran, 18m.



18m

Yellow oil (7.2 mg, 19%):ν_{max} (liquid film) 2935, 2889, 1146, 1373, 1290, 1213, 1151; δH (200 MHz; $CDCl_3$) 7.88 – 7.82 (2H, m, ArH_{ortho}), 7.60 – 7.47 (3H, m, ArH_{meta} and ArH_{para}), 7.39 – 7.32 (1H, m, H1´), 6.58 – 6.35 (2H, m, H4 and H2´), 5.59 (1H, dd, *J* = 10.0, 3.3 Hz, H3), 4.66 (2H, s, O-CH_2-O), 4.27 – 4.21 (3H, m, H1 and H3´), 4.07 (2H, dd, *J* = 14.7, 6.2, H2´´), 3.92 (1H, dd, *J* = 8.7, 6.2 Hz, H1´´), 3.38 (3H, s, CH_3-O), 1.37 (3H, s, $(CH_3)_2$-C), 1.31 (3H, s, $(CH_3)_2$-C); δC (50 MHz; $CDCl_3$) 156.7 (C, C6), 142.8 (C, ArC_{ipso}), 137.1 (CH, C2´), 133.1 (CH, ArC_{para}), 129.4 (2CH, ArC_{meta}), 126.9 (2CH, ArC_{ortho}), 125.3 (CH, C3), 121.9 (CH, C1´), 120.6 (CH, C4), 116.5 (C, C5), 110.4 (C, $(CH_3)_2$-C), 96.3 (CH_2, O-CH_2-O), 76.3 (CH, C1), 76.2 (CH, C1´´), 69.1 (CH_2, C2´´), 67.0 (CH_2, C3´), 55.6 (CH_3, CH_3-O), 26.8 (CH_3, $(CH_3)_2$-C), 25.3 (CH_3, $(CH_3)_2$-C); EIHRMS: Calcd. for $C_{21}H_{26}O_7S$ (M+Na): 445.1297; found: 445.1291 (M+Na).

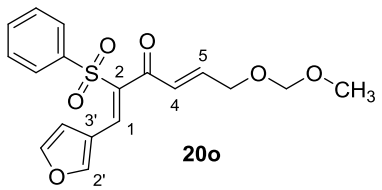
9.9. (1*Z*,4*E*)-1-(furan-2-yl)-6-(methoxymethoxy)-2-(phenylsulfonyl)hexa-1,4-dien-3-one, 20n.



20n

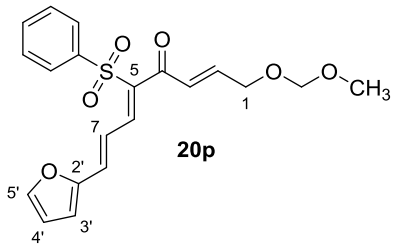
Yellow oil (28.3 mg, 87%):ν_{max} (liquid film) 2947, 2889, 1659, 1622, 1446, 1319, 1197, 1149; δH (400 MHz; $CDCl_3$) 7.86 (2H, dd, *J* = 8.4, 1.3 Hz, ArH_{ortho}), 7.64 – 7.57 (2H, m, H1 and ArH_{para}), 7.57-7.49 (2H, m, ArH_{meta}), 7.49 – 7.43 (1H, m, H5´), 6.84 (1H, dt, *J* = 16.0, 4.1 Hz, H5), 6.78 (1H, d, *J* = 3.5 Hz, H3´), 6.54 (1H, dt, J = 16.0, 2.0 Hz, H4), 6.46 (1H, dd, J = 3.5, 1.8 Hz, H4´), 4.60 (2H, s, O-CH_2-O), 4.21 (2H, dd, *J* = 4.1, 2.0 Hz, H6), 3.33 (3H, s, CH_3-O); δC (101 MHz; $CDCl_3$) 190.1 (C, C3), 147.9 (CH, C5), 147.5 (C, C2´), 146.9 (CH, C5´), 139.8 (C, ArC_{ipso}), 135.7 (C, C2), 133.6 (CH, ArC_{para}), 129.8 (CH, C4), 129.1 (2CH, ArC_{meta}), 128.3 (2CH, ArC_{ortho}), 126.9 (CH, C1), 119.3 (CH, C4´), 112.8 (CH, C3´), 96.0 (CH_2, O-CH_2-O), 65.7 (CH_2, C6), 55.4 (CH_3, O-CH_3); EIHRMS: Calcd. for $C_{18}H_{18}O_6S$ (M+Na): 385.0716; found: 385.0716 (M+Na).

9.10. (1*Z*,4*E*)-1-(furan-3-yl)-6-(methoxymethoxy)-2-(phenylsulfonyl)hexa-1,4-dien-3-one, 20o.



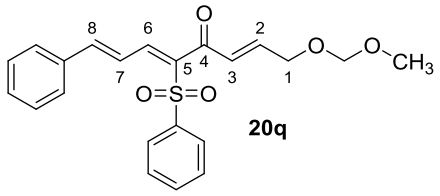
Yellow oil (32.2 mg, 99%):ν_{max} (liquid film) 2949, 2889, 1654, 1622, 1446, 1309, 1205, 1149; δH (400 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 8.5, 1.3 Hz, ArH_{ortho}), 7.74 (1H, dd, *J* = 1.1, 0.5 Hz, H1), 7.72 – 7.71 (1H, m, H2´), 7.63 – 7.58 (1H, m, ArH_{para}), 7.55 – 7.49 (2H, m, ArH_{meta}), 7.40 – 7.35 (1H, m, H5´), 6.92 (1H, dt, J = 15.9, 4.0 Hz, H5), 6.55 (1H, dt, J = 15.9, 2.1 Hz, H4), 6.29 (1H, dtd, J = 1.4, 0.9, 0.4 Hz, H4´), 4.60 (2H, s, O-CH_2-O), 4.22 (2H, dd, J = 4.0, 2.1 Hz, H6), 3.33 (3H, s, CH_3-O); δC (101 MHz; $CDCl_3$) 191.2 (C, C3), 149.5 (CH, C5), 147.3 (CH, C2´), 144.7 (CH, C5´), 139.7 (C, ArC_{ipso}), 138.1 (C, C2), 136.6 (CH, ArC_{para}), 131.6 (CH, C1), 129.1 (2CH, ArC_{meta}), 129.0 (CH, C4), 128.3 (2CH, ArC_{ortho}), 119.0 (C, C3´), 109.3 (CH, C4´), 96.0 (CH_2, O-CH_2-O), 65.7 (CH_2, C6), 55.4 (CH_3, O-CH_3); EIHRMS: Calcd. for $C_{18}H_{18}O_6S$ (M+Na): 385.0716; found: 385.0716 (M+Na).

9.11. (2*E*,5*Z*,7*E*)-8-(furan-2-yl)-1-(methoxymethoxy)-5-(phenylsulfonyl)octa-2,5,7-trien-4-one, 20p.



Yellow oil (19.6 mg, 56%):ν_{max} (liquid film) 2933, 2889, 1647, 1616, 1583, 1463, 1446, 1307, 1147; δH (400 MHz; $CDCl_3$) 7.88 (2H, d, *J* = 7.9 Hz, ArH_{ortho}), 7.72 – 7.43 (5H, m, H6, ArH_{meta}, ArH_{para} and H5´), 7.00 – 6.80 (3H, m, H2, H7 and H8), 6.71 (1H, d, *J* = 15.7 Hz, H3), 6.62 – 6.58 (1H, m, H3´), 6.48 – 6.45 (1H, m, H4´), 4.65 (2H, s, O-CH_2-O), 4.33 – 4.22 (2H, m, H1), 3.37 (3H, s, CH_3-O); δC (101 MHz; $CDCl_3$) 188.5 (C, C4), 151.5 (C, C2´), 148.0 (CH, C2), 145.1 (CH, C5´), 143.5 (CH, C6), 140.5 (C, ArC_{ipso}), 138.6 (C, C5), 133.4 (CH, ArC_{para}), 132.2 (CH, C7), 129.0 (3CH, C3 and ArC_{meta}), 128.1 (2CH, ArC_{ortho}), 119.9 (C, C8), 114.9 (CH, C3´), 112.6 (CH, C4´), 96.1 (CH_2, O-CH_2-O), 65.9 (CH_2, C6), 55.4 (CH_3, O-CH_3); EIHRMS: Calcd. for $C_{20}H_{20}O_6S$ (M+Na): 411.0873; found: 411.0873 (M+Na).

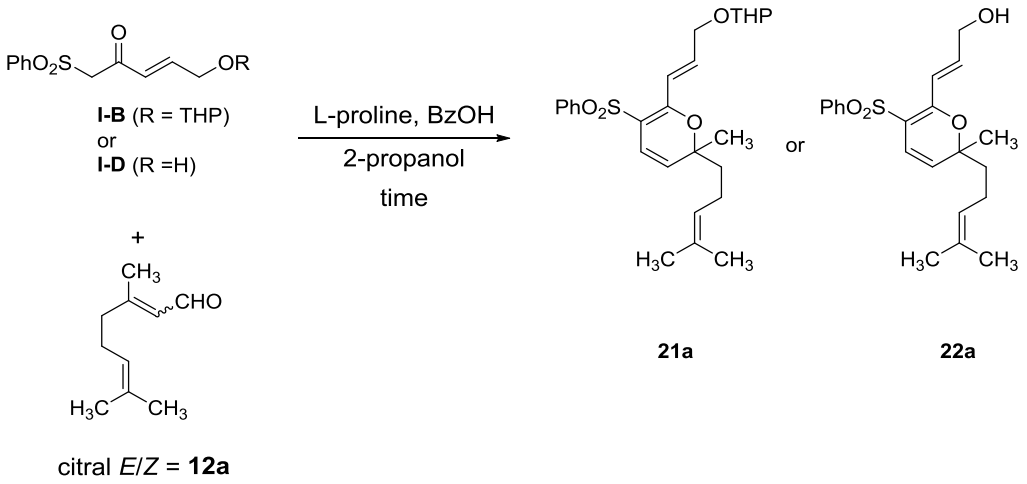
9.12. (2*E*,5*Z*,7*E*)-1-(methoxymethoxy)-8-phenyl-5-(phenylsulfonyl)octa-2,5,7-trien-4-one, 20q.



20q

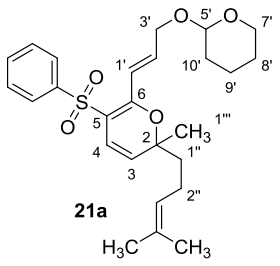
Yellow oil (7.9 mg, 22%):ν_{max} (liquid film) 3061, 2927, 2891, 1653, 1618, 1577, 1448, 1317, 1309, 1149; δH (400 MHz; $CDCl_3$) 7.94 – 7.86 (2H, m, SO_2-ArH_{ortho}), 7.73 (1H, d, *J* = 11.5 Hz, H6), 7.65 – 7.57 (1H, SO_2-ArH_{para}), 7.55 – 7.51 (2H, m, SO_2-ArH_{meta}), 7.48 – 7.41 (1H, m, ArH_{para}), 7.38 – 7.33 (4H, m, ArH_{ortho} and ArH_{meta}), 7.15 (1H, d, *J* = 15.4 Hz, H8), 6.95 – 6.89 (2H, m, H2 and H7), 6.73 (1H, dt, *J* = 15.7, 2.0 Hz, H3), 4.65 (2H, s, O-CH_2-O), 4.27 (2H, dd, *J* = 3.9, 2.0 Hz, H1), 3.36 (3H, s, CH_3-O); δC (100 MHz; $CDCl_3$) 188.6 (C, C=O), 148.3 (CH, C2), 146.7 (CH, C8), 143.8 (CH, C6), 140.4 (C, SO_2-ArC_{ipso}), 139.1 (C, C5), 135.1 (C, ArC_{ipso}), 133.5 (CH, SO_2-ArC_{para}), 130.4 (2CH, ArC_{meta}), 129.1 (2CH, SO_2-ArC_{meta}), 128.9 (3CH, C3 and ArC_{ortho}), 128.2 (2CH, SO_2-ArC_{ortho}), 127.9 (CH, ArC_{para}), 121.8 (CH, C7), 96.1 (CH_2, O-CH_2-O), 65.9 (CH_2, C1), 55.4 (CH_3, CH_3-O); EIHRMS: Calcd. for $C_{22}H_{22}O_5S$ (M+Na): 421.1086; found: 421.1080 (M+Na).

10. General procedure for the synthesis of 2*H*-pyrans, 21a and 22a.



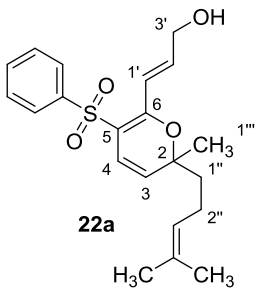
β-ketosulfone (**I-B or I-D)** (17.6 mmol) and *E/Z*-citral **12a** (8.7 mmol) were dissolved in 1 mL of the 2-propanol. Next, *L*-Proline (20 mol%), and benzoic acid (20 mol%), was added and left stirring for the appropriate time. All products were purified by flash chromatography on silica gel using different mixtures of *n*-Hexane/EtOAc.

10.1. (*E*)-2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-en-1-yl)-2*H*-pyran, 21a.



Yellow oil (Using **I-B**: 40.0 mg, 97%; using **I-C**: 36.3 mg, 88%): ν_{max} (liquid film) 2926, 1647, 1537, 1446, 1377, 1321, 1153; δH (200 MHz; $CDCl_3$) 7.94 – 7.77 (2H, m, ArH_{ortho}), 7.60 – 7.45 (3H, m, ArH_{meta}, ArH_{para}), 7.45 – 7.32 (1H, m, H1´), 6.58 (1H, dt, *J* = 15.3, 5.0 Hz, H2´), 6.38 (1H, d, *J* = 10.0 Hz, H4), 5.33 (1H, d, *J* = 10.0 Hz, H3), 5.05 – 4.92 (1H, m, H3´´), 4.67 (1H, t, *J* = 3.2 Hz, O-CH-O), 4.50 – 4.33 (1H, m, $H3´_a$), 4.27 – 4.07 (1H, m, $H3´_b$), 3.94 – 3.76 (1H, m, $H7´_A$), 3.60 – 3.45 (1H, m, $H7´_B$), 2.06 –1.86 (2H, m, H2´´), 1.64 (6H, s, $(CH_3)_2$-C4´´), 1.60 – 1.53 (4H, m, H10´ and H1´´), 1.53 – 1.44 (4H, m, H8´ and H9´), 1.27 (3H, s, CH_3-C2); δC (50 MHz; $CDCl_3$) 156.5 (C, C6), 143.4 (C, ArC_{ipso}), 136.8 (CH, C2´), 132.8 (CH, C2´), 132.8 (C, ArC_{para}), 132.3 (C, C4´´), 129.2 (2CH, ArC_{meta}), 128.4 (C, C4´), 126.7 (2CH, ArC_{ortho}), 124.3 (CH, C3), 123.7 (CH, C3´´), 121.3 (CH, C1´), 119.5 (CH, C4), 114.3 (C, C5), 98.4 (CH, O-CH-O), 80.8 (C, C2), 66.8 (CH_2, C3´), 62.3 (CH_2, C7´), 40.8 (CH_2, C1´´), 30.7 (CH_2, C10´), 25.9 (CH_3, C1´´´), 25.8 (CH_3, $C5´´_B$), 25.7 (CH_2, C8´), 22.5 (CH_2, C2´´), 19.5 (CH_3, C9´), 17.8 (CH_3, $C5´´_A$); EIHRMS: Calcd. for $C_{26}H_{34}O_5S$ (M+Na): 481.2025; found: 481.2019 (M+Na).

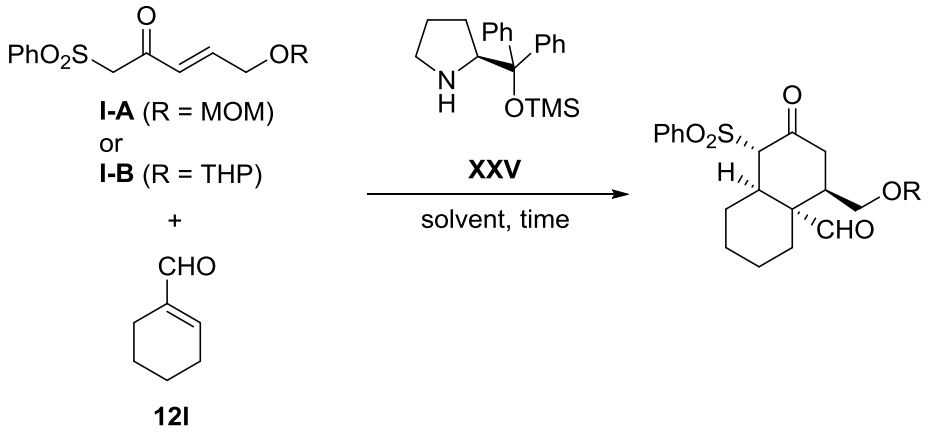
10.2. (*E*)-3-(2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2H-pyran-6-yl)prop-2-en-1-ol, 22a.



22a

Yellow oil (21.5 mg, 64%):ν_{max} (liquid film) 3493, 2968, 2916, 2850, 1645, 1621, 1537, 1446, 1317, 1155, ; δH (200 MHz; $CDCl_3$) 7.91 – 7.78 (2H, m, ArH_{ortho}), 7.60 –7.47 (3H, m, ArH_{meta}, ArH_{para}), 7.41 (1H, dt, *J* = 15.3, 1.8 Hz, H1´), 6.64 (1H, dt, *J* = 15.3, 4.9 Hz, H2´), 6.36 (1H, d, *J* = 10.0 Hz, H4), 5.34 (1H, d, *J* = 10.0 Hz, H3), 5.07 – 4.94 (1H, m, H3´´), 4.43 – 4.30 (2H, m, H3´), 2.02 – 1.88 (2H, m, H2´´), 1.76 – 1.51 (8H, m, H1´´ and $(CH_3)_2$-C4´´), 1.27 (3H, s, CH_3-C2); δC (50 MHz; $CDCl_3$) 156.3 (C, C6), 143.2 (C, ArC_{ipso}), 139.2 (CH, C2´), 132.9 (C, ArC_{para}), 132.3 (C, C4´´), 129.3 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 124.4 (CH, C3), 123.6 (CH, C3´´), 120.6 (CH, C1´), 119.4 (CH, C4), 114.5 (C, C5), 80.9 (C, C2), 63.2 (CH_2, C3´), 40.8 (CH_2, C1´´), 25.9 (CH_3, C1´´´), 25.8 (CH_3, $C5''_B$), 22.5 (CH_2, C2´´), 17.8 (CH_3, $C5''_A$); EIHRMS: Calcd. for $C_{21}H_{26}O_4S$ (M+Na): 397.1444; found: 397.1447 (M+Na).

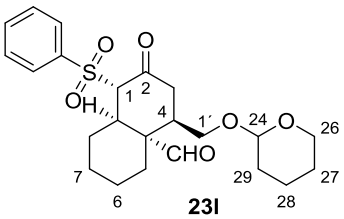
11. General procedure for the synthesis of chiral *cis*-decalines 23l, 23r-s and 25l.



β−ketosulfone **I-A** or **I-B** (0.15 mmol) and the corresponding aldehyde **12l** (0.07 mmol) were dissolved in 1 mL of EtOH. Next, catalyst **XXV** (20 mol%) was added and left stirring a room temperature for 48-72 hours. Then were concentrated in vacuum and the residues were purified by flash chromatography on silica gel using different mixtures of *n*-Hexane/EtOAc. Note: for the synthesis of enantiomeric derivativesm catalyst ***ent*-XXV** was used instead.

11.1. (1*S*,4*R*,4a*S*,8a*R*)-2-oxo-1-(phenylsulfonyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)decahydronaphthalene-4a-carbaldehyde, 23l.

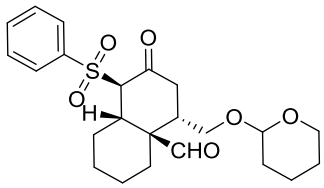
Note: the presence of THP protecting group makes many of NMR signals, both ^{1}H and ^{13}C, to appear twice. Hence, for compounds with THP group only NMR shift values for one isomer are given here.



23l

Colorless oil (15.3 mg, 51%): ν_{max} (liquid film) 2939, 2868, 1716, 1448, 1321, 1309, 1149; δH (200 MHz; $CDCl_3$) 9.63 (1H, s, CHO), 7.86 (2H, d, *J* = 7.2 Hz, ArH_{ortho}), 7.70 (1H, d, *J* = 6.9 Hz, ArH_{para}), 7.66 – 7.51 (2H, m, *J* = 7.2 Hz, ArH_{meta}), 4.51 (1H, d, *J* = 12.4 Hz, H24), 3.82 – 3.64 (2H, m, H1 and $H26_A$), 3.62 – 3.36 (3H, m, H8a and H1´), 3.26 – 3.10 (1H, m, $H26_B$), 3.02 – 2.70 (2H, m, H3), 2.23 – 1.92 (2H, m, H4 and $H5_A$), 1.66 – 1.48 (13H, m, H27, H28, H29, $H5_B$, H6, H7 and H8); δC (50 MHz; $CDCl_3$) 203.8 (CH, CHO), 202.2 (C, C=O), 137.3 (C, ArC_{ipso}), 134.7 (CH, ArC_{para}), 129.5 (2CH, ArC_{meta}), 129.2 (2CH, ArC_{ortho}), 98.9 (CH, C24), 75.4 (CH, C1), 66.6 (CH_2, C1´), 62.3 (CH_2, C26), 50.0 (C, C4a), 39.8 (CH, C4), 37.8 (CH_2, C3), 35.6 (CH, C8a), 30.4 (CH_2, C29), 30.2 (CH_2,C5), 25.5 (CH_2, C27), 22.2 (CH_2, C8), 21.4 (CH_2, C7), 19.7 (CH_2, C6), 19.1 (CH_2, 28); EIHRMS: Calcd. for $C_{23}H_{30}O_6S$ (M+Na): 457.1661; found 457.1655 (M+Na); ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R (minor) = 19.1, 20.8 min; t_R (major) = 26.5, 37.5 min; $[\alpha]_D^{25}$ = - 8.66 (c = 2. 65, $CHCl_3$).

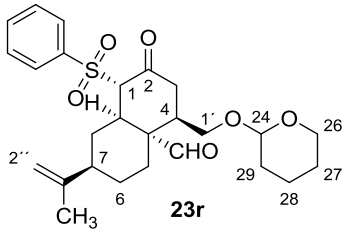
11.2. (1*R*,4*S*,4a*R*,8a*S*)-2-oxo-1-(phenylsulfonyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)decahydronaphthalene-4a-carbaldehyde, *ent*-23l.



***ent*-23l**

Colorless oil (15.3 mg, 51%): $[\alpha]_D^{25}$ = + 12.9 (c = 1.54, $CHCl_3$).

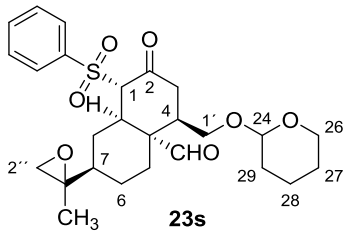
11.3. (1*S*,4*R*,4a*S*,7*R*,8a*R*)-2-oxo-1-(phenylsulfonyl)-7-(prop-1-en-2-yl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)decahydronaphthalene-4a-carbaldehyde, 23r.



23r

Colorless oil (15.3 mg, 51%): ν_{max} (liquid film) 2939, 2870, 1714, 1448, 1319, 1309, 1149; δH (200 MHz; $CDCl_3$) 9.63 (1H, s, CHO), 7.96 – 7.79 (2H, m, ArH_{ortho}), 7.78 – 7.49 (3H, m, ArH_{meta} and ArH_{para}), 4.64 (2H, d, *J* = 15.5 Hz, H2´´), 4.51 (1H, d, *J* = 12.2 Hz, H24), 3.86 – 3.64 (2H, m, H1 and $H26_A$), 3.64 – 3.44 (3H, m, H8a and H1´), 3.27 – 3.11 (1H, m, $H26_B$), 3.11 – 2.65 (2H, m, H3), 2.29 – 1.99 (2H, m, H4 and $H5_A$), 1.66 – 1.48 (15H, m, H27, H28, H29, $H5_B$, H6, H7, H8 and CH_3-C1´´); δC (50 MHz; $CDCl_3$) 203.5 (CH, CHO), 202.1 (C, C=O), 148.2 (C, C1´´), 137.2 (C, ArC_{ipso}), 134.8 (CH, ArC_{para}), 129.6 (2CH, ArC_{meta}), 129.2 (2CH, ArC_{ortho}), 109.9 (CH_2, C2´´), 98.9 (CH, C24), 75.9 (CH, C1), 66.7 (CH_2, C1´), 62.1 (CH_2, C26), 49.7 (C, C4a), 39.5 (CH, C4), 37.7 (CH_2, C3), 36.1 (CH, C7), 35.3 (CH, C8a), 30.4 (CH_2, C29), 30.2 (CH_2,C5), 25.5 (CH_2, C27), 22.4 (CH_2, C8), 22.3 (CH_2, C6), 20.9 (CH_3, CH3-C1´´), 22.2 (CH_2, C6), 19.1 (CH_2, 28); EIHRMS: Calcd. for $C_{26}H_{34}O_6S$ (M+Na): 497.1974; found 497.1968 (M+Na); ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R (major) = 19.7, 25.5 min; t_R (minor) = 46.6, 53.2, 61.4 min; $[\alpha]_D^{25}$ = + 17.5 (c = 3.4, $CHCl_3$).

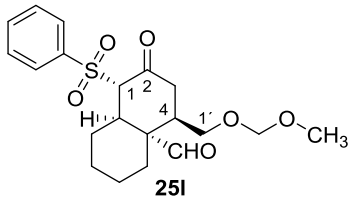
11.4. (1*S*,4*R*,4a*S*,7*R*,8a*R*)-7-(2-methyloxiran-2-yl)-2-oxo-1-(phenylsulfonyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)decahydronaphthalene-4a-carbaldehyde, 23s.



23s

Colorless oil (13.4 mg, 39%): ν_{max} (liquid film) 3478, 2941, 2872, 1720, 1660, 1447, 1321, 1309, 1150; δH (200 MHz; $CDCl_3$) 9.62 (1H, s, CHO), 8.02 – 7.79 (2H, m, ArH_{ortho}), 7.79 – 7.52 (3H, m, ArH_{meta} and ArH_{para}), 4.51 (1H, d, *J* = 14.6 Hz, H24), 3.81 – 3.41 (5H, m, H1, $H26_A$, H1´ and H8a), 3.25 – 3.09 (1H, m, $H26_B$), 2.95 – 2.71 (2H, m, H3), 2.50 (2H, s, H2´´), 2.27 – 2.03 (2H, m, H4 and $H5_A$), 1.81 – 1.40 (m, 12H), 1.14 (3H, s, CH_3-C1´´). EIHRMS: Calcd. for $C_{26}H_{34}O_7S$ (M+Na): 513.1923; found 513.1917 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [80/20 (v/v)]; flow rate: 1.0 mL/min; λ = 290 nm t_R = 26.9, 29.0, 33.3, 35.8, 45.9, 49.7 min; $[\alpha]_D^{25}$ = -0.3 (c = 2.3, $CHCl_3$).

11.5. (1*S*,4*R*,4a*S*,8a*R*)-4-((methoxymethoxy)methyl)-2-oxo-1-(phenylsulfonyl)octahydronaphthalene-4a(2H)-carbaldehyde, 25l.



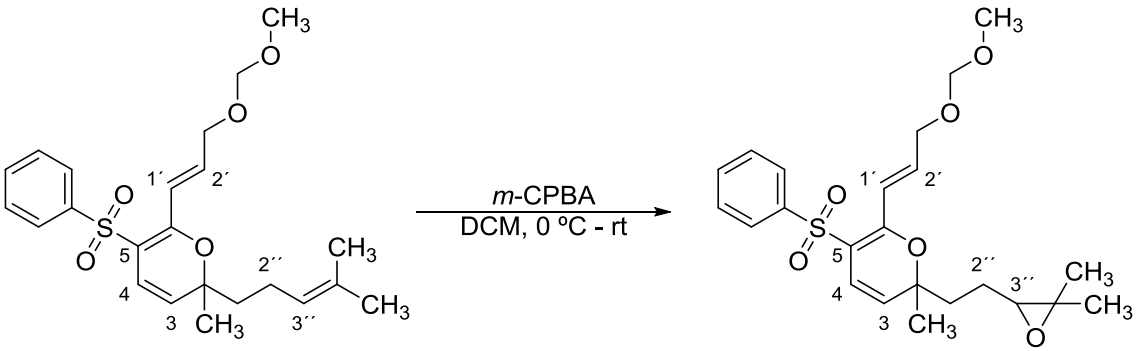
25l

Colorless oil (151 mg, 60%): v_{max} (liquid film) 2937, 2868, 1718, 1448, 1321, 1307, 1149; δH (200 MHz; $CDCl_3$) 9.61 (1H, s, CHO), 7.96 – 7.78 (2H, m, ArH_{ortho}), 7.67 – 7.53 (3H, m, ArH_{meta} and ArH_{para}), 4.51 (2H, s, O-CH_2-O), 3.71 (1H, d, *J* = 4.7 Hz, H1), 3.52 – 3.35 (3H, m, H8a and H1´), 3.32 (3H, s, CH_3-O), 3.05 – 2.76 (2H, m, H3), 2.24 – 1.97 (2H, m, H4 and $H5_A$), 1.81 – 1.33 (7H, m, $H5_B$, H6, H7 and H8); δC (50 MHz; $CDCl_3$) 203.7 (CH, CHO), 202.1 (C, C=O), 137.2 (C, ArC_{ipso}), 134.8 (CH, ArC_{para}), 129.6 (2CH, ArC_{meta}), 129.2 (2CH, ArC_{ortho}), 96.6 (CH_2, O-CH_2-O), 75.3 (CH, C1), 66.9 (CH_2, C1´), 55.9 (CH_3, CH_3-O), 50.1 (C, C4a), 39.4 (CH, C4), 37.9 (CH_2, C3), 35.7 (CH, C8a), 30.2 (CH_2, C5), 22.2 (CH_2, C8), 21.3 (CH_2, C7), 19.8 (CH_2, C6); EIHRMS: Calcd. for $C_{20}H_{26}O_6S$ (M+Na): 417.1348; found: 417.1242 (M+Na); ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R (minor) = 16.8 min; t_R (major) = 39.5 min; $[\alpha]_D^{25}$ = -8.66 (c=0.75, $CHCl_3$).

12. Transformation of obtained products for diversity oriented synthesis (DOS).

12.1. DOS with pyran derivatives.

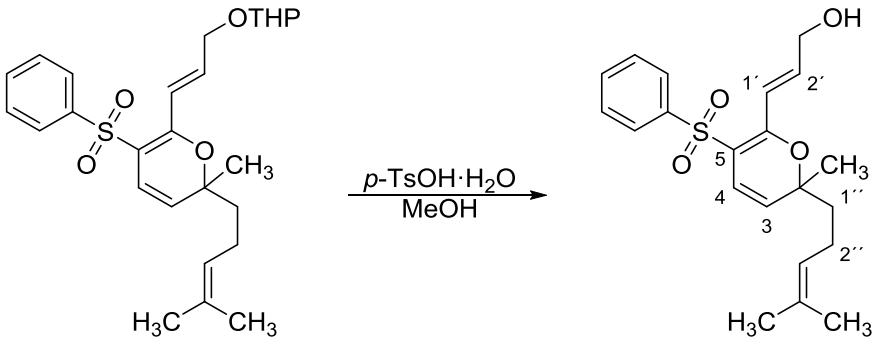
12.1.i (*E*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-6-(3-(methoxymethoxy)prop-1-en-1-yl)-2-methyl-5-(phenylsulfonyl)-2*H*-pyran, 26.



18a **26**

m-CPBA (77%, 46.6 mg, 0.21 mmol) was added to a solution of pyran **18a** (86.9 mg, 0.21 mmol) in DCM (2 mL) at 0 ºC and the whole mixture was left to stirr and warm up to room temperature for 3 hours. The reaction was quenched with $NaHSO_3$ (10 % aq.) and after 15 minutes it was extracted with EtOAc. The organic layers were washed with $NaHCO_3$ (5%), H_2O and brine, dried over Na_2SO_4, filtered and all the volatiles were removed *in vacuo* to afford **26** (85.7 mg, 95%). ν_{max} (liquid film) 2927, 1539, 1446, 1321, 1153; δH (400 MHz; $CDCl_3$) 7.92 – 7.77 (2H, m, ArH_{ortho}), 7.59 – 7.48 (3H, m, ArH_{meta} and ArH_{para}), 7.43 (1H, ddt, *J* = 15.3, 7.6, 1.8 Hz, H1´), 6.55 (1H, dtd, *J* = 15.3, 5.2, 1.8 Hz, H2´), 6.39 (1H, dd, *J* = 10.0, 2.8 Hz, H4), 5.33 (1H, dd, *J* = 10.0, 3.3 Hz, H3), 4.68 (2H, s, O-CH_2-O), 4.25 (2H, dt, *J* = 5.2, 1.8 Hz, H3´), 3.40 (3H, s, CH_3-O), 2.67 – 2.59 (1H, m, H3´´), 1.88 – 1.74 (2H, m, H1´´), 1.30 – 1.24 (8H, m, CH_3-C2, CH_3-C-O, H2´´), 1.18 (3H, s, CH_3-C-O); δC (100 MHz; $CDCl_3$) 156.1 (C, C6), 143.2 (C, ArC_{ipso}), 136.6 (CH, C2´), 132.9 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 126.7 (2CH, ArC_{ortho}), 124.3 (CH, C3), 121.5 (CH, C1´), 119.9 (CH, C4), 114.8 (C, C5), 96.3 (CH_2, O-CH_2-O), 80.7 (C, C1), 67.1 (CH_2, C3´), 64.1 (CH, C3´´), 58.6 (C, C4´´), 55.6 (CH_3, CH_3-O), 37.6 (CH_2, C1´´), 26.2 (CH_3, CH_3-C2), 25.0 (CH_3, $(CH_3)_2$-C), 23.8 (CH_2, C2´´), 18.8 (CH_3, $(CH_3)_2$-C); EIHRMS: Calcd. for $C_{23}H_{30}O_6S$ (M+Na): 457.1661; found: 457.1655 (M+Na).

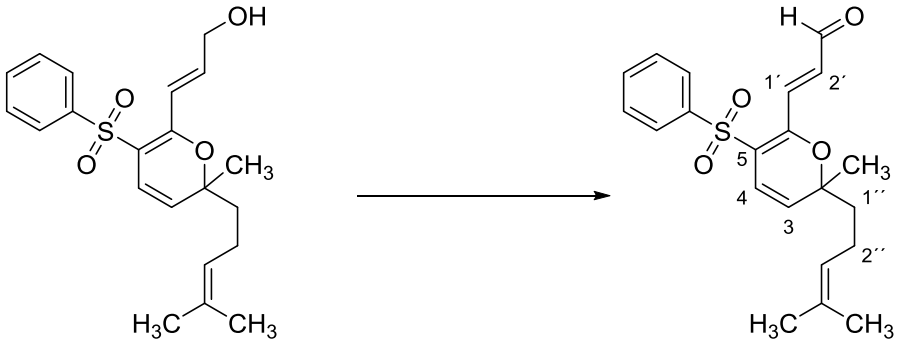
12.1.iiSynthtesis of pyran 22a by deprotection of 21a.



21a **22a**

21a (26.5 mg, 0.06 mmol) and *p*-toluenesulfonic acid monohydrate (5.7 mg, 0.03 mmol) were dissolved in 6 mL of a MeOH, and the whole mixture was stirred for 14 hours. The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **22a** (see spectral properties at section 10.2).

12.1.iii Synthesis of (*E*)-3-(2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2H-pyran-6-yl)acrylaldehyde, 27.



22a **27**

Oxidation with TPAP/NMO:

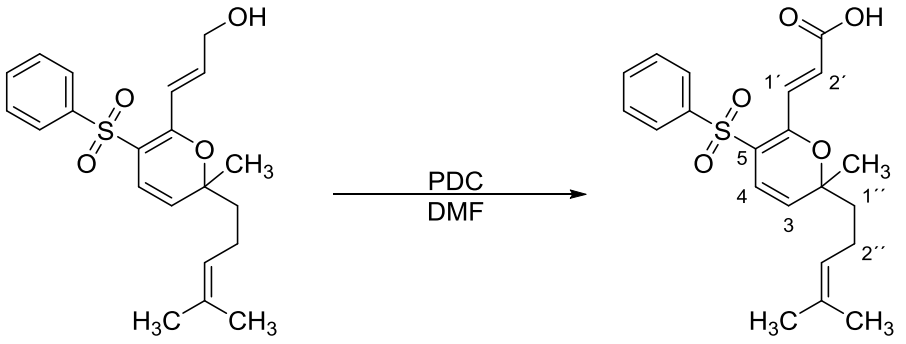
22a (13.4 mg, 0.04 mmol), NMO·H_2O (9.7 mg, 0.08 mmol), and molecular sieves were dissolved in DCM (0.7 mL) under argon. Next TPAP (3.2 mg, 0.01 mmol) was added and the whole mixture was left to stir for 30 minutes. The reaction was stopped and chromatographied simultanuosly by filtering through a pad of Celite®/Silica-gel eluting with a mixture of *n*-Hexane/EtOAc (8/2) affording **27** (6.7 mg, 50%).

Jones oxidation:

H_5IO_6 (1.14 g, 5 mmol) and CrO_3 (2.3 mg, 0.09 mmol) were dissolved in CH_3CN/H_2O (3/1, 12 mL) for 4 hours. Next, **22a** (20 mg, 0.05 mmol) was dissolved in CH_3CN/H_2O (3/1, 0.3 mL) and 0.3 mL of previous mix were added at 0 ºC in two fractions separated 15 minutes in time. The whole mixture was left to stir for 12 hours and warm up to room temperature. The reaction was quenched with 0.3 mL of Na_2HPO_4 (600 mg in 10 mL). After adding toluene to the mixture, the organic layer was washed with brine/H_2O (1/1), $NaHSO_3$ (10% aq.) and brine. The organic layers were dried over anhydrous sodium sulphate. Following filtration the solution was evaporated. Flash chromatography afforded (*n*-Hexane/EtOAc 7/3) **27** (15.2 mg, 76%). ν_{max} (liquid film) 2962, 2924, 2852, 1681, 1531, 1446, 1323, 1155; δH (200 MHz; $CDCl_3$) 9.80 (1H, d, *J* = 8.1 Hz, CHO), 8.33 (1H, d, *J* = 15.4 Hz, H1´), 7.87 (2H, d, *J* = 6.3 Hz, ArH_{ortho}), 7.69 – 7.48 (3H, m, 3H), 6.70 (1H, dd, *J* = 15.4, 8.1 Hz, H2´), 6.34 (1H, d, *J* = 10.1 Hz, H4), 5.52 (1H, d, *J* = 10.1 Hz, H3), 5.07 – 4.88 (1H, m, H3´´), 2.09 – 1.89 (2H, m, H2´´), 1.70 – 1.46 (8H, m, $(CH_3)_2$-C3´´ and H1´´), 1.30 (3H, s, CH_3-C2); δC (50 MHz; $CDCl_3$) 193.7 (CH, CHO), 153.4 (C, C6), 142.1 (C, ArC_{ipso}), 133.6 (CH, C2´), 132.7 (CH, ArC_{para}), 129.7 (2CH, ArC_{meta}), 126.9 (2CH, ArC_{ortho}), 123.9 (CH, C3), 123.3 (CH, C3´´), 123.2 (CH, C1´), 119.1 (CH, C4), 114.3 (C, C5), 81.6 (C, C2), 40.9 (CH_2, C1´´), 29.9 (CH_3, C1´´´), 25.9 (CH_3, C5´´$_B$), 22.5 (CH_2, C2´´), 17.7 (CH_3, C5´´$_A$); EIHRMS: Calcd. for $C_{21}H_{24}O_4S$ (M+Na): 395.1293; found: 395.1287 (M+Na).

12.1.iv Synthesis of (*E*)-3-(2-methyl-2-(4-methylpent-3-en-1-yl)-5-(phenylsulfonyl)-2*H*-pyran-6-yl)acrylic acid, 28.

Caution: the name does not correspond to the numeration used.

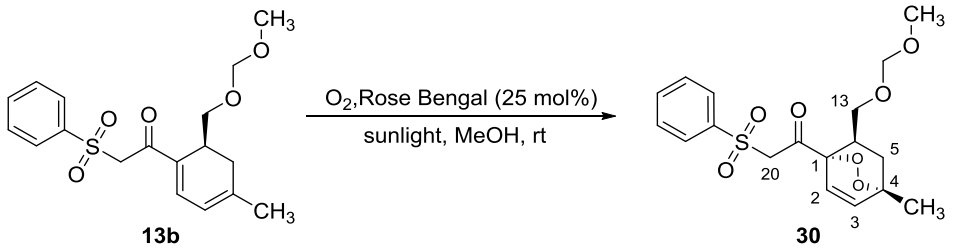


22a **28**

22a (16.0 mg, 0.043 mmol) and PDC (113 mg, 0.301 mmol) were dissolved in DMF (0.4 mL) under argon and the whole mixture was left to stir for 15 hours. The reaction was quenched with ice water. After extracting with Et_2O, the organic layers were washed with H_2O and Brine, dried over Na_2SO_4, filtered and the volatiles removed *in vacuo* to afford **28** (16.1, 96%). ν_{max} (liquid film) 3150, 2966, 2924, 2852, 1693, 1537, 1446, 1323, 1155; δH (200 MHz; $CDCl_3$) 8.44 (1H, d, *J* = 15.3 Hz, H1´), 7.88 (2H, d, *J* = 6.0 Hz, ArH_{ortho}), 7.62 – 7.51 (3H, m, ArH_{meta} and ArH_{para}), 6.49 (1H, d, *J* = 15.3 Hz, H2´), 6.40 (1H, d, *J* = 10.1 Hz, H4), 5.50 (1H, d, *J* = 10.1 Hz, H3), 5.09 – 4.92 (1H, m, H3´´), 2.06 – 1.90 (2H, m, H2´´), 1.77 – 1.17 (11H, m, H1´´, $(CH_3)_2$-C4´´ and CH_3-C2).); δC (50 MHz; $CDCl_3$) 183.5 (C, COOH), 153.2 (C, C6), 142.4 (C, ArC_{ipso}), 133.4 (CH, C2´), 132.6 (CH, ArC_{para}), 129.6 (2CH, ArC_{meta}), 127.0 (2CH, ArC_{ortho}), 124.1 (CH, C3), 123.3 (CH, C3´´), 123.2 (CH, C1´), 119.1 (CH, C4), 114.5 (C, C5), 81.4 (C, C2), 40.9 (CH_2, C1´´), 29.9 (CH_3, C1´´´), 25.8 (CH_3, $C5´´_B$), 22.5 (CH_2, C2´´), 17.8 (CH_3, $C5´´_A$);

12.2. DOS with chiral cyclohexa-1,3-dienes.

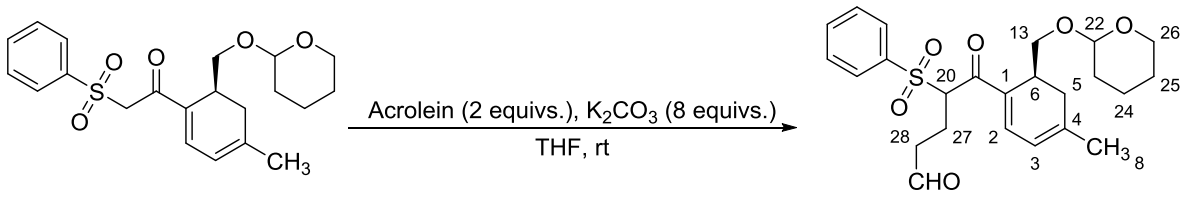
12.2.i Synthesis of 1-((1*S*,4*S*,7*R*)-7-((methoxymethoxy)methyl)-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-en-1-yl)-2-(phenylsulfonyl)ethan-1-one, 30.



13b **30**

13b (22 mg, 0.06 mmol) and Rose Bengal (15 mg, 0.015 mmol) were dissolved in 1 mL of MeOH and left to stir under O_2 atmosphere and solar light for 4 hours. After the solvent was evaporated *in vacuo*, flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **30** as a yellow oil (7 mg, 33%). ν_{max} (liquid film) 2957, 2929, 2873, 1728, 1448, 1323, 1311, 1290, 1149; δH (200 MHz; $CDCl_3$) 8.01 (2H, d, *J* = 8.2 Hz, ArH_{ortho}), 7.75 – 7.52 (3H, m, ArH_{meta}, ArH_{para}), 6.80 (1H, d, *J* = 8.5 Hz, H2), 6.46 (1H, d, *J* = 8.5 Hz, H3), 4.74 – 4.36 (2H, m, H20), 4.22 (2H, s, O-CH_2-O), 3.45 – 3.26 (2H, m, H13), 3.19 (3H, s, CH_3-O), 3.18 – 3.06 (1H, m, H6), 2.41 – 2.15 (2H, m, H5), 1.48 (3H, s, H7); δC (50 MHz; $CDCl_3$) 191.3 (C, C=O), 139.9 (C, ArC_{ipso}), 137.4 (CH, C2), 134.2 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 129.0 (2CH, ArC_{ortho}), 128.0 (CH, C3), 96.5 (CH_2, O-CH_2-O), 83.6 (C, C1), 76.3 (C, C4), 68.9 (CH_2, C13), 62.4 (CH_2, C20), 55.8 (CH_3, O-CH_3), 39.0 (CH, C6), 33.1 (CH_2, C5), 21.1 (CH_3, C7); EIHRMS: Calcd. for $C_{18}H_{22}O_7S$ (M+Na): 405.0984; found: 405.0978 (M+Na). $[\alpha]_D^{25}$ = +8.15 (c=0.92, $CHCl_3$).

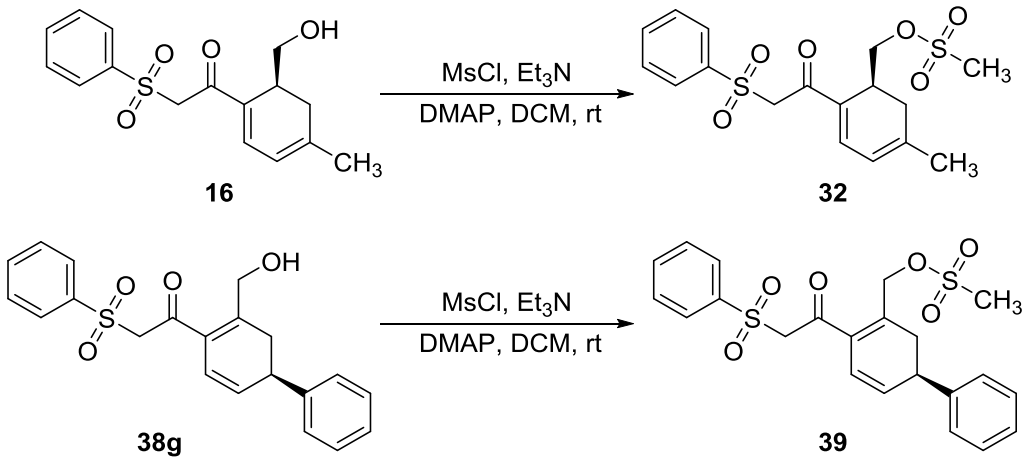
12.2.iiSynthesis of 5-((6*S*)-4-methyl-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)cyclohexa-1,3-dien-1-yl)-5-oxo-4-(phenylsulfonyl)pentanal, 31.



13b **31**

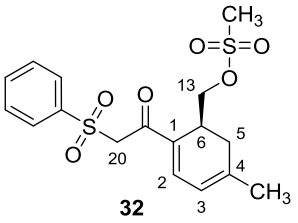
A mixture of compound **13b** (26 mg, 0.067 mmol) and potassium carbonate (74 mg, 0.536 mmol) was suspended in THF (0.7 mL) under an Argon atmosphere. The suspension was stirred at room temperature for 10 min, and acrolein (9 μL, 0.133 mmol) was then added. The reaction mixture was stirred for 17 h and then filtered through Celite®, which was washed with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and all the volatiles evaporated. Flash chromatography (*n*-Hexane/EtOAc, 7/3) afforded **31** as a yellow oil (15 mg, 48%). ν_{max} (liquid film) 2941, 2870, 1722, 1651, 1637, 1566, 1446, 1386, 1321, 1309, 1288, 1149; δH (200 MHz; $CDCl_3$) 9.68 (1H, s, CHO), 7.91 – 7.29 (5H, m, ArH_{ortho}, ArH_{meta} and ArH_{para}), 6.97 (1H, dd, *J* = 11.7, 5.8 Hz, H3), 5.99 – 5.79 (1H, m, H3), 4.93 (1H, dd, *J* = 9.3 H, 4.8 Hz, H20), 4.61 – 4.40 (1H, m, H22), 3.97 – 3.62 (1H, m, $H26_A$), 3.62 – 3.24 (2H, m, $H13_A$ and $H26_B$), 3.24 – 2.89 (2H, m, H6, $H13_B$), 2.75 – 2.10 (3H, m, $H5_B$, and H28), 1.92 (3H, s, H7), 1.77 – 1.39 (9H, m, $H5_B$ H23, H24, H25 and H27); δC (50 MHz; $CDCl_3$) 200.5 (CH, CHO), 190.3 (C, C=O), 148.8 (C, C1), 140.0 (CH, C2), 136.9 (C, ArC_{ipso}), 133.9 (CH, ArC_{para}), 133.8 (C, C4), 129.9 (2CH, ArC_{meta}), 129.1 (2CH, ArC_{ortho}), 119.2 (CH, C3), 98.7 (CH, O-CH-O), 67.0 (CH, C20), 62.6 (CH_2, C13), 62.4 (CH_2, C26), 40.6 (CH_2, C28), 31.1 (CH_2, C5), 30.9 (CH, C6), 30.7 (CH_2, C23), 25.7 ($2CH_2$, C25 and C27), 24.4 (CH_3, C7), 19.7 (CH_2, C24); EIHRMS: Calcd. for $C_{24}H_{30}O_6S$ (M+Na+MeOH): 501.1923; found: 501.1917 (M+Na+MeOH). $[\alpha]_D^{25}$ = -2.34 (c=1.45, $CHCl_3$).

12.2.iii General procedure for mesylation reaction: synthesis of compounds 32 and 39.



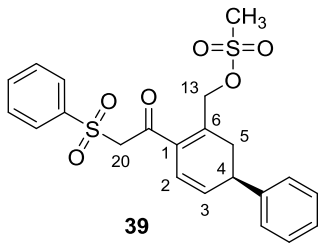
Hydroxyl derivative (1 mmol), DMAP (0.2 mmol) and Et_3N (1.3 mmol) were dissolved in 10 mL of DCM, and then methanesulfonyl chloride (1.2 mmol) was added. The mixture was stirred at room temperature for 40 minutes. The reaction was quenched with H_2O and extracted with ethyl acetate after 10 minutes. The organic layers were washed with HCl (2M), $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the desired product.

12.2.iii.1. (*S*)-1-(6-(methanesulfonyl)oxymethyl)-4-(4-methyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 32.



Yellow oil (380.2 mg, 99%): ν_{max} (liquid film) 2939, 1718, 1651, 1637, 1568, 1446, 1323, 1309, 1292, 1153; δH (200 MHz; $CDCl_3$) 7.95 – 7.84 (2H, m, ArH_{ortho}), 7.72 – 7.50 (3H, m, ArH_{meta}, ArH_{para}), 7.10 (1H, d, *J* = 5.9 Hz, H2), 5.94 (1H, d, *J* = 5.9 Hz, H3), 4.51 (1H, d, *J* = 13.5 Hz, $H20_A$), 4.38 (1H, d, *J* = 13.5 Hz, $H20_B$), 3.91 (1H, dd, *J* = 10.7, 8.3 Hz, $H13_A$), 3.79 (1H, dd, *J* = 10.7, 5.0 Hz, $H13_B$), 3.31 – 3.16 (1H, m, H6), 2.95 (3H, s, CH_3-SO_3), 2.50 – 2.35 (2H, m, H5), 1.94 (3H, s, H7); δC (50 MHz; $CDCl_3$) 186.6 (C, C=O), 148.9 (C, C1), 142.2 (CH, C2), 139.0 (C, ArC_{ipso}), 134.5 (CH, ArC_{para}), 130.7 (C, C4), 129.5 (2CH, ArC_{meta}), 128.6 (2CH, ArC_{ortho}), 119.4 (CH, C3), 67.8 (CH_2, C13), 62.7 (CH_2, C20), 37.5 (CH_3, MsO), 30.8 (CH_2, C5), 30.4 (CH, C6), 24.3 (CH_3, C7); EIHRMS: Calcd. for $C_{17}H_{20}O_6S_2$ (M+Na): 407.0599; found: 407.0593 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (minor) = 69.0 min; t_R (major) = 79.0 min; $[\alpha]_D^{25}$ = -9.00 (c=1.1, $CHCl_3$).

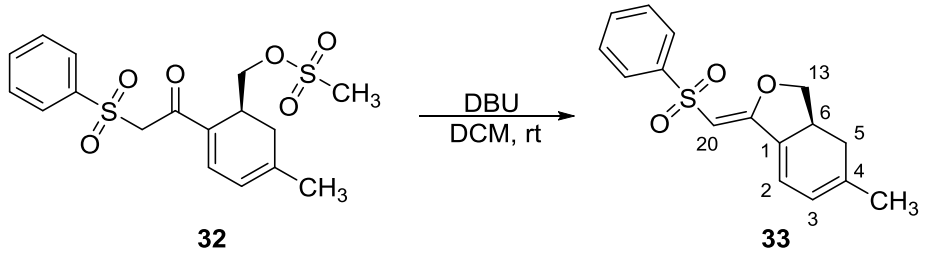
12.2.iii.2. (*R*)-1-(6-(methanesulfonyl)oxymethyl)-4-(4-phenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 39.



39

Yellow oil (223.0 mg, 50%): ν_{max} (liquid film) 2963, 2932, 1718, 1650, 1541, 1446, 1354, 1323, 1309, 1292, 1174, 1153; δH (200 MHz; $CDCl_3$) 7.92 (2H, d, *J* = 7.9 Hz, SO_2-ArH_{ortho}), 7.76 – 7.49 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.49 – 7.37 (5H, m, ArH_{ortho}, ArH_{meta} and ArH_{para}), 7.34 (1H, d, *J* = 6.2 Hz, H2), 6.58 (1H, dd, *J* = 6.3, 2.7 Hz, H3), 4.58 (1H, d, *J* = 13.4 Hz, $H20_A$), 4.44 (1H, d, *J* = 13.4 Hz, $H20_B$), 4.22 (1H, d, *J* = 5.7 Hz, $H13_A$), 3.96 (1H, t, *J* = 6.7 Hz, $H13_B$), 3.49 – 3.38 (1H, m, H6), 2.93 (3H, s, CH_3-SO_3), 2.78 (2H, ddd, *J* = 11.3, 9.0, 2.8 Hz, H5); δC (50 MHz; $CDCl_3$) 186.3 (C, C=O), 146.4 (C, C6), 141.5 (CH, C2), 138.6 (C, SO_2-ArC_{ipso}), 134.4 (CH, SO_2-ArC_{para}), 132.1(C, C1), 130.9 (C, ArC_{ipso}), 129.6 (CH, Ar-ArC_{para}), 129.4 (2CH, SO_2-ArC_{meta}), 128.5 (4CH, SO_2-ArC_{ortho} and ArC_{meta}), 126.1 (2CH, ArC_{ortho}), 119.2 (CH, C3), 67.6 (CH_2, C13), 62.7 (CH_2, C20), 37.2 (CH_3, MsO), 30.4 (C, C4), 27.8 (CH_2, C5); EIHRMS: Calcd. for $C_{22}H_{22}O_6S_2$ (M+Na): 469.0755; found: 469.0750 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ = 325 nm t_R (minor) = 17.9 min; t_R (major) = 23.2 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +7.22 (c=0.36, $CHCl_3$).

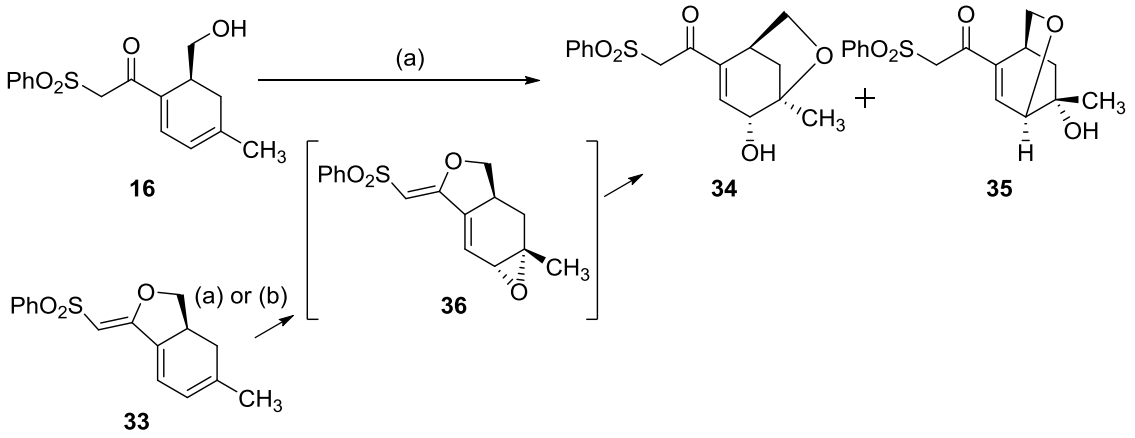
12.2.iv Synthesis of (*S,Z*)-5-methyl-1-((phenylsulfonyl)methylene)-1,3,3a,4-tetrahydroisobenzofuran, 33.



32 **33**

32 (162 mg, 0.38 mmol) was dissolved in 4 mL of DCM, and then 1,8-diazabicyclo[5.4.0]undec-7-ene (85 µl, 0.57 mmol) was added. The mixture was stirred at room temperature for 35 minutes. The reaction was quenched with H_2O and extracted with ethyl acetate after 10 minutes. The organic layers were washed with H_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **33** as a yellow oil (56.1 mg, 50%). v_{max} (liquid film) 3066, 2929, 2900, 1610, 1579, 1446, 1304, 1140; δH (200 MHz; Benzene-d_6) 8.32 – 8.21 (2H, m, ArH_{ortho}), 7.14 – 6.97 (3H, m, ArH_{meta}, ArH_{para}), 5.92 (1H, s, H20), 5.84 – 5.73 (1H, m, H2), 5.43 – 5.35 (1H, m, H3), 4.01 (1H, t, J = 8.6 Hz, $H13_A$), 3.19 – 3.02 (1H, m, $H13_B$), 2.26 – 2.01 (1H, m, H6), 1.37 (3H, s, H7), 1.32 – 1.08 (2H, m, H5); δC (50 MHz; Benzene-d_6) 162.1 (C, C-O), 145.4 (C, ArC_{ipso}), 140.2 (C, C4), 131.9 (CH, ArC_{para}), 130.4 (C, C1), 128.6 (2CH, ArC_{meta}), 127.9 (2CH, ArC_{ortho}), 122.8 (CH, C2), 120.2 (CH, C3), 97.0 (CH, C20), 77.9 (CH_2, C13), 35.3 (CH, C6), 31.2 (CH_2, C5), 22.9 (CH_3, C7); EIHRMS: Calcd. for $C_{16}H_{16}O_3S$ (M+H): 289.0898; found: 289.0893 (M+H). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (minor) = 16.9 min; t_R (major) = 19.4 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -86.50 (c=1.57, MeOH).

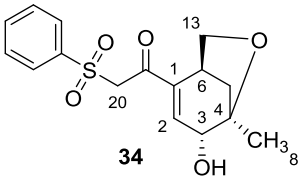
12.2.vSynthesis of compounds 34, 35 and 36.



Procedure a: To a solution of 1 mmol of starting material (**16**, 45.9 mg, 0.15 mmol or **33**, 46.1 mg, 0.16 mmol) in $CDCl_3$ (10 mL) was added *m*-CPBA (70% pure, 1 equiv.) and the reaction was left to stir for the specified time (15 hours for compound **16** and 6 hours for compound **33**). Flash chromatography (EtOAc/MeOH, 95/5) afforded the corresponding product (1/1 mixture of **34**/**35**, 18.4 mg, 38% starting from **16**; only **34**, 31.9 mg, 62% starting from **33**).

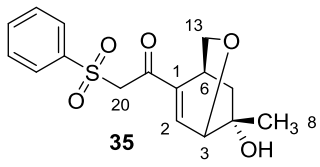
Procedure b: A solution of **33** (38.4 mg, 0.13 mmol) in $CHCl_3$ (1 mL) was heated at 37 ºC under normal air atmosphere for 72 hours. Flash chromatography (EtOAc/MeOH, 95/5) afforded **34** (22.1 mg, 53%).

12.2.v.1. 1-((1*S*,4*R*,5*R*)-4-hydroxy-5-methyl-6-oxabicyclo[3.2.1]oct-2-en-2-yl)-2-(phenylsulfonyl)ethan-1-one, 34.



Yellow oil: v_{max} (liquid film) 3471, 2970, 2932, 2873, 1712, 1666, 1625, 1448, 1379, 1321, 1309, 1259, 1150; δH (600 MHz; $CDCl_3$) 7.95 – 7.80 (2H, m, ArH_{ortho}), 7.75 – 7.47 (3H, m, ArH_{meta}, ArH_{para}), 6.72 (1H, d, *J* = 3.9 Hz, H3), 4.49 (2H, s, H20), 3.91 – 3.85 (1H, m, H3), 3.85 – 3.79 (1H, m, $H13_A$), 3.48 – 3.38 (1H, m, H6), 3.34 (1H, d, *J* = 7.5 Hz, $H13_B$), 1.63 (1H, d, *J* =8.0 Hz, $H5_A$), 1.56 (1H, dd, *J* = 8.0 Hz, 4.0 Hz, $H5_B$), 1.45 (3H, s, CH_3); δC (150 MHz; $CDCl_3$) 187.3 (C, C=O), 144.2 (C, C1), 141.9 (CH, C2), 138.7 (C, ArC_{ipso}), 134.4 (CH, ArC_{para}), 129.4 (2CH, ArC_{meta}), 128.5 (2CH, ArC_{ortho}), 81.4 (C, C4), 73.7 (CH_2, C13), 72.4 (CH, C3), 62.4 (CH, C20), 35.7 (CH, C6), 35.3 (CH_2, C5), 21.8 (CH_3, C8); EIHRMS: Calcd. for $C_{16}H_{18}O_5S$ (M+Na): 345.0773; found: 345.0767 (M+Na). $[\alpha]_D^{25}$ = -13.05 (c=0.95, $CHCl_3$).

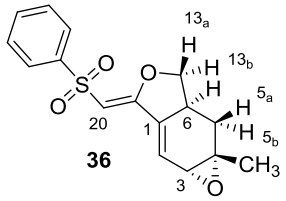
12.2.v.2. 1-((4*S*,7*S*)-7-hydroxy-7-methyl-2-oxabicyclo[2.2.2]oct-5-en-5-yl)-2-(phenylsulfonyl)ethan-1-one, 35.



35

Yellow oil: ν_{max} (liquid film) 3464, 2929, 1710, 1664, 1626, 1448, 1321, 1309, 1153; δH (600 MHz; $CDCl_3$) 7.98 – 7.80 (2H, m, ArH_{ortho}), 7.74 – 7.50 (3H, m, ArH_{meta}, ArH_{para}), 7.32 (1H, d, J = 4.6 Hz, H2), 4.59 (1H, d, J = 13.6 Hz, $H20_A$), 4.38 (1H, d, J = 13.6 Hz, $H20_B$), 3.59 – 3.30 (3H, m, H6 and H13), 2.21 (1H, d, J = 15.4 Hz, H3), 2.09 – 1.83 (2H, m, H5), 1.51 (3H, s, CH_3); δC (150 MHz; $CDCl_3$) 187.6 (C, C=O), 141.9 (C, C1), 141.1 (CH, C2), 138.5 (C, ArC_{ipso}), 134.4 (CH, ArC_{para}), 129.3 (2CH, ArC_{meta}), 128.5 (2CH, ArC_{ortho}), 82.0 (C, C4), 66.3 (CH_2, C13), 63.0 (CH, C20), 53.8 (CH, C3), 35.2 (CH, C6), 30.9 (CH_2, C5), 21.8 (CH_3, C8); EIHRMS: Calcd. for $C_{16}H_{18}O_5S$ (M+Na): 345.0773; found: 345.0771 (M+Na). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -99.95 (c=0.19, $CHCl_3$).

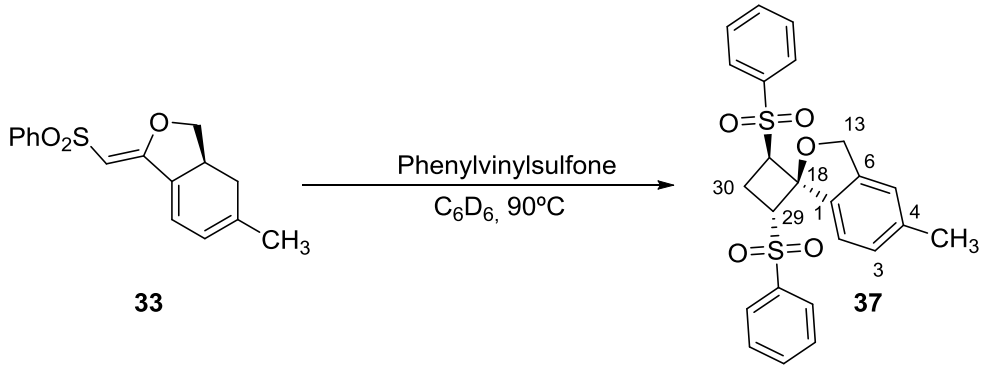
12.2.v.3. (1a*S*,2a*S*,6a*R*,*Z*)-1a-methyl-5-((phenylsulfonyl)methylene)-1a,2,2a,3,5,6a-hexahydrooxireno[2,3-f]isobenzofuran, 36.



36

Yellow oil: ν_{max} (liquid film) 2961, 2928, 1614, 1446, 1304, 1142; δH (600 MHz; Benzene-d_6) 8.22 (2H, dd, J = 7.8, 1.8 Hz, ArH_{ortho}), 7.06 – 6.92 (3H, m, ArH_{meta}, ArH_{para}), 5.84 (1H, s, H20), 5.51 (1H, t, J = 3.7 Hz, H2), 3.71 (1H, t, J = 8.7 Hz, $H13_A$), 3.00 – 2.80 (1H, m, $H13_B$), 2.47 (1H, d, J = 3.7 Hz, H3), 2.19 – 2.03 (1H, m, H6), 1.18 (1H, dd, J = 13.9, 7.5 Hz, $H5_B$), 0.91 (3H, s; H7), 0.14 (1H, dd, J = 13.9, 11.5 Hz, $H5_A$); δC (150 MHz; Benzene-d_6) 161.5 (C, C-O), 144.7 (C, ArC_{ipso}), 137.8 (C, C1), 131.9 (CH, ArC_{para}), 128.4 (2CH, ArC_{meta}), 127.5 (2CH, ArC_{ortho}), 122.7 (CH, C2), 98.2 (CH, C20), 76.6 (CH_2, C13), 59.9 (C, C4), 53.1 (C, C3), 34.6 (CH, C6), 29.0 (CH_2, C5), 20.5 (CH_3, C7); EIHRMS: Calcd. for $C_{16}H_{16}O_4S$ (M+H): 305.0848; found: 305.0843 (M+H). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +101.61 (c=0.31, $CHCl_3$).

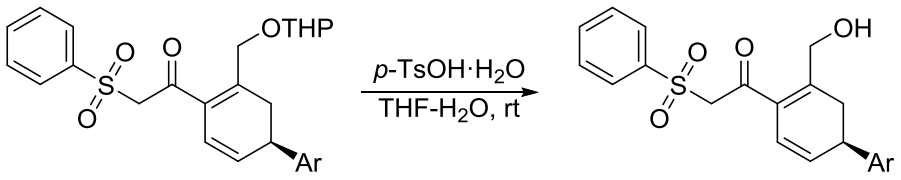
12.2.vi **Synthesis of (2*R*,4*R*)-5´-methyl-2,4-bis(phenylsulfonyl)-3´*H*-spiro[cyclobutane-1,1´-isobenzofuran], 37.**



33 **37**

33 (56 mg, 0.19 mmol) and phenyl vinyl sulfone (66 mg, 0.39 mmol) were dissolved in 1 mL of benzene-d_6. The mixture was stirred at reflux for 2.5 hours. Flash chromatography (*n*-Hexane/EtOAc, 6/4) afforded **37** as a yellow oil (36.2 mg, 42%). ν_{max} (liquid film) 3062, 2970, 2926, 1714, 1381, 1146, 1319, 1148; δH (600 MHz; Benzene-d_6) 8.01 – 7.83 (4H, m, ArH_{ortho}), 7.08 – 6.70 (9H, m, ArH_{meta}, ArH_{para}, H2, H3 and H5), 5.26 (1H, dd, J = 9.8, 4.3 Hz, H31), 5.04 (1H, d, J = 15.0 Hz, $H13_A$), 4.70 (1H, d, J = 4.8 Hz, H29), 3.90 (1H, d, J = 15.0 Hz, $H13_B$), 2.04 (3H, s, H7), 1.90 – 1.75 (2H, m, H30); δC (150 MHz; Benzene-d_6) 145.3 (C, C1), 143.7 (C, C6), 142.0 (2C, ArC_{ipso}), 138.0 (C, C4), 129.1 (2CH, ArC_{para}), 128.7 (2CH, ArC_{meta}), 128.2 (2CH, ArC_{ortho}), 127.9 (2CH, ArC_{meta}), 127.8 (2CH, ArC_{ortho}), 121.4 (CH, C3), 119.9 (CH, C2), 119.4 (CH, C5), 85.5 (C, C18), 78.9 (CH, C29), 62.7 (CH, C31), 56.2 (CH_2, C13), 33.2 (CH_2, C30), 19.6 (CH_3, C7); EIHRMS: Calcd. for $C_{24}H_{22}O_5S_2$ ($M+NH_4$): 472.1247; found: 472.1247 ($M+NH_4$). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -6.67 (c=0.81, MeOH).

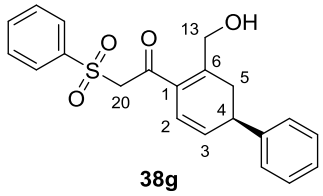
12.2.vii General procedure for the synthesis of deprotected compounds 38g-j.



15g-j **38g-j**

Tetrahydropyanyl derivative (1 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 mmol) were dissolved in 10 mL of a 1 : 1 mixture of THF–H_2O, and the whole mixture was stirred until no starting material was observed (typically 3-7 days). The reaction was quenched with H_2O, extracted with EtOAc and the combined organics were washed with $NaHCO_3$ (5%), H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the desired product.

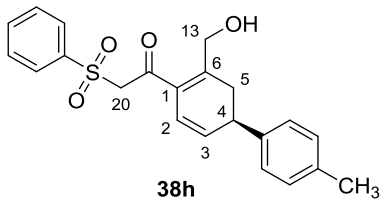
12.2.vii.1. (*R*)-2-(6-(hydroxymethyl)-5-(phenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 38g.



38g

Yellow oil (364.3 mg, 99%): ν_{max} (liquid film) 3487, 3061, 2931, 2872, 1718, 1645, 1544, 1446, 1314, 1309, 1153; δH (200 MHz; $CDCl_3$) 7.92 (2H, d, *J* = 7.0 Hz, SO_2-ArH_{ortho}), 7.74 – 7.48 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.47 – 7.32 (5H, m, ArH_{ortho}, ArH_{meta} and ArH_{para}), 7.24 (1H, d, *J* = 6.2 Hz, H2), 6.53 (1H, dd, *J* = 6.2, 2.7, H3), 4.52 (1H, d, *J* = 13.5 Hz, $H20_A$), 4.28 – 4.10 (1H, m, $H20_B$), 3.61 – 3.32 (2H, m, $H5_A$ and $H13_A$), 3.29 – 3.09 (1H, m, H4), 3.04 (1H, d, *J* = 1.6 Hz, $H13_B$), 2.76 (1H, dd, *J* = 17.9, 8.6 Hz, $H5_B$); δC (50 MHz; $CDCl_3$) 187.5 (C, C=O), 146.4 (C, C6), 140.3 (CH, C2), 139.2 (C, SO_2-ArC_{ipso}), 134.8 (2C, ArC_{ipso} and C1), 134.2 (CH, SO_2-ArC_{para}), 129.2 (2CH, SO_2-ArC_{meta}), 128.7 (2CH, SO_2-ArC_{ortho}), 128.5 (CH, ArC_{para}), 125.9 (4CH, ArC_{ortho}, ArC_{meta}), 119.2 (CH, C3), 62.5 (CH_2, C13), 62.7 (CH_2, C20), 33.6 (CH, C4), 28.1 (CH_2, C5); EIHRMS: Calcd. for $C_{21}H_{20}O_4S$ (M+H): 369.1161; found: 369.1155 (M+H). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 430 nm t_R (minor) = 35.9 min; t_R (major) = 39.3 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +13.62 (c=0.94, $CHCl_3$).

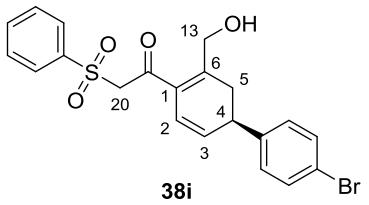
12.2.vii.2. (*R*)-2-(6-(hydroxymethyl)-5-(4-methylphenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 38h.



38h

Yellow oil (378.2 mg, 99%): ν_{max} (liquid film) 3442, 2923, 2873, 1714, 1643, 1514, 1446, 1354, 1309, 1153; δH (200 MHz; $CDCl_3$) 7.96 – 7.81 (2H, m, SO_2-ArH_{ortho}), 7.73 – 7.41 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.28 – 7.13 (5H, m, H2, ArH_{ortho} and ArH_{meta}), 6.50 (1H, dd, *J* = 6.2, 2.6, H3), 4.60 (1H, d, *J* = 13.5 Hz, $H20_A$), 4.43 (1H, d, *J* = 13.5 Hz, $H20_B$), 3.57 – 3.30 (2H, m, $H5_A$ and $H13_A$), 3.26 – 3.08 (1H, m, H4), 3.02 (1H, d, *J* = 4.7 Hz, $H13_B$), 2.73 (1H, dd, *J* = 20.5, 8.6 Hz, $H5_B$), 2.37 (3H, s, CH_3-Ar); δC (50 MHz; $CDCl_3$) 187.6 (C, C=O), 146.7 (C, C6), 140.8 (CH, C2), 138.9 (2C, ArC_{ipso} and ArC-CH_3), 136.4 (C, C1), 134.4 (CH, SO_2-ArC_{para}), 130.0 (2CH, ArC_{ortho}), 128.9 (2CH, SO_2-ArC_{meta}), 128.8 (2CH, SO_2-ArC_{ortho}), 126.1 (2CH, ArC_{meta}), 118.5 (CH, C3), 62.9 (CH_2, C13), 62.8 (CH_2, C20), 33.8 (CH, C4), 28.3 (CH_2, C5), 21.5 (CH_3, Ar-CH_3); EIHRMS: Calcd. for $C_{22}H_{22}O_4S$ (M+Na): 405.1136; found: 405.1141 (M+Na).

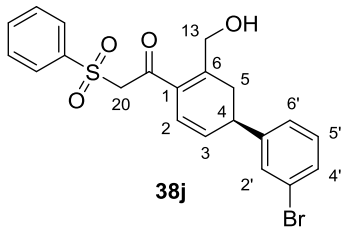
12.2.vii.3. (*R*)-2-(6-(hydroxymethyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 38i.



38i

Yellow oil (441.5 mg, 99%): ν_{max} (liquid film) 3477, 2941, 2872, 1718, 1643, 1543, 1489, 1446, 1312, 1309, 1153; δH (200 MHz; $CDCl_3$) 7.91 (2H, d, *J* = 8.3 Hz, SO_2-ArH_{ortho}), 7.73 – 7.48 (3H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}), 7.47 – 7.36 (4H, m, ArH_{ortho} and ArH_{meta}), 7.23 (1H, d, *J* = 6.1 Hz, H2), 6.52 (1H, dd, *J* = 6.2, 2.7 Hz, H3), 4.60 (1H, d, *J* = 13.4 Hz, $H20_A$), 4.43 (1H, d, *J* = 13.5 Hz, $H20_B$), 3.62 – 3.26 (1H, m, $H13_A$), 3.26 – 3.05 (2H, m, H4 and $H5_A$), 3.00 (1H, d, *J* = 1.7 Hz, $H13_B$), 2.87 – 2.64 (1H, m, $H5_B$); δC (50 MHz; $CDCl_3$) 187.4 (C, C=O), 144.9 (C, C6), 139.9 (CH, C2), 138.7 (C, SO_2-ArC_{ipso}), 138.0 (C, ArC_{ipso}), 135.1 (C, C1), 134.3 (CH, SO_2-ArC_{para}), 129.3 (2CH, ArC_{ortho}), 128.5 (2CH, ArC_{meta}), 127.5 (2CH, SO_2-ArC_{meta}), 127.4 (2CH, SO_2-ArC_{ortho}), 123.4 (C, ArC-Br), 119.5 (CH, C3), 62.7 (CH_2, C20), 62.3 (CH_2, C13), 33.5 (CH, C4), 27.8 (CH_2, C5); EIHRMS: Calcd. for $C_{21}H_{19}O_4SBr$ (M+Na): 469.0085; found: 469.0079 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 350 nm t_R (minor) = 30.6 min; t_R (major) = 38.8 min; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +5.88 (c=1.75, $CHCl_3$).

12.2.vii.4. (*R*)-2-(6-(hydroxymethyl)-5-(4-bromophenyl)cyclohexa-1,3-dien-1-yl)-2-(phenylsulfonyl)ethan-1-one, 38j.

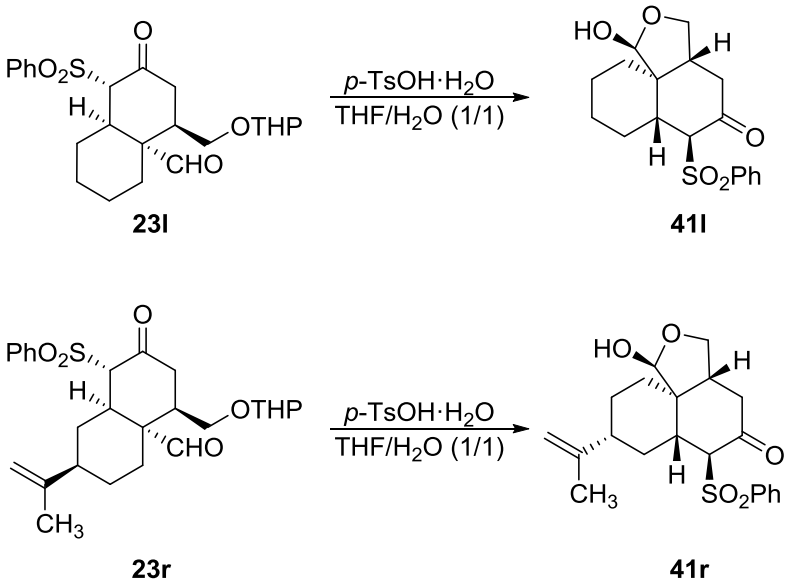


38j

Yellow oil (437.1 mg, 98%): ν_{max} (liquid film) 3502, 3062, 2929, 2872, 1718, 1645, 1545, 1473, 1446, 1312, 1309, 1153; δH (200 MHz; $CDCl_3$) 8.00 – 7.82 (2H, m, SO_2-ArH_{ortho}), 7.77 – 7.41 (7H, m, SO_2-ArH_{meta}, SO_2-ArH_{para}, ArH_{ortho}, ArH_{meta} and ArH_{para}), 7.30 (1H, s, ArH_{ortho}), 7.25 – 7.19 (1H, m, H2), 6.52 (1H, dd, J = 6.2, 2.7 Hz, H3), 4.61 (1H, d, J = 13.5 Hz, $H20_A$), 4.43 (1H, d, J = 13.5 Hz, $H20_B$), 3.42 (1H, d, J = 12.3 Hz, $H13_A$), 3.29 – 3.11 (2H, m, H4 and $H5_A$), 2.99 (1H, d, J = 1.7 Hz, $H13_B$) 2.86 – 2.60 (1H, m, $H5_B$); δC (50 MHz; $CDCl_3$) 187.5 (C, C=O), 144.5 (C, C1), 141.3 (C, C6), 139.6 (CH, C2), 138.7 (2C, SO_2-ArC_{ipso} and C1´), 134.3 (CH, SO_2-ArC_{para}), 132.1 (C1???), 131.9 (CH, C4´), 130.2 (CH, C2´), 129.3 (2CH, SO_2-ArC_{meta}), 128.9 (2CH, SO_2-ArC_{ortho}), 124.5 (CH, C5´), 122.9 (C, ArC-Br), 120.1 (CH, C3), 62.7 (CH_2, C20), 62.3 (CH_2, C13), 33.5 (CH, C4), 27.9 (CH_2, C5); EIHRMS: Calcd. for $C_{21}H_{19}O_4SBr$ (M+Na): 469.0085; found: 469.0079 (M+Na). ee: determined by HPLC: CHIRALPAK AD-H column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 360 nm t_R (minor) = 31.2 min; t_R (major) = 35.1 min; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +23.29 (c=0.97, $CHCl_3$).

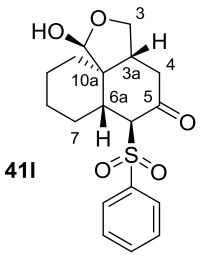
12.3. DOS with chiral cis-decalines.

12.3.i General procedure for the deprotection of THP group. Synthesis of 41l and 41r.



Cis-decaline (**23l** or **22b**23r (0.036 mmol) was dissolved in a 1 mL mixture of 1:1 (THF:H_2O). Then, *p*-T_SOH·H_2O (0.0071 mmol) was added and left stirring a room temperature for 48 hours. Then the mixture was cooled to 0ºC and quenched with H_2O (2mL). The mixture was extracted with EtOAc and the organic layers were washed with saturated $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (*n*-Hexane/EtOAc, 9/1).

12.3.i.1. (1*S*,3a*R*,6*S*,6a*R*,10aS)-1-hydroxy-6-(phenylsulfonyl)octahydro-1*H*-naphtho[1,8a-c]furan-5(3*H*)-one, 41l.

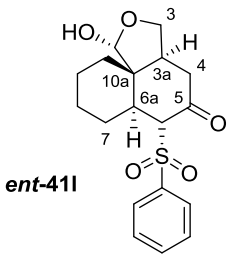


41l

Yield 90%; ν_{max} (liquid film) 3431, 2935, 2866, 1714, 1448, 1307, 1267, 1150; δH (600 MHz; $CDCl_3$) 7.84 (2H, dd, *J* = 8.3, 1.0 Hz, ArH_{ortho}), 7.77 – 7.63 (1H, m, ArH_{para}), 7.58 (2H, t, *J* = 8.3 Hz, ArH_{meta}), 5.41 (1H, s, H1), 4.20 (1H, dd, *J* = 11.0, 6.8 Hz, $H3_A$), 3.65 (1H, d, *J* = 5.9 Hz, H6), 3.46 (1H, dd, *J* = 11.0, 8.0 Hz, $H3_B$), 3.44 – 3.38 (1H, m, H6a), 3.23 – 3.11 (1H, m, H3a), 2.75 (2H, dd, *J* = 19.0, 7.9 Hz, H4), 1.79 – 0.81 (8H, m, H7, H8, H9 and H10) ; δC (150 MHz; $CDCl_3$) 202.9 (C, C=O), 137.4 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 129.2 (2CH, ArC_{meta}), 129.1 (2CH, ArC_{ortho}), 98.7 (CH, C1), 75.1 (CH, C6), 70.0 (CH_2, C3), 46.5 (C, C10a), 38.8 (CH, C3a), 37.3 (CH_2, C4), 34.8 (CH, C6a), 29.4 (CH_2, C10), 23.5 (CH_2, C7), 21.6 (CH_2, C8), 20.1 (CH_2, C9); EIHRMS: Calcd. for $C_{18}H_{22}O_5S$ (M+H): 351.1266; found 351.1261 (M+H); ee: determined by HPLC: CHIRALPAK

IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 190 nm t_R = 12.6, 16.0 min; $[\alpha]_D^{25}$ = + 0.7 (c = 0.87, $CHCl_3$).

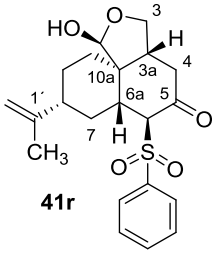
12.3.i.2. (1*R*,3a*S*,6*R*,6a*S*,10a*R*)-1-hydroxy-6-(phenylsulfonyl)octahydro-1*H*-naphtho[1,8a-c]furan-5(3H)-one, *ent*-41l.



***ent*-41l**

Yield 90%; ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R = 17.0, 35.0 min; $[\alpha]_D^{25}$ = - 64.1 (c = 0.44, $CHCl_3$).

12.3.ii(1*S*,3a*R*,6*S*,6a*R*,8*R*,10a*S*)-1-hydroxy-6-(phenylsulfonyl)-8-(prop-1-en-2-yl)octahydro-1H-naphtho[1,8a-c]furan-5(3H)-one, 41r.

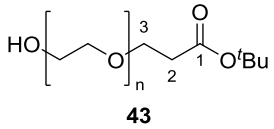


41r

Yield 98%; ν_{max} (liquid film) 3442, 2934, 2868, 1713, 1447, 1310, 1190, 1148; δH (200 MHz; $CDCl_3$) 7.84 (2H, d, *J* = 7.7 Hz, ArH_{ortho}), 7.74 – 7.67 (1H, m, ArH_{para}), 7.62-7.55 (2H, m, ArH_{meta}), 5.33 (1H, s, H1), 4.68 (2H, d, *J* = 11.6 Hz, H2´), 4.25 – 4.07 (1H, m, $H3_A$), 3.64 (1H, d, *J* = 5.7 Hz, H6), 3.54 – 3.42 (2H, m, $H3_B$ and H6a), 3.32 – 3.13 (1H, m), , 2.76 (1H, dd, *J* = 11.2, 7.9 Hz, $H4_A$), 2.20 (1H, dd, *J* = 11.2, 7.1 Hz, $H4_B$), 1.76 – 0.94 (10H, m, H7, H8, H9, H10 and CH_3-C1´); δC (50 MHz; $CDCl_3$) 202.9 (C, C=O), 148.3 (C, C1´), 137.3 (C, ArC_{ipso}), 134.3 (CH, ArC_{para}), 129.2 (2CH, ArC_{meta}), 129.1 (2CH, ArC_{ortho}), 109.5 (CH_2, C2´), 98.6 (CH, C1), 75.6 (CH, C6), 70.0 (CH_2, C3), 46.2 (C, C10a), 38.9 (CH, C3a), 38.3 (CH, C8), 37.2 (CH_2, C4), 35.2 (CH, C6a), 34.6 (CH_2, C9), 27.1 (CH_2, C10), 23.7 (CH_2, C7), 20.9 (CH_3, CH_3-C1´). EIHRMS: Calcd. for $C_{21}H_{26}O_5S$ (M+Na): 413.1399; found 413.1393 (M+Na). ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [70/30 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R = 14.5, 25.0 min; ee: determined by HPLC: CHIRALPAK IC column; *n*-Hexane/2-propanol [80/20 (v/v)]; flow rate: 1.0 mL/min; λ = 210 nm t_R = 19.1, 28.3 min; HPLC mass LC-MSD-trap-XCT; $[\alpha]_D^{25}$ = + 53.9 (c = 1.0, $CHCl_3$).

12.4. Solid support chemistry. Synthesis of PEG-400 derivatives.

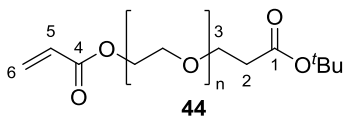
12.4.i *tert*-Butyl ester PEG-400 derivative, 43.



43

A mixture of polyethyleneglycol **42** (average M_n = 400, 6.6 mL, 18.7 mmol, 1 equiv.) and potassium *tert*-butoxide (2.1 g, 18.7 mmol, 1 equiv.) in DCM (37 mL) was stirred for 30 minutes at room temperature, after which *tert*-butyl acrylate (1.37 mL, 9.35 mmol, 0.5 equivs.) was added, and stirring continued for a further 15 hours. The reaction was quenched with 1.5 mL of HCl (9 M). The crude was diluted with some more DCM and H_2O and washed with brine. The organic layers were dried over anhydrous sodium sulphate. Following filtration, the solution was evaporated and the resulting residue dissolved in 60 mL of distilled water and extracted three times with Et_2O (2 x 20 mL) and a mixture of DCM/*n*-Hexane (3/1, 3 x 40 mL). Fractionated extraction afforded **43** (4.112 g, 81%), as a clear oil. ν_{max} (liquid film) 3480, 2867, 1727, 1456, 1392, 1366, 1349, 1279, 1249, 1097, 847, 846, 730, 699; δH (400 MHz, $CDCl_3$) 3.74 – 3.68 (4H, m, H3 and CH_2-OH), 3.68 – 3.58 (44H, m, PEG), 2.50 (2H, t, *J* = 6.6 Hz, H2), 1.44 (9H, s, 9H, O-$(CH_3)_3$); Mass analysis: highest peak at 509.2 corresponding to PEG-CH_2-CH_2COOH + Na^+.

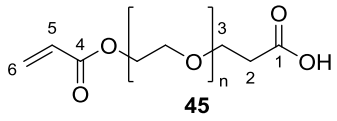
12.4.ii *tert*-Butyl ester PEG-400 acrylic derivative, 44.



44

A mixture of **43** (1.521 g, 3.05 mmol, 1 equiv.), 2,6-di-*tert*-butyl-4-methylphenol (1 small crystal) and triethylamine (0.8 mL, 5.5 mmol, 1.8 equivs.) in DCM (16 mL) was stirred for 5 minutes at 0 ºC, after which acryloyl chloride (0.4 mL, 4.58 mmol, 1.5 equivs.) was added, and stirring continued for a further 21 hours. The reaction was quenched by filtering to a separation funnel and washing the organic layers with 20 mL of HCl (0.9 M), H_2O (20 mL) and $NaHCO_3$ (saturated aqueous solution, 20 mL). The organic layers were dried over anhydrous sodium sulphate. Following filtration the solution was evaporated yielding **44** (1.102 g, 56%) as a yellow-orange oil. ν_{max} (liquid film) 2869, 1724, 1636, 1455, 1407, 1349, 1272, 1245, 1192, 1098, 986, 949, 847, 809, 730, 698; δH (400 MHz, $CDCl_3$) 6.27 (1H, d, *J* = 17.3 Hz, $H6_a$), 6.01 (1H, dd, *J* = 17.4, 10.4 Hz, H5), 5.70 (1H, d, *J* = 10.4 Hz, $H6_b$), 4.20 – 4.10 (2H, m, $\underline{CH_2}$-O-CO-CH-CH_2), 3.74 – 3.28 (46H, m), 2.34 (2H, t, *J* = 6.5 Hz, H2), 1.30 (9H, s, O-$(CH_3)_3$). Mass analysis: highest peak at 663.5 corresponding to APEG-CH_2-CH_2COO^{t}Bu + Na^+.

12.4.iii Carboxylic acid PEG-400 acrylic derivative, 45.



45

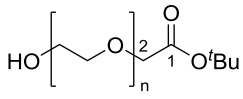
Method A: use of trifluoroacetic acid (TFA).

To a solution of *tert*-butyl ester **44** (1.103 g, 1.66 mmol, 1 equiv.) in DCM (3 mL) was added TFA (2.7 mL, 36 mmol, 21 equivs.). After stirring at room temperature for 4.5 hours, the volatiles were removed *in vacuo*. The oily residue was dissolved in 18 mL of DCM and treated with 2.2 g of Amberlyst A-21. After stirring at room temperature for 1.5 hours, the solids were filtered off. The solvent was removed *in vacuo* to yield **45** (887 mg) but mixed with TFA traces. For this reason it was redissolved in DCM and washed with $NaHCO_3$ (saturated aqueous solution) to remove some more TFA. Eventually 485 mg (65% yield) of **45** were obtained.

Method B: using $ZnBr_2$.

To a solution of *tert*-butyl ester **44** (1.188 g, 2.15 mmol, 1 equiv.) in DCM (11 mL) was added $ZnBr_2$ (2.42 g, 10.75 mmol, 5 equivs.). After stirring at room temperature for 23 hours, it was treated with water (5 mL), and stirred again for 1 hour. The organic phase was separated. The aqueous layer was extracted with DCM. The organic portions were dried over anhydrous sodium sulphate, filtered, and evaporated to yield **45** (813 mg, 76%). ν_{max} (liquid film) 3442, 3176, 2868, 1722, 1635, 1617, 1455, 1407, 1349, 1295, 1249, 1190, 1095, 987, 946, 844, 810; δH (300 MHz, $CDCl_3$) 6.40 (1H, d, J = 17.3 Hz, $H6_a$), 6.12 (1H, dd, J = 17.3, 10.4 Hz, H5), 5.81 (1H, d, J = 10.4 Hz, $H6_b$), 4.29 (2H, dd, J = 5.4, 4.2 Hz, $\underline{CH_2}$-O-CO-CH-CH_2), 3.90 – 3.38 (46H, m), 2.58 (2H, t, J = 6.2 Hz, H2).Mass analysis: highest peak at 563.3 corresponding to APEG-CH_2-CH_2COOH + Na^+.

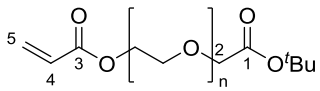
12.4.iv Carboxylic acid PEG-400 acrylic derivative, 46.



46

Polyethyleneglycol **42** (average M_n = 400, 12 mL, 33.8 mmol, 1 equiv.) was dissolved in THF (60 mL) and then NaH (60%, 1.4 g, 33.8 mmol, 1 equiv.) was added. The mixture was stirred for 10 minutes until the bubbles evolution stopped. Then *tert*-butyl bromoacetate (5 mL, 33.8 mmol, 1 equiv.) was added and the solution was stirred at room temperature for 14 hours, then CH_3OH was added to dissolve the white solid appeared and the solvent removed *in vacuo*. The crude product was dissolved in DCM and washed with H_2O (x3), dried over anhydrous sodium sulphate and all the volatiles were removed *in vacuo*. The new crude was dissolved in 70 mL of H_2O and extracted with Et_2O (2 x 20 mL) and DCM/*n*-Hexane (3/1, 5 x 40 mL). Fractionated extraction afforded **46** (2.431 g, 14%), as a clear oil. ν_{max} (liquid film) 3507, 2868, 1745, 1644, 1455, 1367, 1349, 1295, 1227, 1096, 943, 843, 731; Mass analysis: highest peak at 495.3 corresponding to PEG-CH_2COOH + Na^+.

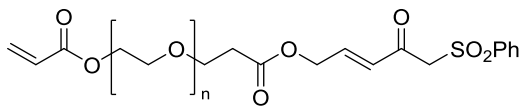
12.4.v *tert*-Butyl ester PEG-400 acrylic derivative, 47.



47

A mixture of **46** (2.43 g, 4.60 mmol, 1 equiv.), 2,6-di-*tert*-butyl-4-methylphenol (1 small crystal) and triethylamine (1.15 mL, 8.28 mmol, 1.8 equivs.) in DCM (23 mL) was stirred for 10 minutes at 0 ºC, after which acryloyl chloride (0.6 mL, 6.90 mmol, 1.5 equivs.) dissolved in DCM (3 mL) was added, and stirring continued for a further 14 hours. The reaction was quenched by filtering to a separation funnel and washing the organic layers with 20 mL of HCl (1 M), H_2O (20 mL) and $NaHCO_3$ (saturated aqueous solution, 20 mL). The organic layers were dried over anhydrous sodium sulphate. Following filtration the solution was evaporated yielding **47** (2.327 g, 87%). ν_{max} (liquid film) 2868, 2725, 1796, 1746, 1724, 1635, 1455, 1407, 1368, 1349, 1295, 1226, 1194, 1099, 987, 946, 843, 810, 731, 700; Mass analysis: highest peak at 549.3 corresponding to APEG-CH_2COOH + Na^+.

12.4.vi Acrylic-PEG-400-phenylsulfonylester, 49.



49

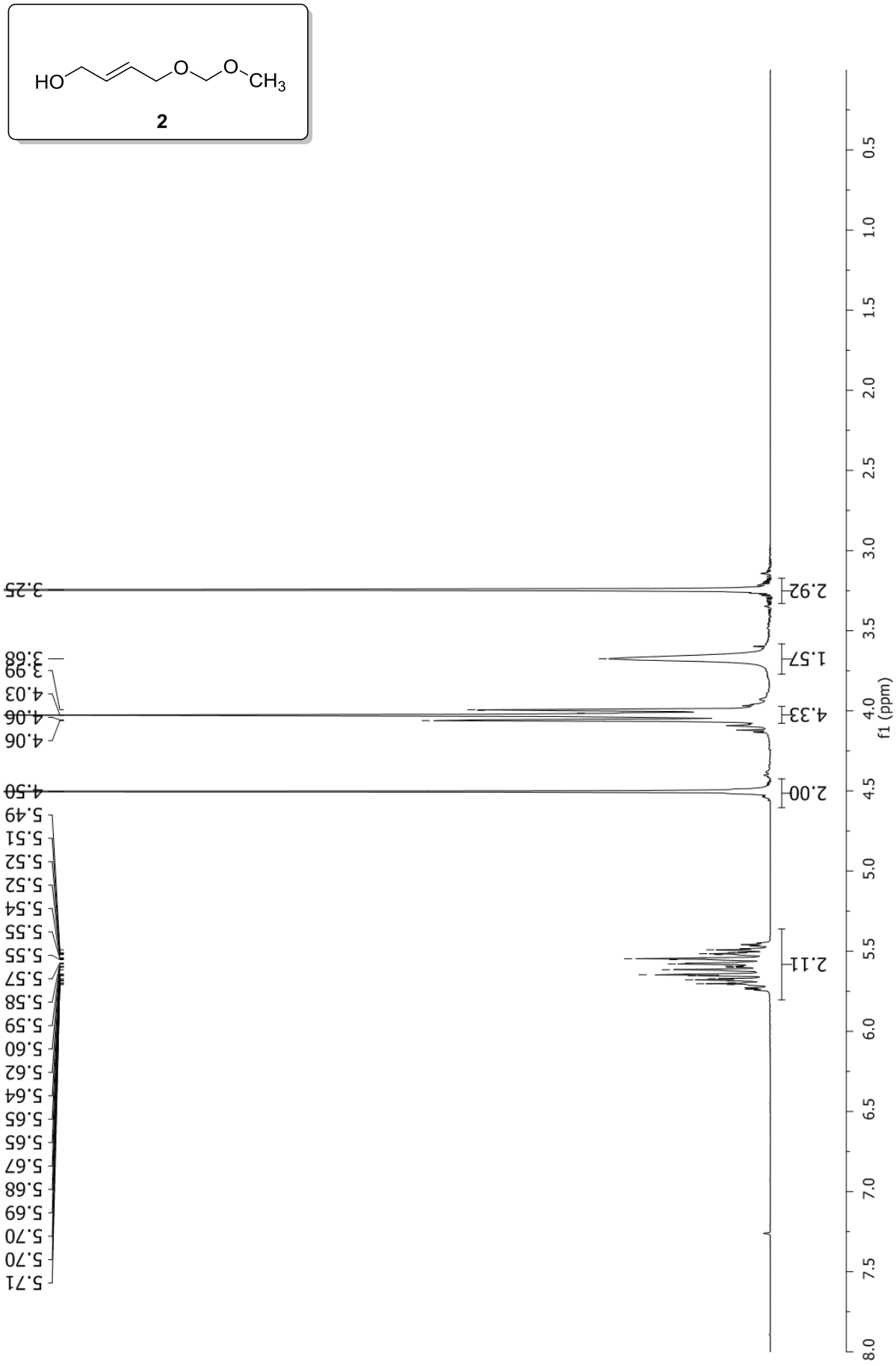
Method A: using EDC and DMAP:

A mixture of **47** (406 mg, 0.753 mmol, 1 equiv.), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC·HCl), triethylamine (Et_3N) and dimethylaminopyridine (DMAP) in DCM (3 mL) was stirred at room temperature for 10 minutes, after which phenylsulfone compound **I-D** (198 mg, 0.83 mmol, 1.1 equivs.) in DCM (1 mL) was added and the whole mixture was stirred for 15 hours. The reaction was quenched with some drops of HCl (0.1 M) and then extracted with DCM (x3). The organic layers were washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous magnesium sulphate, filtered and the volatiles removed *in vacuo* to obtain a dark brown oil. This oil was dissolved in 2 mL of DCM, added to 20 mL of Et_2O and taken into the freezer for 45 minutes. The bottom layer appeared in the process was separated from the supernatant and dried to afford 242 mg of **49**.

Method B: using DCC and DMAP:

A solution of **47** (419 mg, 0.776 mmol, 1 equiv.) in THF (1 mL) was added to a solution of **I-D** (223 mg, 0.931 mmol, 1.2 equivs.), *N*,*N′*-dicyclohexylcarbodiimide (DCC) (192 mg, 0.931 mmol, 1.2 equivs.) and DMAP (9.5 mg, 0.08 mmol, 0.1 equivs.) in THF (0.5 mL). The resulting brown-red mixture was stirred at room temperature for 24 hours, followed by filtration to remove the solid byproduct. Removal of the solvent under reduced pressure afforded 605 mg of **49**. **Data analyses for **49** are currently in progress.*

SPECTROSCOPY


HO
O
O
CH3
2
3.25
3.68
3.99
4.03
4.06
4.06
4.50
5.49
5.51
5.52
5.52
5.54
5.55
5.55
5.57
5.58
5.59
5.60
5.62
5.64
5.65
5.65
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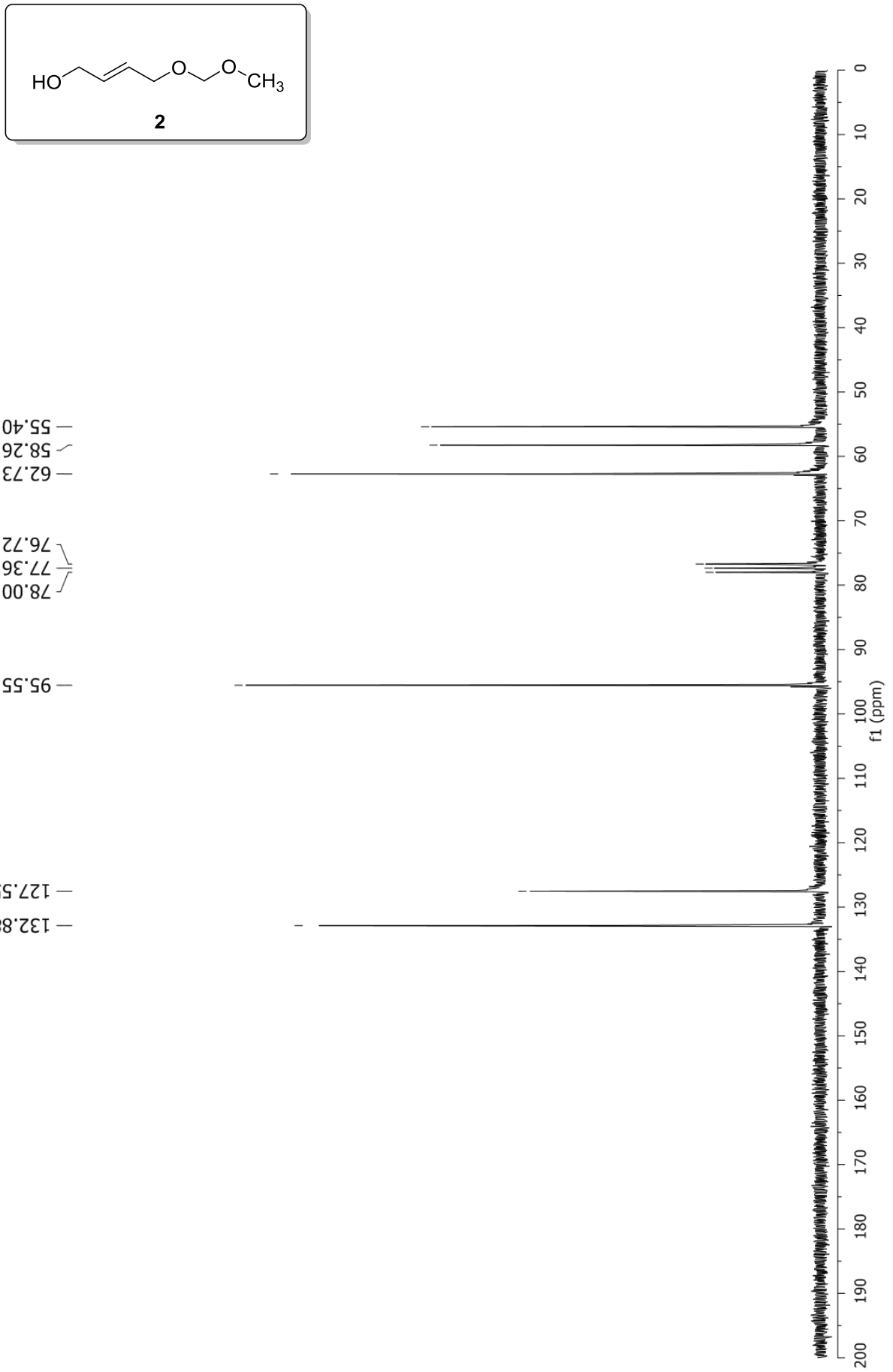
2.92
1.57
4.33
2.00
2.11
f1 (ppm)


HO
O
O
CH3
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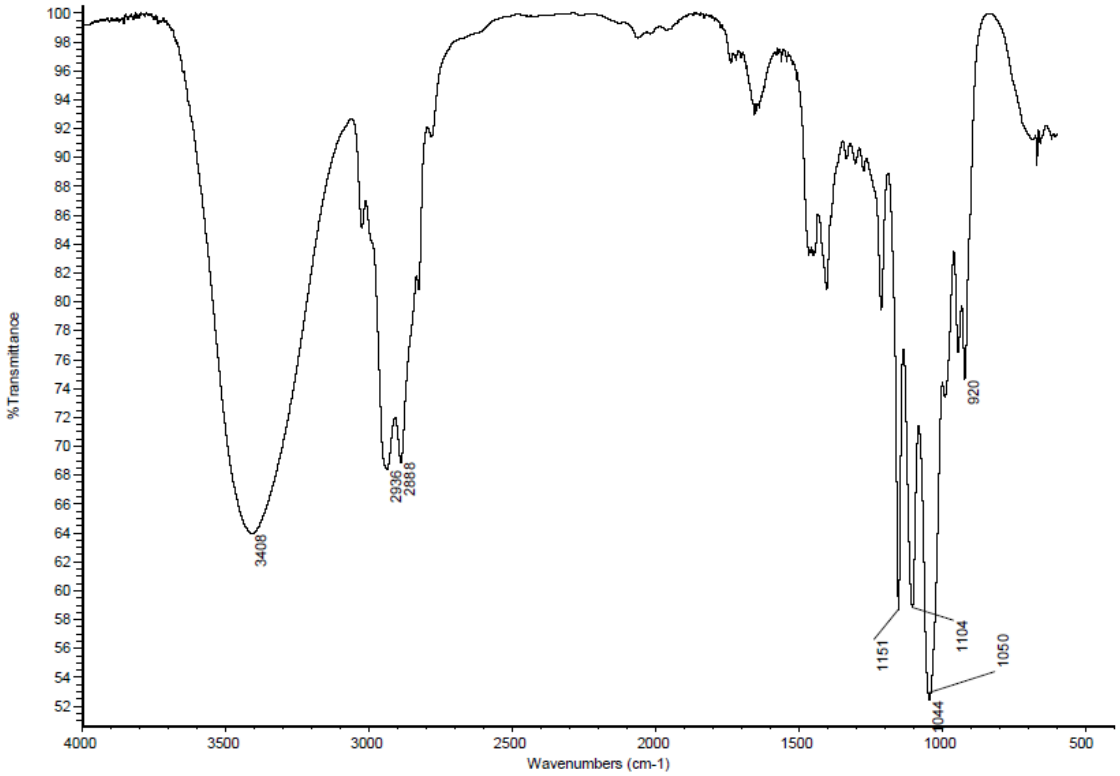
95.55
127.55
132.88
f1 (ppm)


%Transmittance
Wavenumbers (cm-1)
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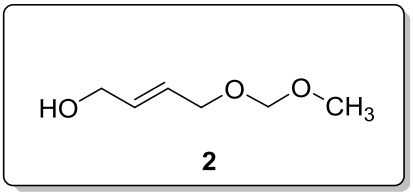
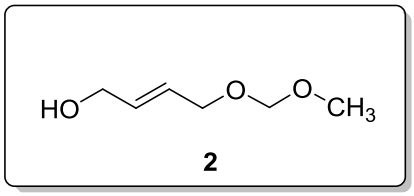
2936
2888
1151
1104
1050
1044
920

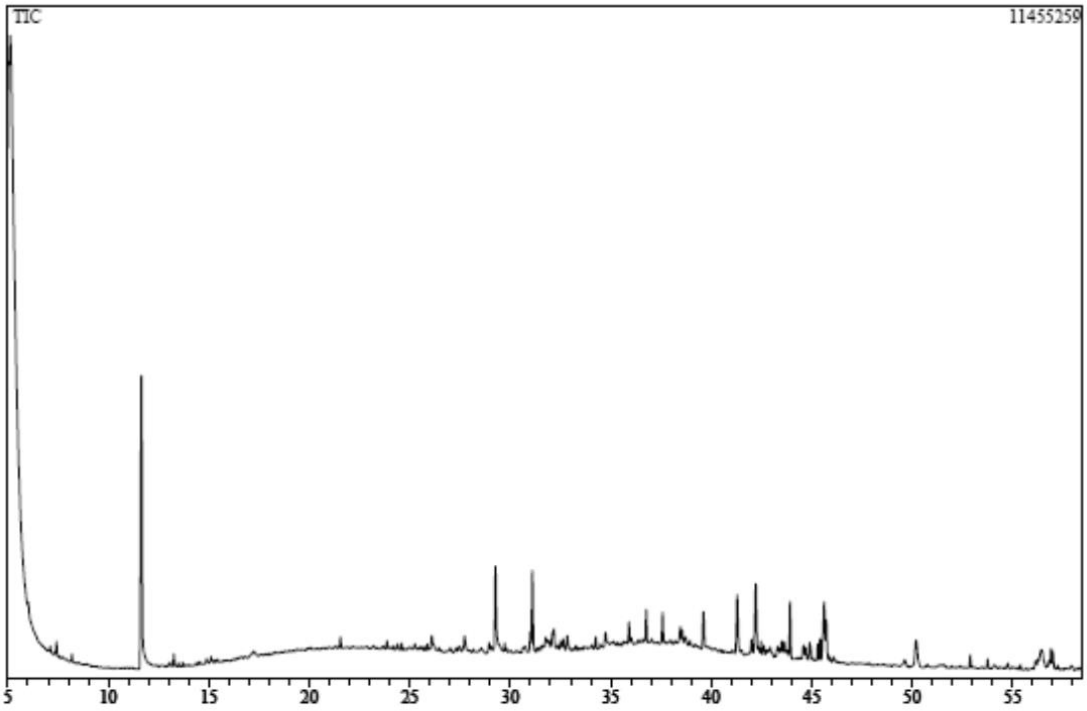

HO
O
O
CH3

2

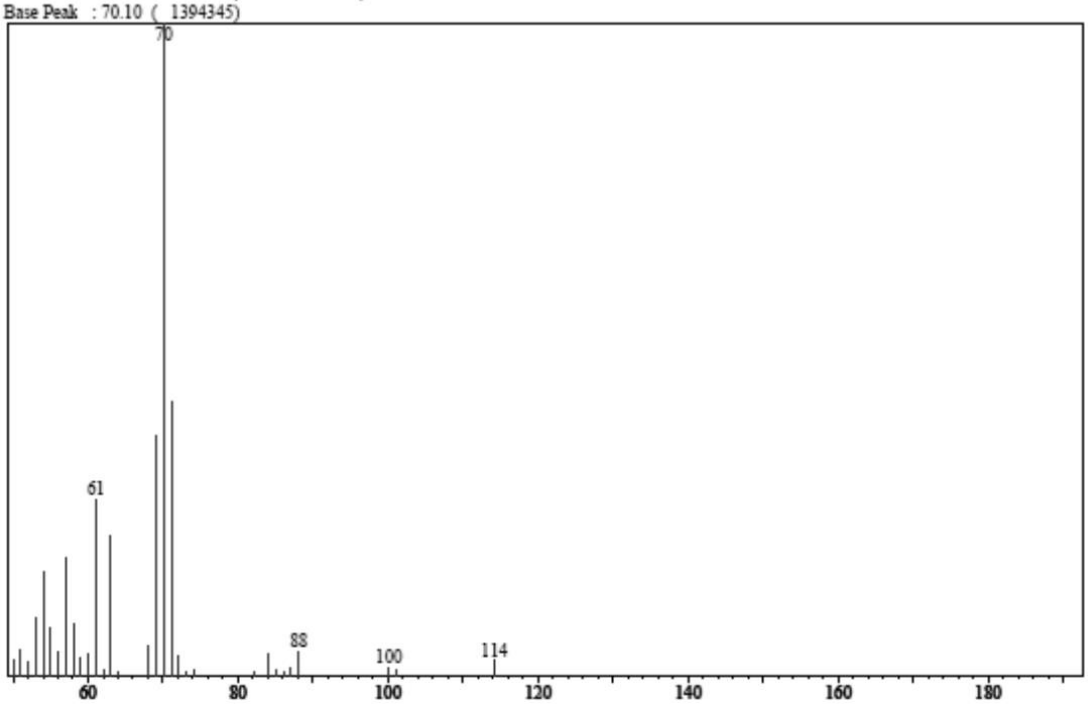


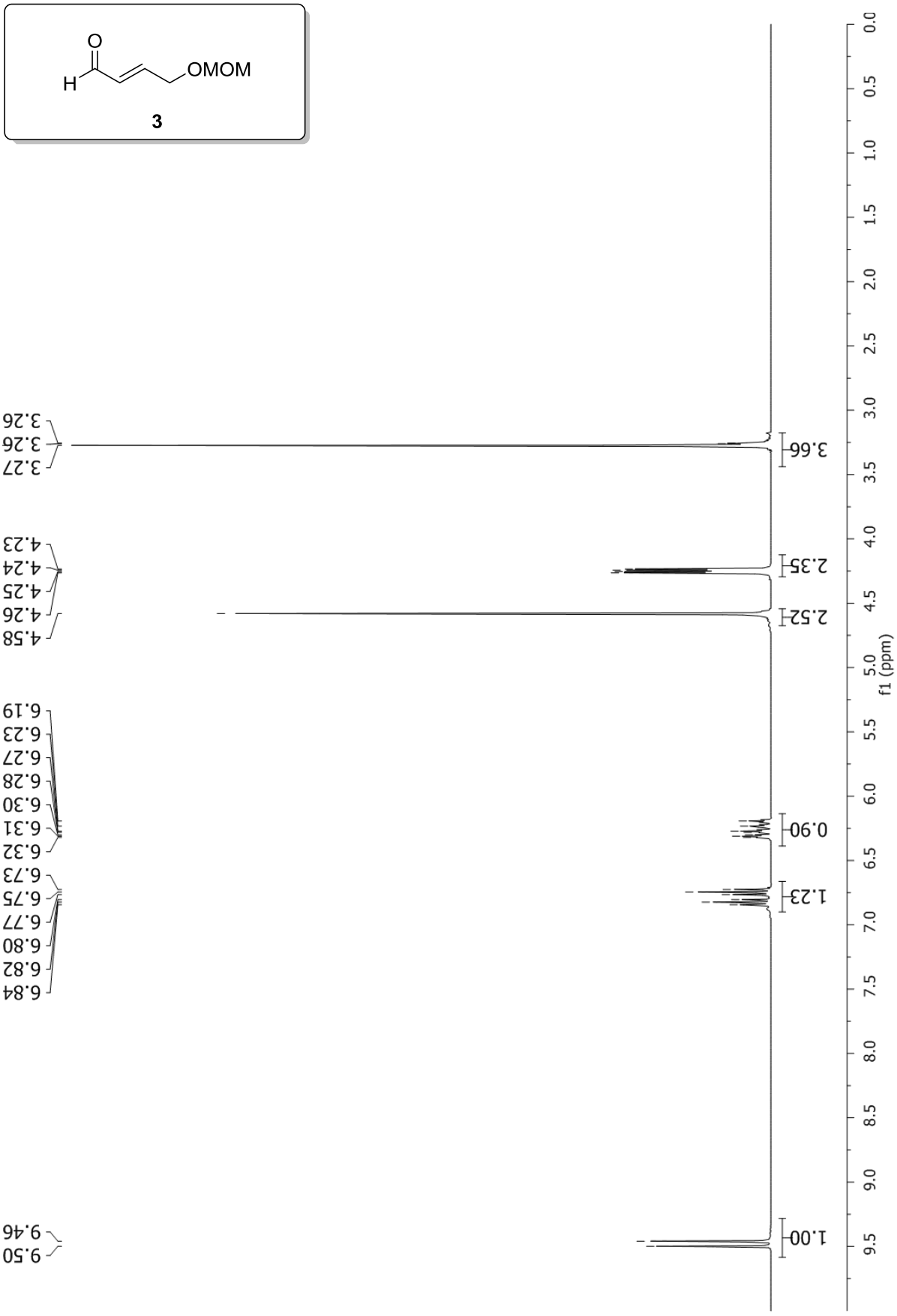
2

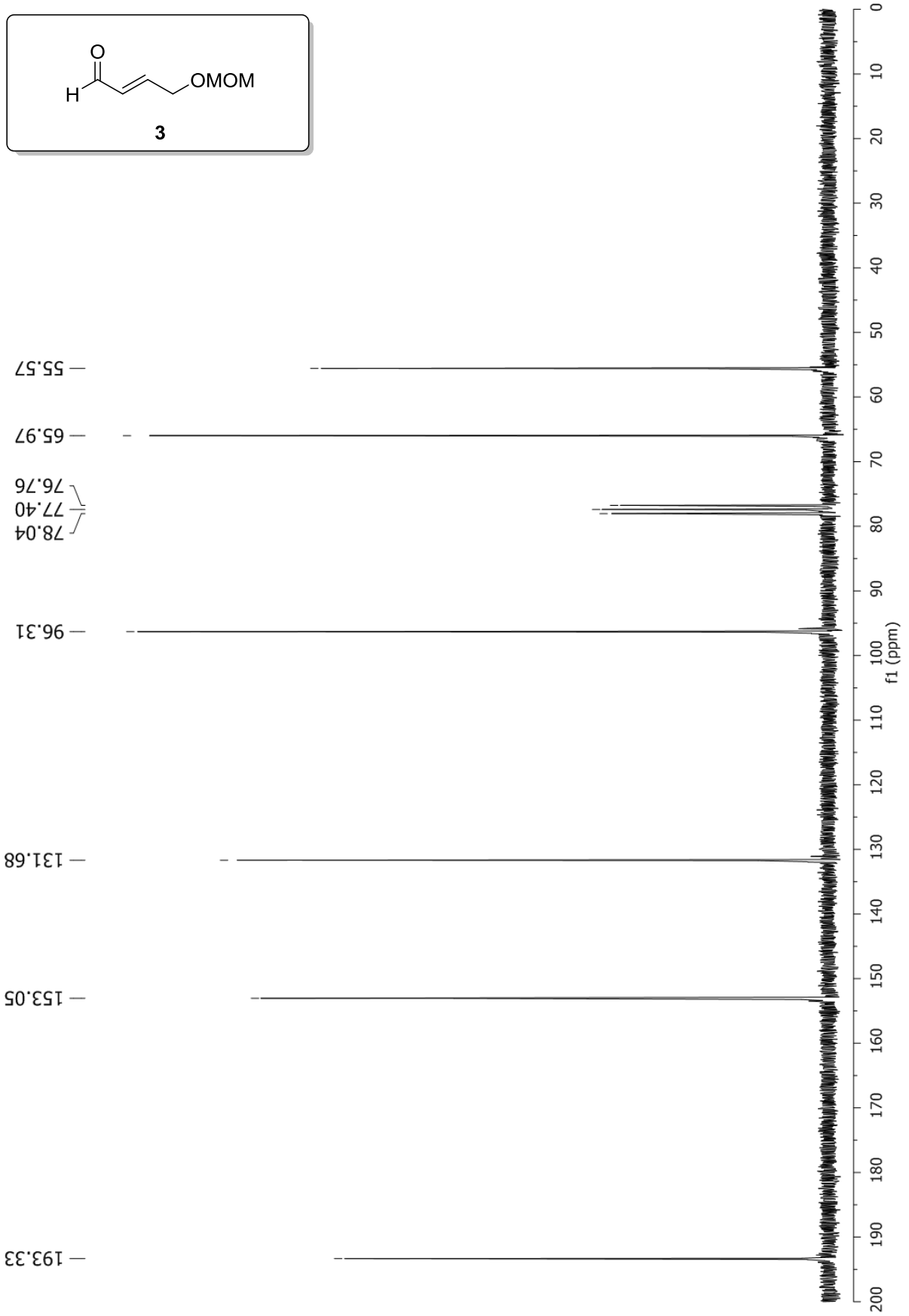
Data : JULIO.D01
Sample : PR-147-crudo
Method File Name : NMG3.MET

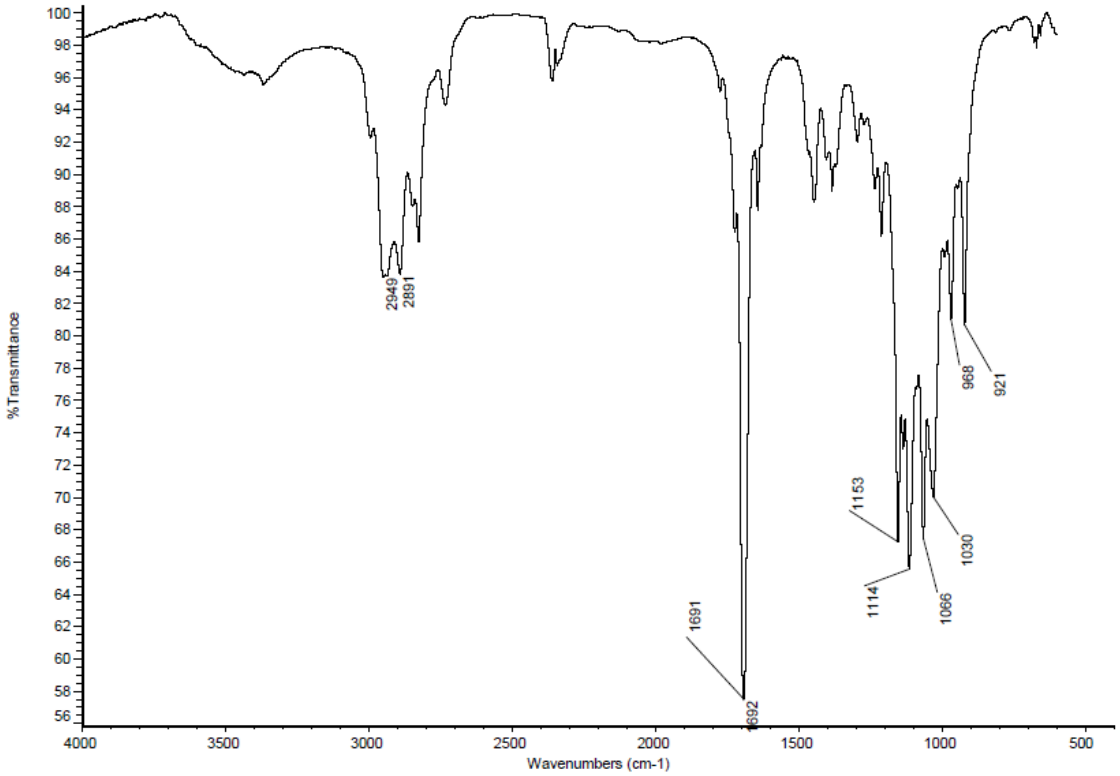


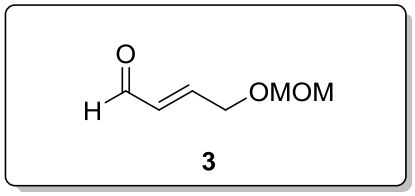
Scan # : (794 - 802) B.G. Scan # : (742 - 769)
Mass Peak # : 31 Ret. Time : (11.608 - 11.675)
Base Peak : 70.10 (1394345)



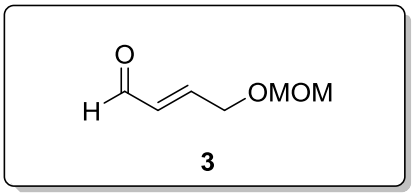

O
H
OMOM
3
9.50
9.46
6.84
6.82
6.80
6.77
6.75
6.73
6.32
6.31
6.30
6.28
6.27
6.23
6.19
4.58
4.26
4.25
4.24
4.23
3.27
3.26
3.26
1.00
1.23
0.90
2.52
2.35
3.66
f1 (ppm)


O
H
OMOM
3
55.57
65.97
76.76
77.40
78.04
96.31
131.68
153.05
193.33
f1 (ppm)


%Transmittance
Wavenumbers (cm-1)
2949
2891
1691
1692
1153
1114
1066
1030
968
921

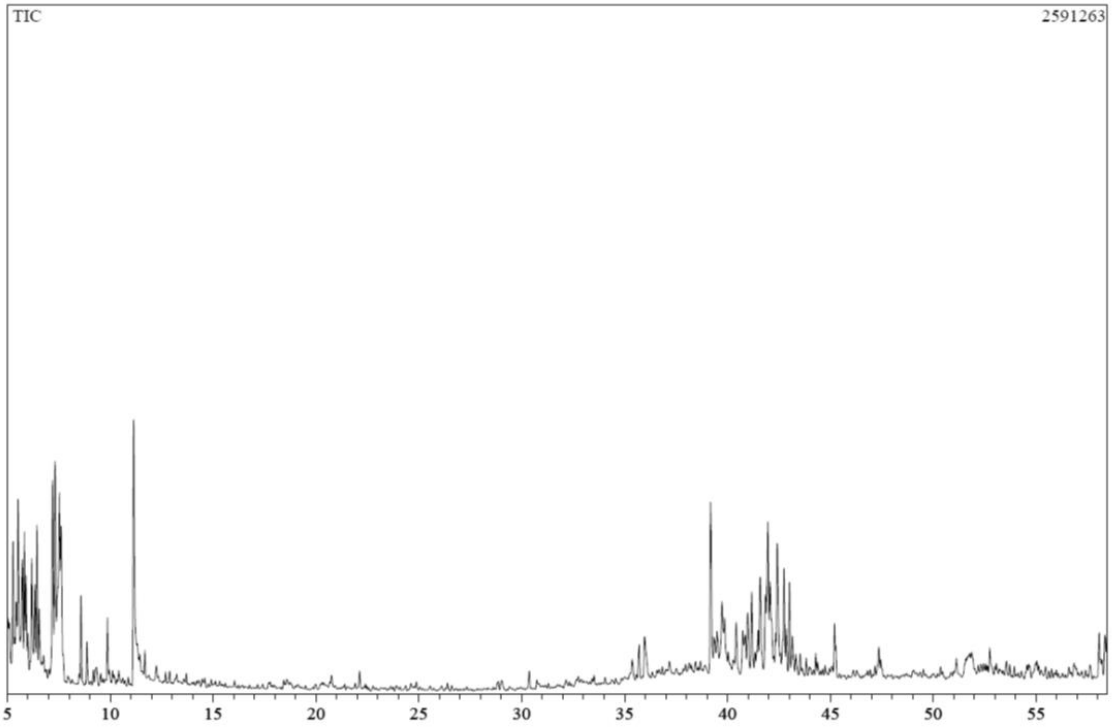

O
H
OMOM

3

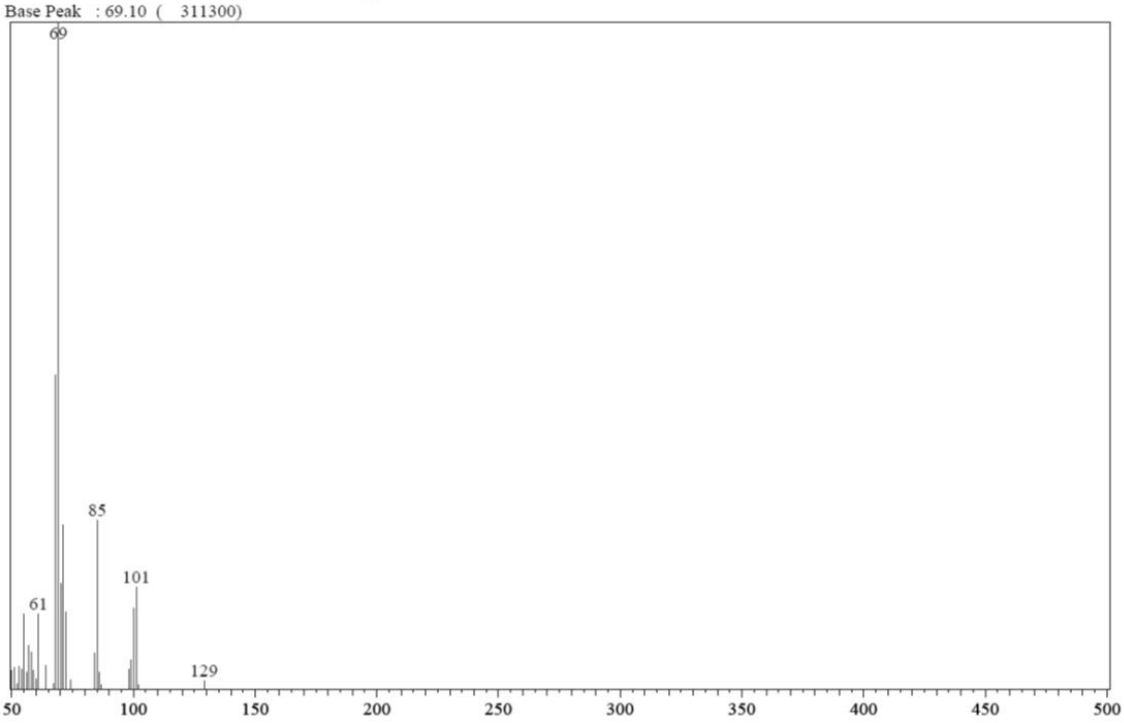


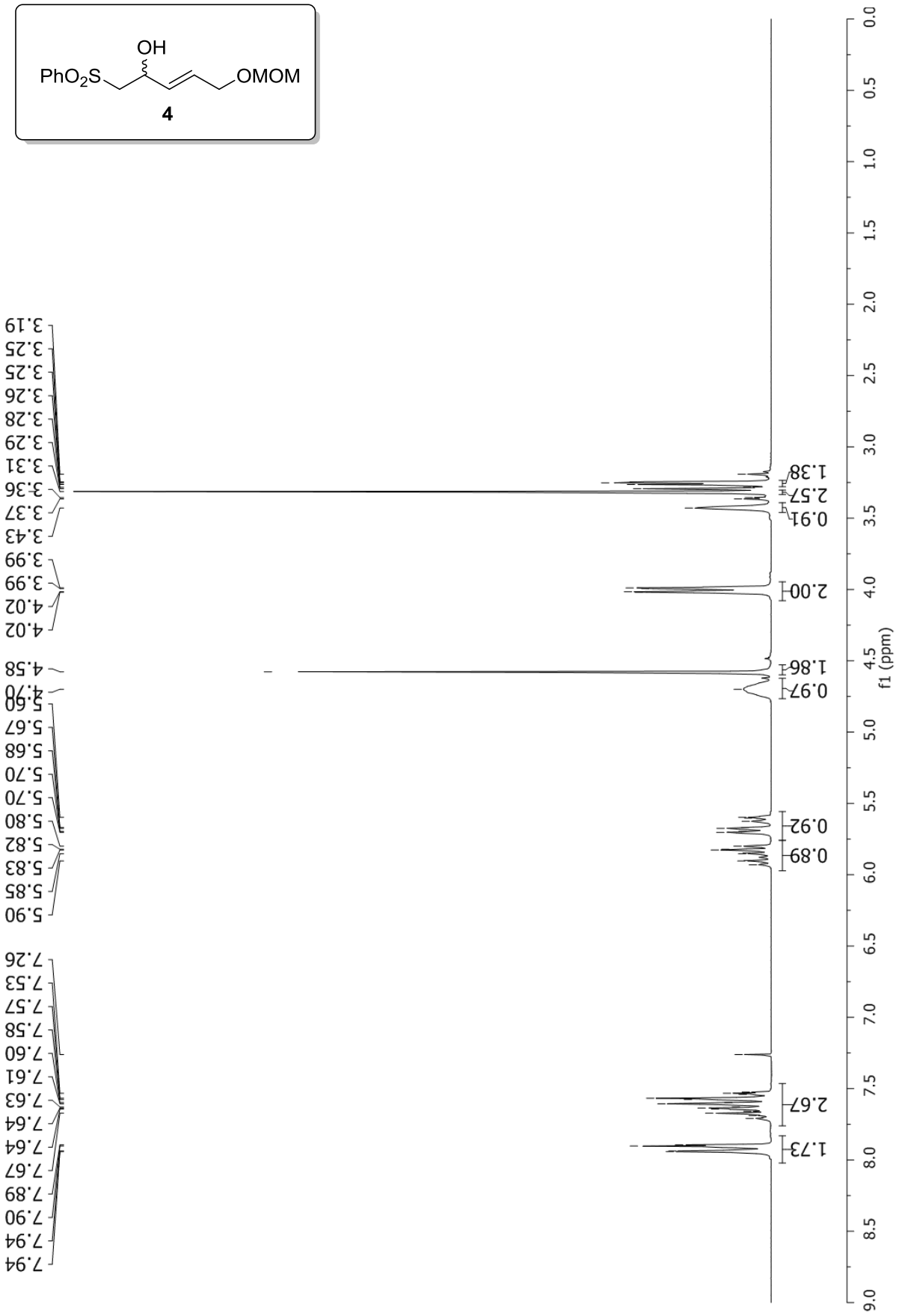
3

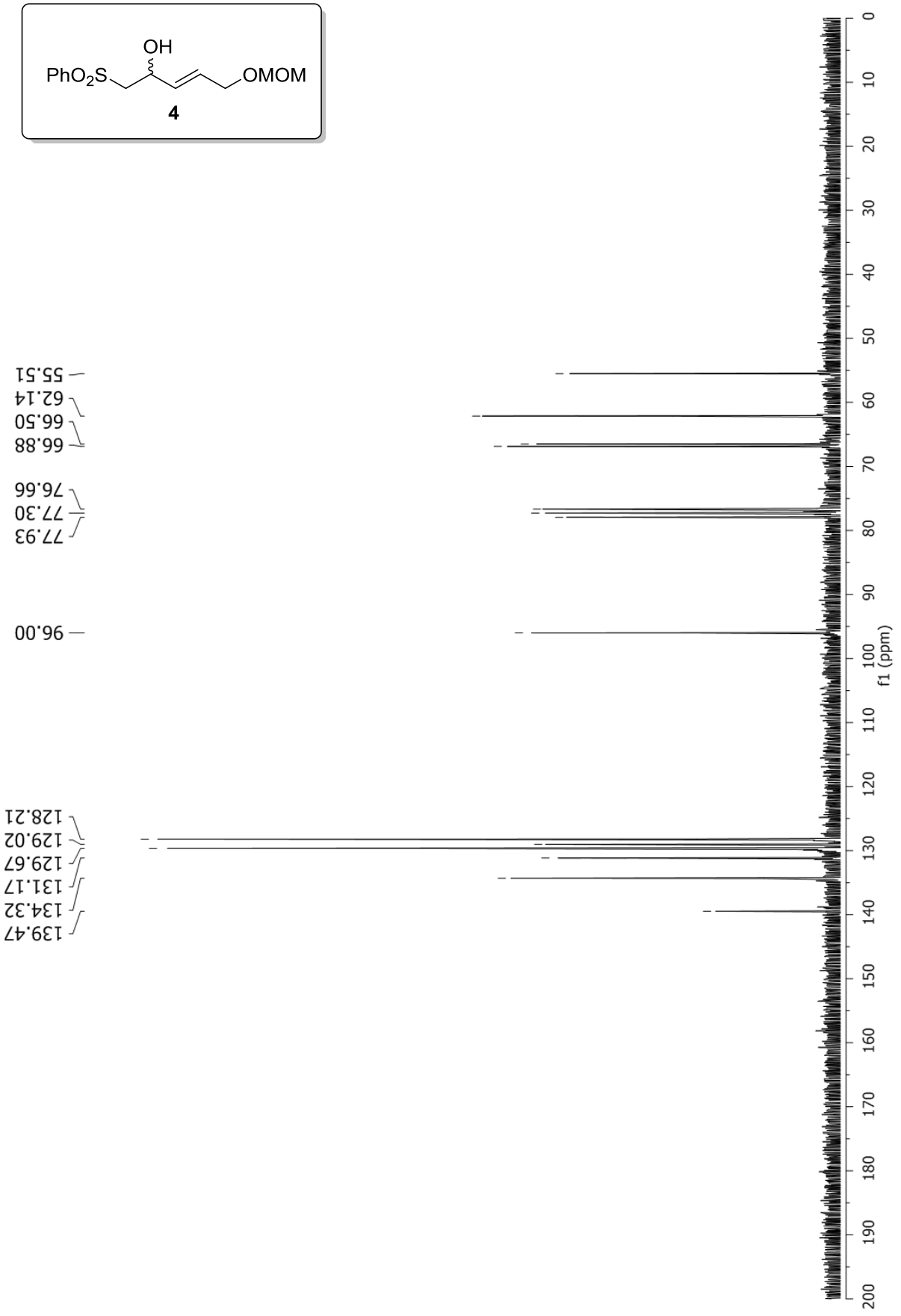
Data : JULIO.D02
Sample : PR-148-Crudo
Method File Name : NMG3.MET

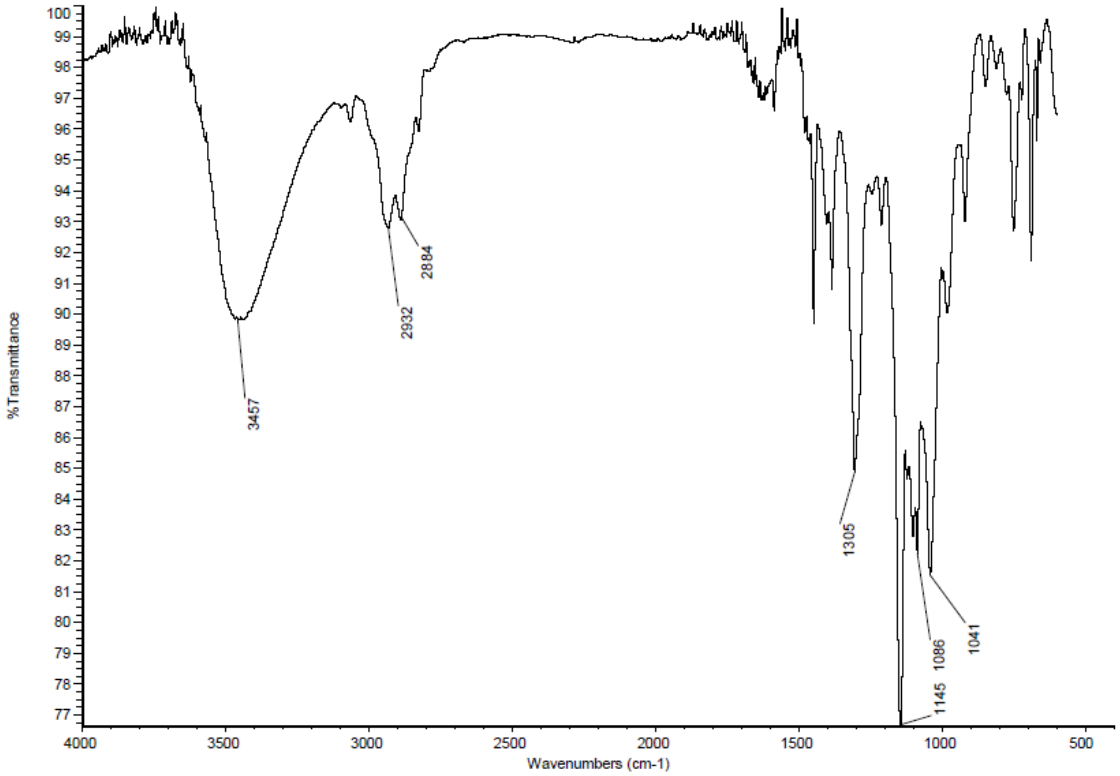


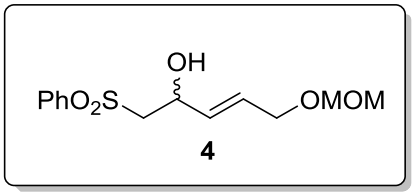
Scan # : (735 - 741)
Mass Peak # : 30 Ret. Time : (11.115 - 11.163)
Base Peak : 69.10 (311300)



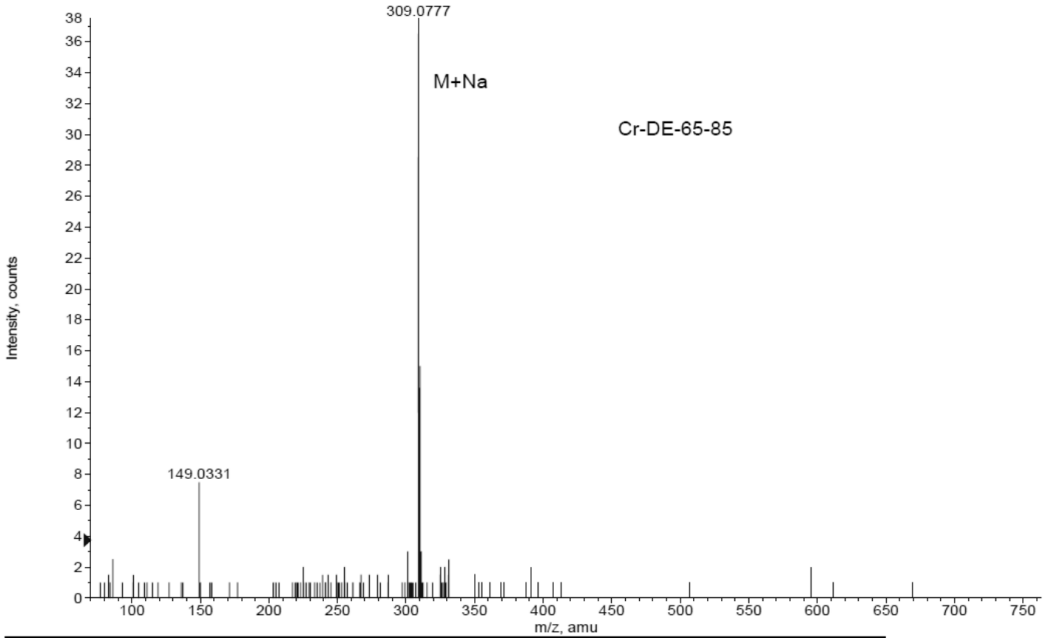

OH
PhO2S
OMOM
4
f1 (ppm)


OH
PhO2S
OMOM
4
55.51
62.14
66.50
66.88
76.66
77.30
77.93
96.00
128.21
129.02
129.67
131.17
134.32
139.47
f1 (ppm)

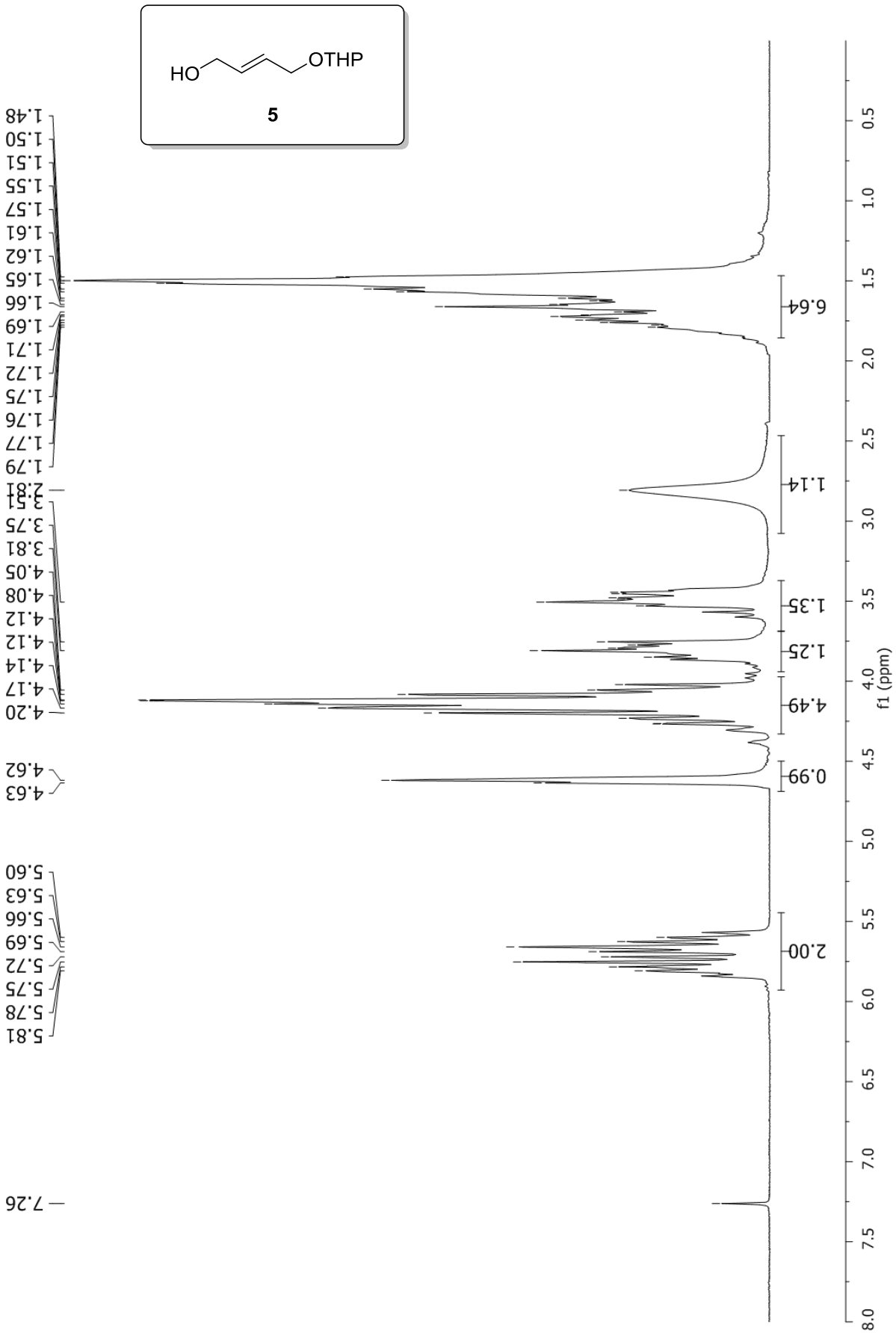


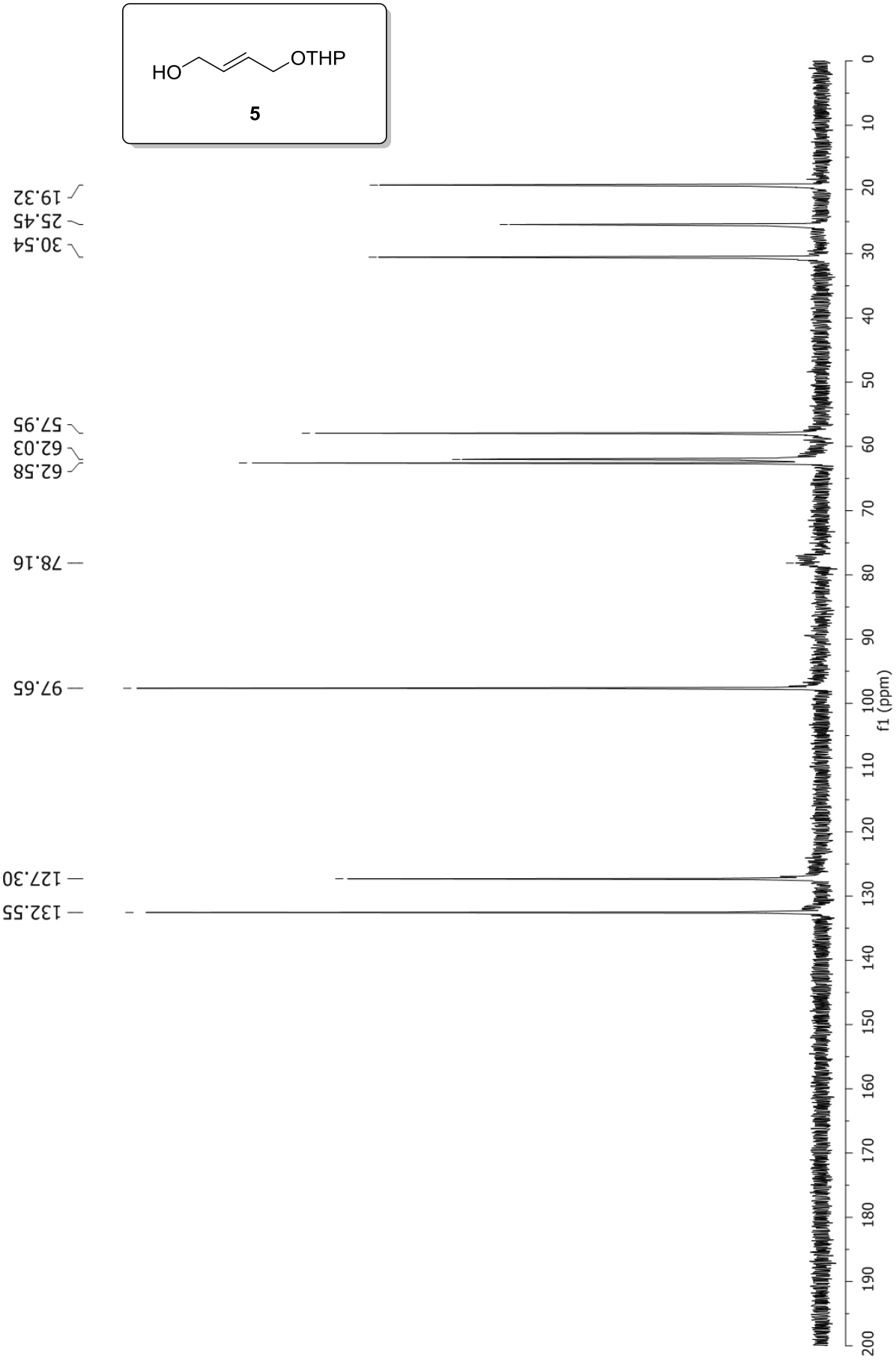


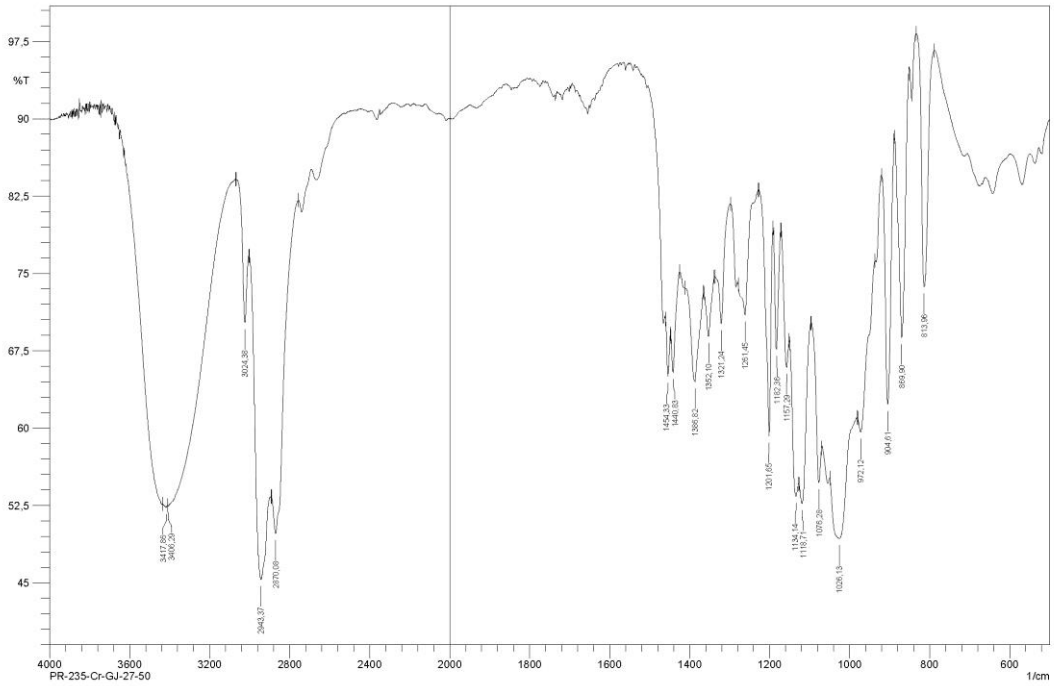
4

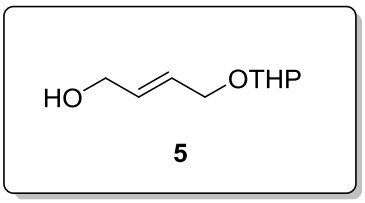


Formula	CalculatedMass	mDaError	ppmError	RDB
C14 H14 N4 O Na S	309.078054	-0.354152	-1.145833	9.5
C13 H18 O5 Na S	309.076717	0.98316	3.180942	4.5

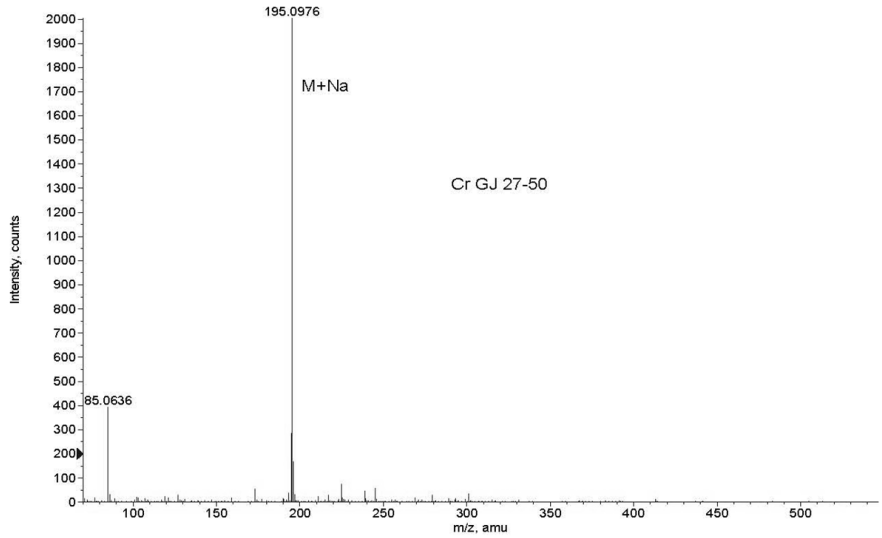

HO
OTHP
5
1.48
1.50
1.51
1.55
1.57
1.61
1.62
1.65
1.66
1.69
1.71
1.72
1.75
1.76
1.77
1.79
2.81
3.51
3.75
3.81
4.05
4.08
4.12
4.12
4.14
4.17
4.20
4.62
4.63
5.60
5.63
5.66
5.69
5.72
5.75
5.78
5.81
7.26
6.64
1.14
1.35
1.25
4.49
0.99
2.00
f1 (ppm)


HO
OTHP
5
19.32
25.45
30.54
57.95
62.03
62.58
78.16
97.65
127.30
132.55
f1 (ppm)

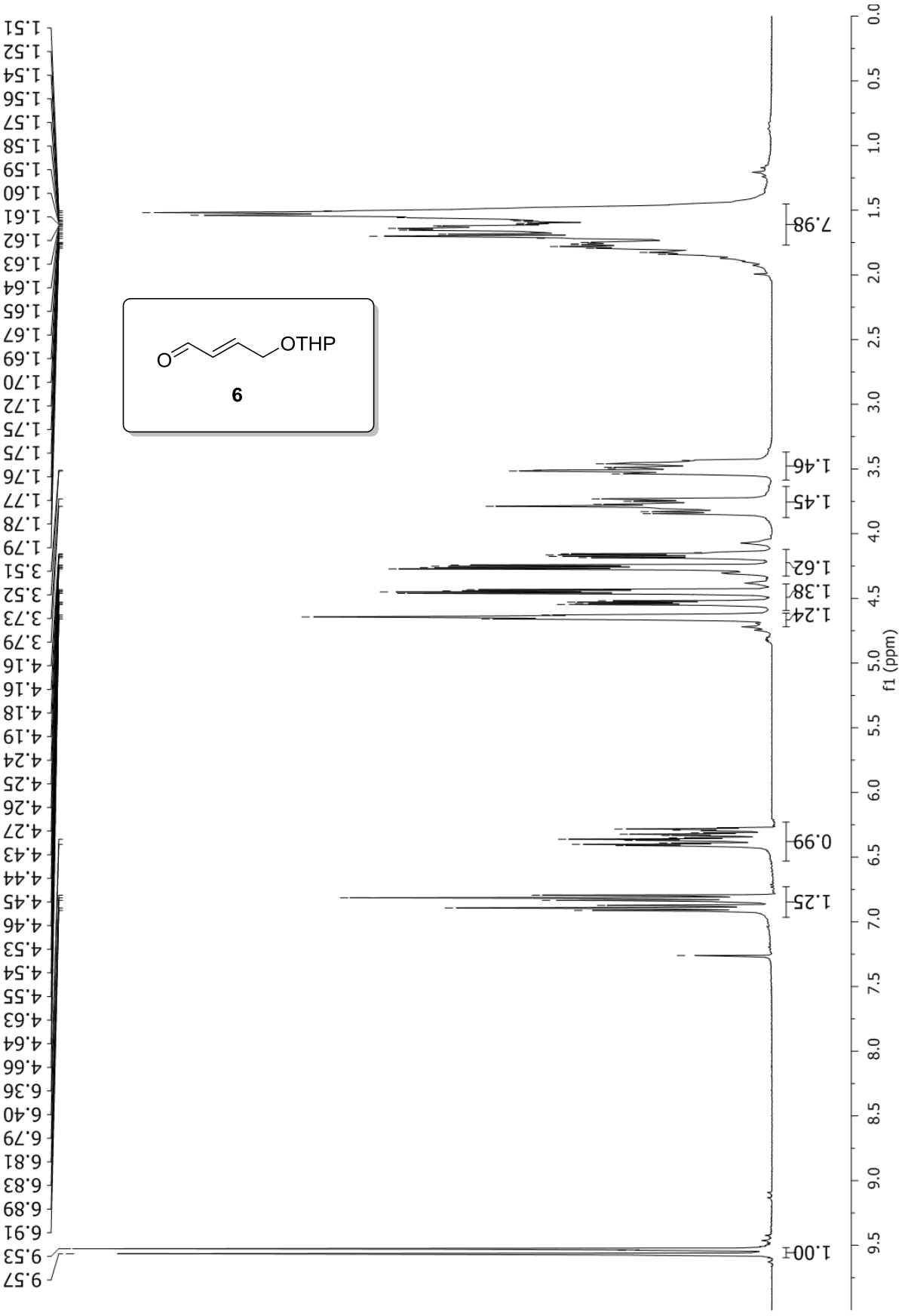


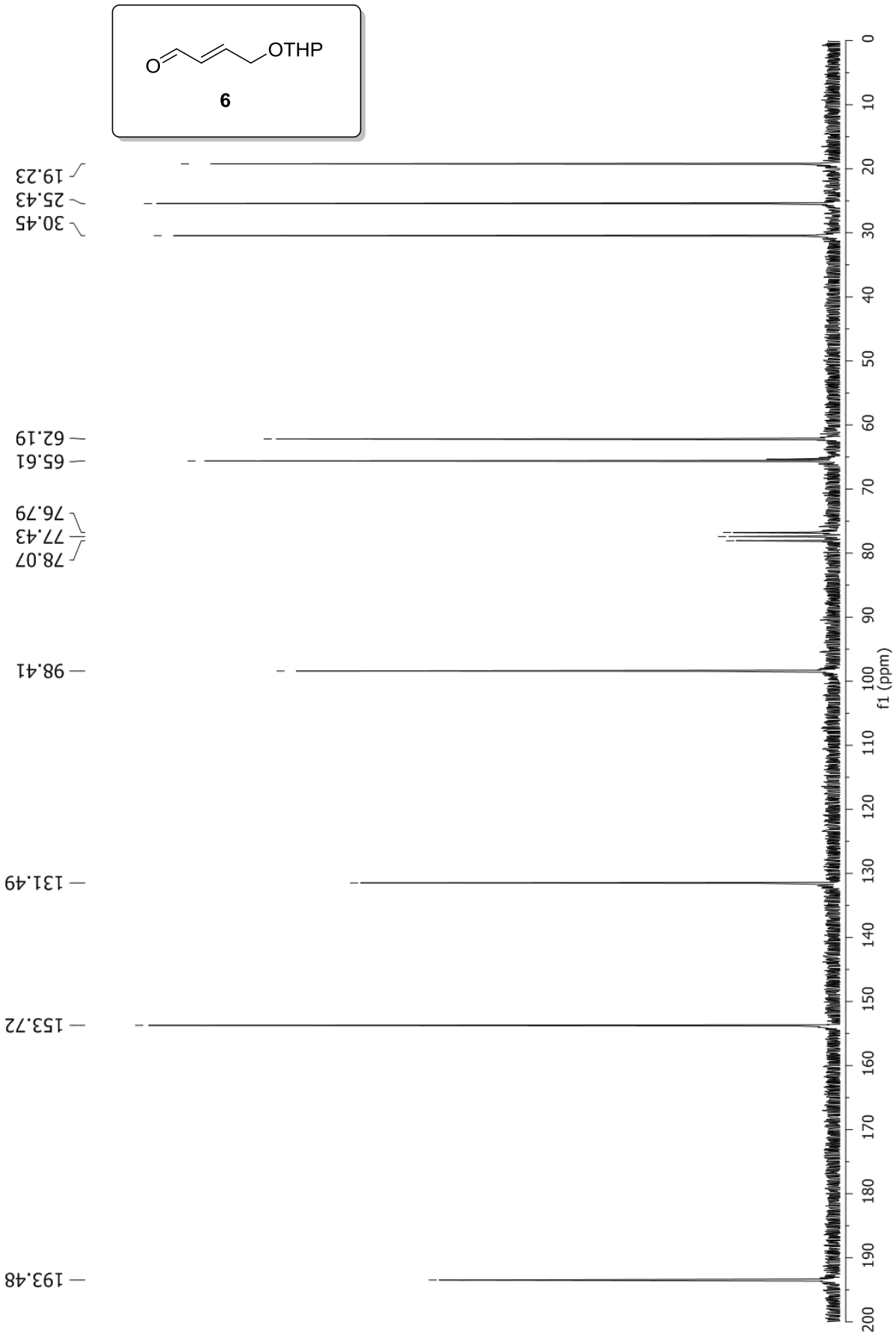


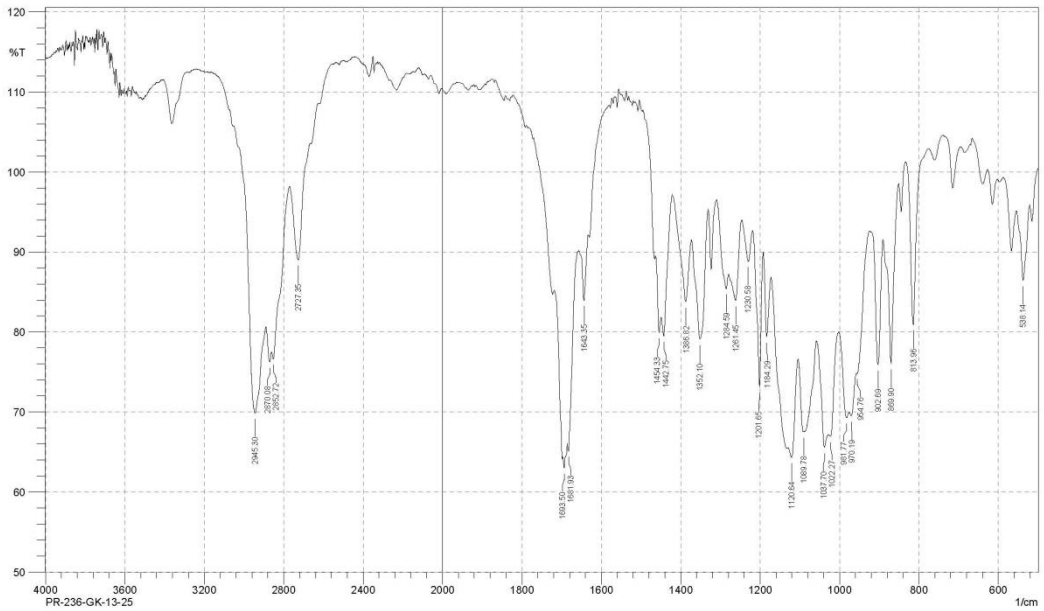
5

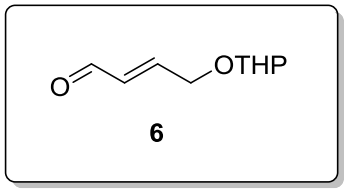


Formula	CalculatedMass	mDaError	ppmError	RDB
C6 H15 N2 O5	195.097548	0.051764	0.265323	0.5
C5 H12 N6 O Na	195.09648	1.119712	5.739224	2.5
C7 H11 N6 O	195.098886	-1.285548	-6.589237	5.5
C9 H16 O3 Na	195.099166	-1.56568	-8.025089	1.5

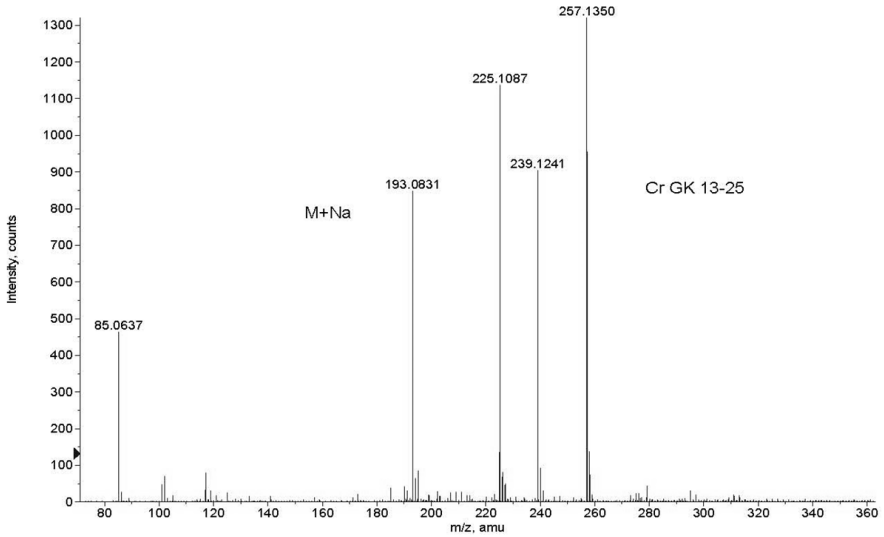

OTHP
6
1.00
0.99
1.25
1.24
1.38
1.62
1.45
1.46
7.98
f1 (ppm)


OTHP
6
19.23
25.43
30.45
62.19
65.61
76.79
77.43
78.07
98.41
131.49
153.72
193.48
f1 (ppm)

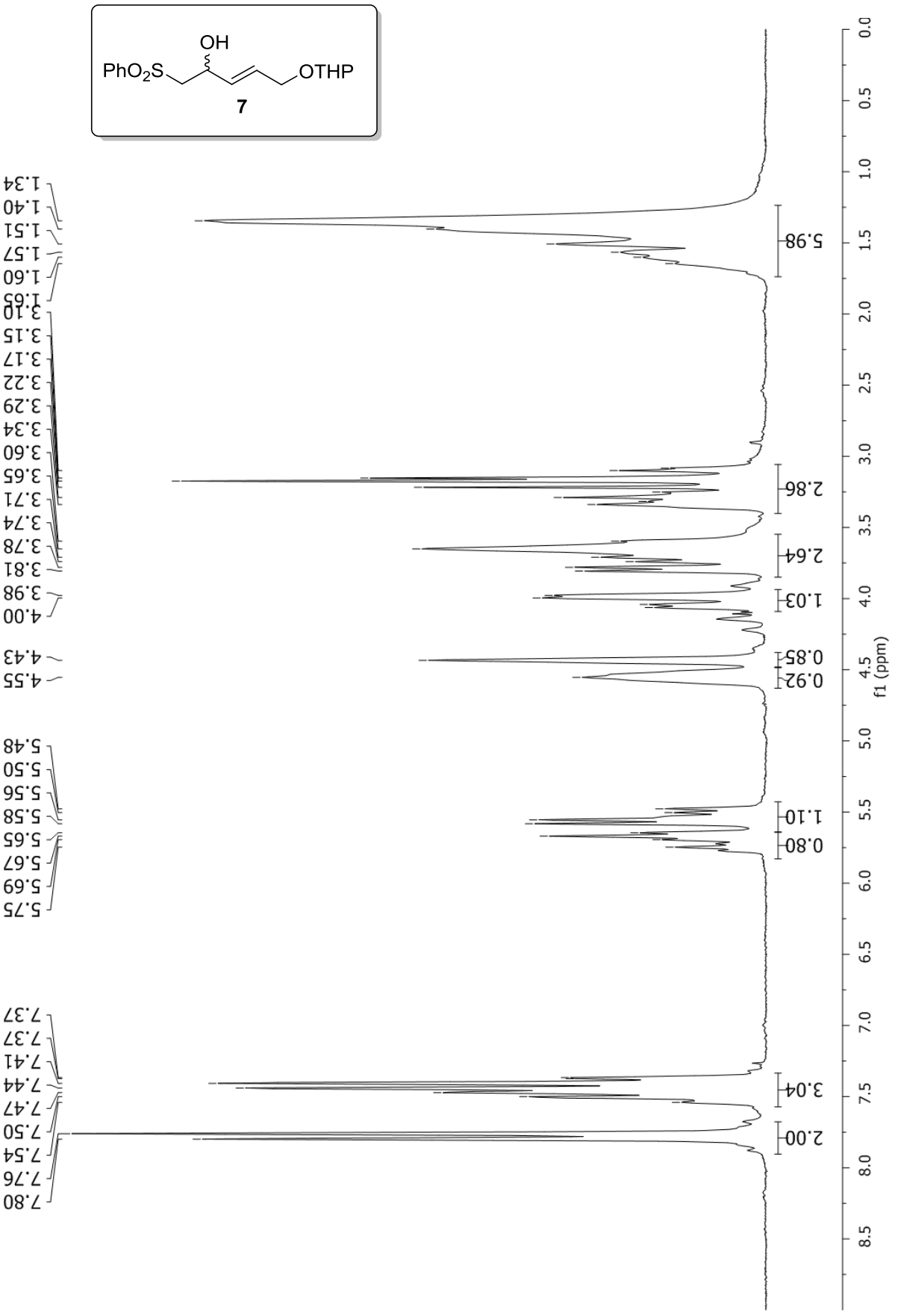


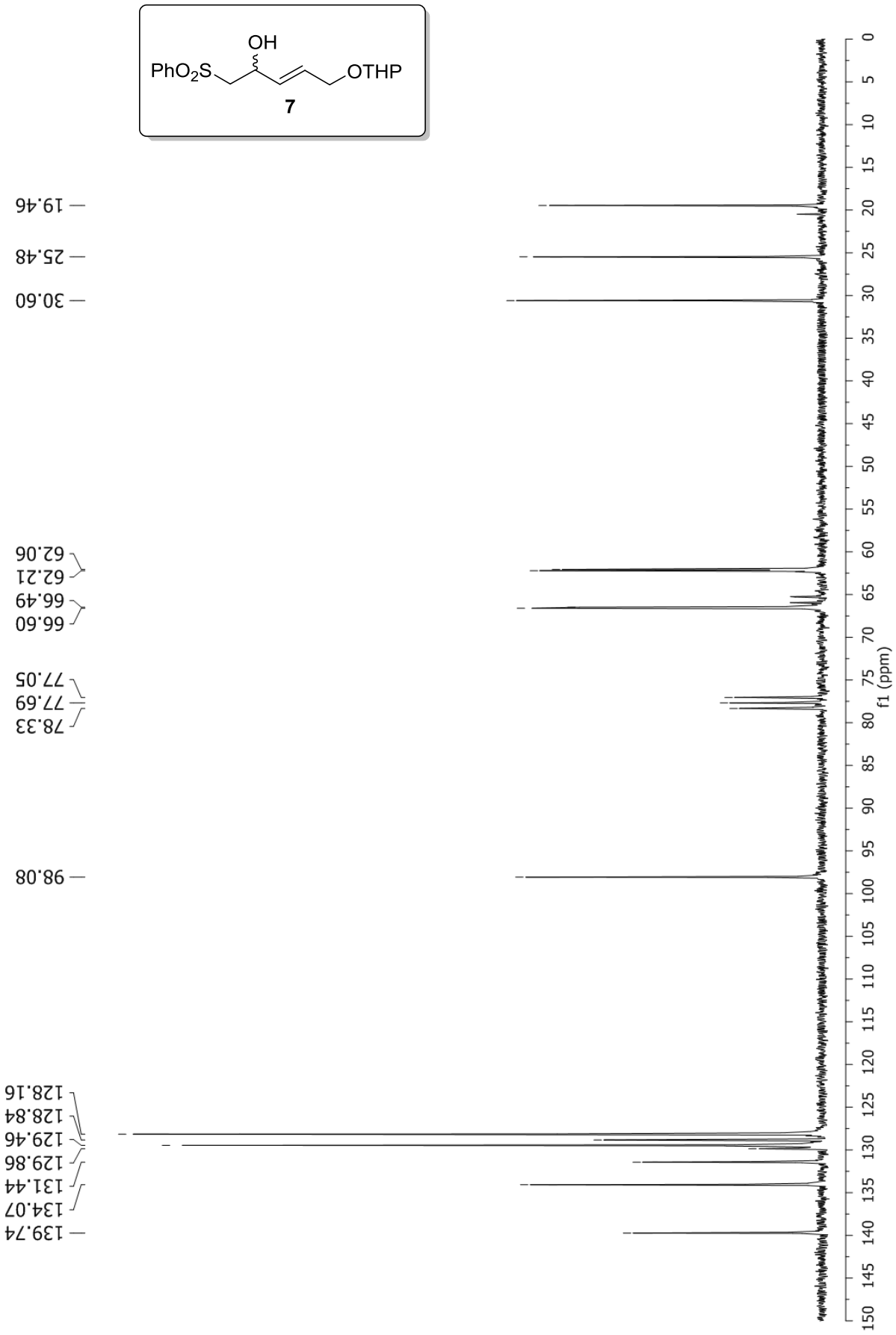


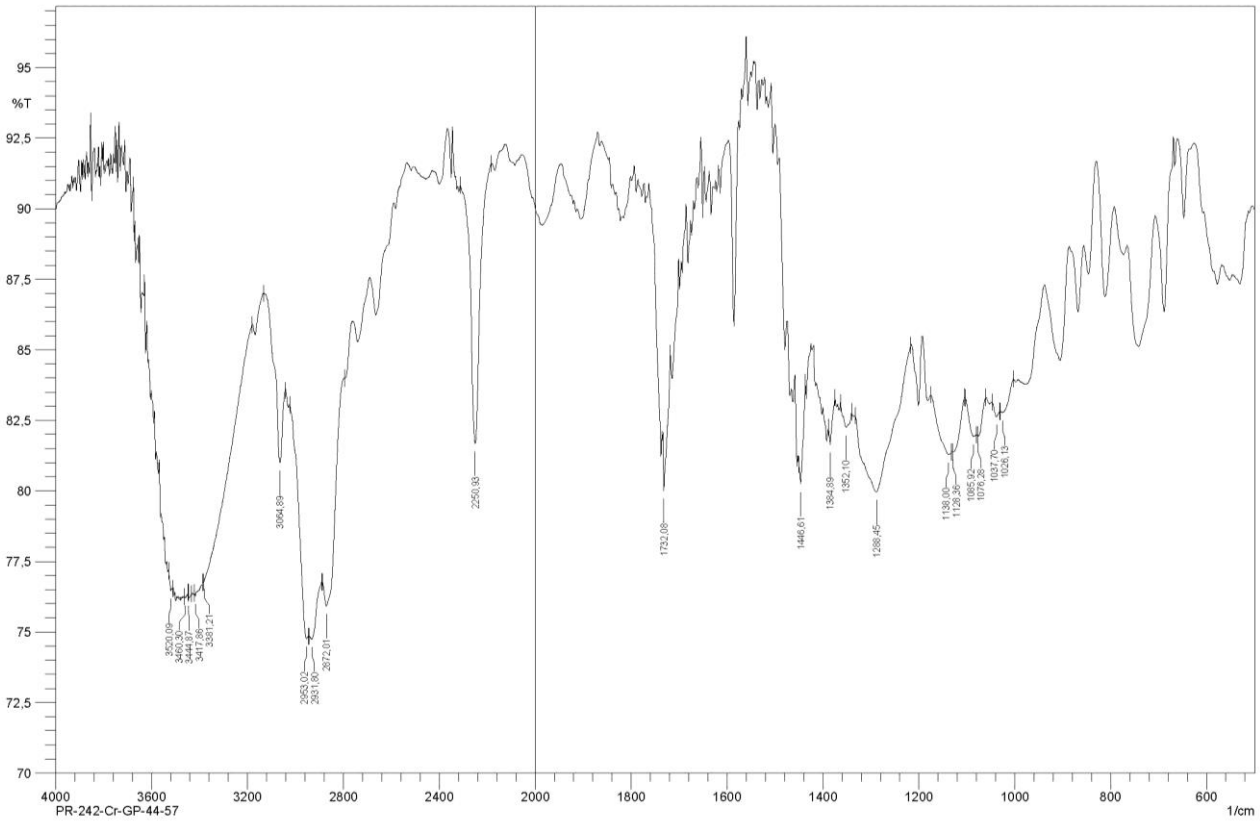
6

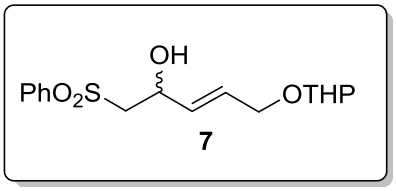


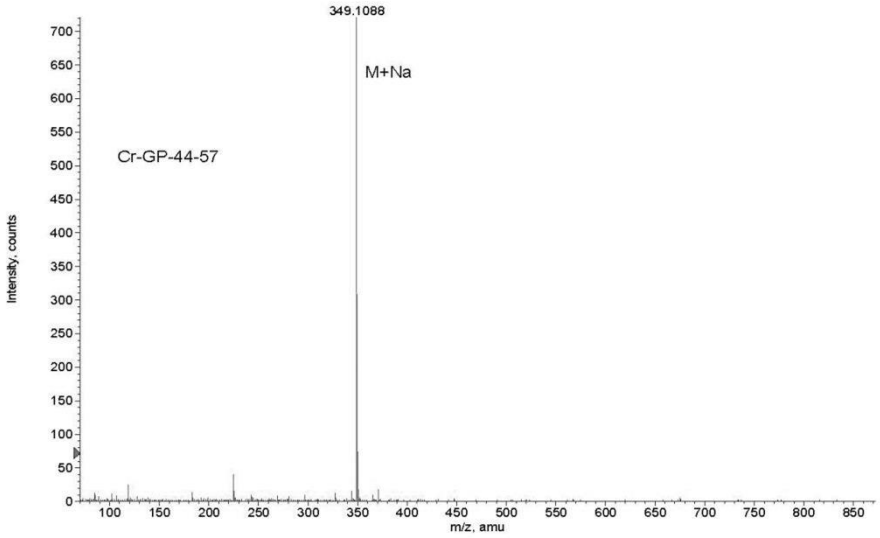
Formula	CalculatedMass	mDaError	ppmError	RDB
C7 H9 N6 O	193.083235	-0.135468	-0.701603	6.5
C9 H14 O3 Na	193.083516	-0.4156	-2.152435	2.5
C6 H13 N2 O5	193.081898	1.201844	6.224473	1.5


OH
PhO2S
OTHP
7
1.34
1.40
1.51
1.57
1.60
1.65
3.10
3.15
3.17
3.22
3.29
3.34
3.60
3.65
3.71
3.74
3.78
3.81
3.98
4.00
4.43
4.55
5.48
5.50
5.56
5.58
5.65
5.67
5.69
5.75
7.37
7.37
7.41
7.44
7.47
7.50
7.54
7.76
7.80
5.98
2.86
2.64
1.03
0.85
0.92
1.10
0.80
3.04
2.00
f1 (ppm)

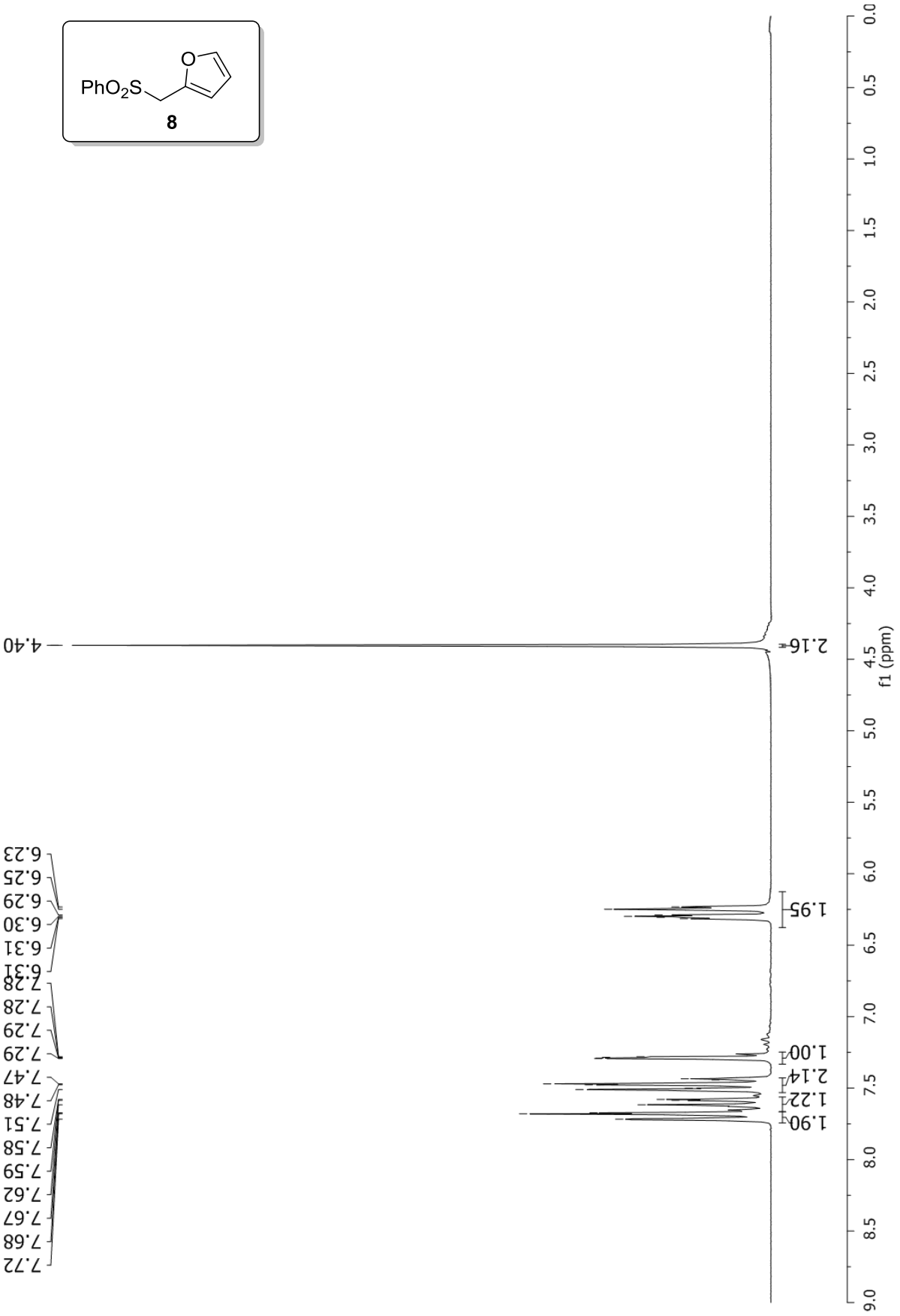

OH
PhO2S
OTHP
7
19.46
25.48
30.60
62.06
62.21
66.49
66.60
77.05
77.69
78.33
98.08
128.16
128.84
129.46
129.86
131.44
134.07
139.74
f1 (ppm)

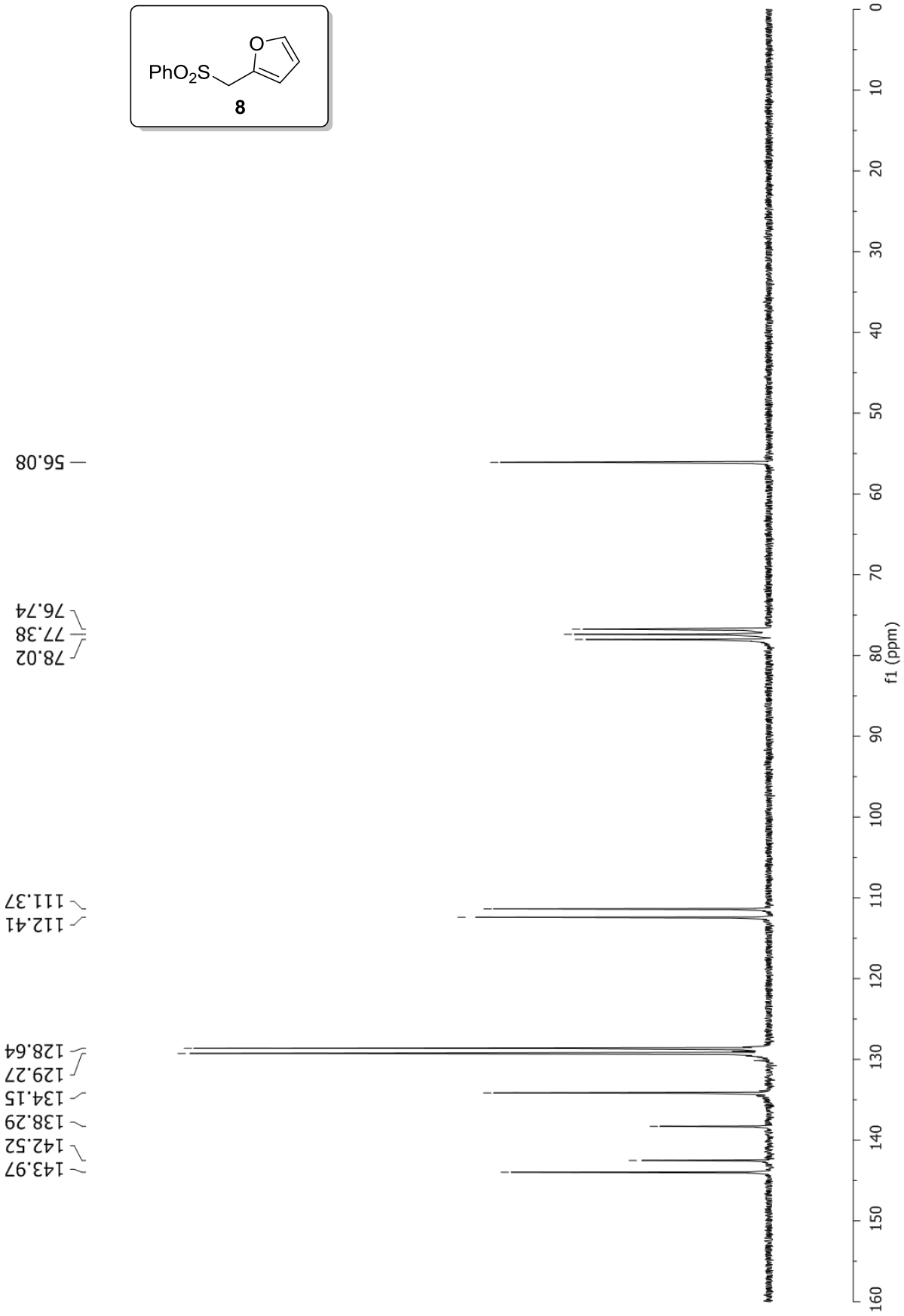


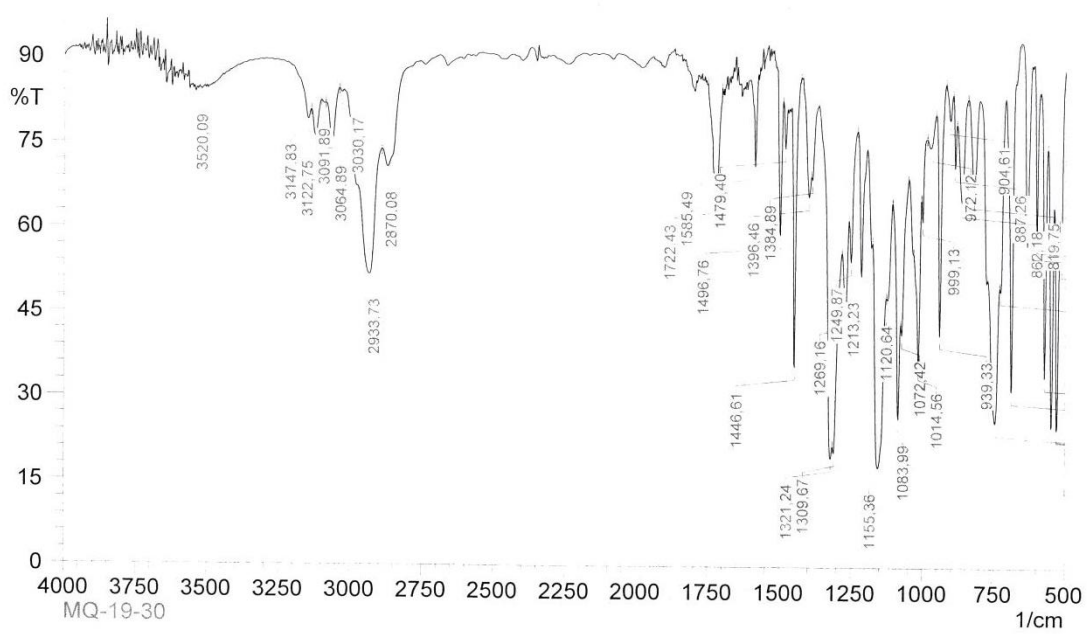


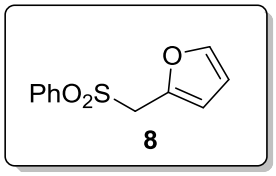


Formula	CalculatedMass	mDaError	ppmError	RDB
C17 H18 N4 O Na S	349.109354	-0.554312	-1.587789	10.5
C16 H22 O5 Na S	349.108017	0.783	2.24285	5.5
C14 H17 N6 O3 S	349.107737	1.063132	3.045269	9.5
C18 H21 O5 S	349.110422	-1.62226	-4.646854	8.5
C3 H17 N12 O6 S	349.110925	-2.124836	-6.086448	1.5
C13 H21 N2 O7 S	349.1064	2.400444	6.875909	4.5
C19 H17 N4 O S	349.11176	-2.959572	-8.477493	13.5
C12 H18 N6 O3 Na S	349.105332	3.468392	9.934973	6.5

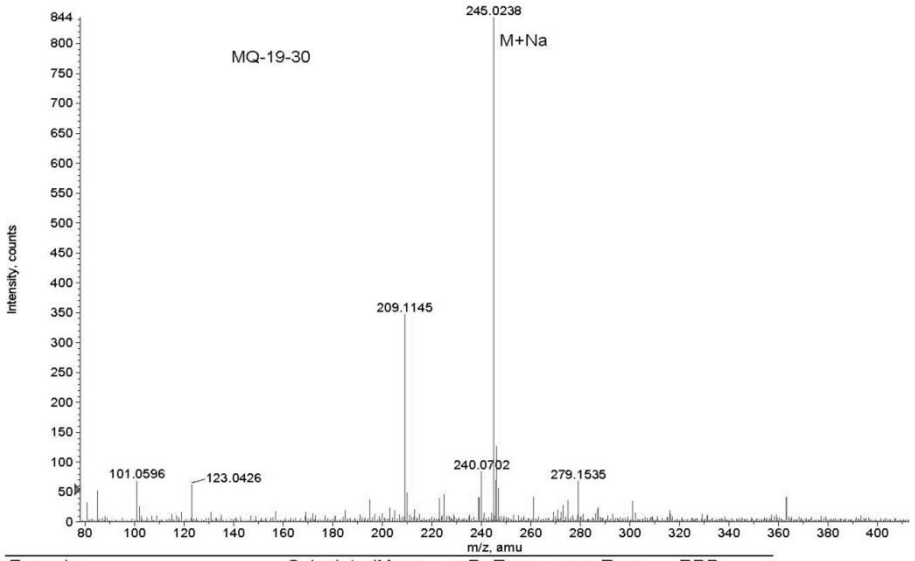

PhO2S
O
8
4.40
2.16
1.95
1.00
2.14
1.22
1.90
7.72
7.68
7.67
7.62
7.59
7.58
7.51
7.48
7.47
7.29
7.29
7.28
7.28
6.31
6.31
6.30
6.29
6.25
6.23
f1 (ppm)


PhO2S
O
8
56.08
76.74
77.38
78.02
111.37
112.41
128.64
129.27
134.15
138.29
142.52
143.97
f1 (ppm)

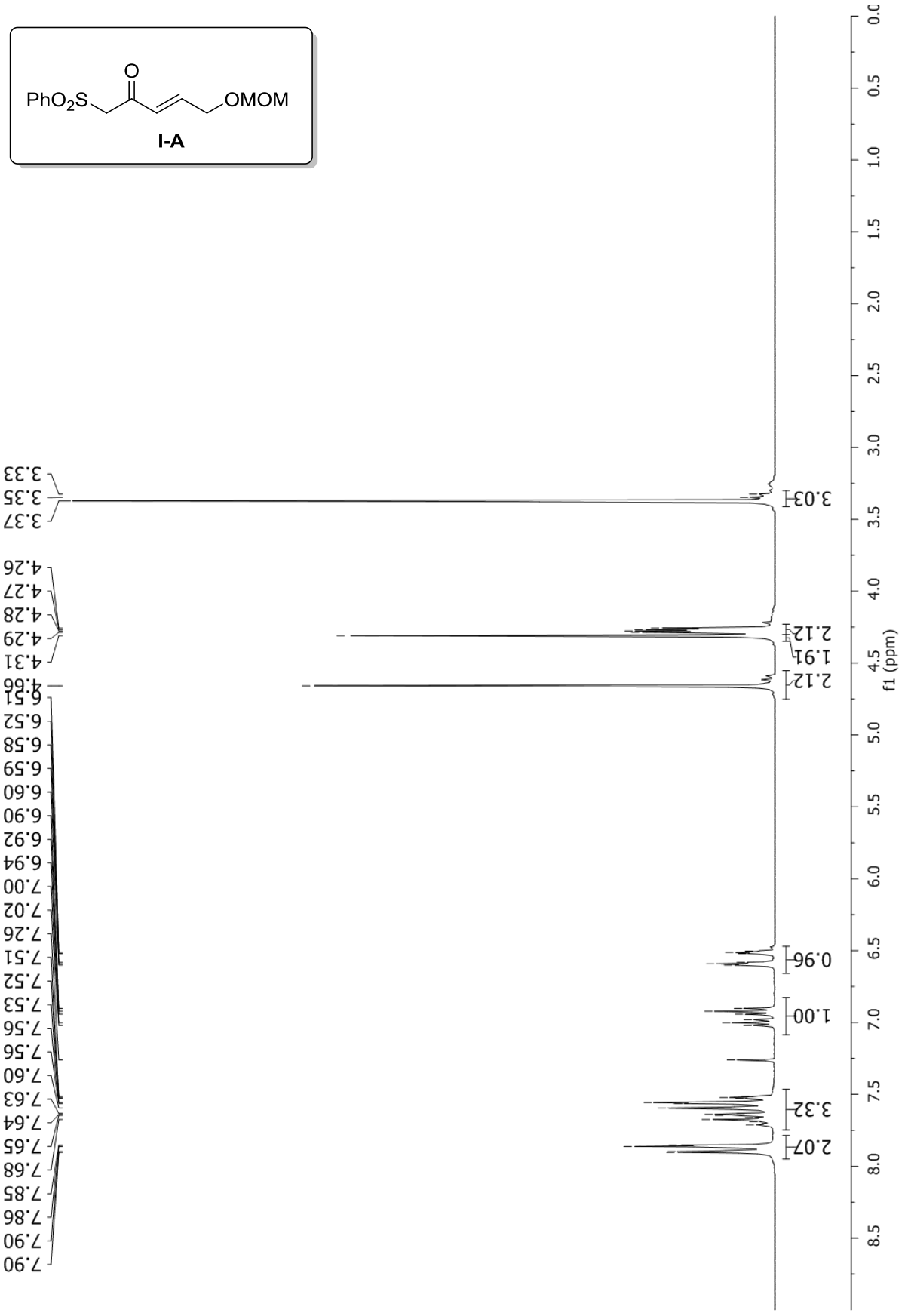


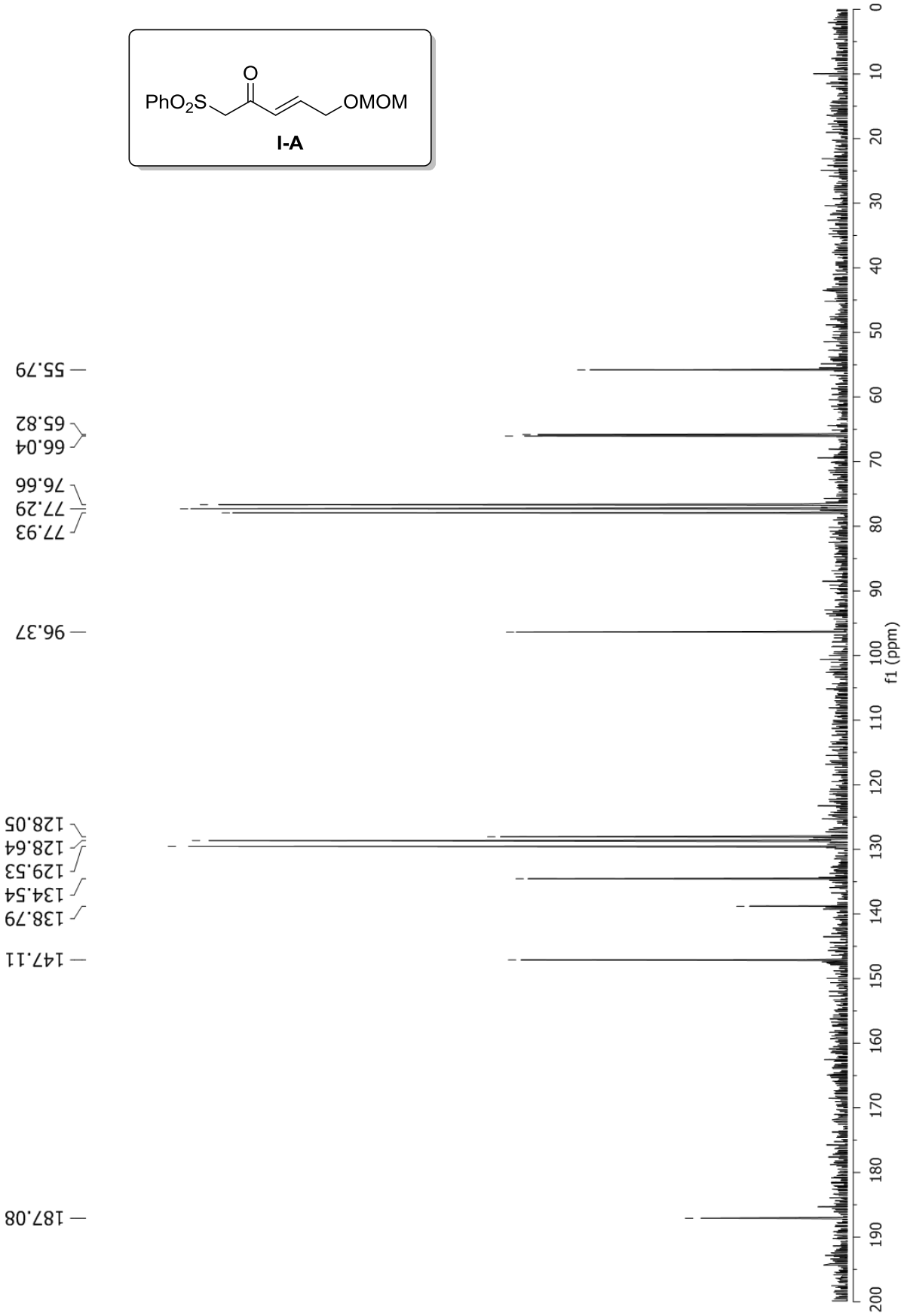


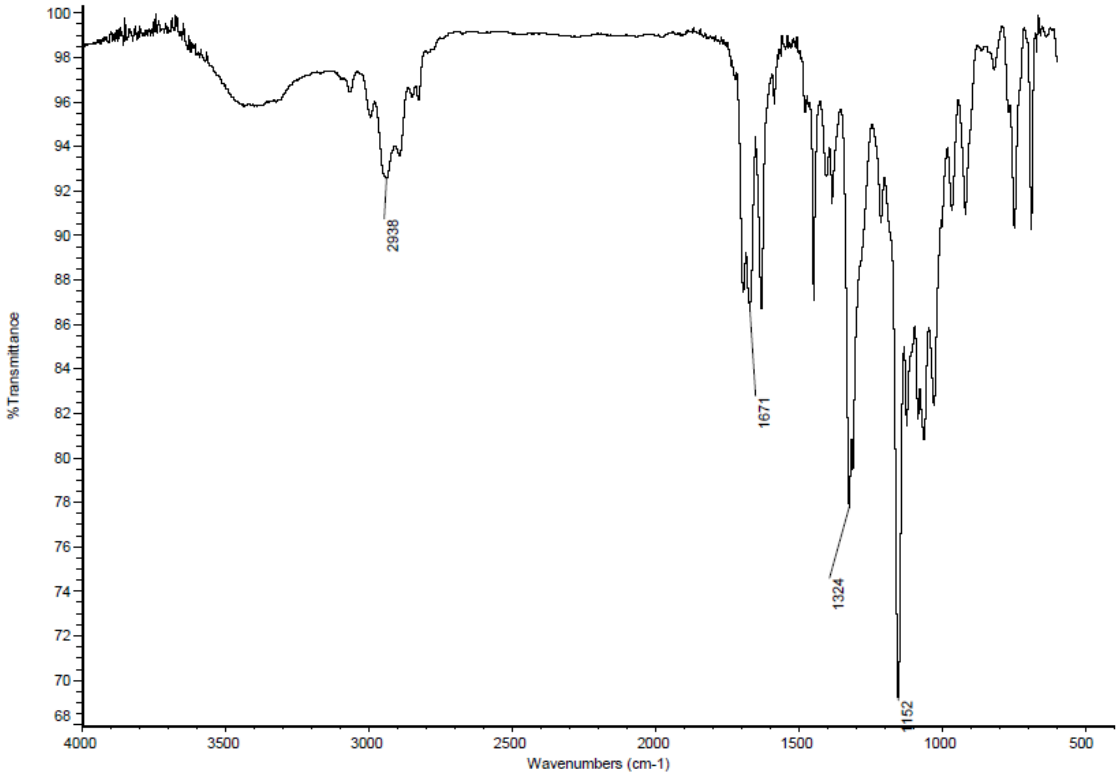
8

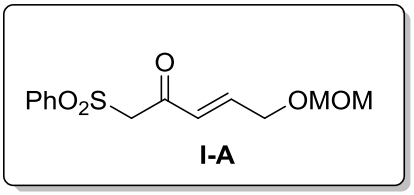


Formula	CalculatedMass	mDaError	ppmError	RDB
C9 H5 N6 O S	245.024007	-0.207108	-0.845255	10.5
C3 H6 N6 O6 Na	245.024103	-0.303248	-1.237624	3.5
C16 H5 O3	245.023321	0.47946	1.956785	14.5
C11 H10 O3 Na S	245.024287	-0.48724	-1.988537	6.5

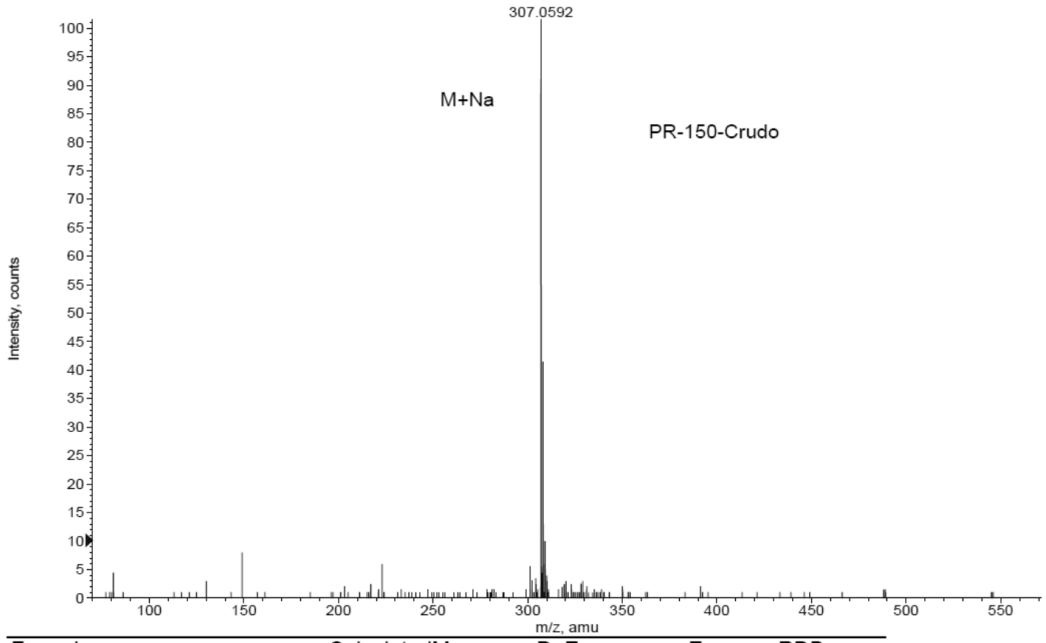

PhO2S
O
OMOM
I-A
f1 (ppm)


PhO2S
O
OMOM
I-A
55.79
65.82
66.04
76.66
77.29
77.93
96.37
128.05
128.64
129.53
134.54
138.79
147.11
187.08
f1 (ppm)

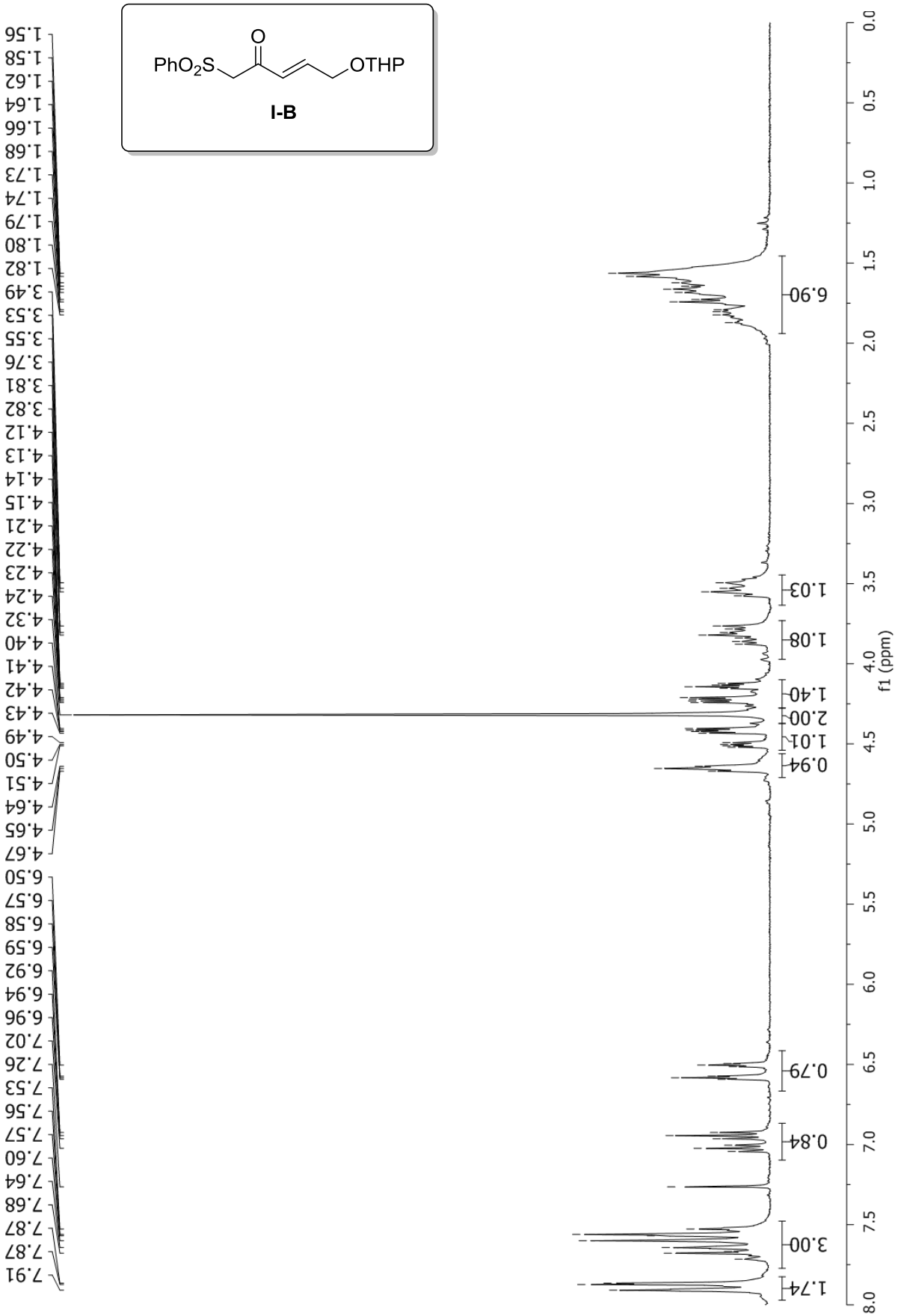


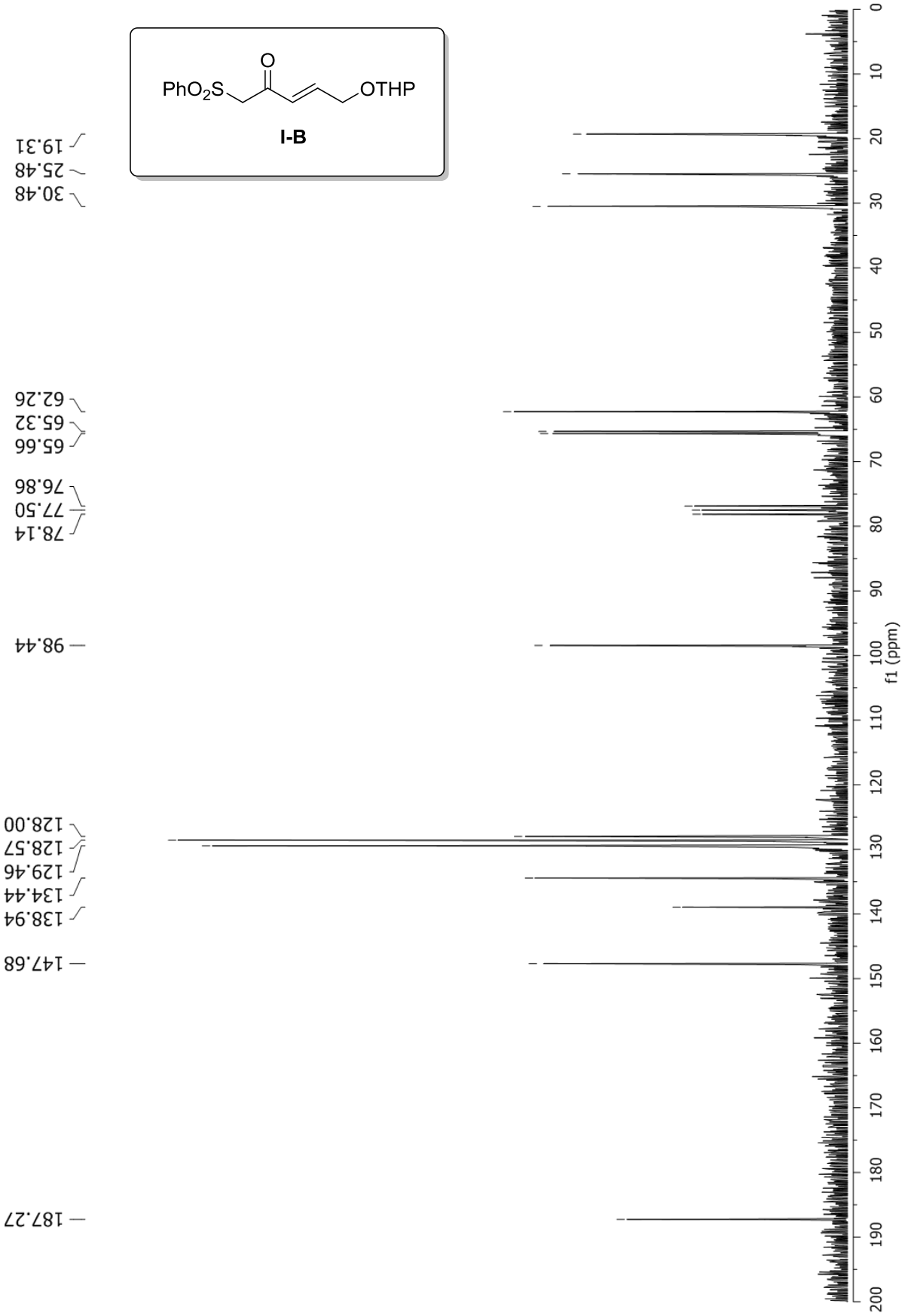


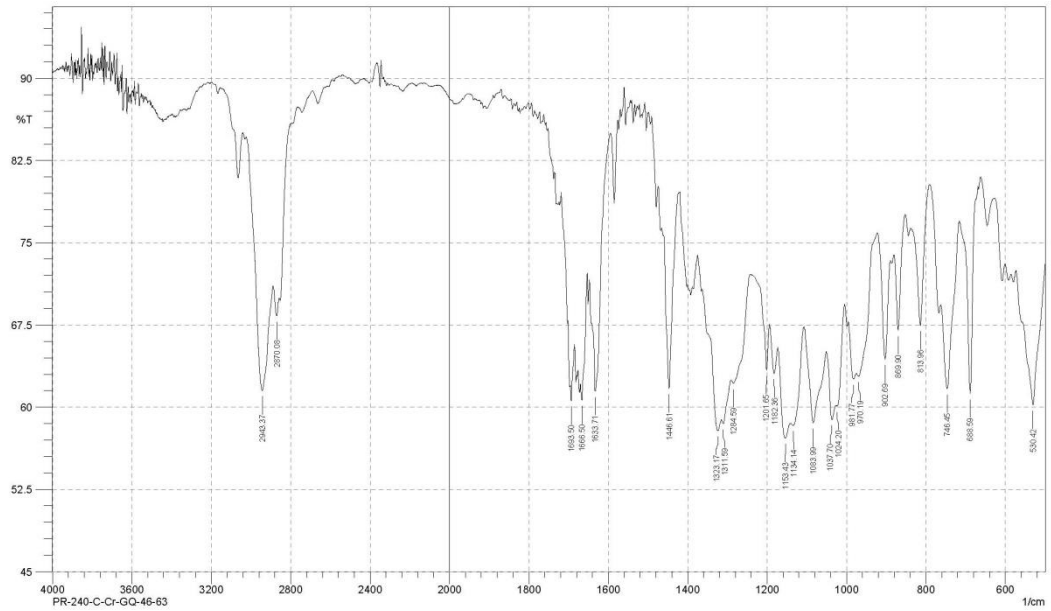
I-A



Formula	CalculatedMass	mDaError	ppmError	RDB
C10 H15 N2 O7 S	307.059449	-0.249316	-0.811946	4.5
C9 H12 N6 O3 Na S	307.058381	0.818632	2.666035	6.5
C7 H7 N12 O S	307.058101	1.098764	3.578339	10.5
C11 H11 N6 O3 S	307.060787	-1.586628	-5.167164	9.5
C22 H11 S	307.057599	1.60134	5.215076	17.5
C13 H16 O5 Na S	307.061067	-1.86676	-6.079468	5.5


PhO2S
O
OTHP
I-B
f1 (ppm)


PhO2S
O
OTHP
I-B
19.31
25.48
30.48
62.26
65.32
65.66
76.86
77.50
78.14
98.44
128.00
128.57
129.46
134.44
138.94
147.68
187.27
f1 (ppm)



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PR-240-C-Cr-GQ-46-63

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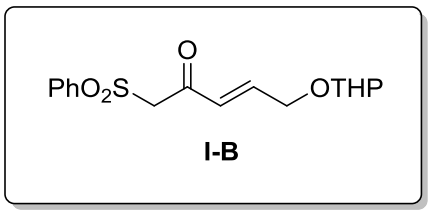
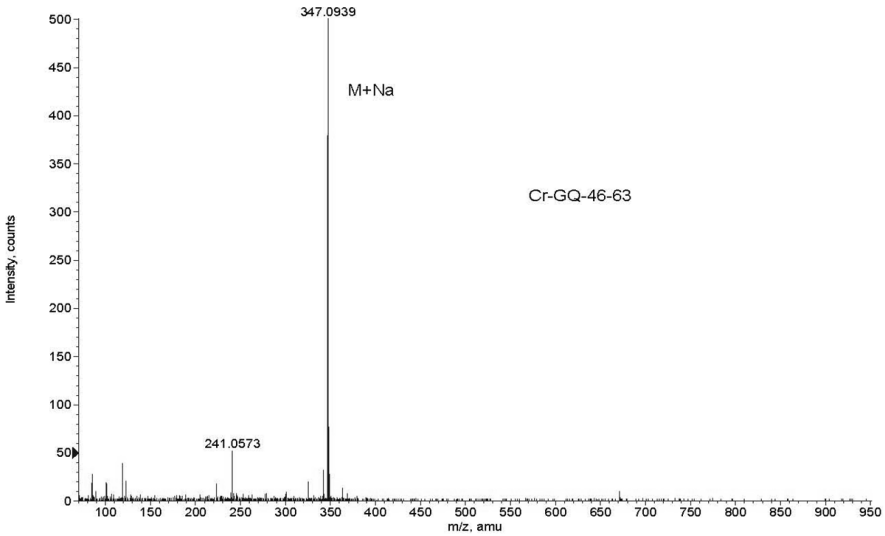
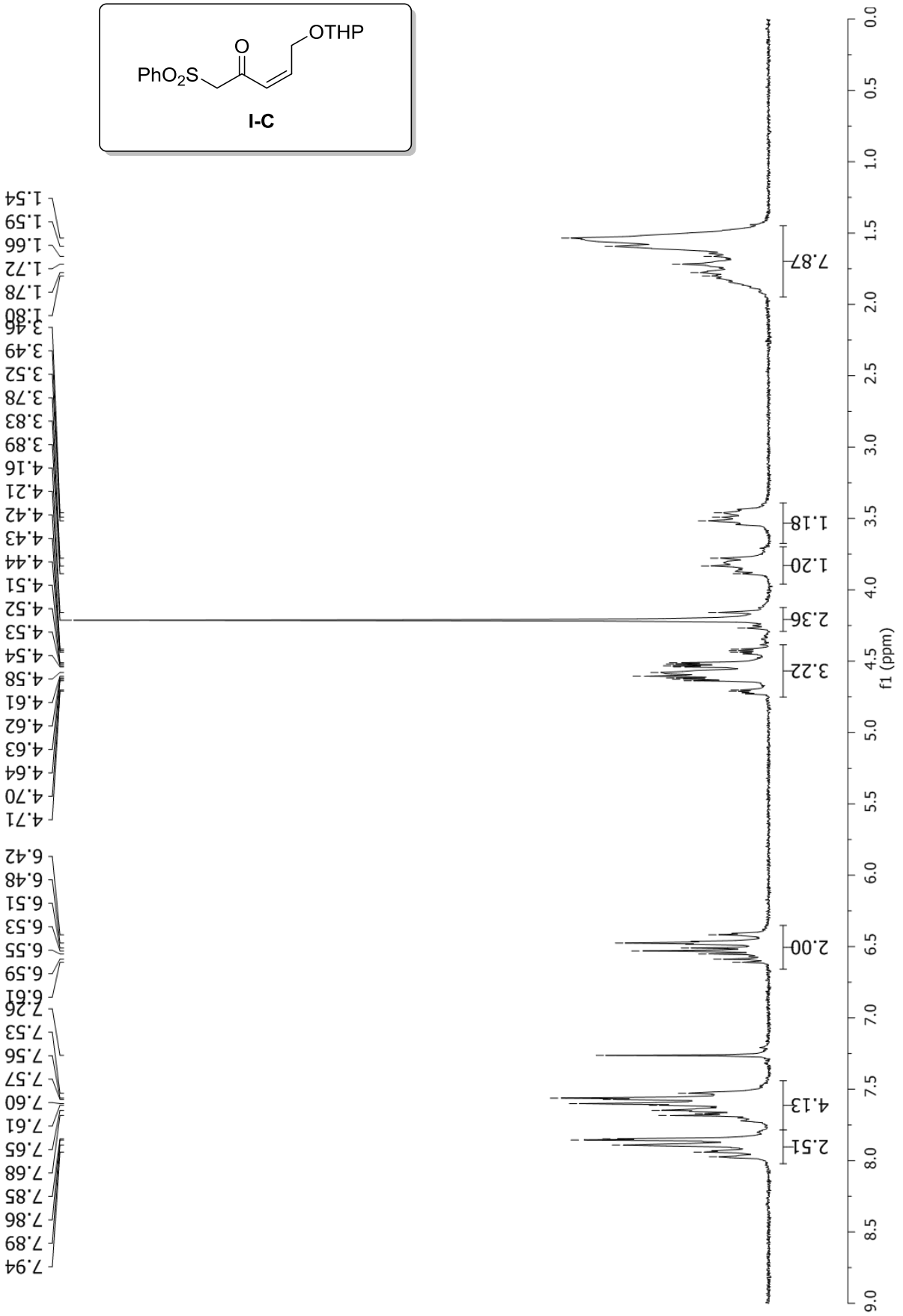
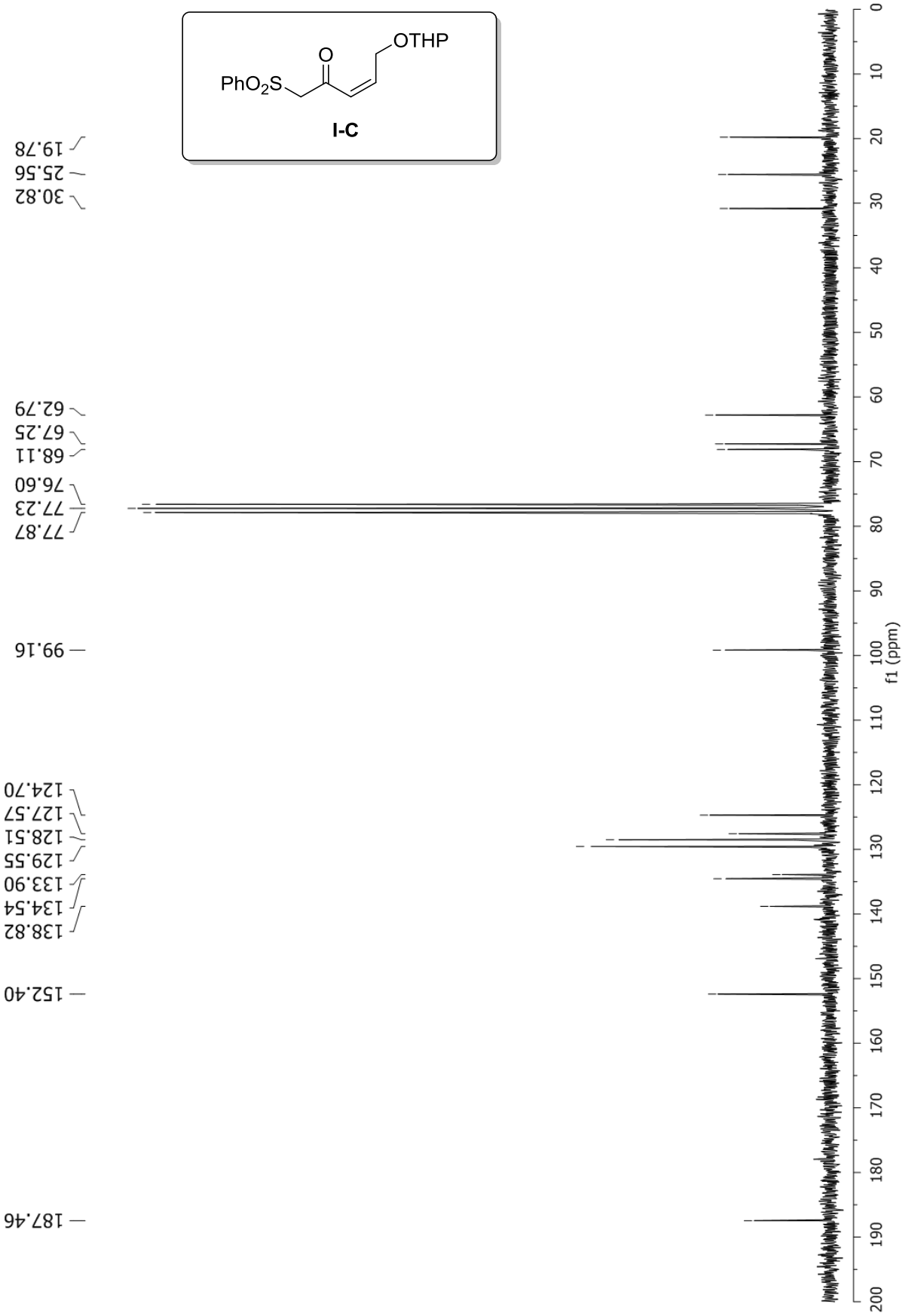


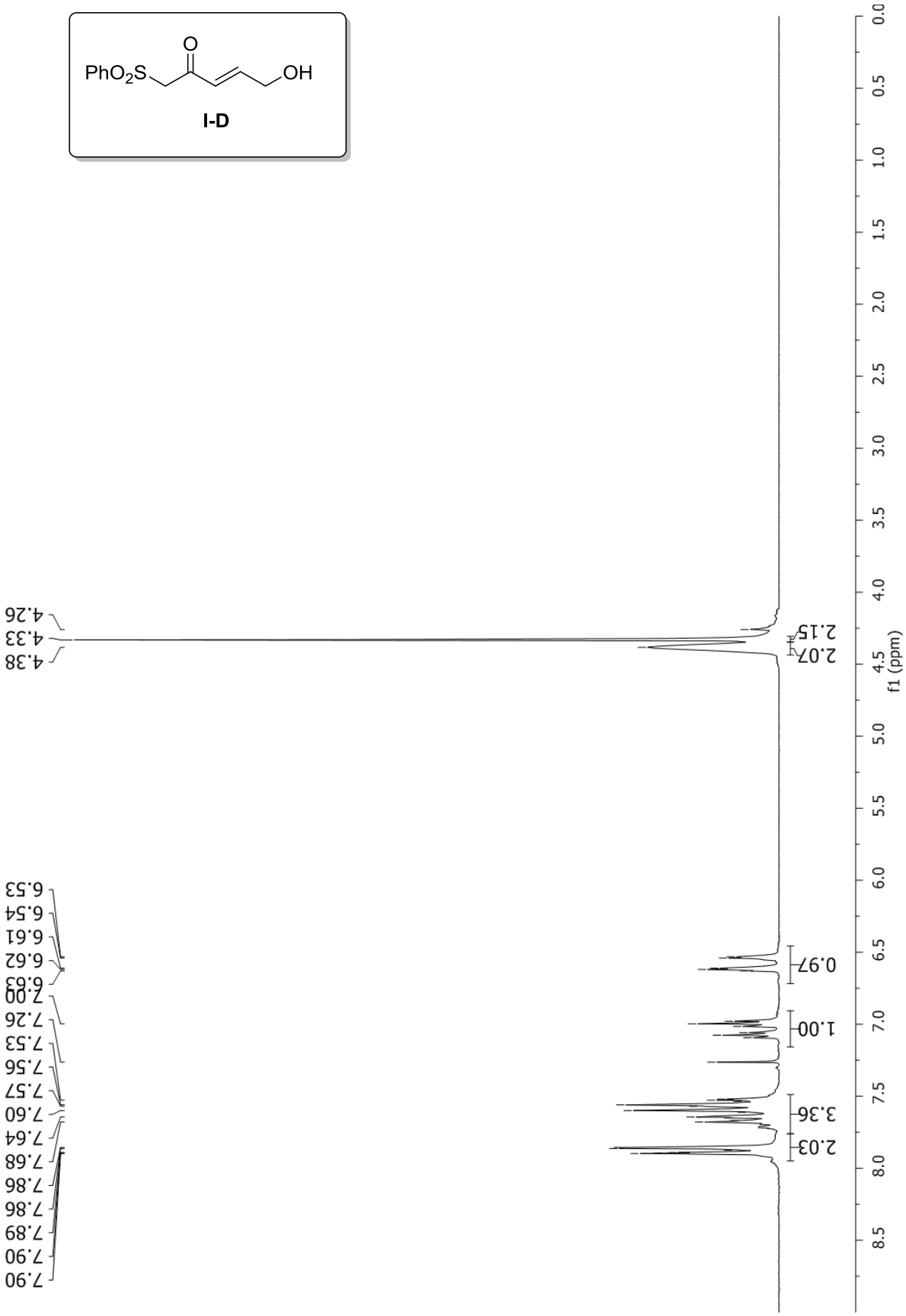
I-B

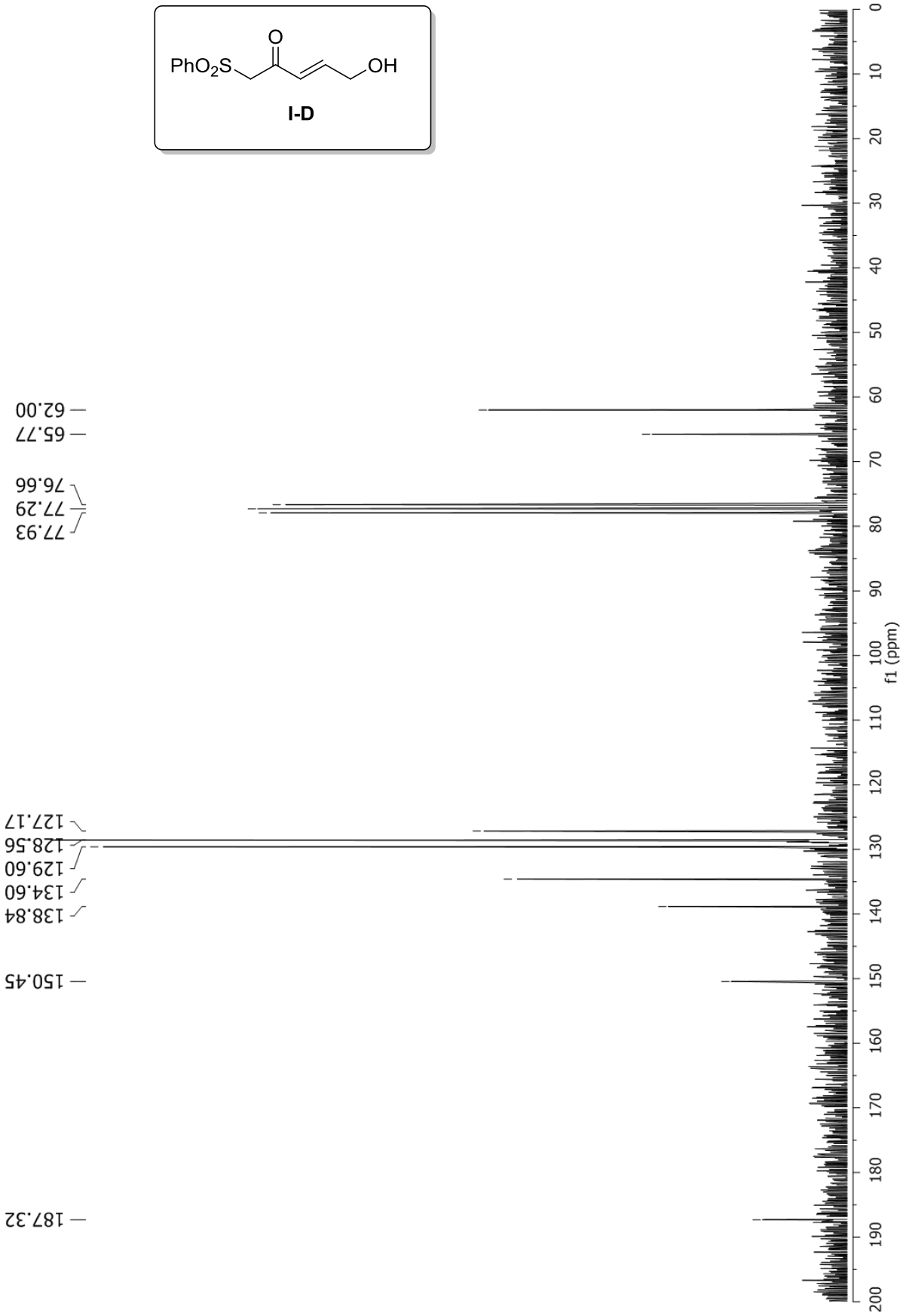


Formula	CalculatedMass	mDaError	ppmError	RDB
C17 H16 N4 O Na S	347.093704	0.195768	0.564019	11.5
C9 H12 N10 O4 Na	347.09352	0.37976	1.094111	8.5
C9 H19 N2 O12	347.093251	0.649124	1.870165	1.5
C10 H15 N6 O8	347.094588	-0.688188	-1.982711	6.5
C18 H19 O5 S	347.094772	-0.87218	-2.512803	9.5
C10 H8 N14 Na	347.094858	-0.957552	-2.758765	13.5
C12 H20 O10 Na	347.094868	-0.96832	-2.789788	2.5
C H16 N12 O6 Na S	347.092869	1.030504	2.968944	-0.5
C22 H11 N4 O	347.092738	1.162468	3.34914	19.5
C3 H15 N12 O6 S	347.095275	-1.374756	-3.960755	2.5
C16 H20 O5 Na S	347.092367	1.53308	4.416896	6.5


OTHP
O
PhO2S
I-C
f1 (ppm)


OTHP
O
PhO2S
I-C
19.78
25.56
30.82
62.79
67.25
68.11
76.60
77.23
77.87
99.16
124.70
127.57
128.51
129.55
133.90
134.54
138.82
152.40
187.46
f1 (ppm)


O
PhO2S
OH
I-D
4.26
4.33
4.38
2.15
2.07
6.53
6.54
6.61
6.62
6.63
7.00
7.26
7.53
7.56
7.57
7.60
7.64
7.68
7.86
7.86
7.89
7.90
7.90
0.97
1.00
3.36
2.03
f1 (ppm)


O
PhO2S
OH
I-D
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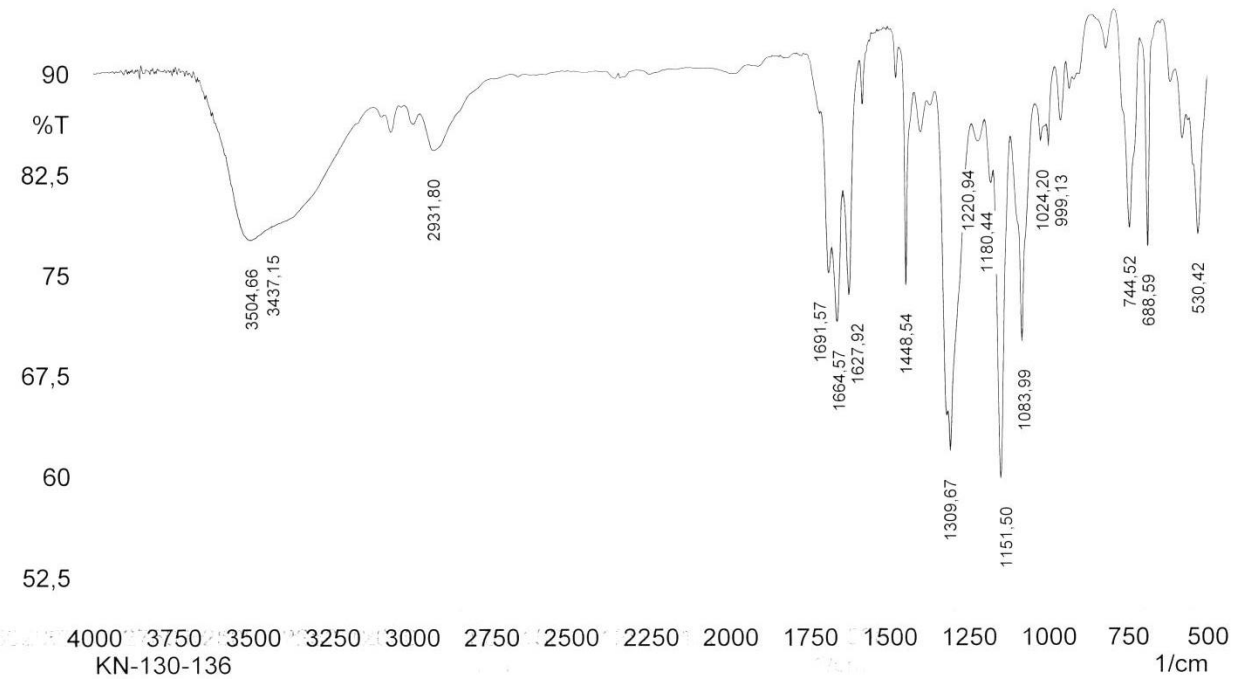
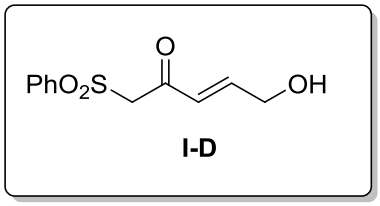
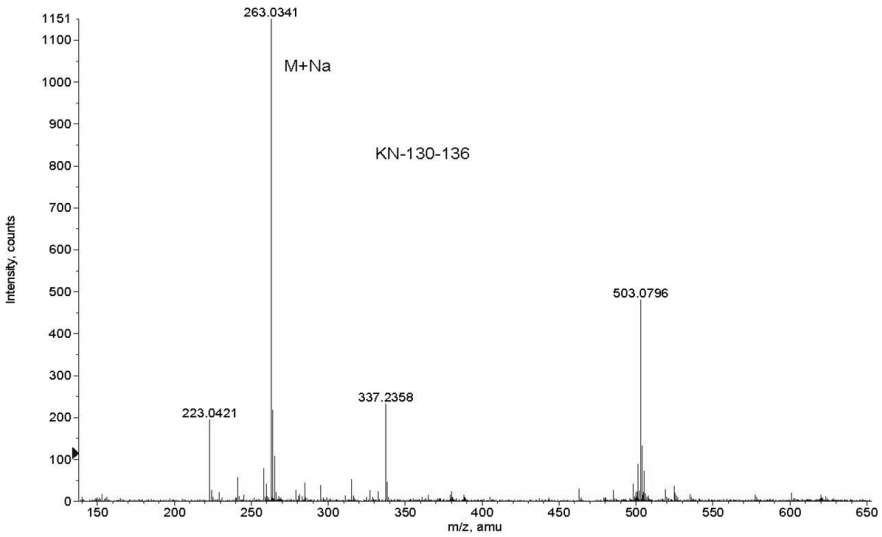
127.17
128.56
129.60
134.60
138.84
150.45
187.32
f1 (ppm)

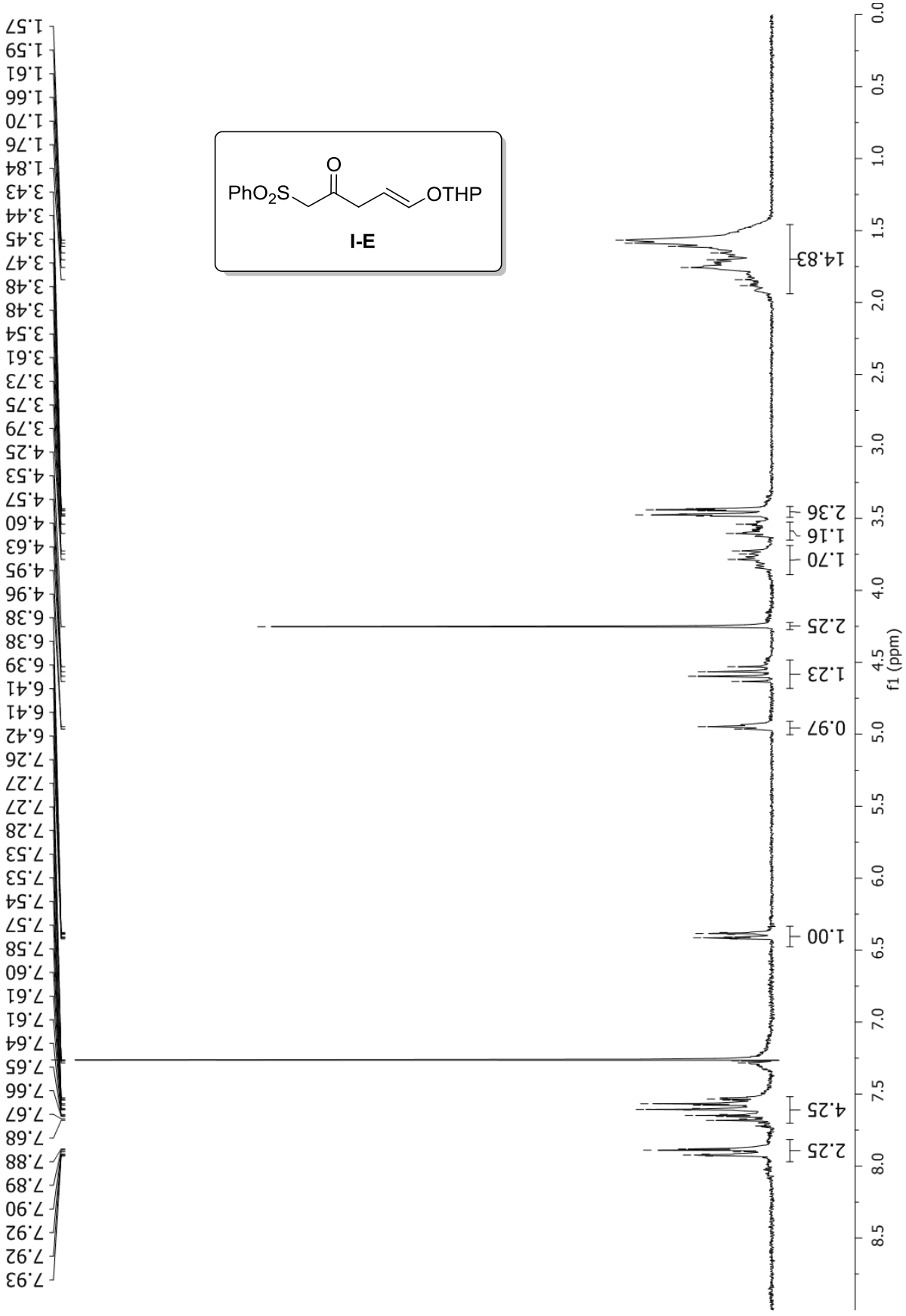


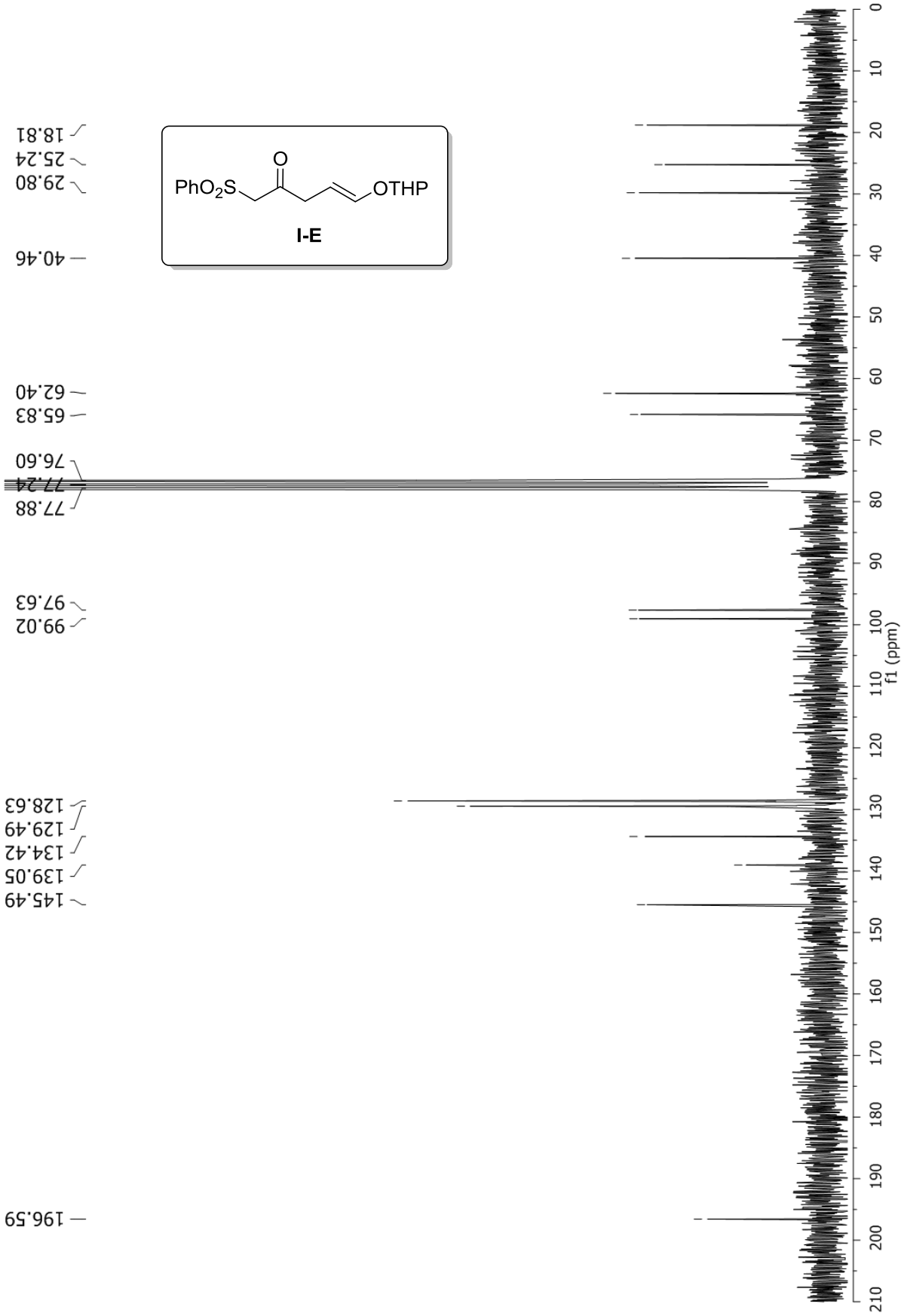


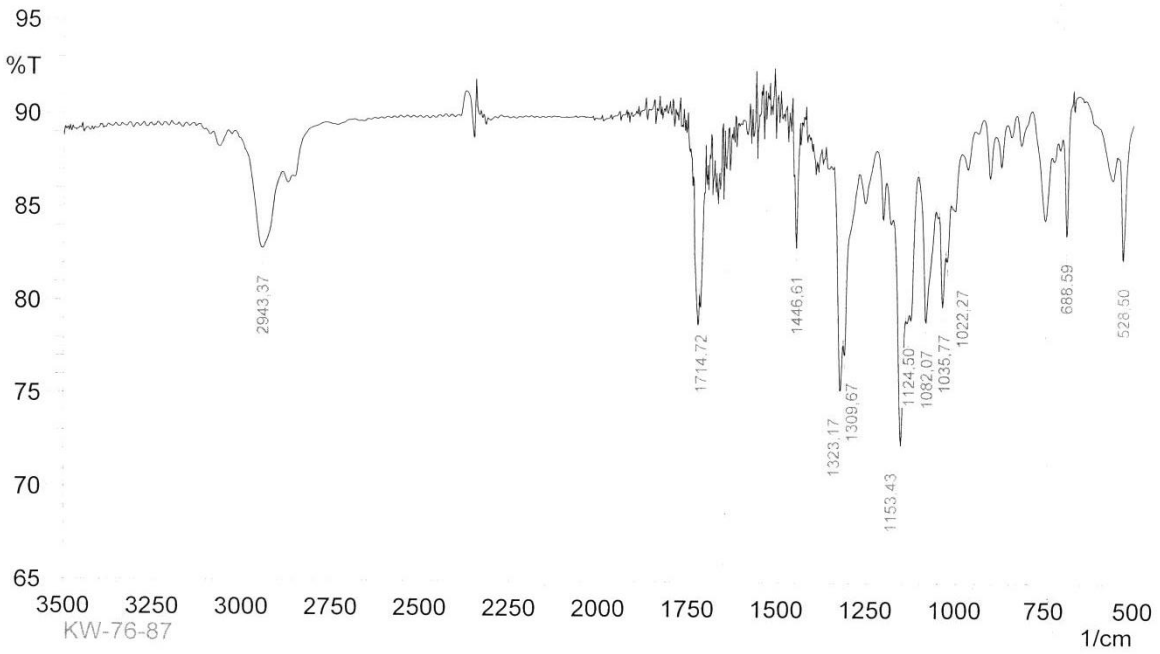
I-D

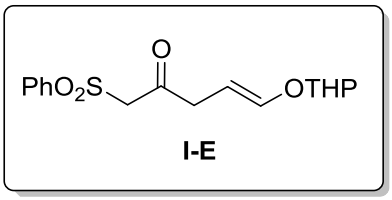


Formula	CalculatedMass	mDaError	ppmError	RDB
C9 H7 N6 O2 S	263.034572	-0.471828	-1.793786	9.5
C11 H12 O4 Na S	263.034852	-0.75196	-2.858787	5.5
C8 H11 N2 O6 S	263.033235	0.865484	3.29038	4.5
C7 H8 N6 O2 Na S	263.032167	1.933432	7.350484	6.5
C12 H8 N4 Na S	263.036189	-2.089272	-7.942954	10.5

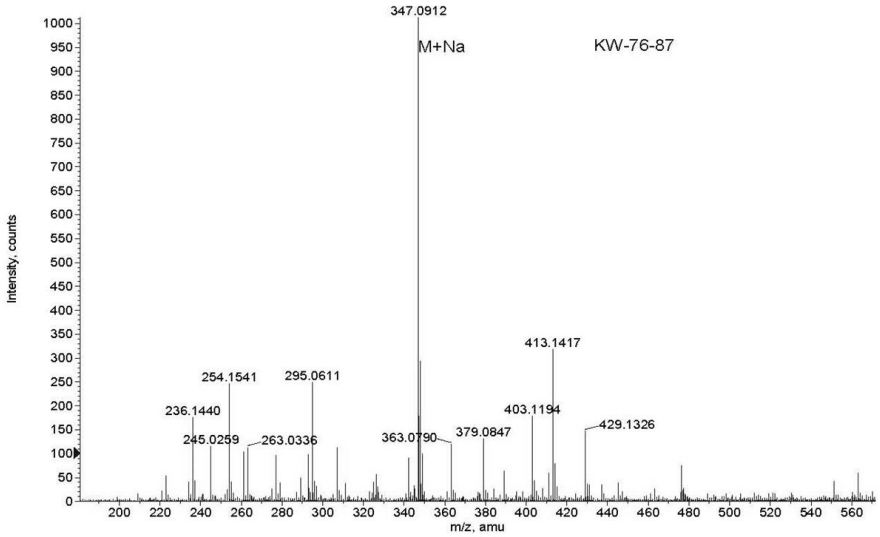

PhO2S
O
OTHP
I-E
14.83
2.36
1.16
1.70
2.25
1.23
0.97
1.00
4.25
2.25
f1 (ppm)


PhO2S
O
OTHP
I-E
18.81
25.24
29.80
40.46
62.40
65.83
76.60
77.24
77.88
97.63
99.02
128.63
129.49
134.42
139.05
145.49
196.59
f1 (ppm)

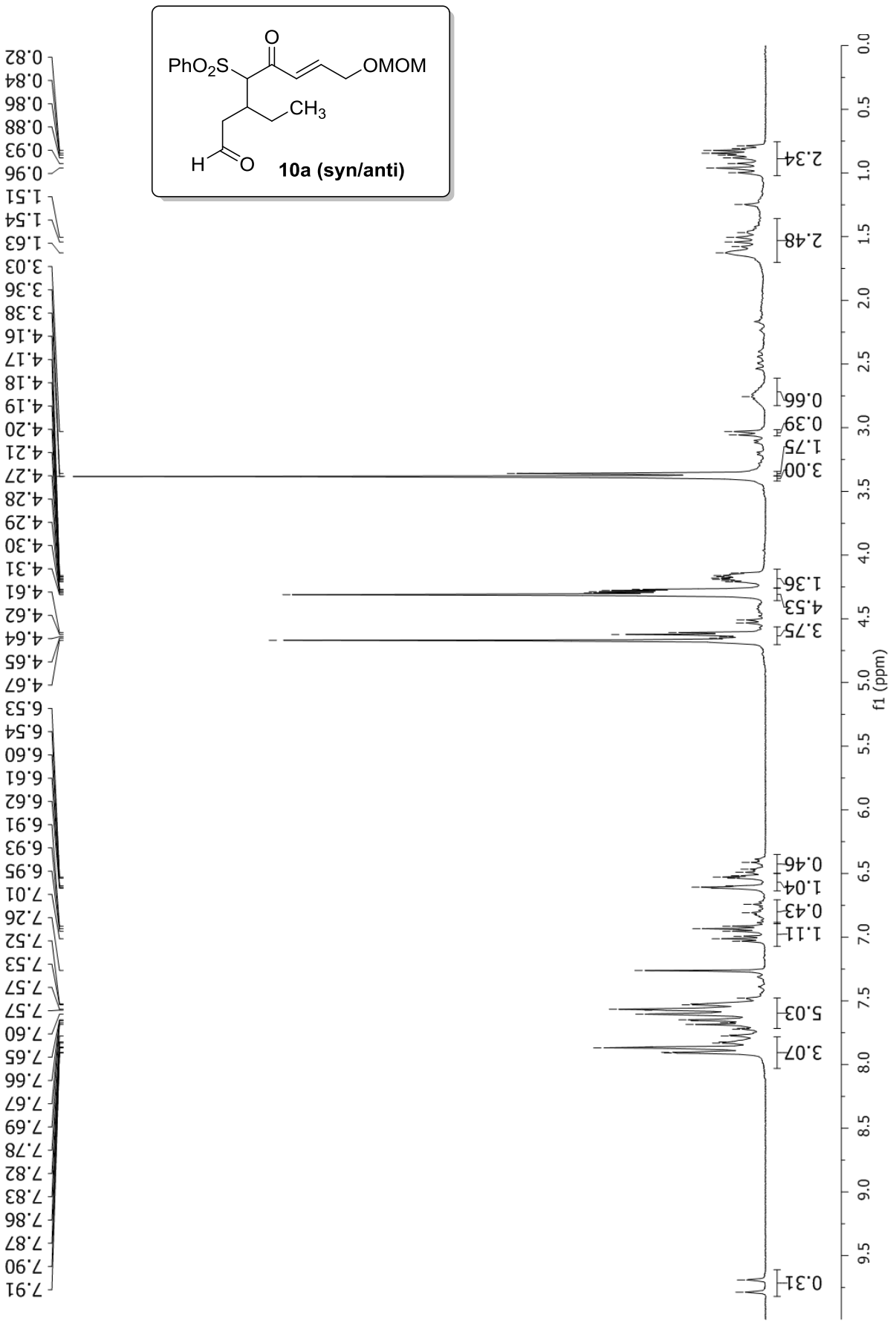


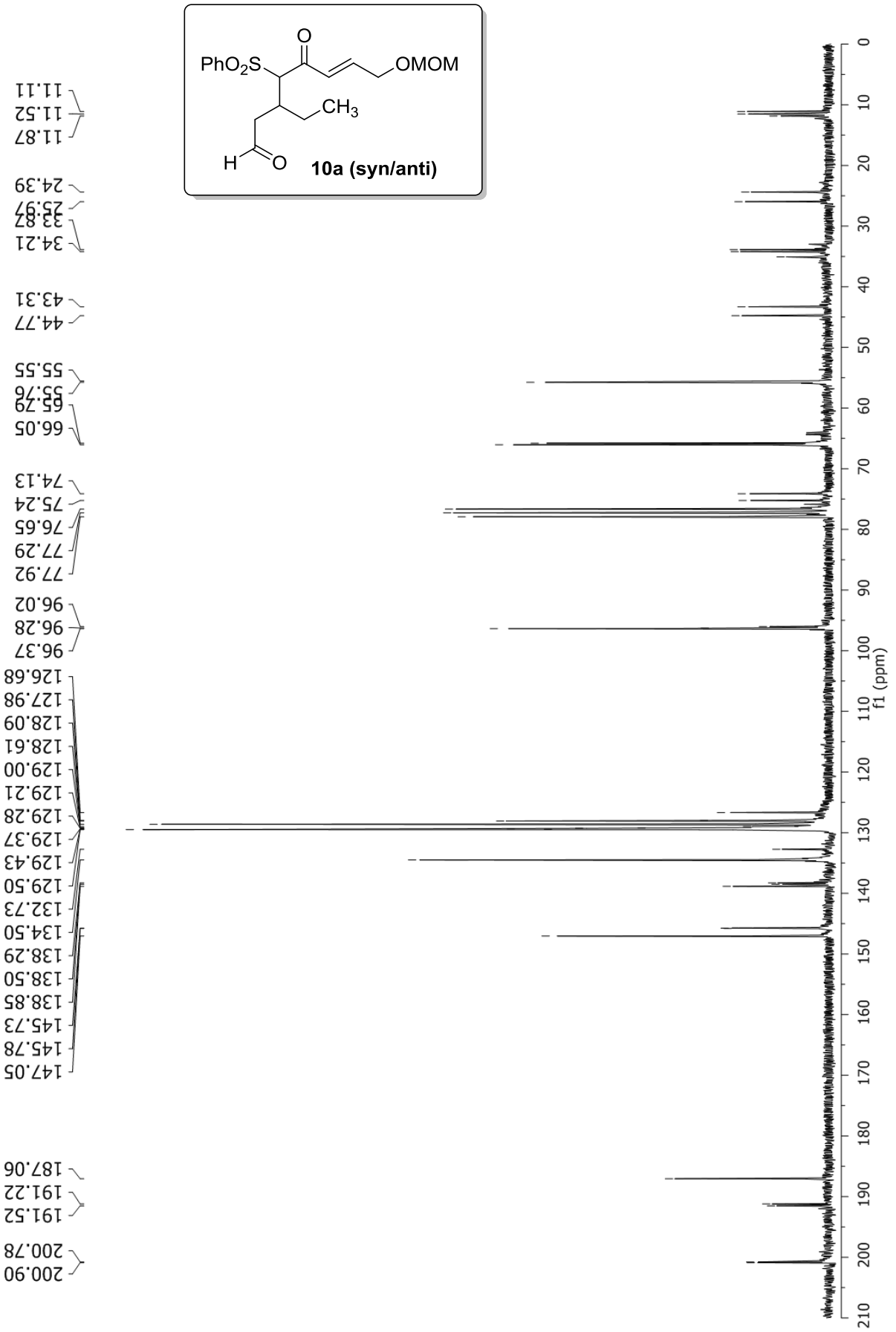


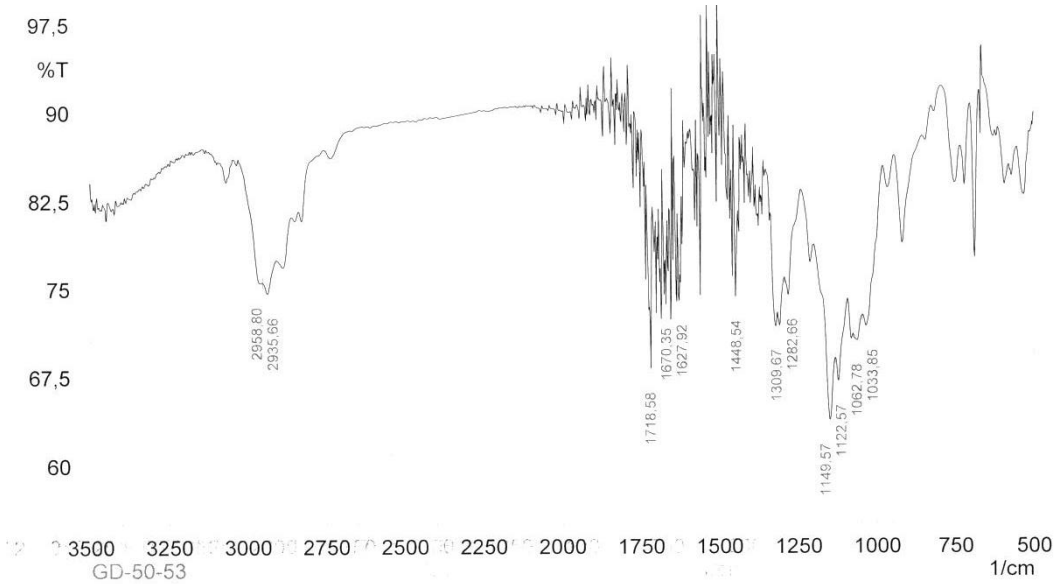
I-E

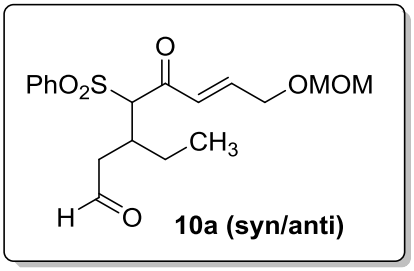


Formula	CalculatedMass	mDaError	ppmError	RDB
C21 H15 O5	347.0914	-0.20022	-0.57685	14.5
C13 H19 N2 O7 S	347.090749	0.450524	1.297997	5.5
C16 H20 O5 Na S	347.092367	-1.16692	-3.361993	6.5
C19 H16 O5 Na	347.088995	2.20504	6.352902	11.5
C25 H15 S	347.088899	2.30118	6.62989	18.5
C11 H20 N2 O7 Na S	347.088344	2.855784	8.22775	2.5

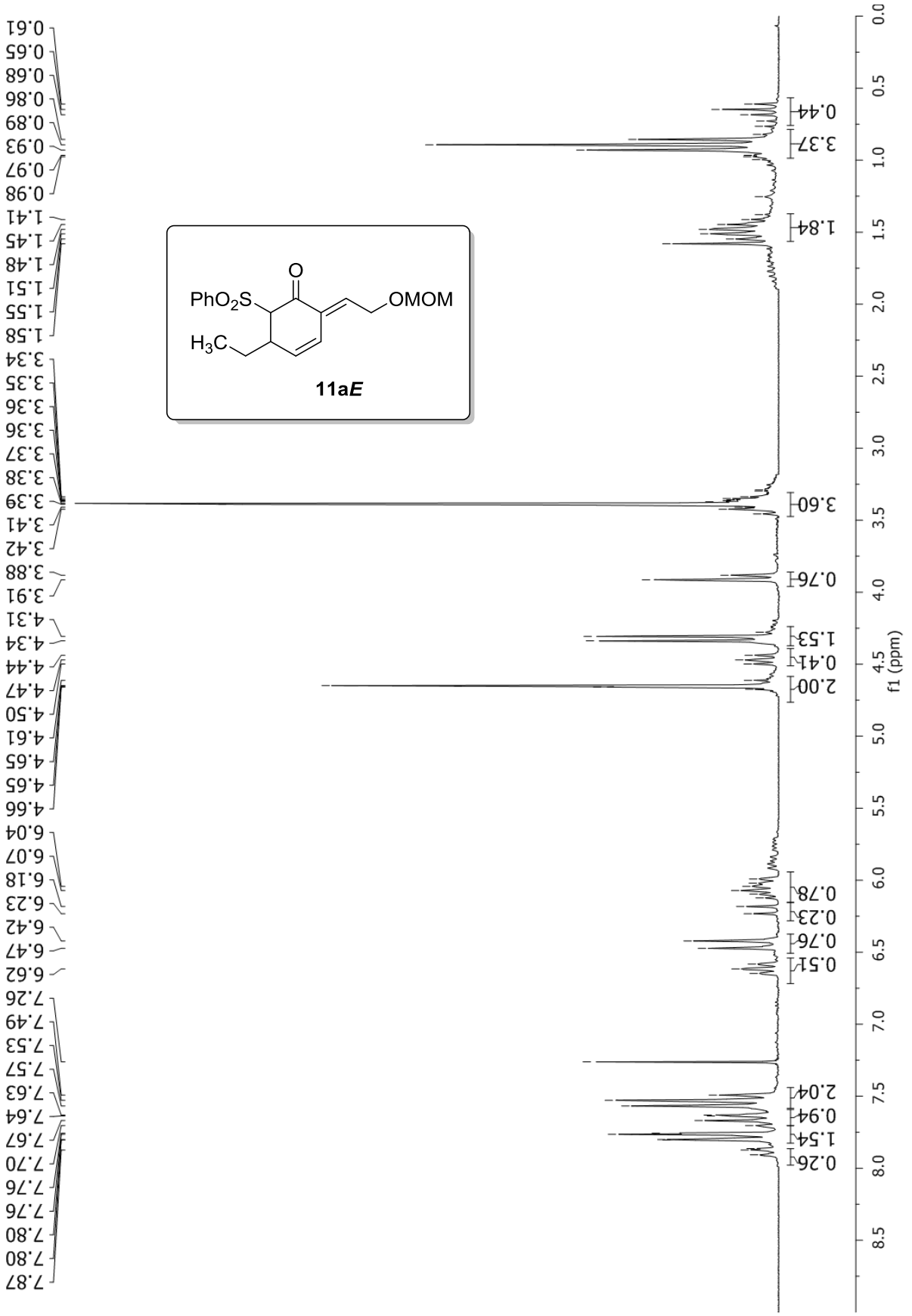

PhO2S
O
OMOM
CH3
H
O
10a (syn/anti)
f1 (ppm)

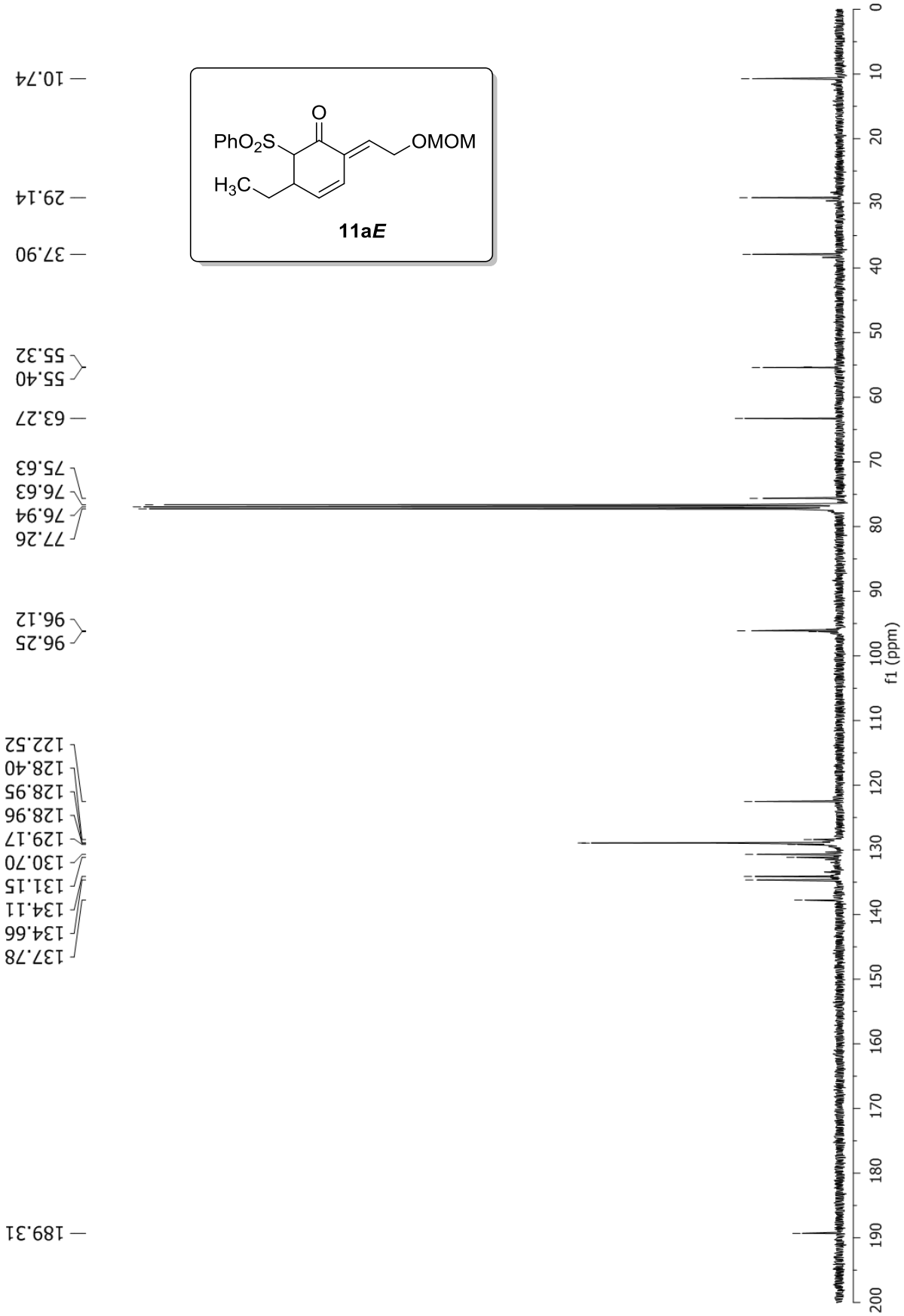

PhO2S
O
OMOM
CH3
H
O
10a (syn/anti)
11.11
11.52
11.87
24.39
25.97
33.87
34.21
43.31
44.77
55.55
55.76
65.29
66.05
74.13
75.24
76.65
77.29
77.92
96.02
96.28
96.37
126.68
127.98
128.09
128.61
129.00
129.21
129.28
129.37
129.43
129.50
132.73
134.50
138.29
138.50
138.85
145.73
145.78
147.05
187.06
191.22
191.52
200.78
200.90
f1 (ppm)


97,5
%T
90
82,5
75
67,5
60
2958,80
2935,66
1718,58
1670,35
1627,92
1448,54
1309,67
1282,66
1149,57
1122,57
1062,78
1033,85
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1/cm
GD-50-53


O
PhO2S
OMOM
CH3
H
O

10a (syn/anti)


O
PhO2S
OMOM
H3C
11aE
f1 (ppm)


O
PhO2S
OMOM
H3C
11aE
10.74
29.14
37.90
55.32
55.40
63.27
75.63
76.63
76.94
77.26
96.12
96.25
122.52
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128.96
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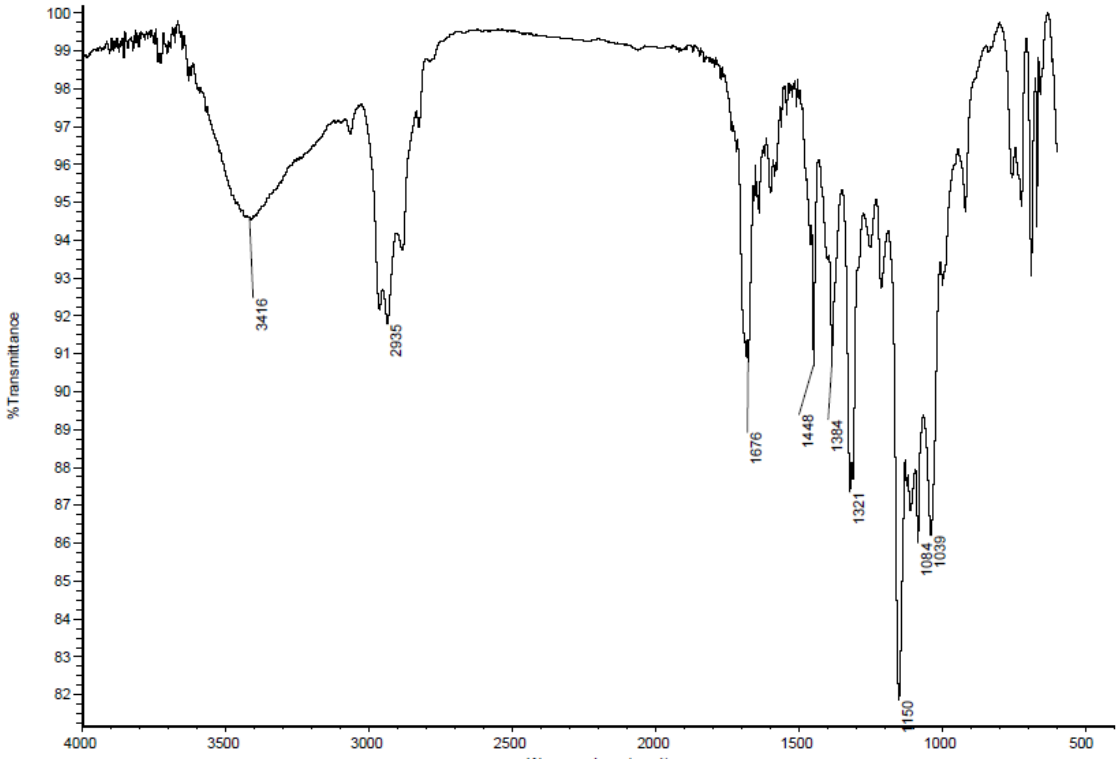
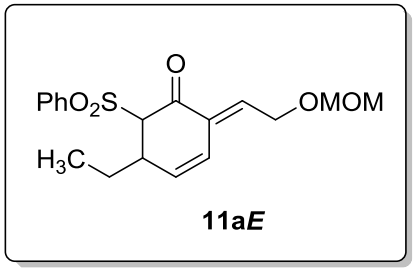
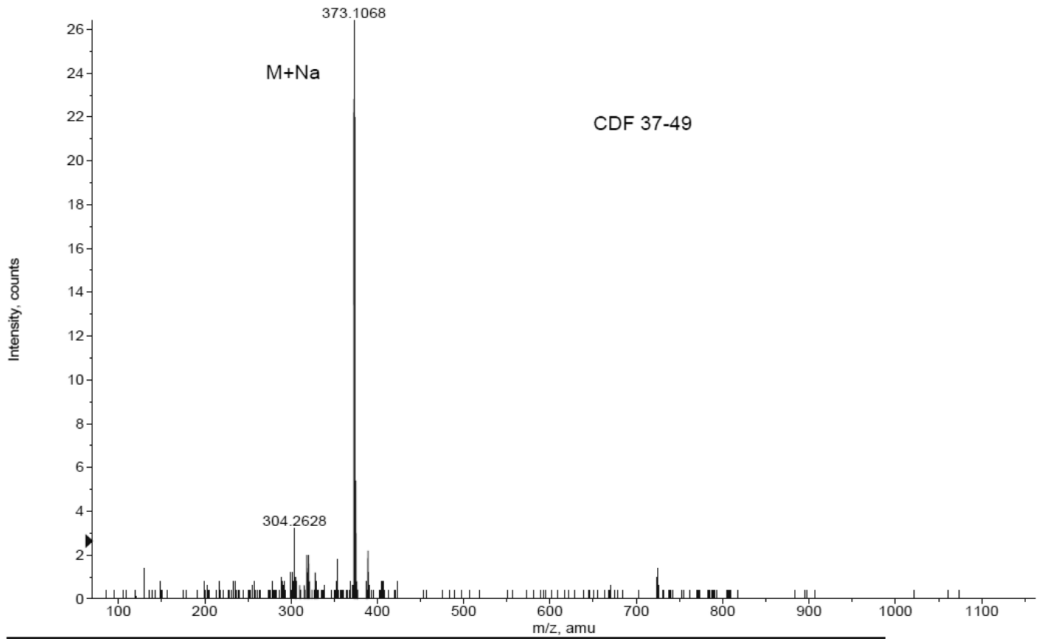
130.70
131.15
134.11
134.66
137.78
189.31
f1 (ppm)

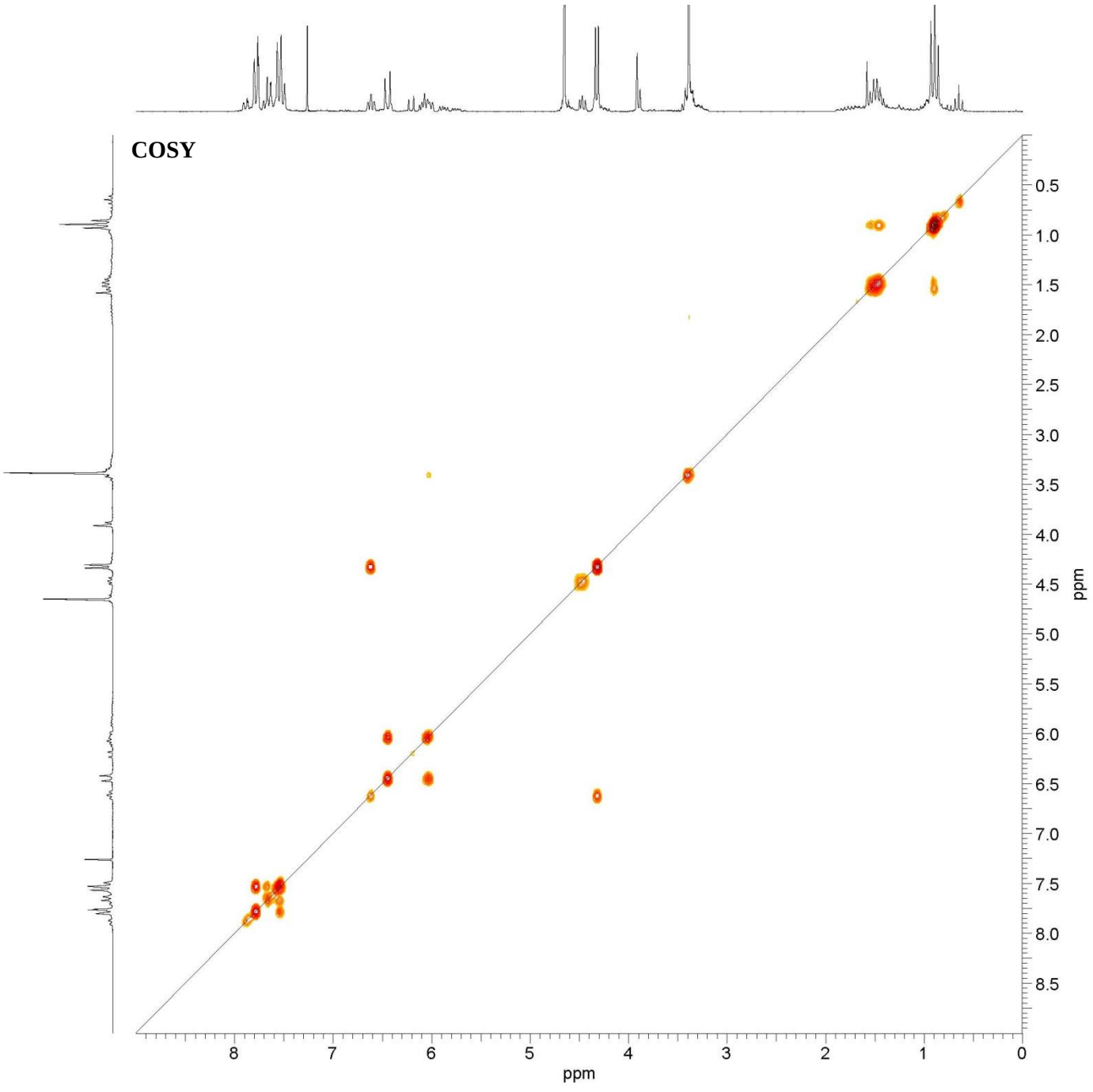


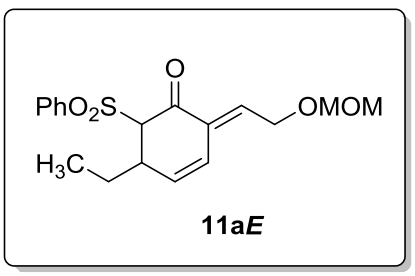


11a*E*

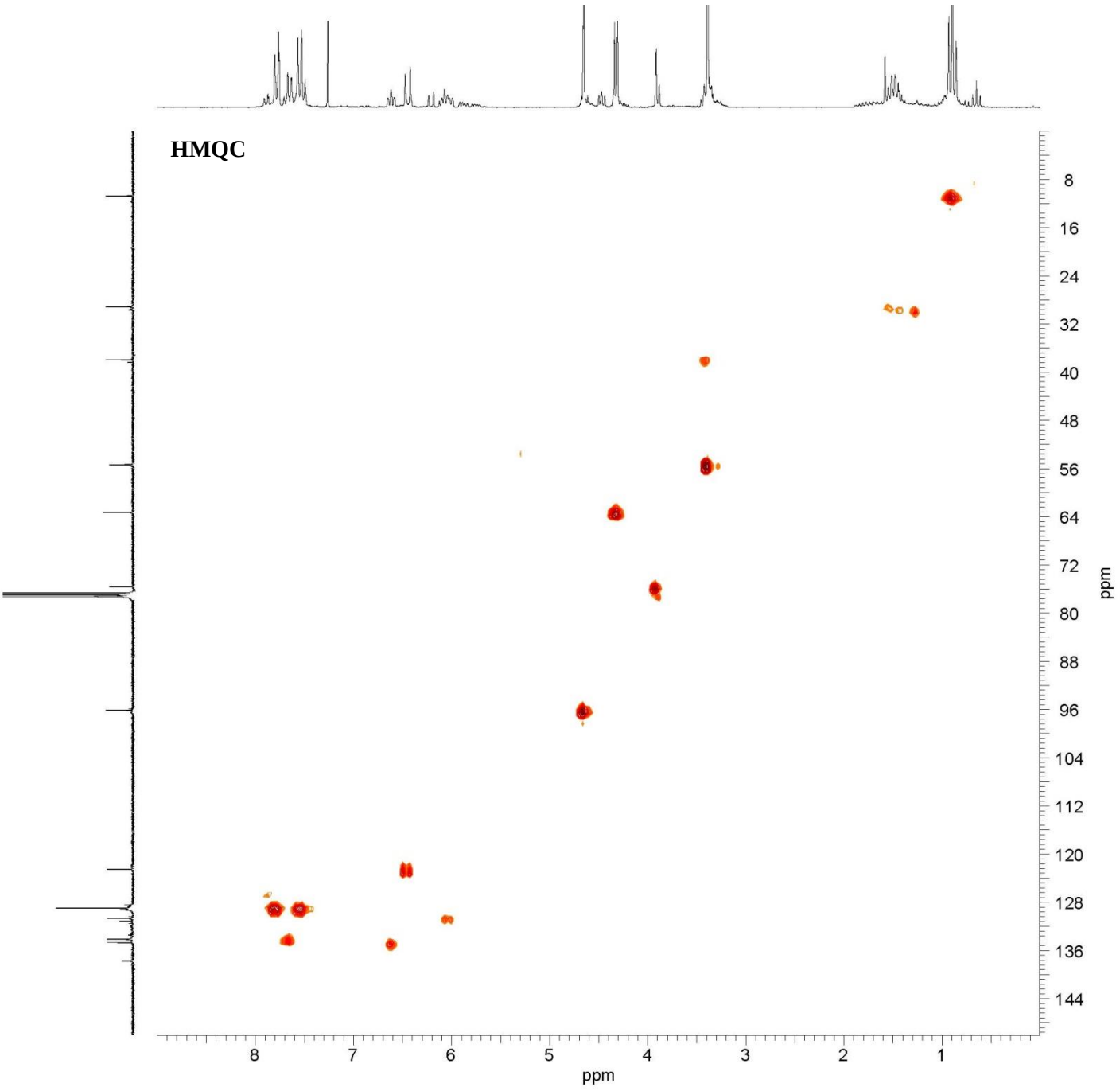


Formula	CalculatedMass	mDaError	ppmError	RDB
H17 N14 O8 S	373.106902	-0.102132	-0.273734	-0.5
C15 H21 N2 O7 S	373.1064	0.400444	1.073268	6.5
C16 H17 N6 O3 S	373.107737	-0.936868	-2.510988	11.5
C18 H22 O5 Na S	373.108017	-1.217	-3.261796	7.5





11a*E*


HMQC
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16
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104
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120
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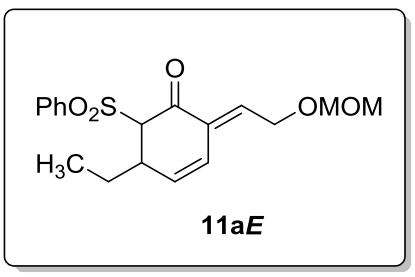
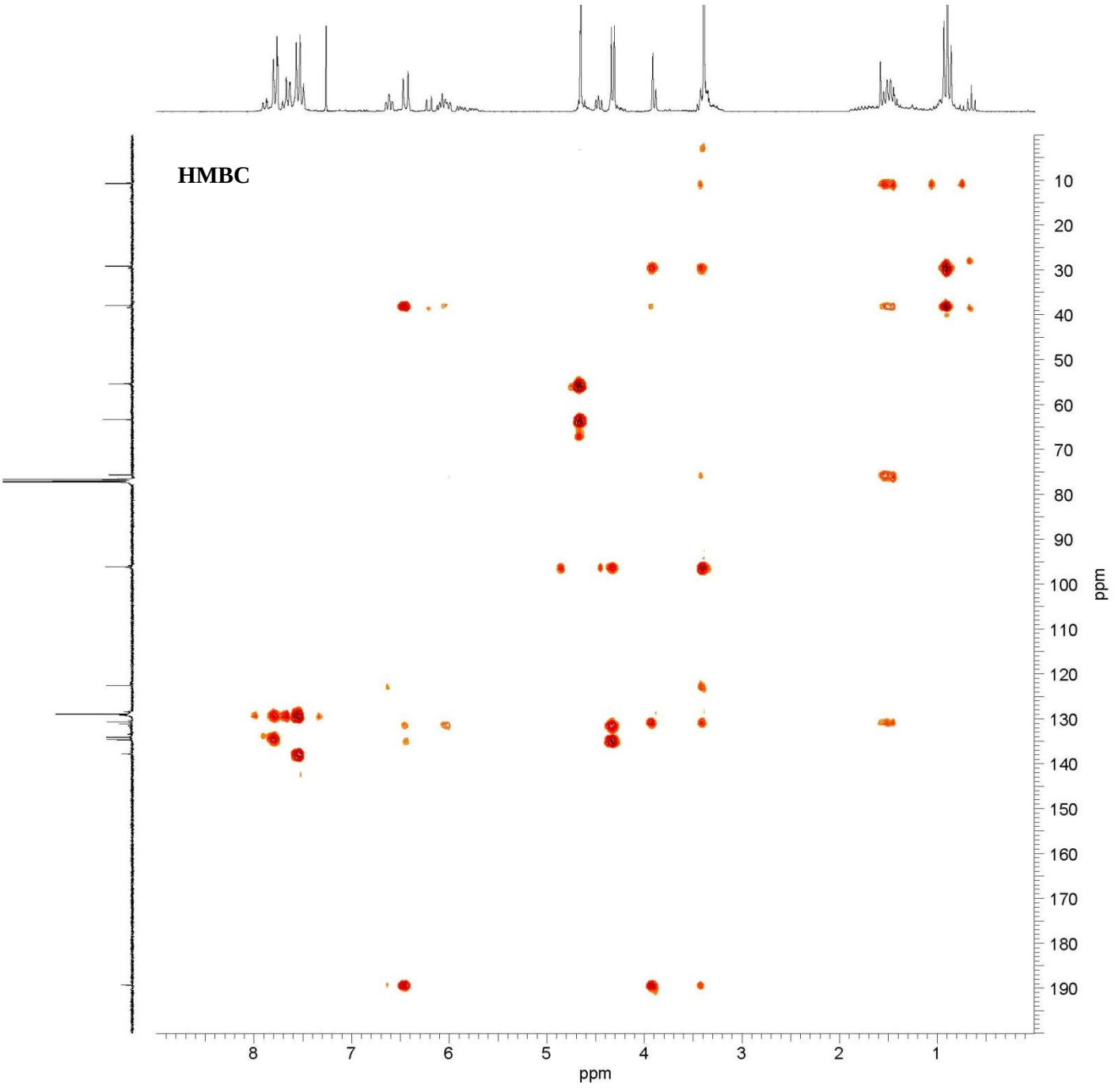
136
144
ppm
8
7
6
5
4
3
2
1
ppm


O
PhO2S
OMOM
H3C

11a*E*


HMBC
10
20
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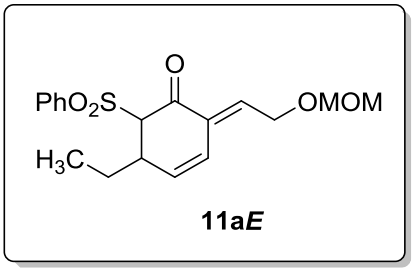
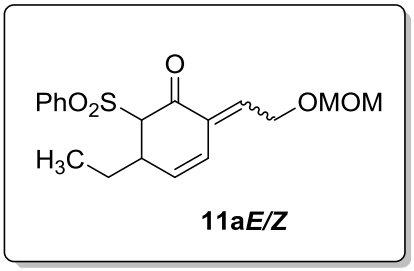
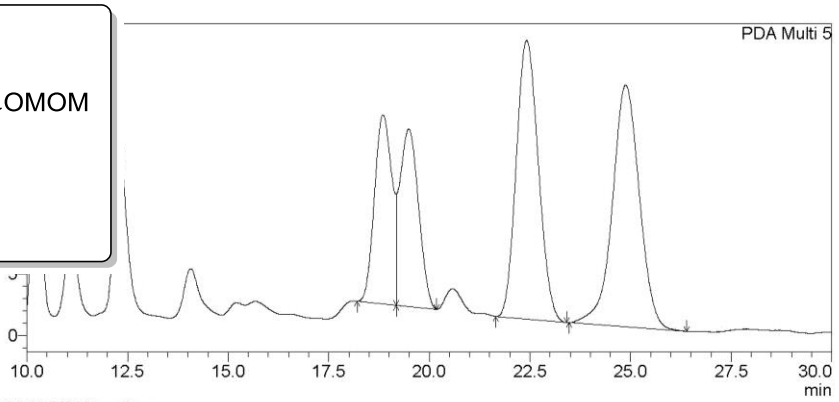
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm
8
7
6
5
4
3
2
1
ppm


O
PhO2S
OMOM
H3C

11a*E*



11a*E/Z*

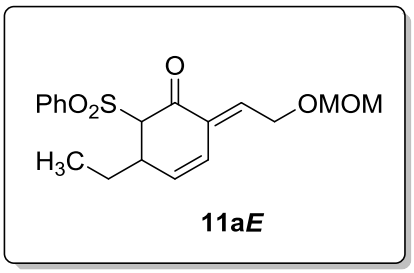


1 PDA Multi 5/218nm 4nm

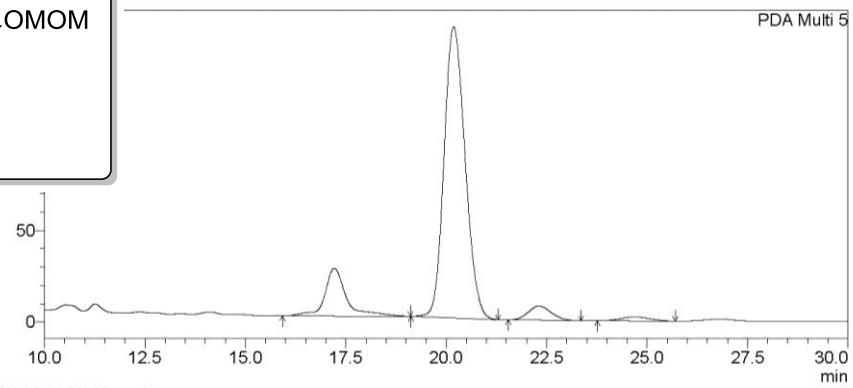
PeakTable

PDA Ch5 218nm 4nm

Peak#	Ret. Time	Area %
1	18.843	17.247
2	19.483	17.154
3	22.411	31.830
4	24.875	33.770
Total		100.000



11a*E*

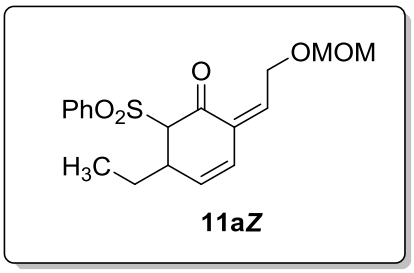


1 PDA Multi 5/218nm 4nm

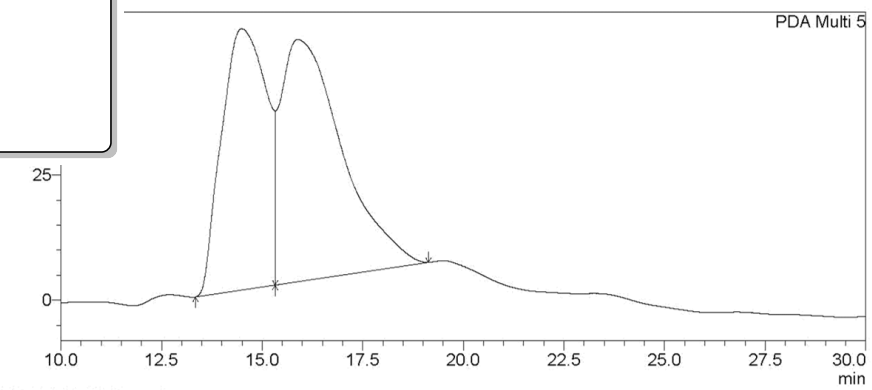
PeakTable

PDA Ch5 218nm 4nm

Peak#	Ret. Time	Area %
1	17.210	13.438
2	20.179	80.791
3	22.301	4.248
4	24.675	1.524
Total		100.000



11a*Z*

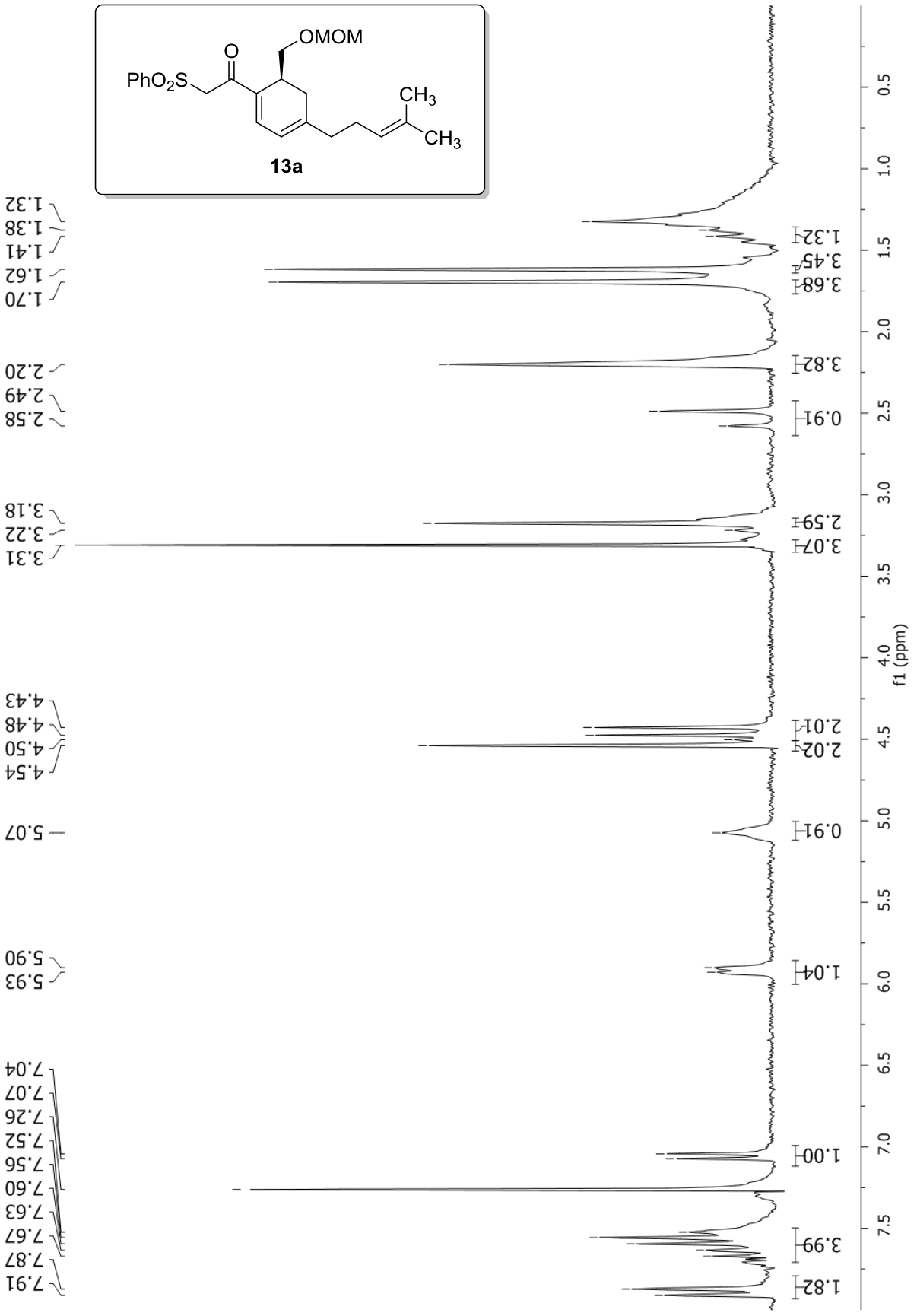


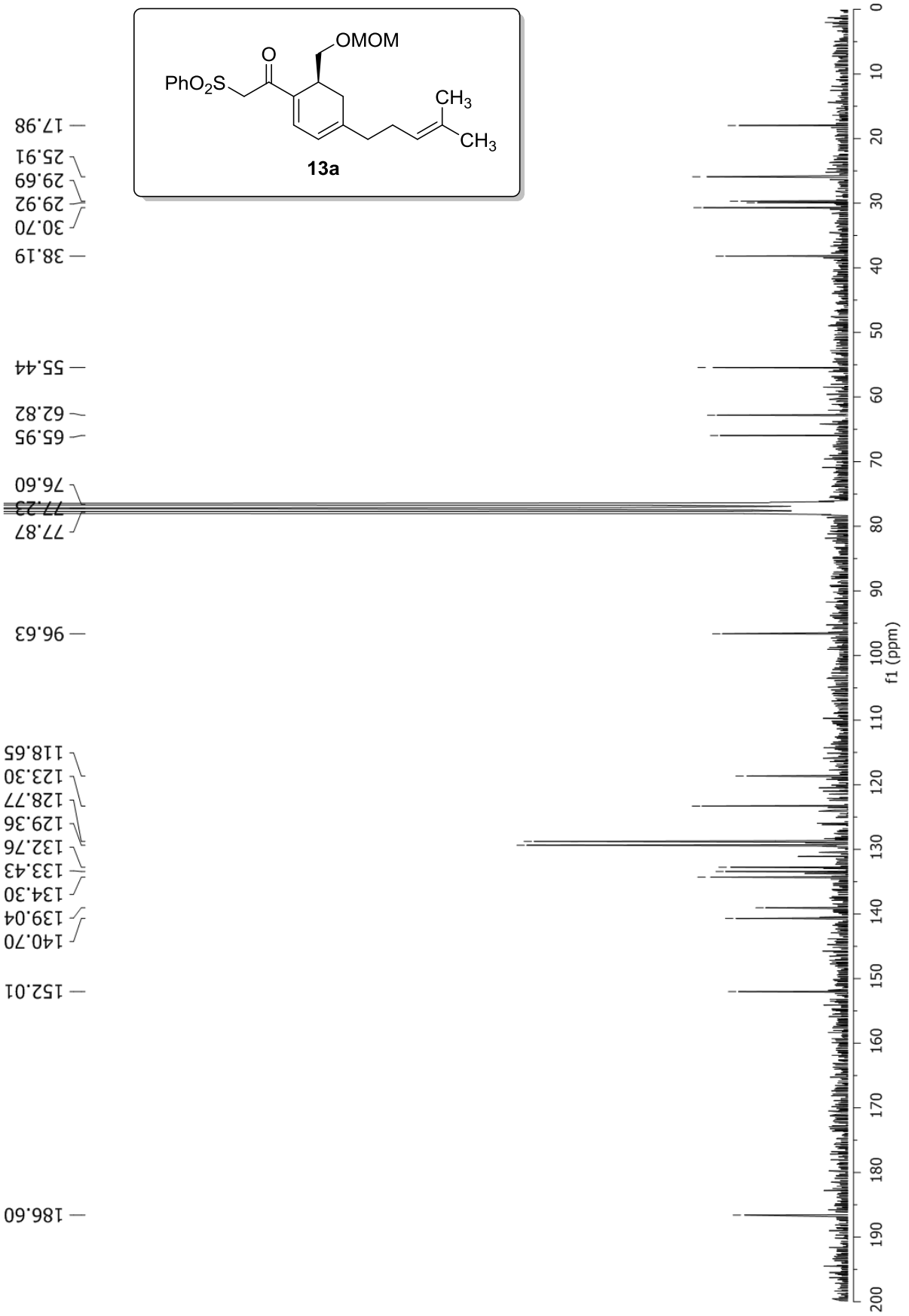
1 PDA Multi 5/218nm 4nm

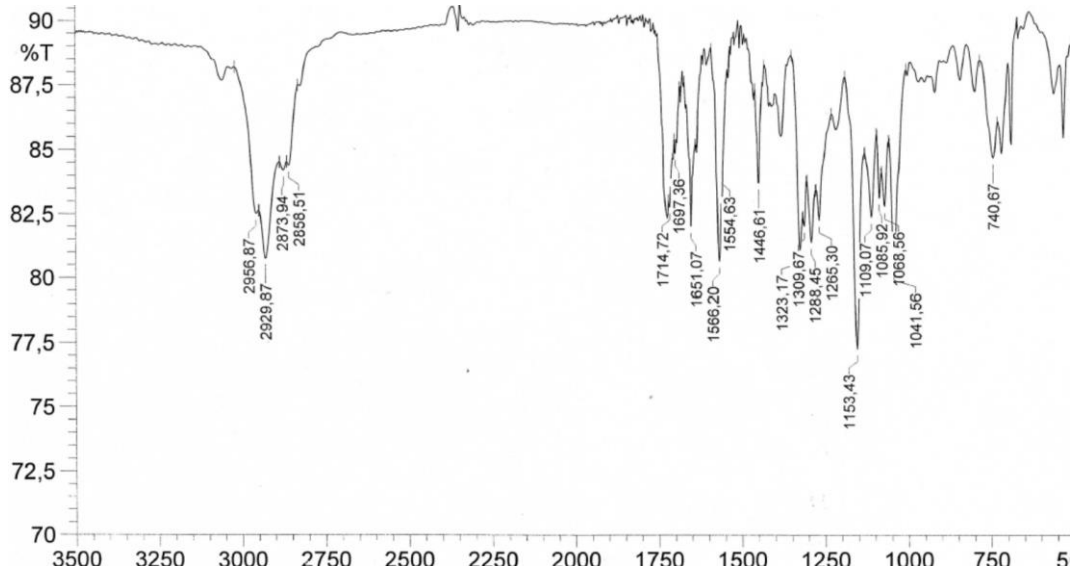
PeakTable

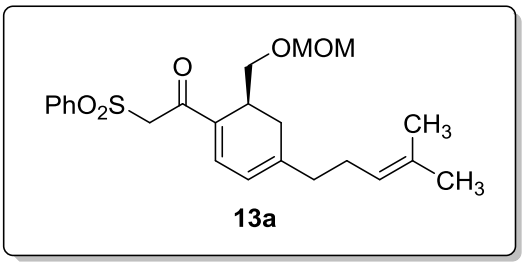
PDA Ch5 218nm 4nm

Peak#	Ret. Time	Area %
1	14.487	44.166
2	15.887	55.834
Total		100.000

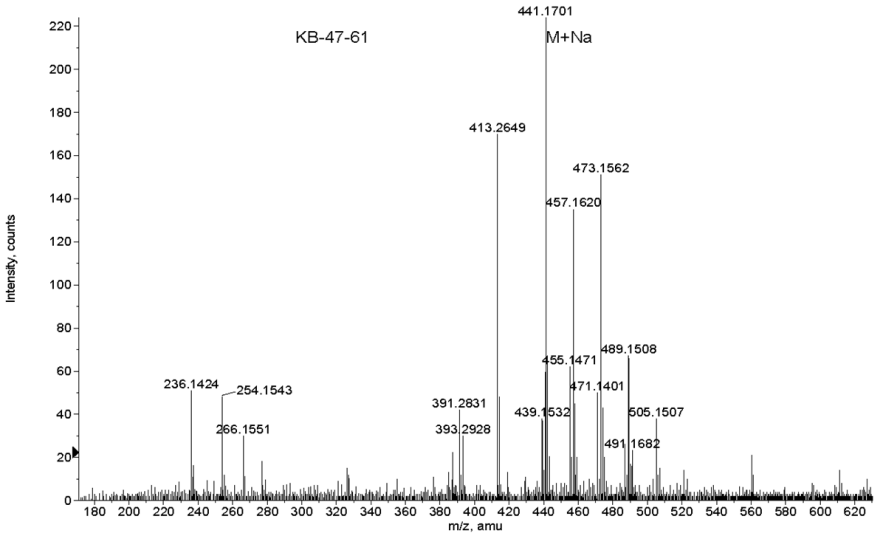

OMOM
O
PhO2S
CH3
CH3
13a
f1 (ppm)


OMOM
O
PhO2S
CH3
CH3
13a
17.98
25.91
29.69
29.92
30.70
38.19
55.44
62.82
65.95
76.60
77.23
77.87
96.63
118.65
123.30
128.77
129.36
132.76
133.43
134.30
139.04
140.70
152.01
186.60
f1 (ppm)

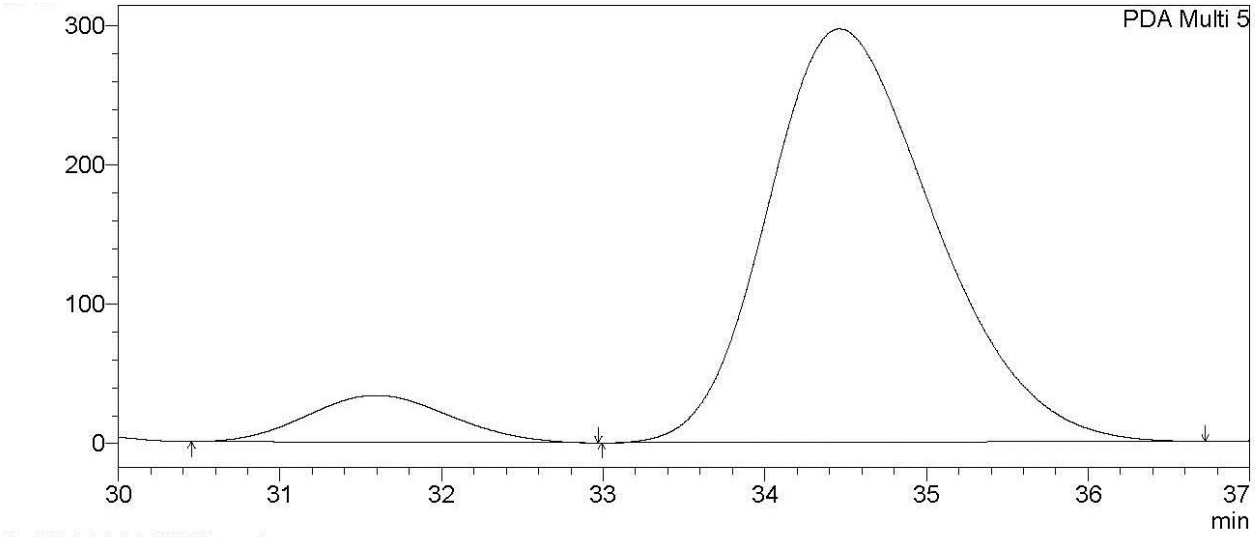




13a



Formula	CalculatedMass	mDaError	ppmError	RDB
C21 H25 N6 O3 S	441.170337	-0.237188	-0.537633	12.5
C23 H30 O5 Na S	441.170617	-0.51732	-1.172607	8.5

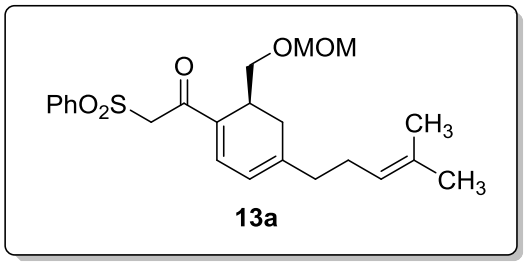


1 PDA Multi 5/325nm 4nm

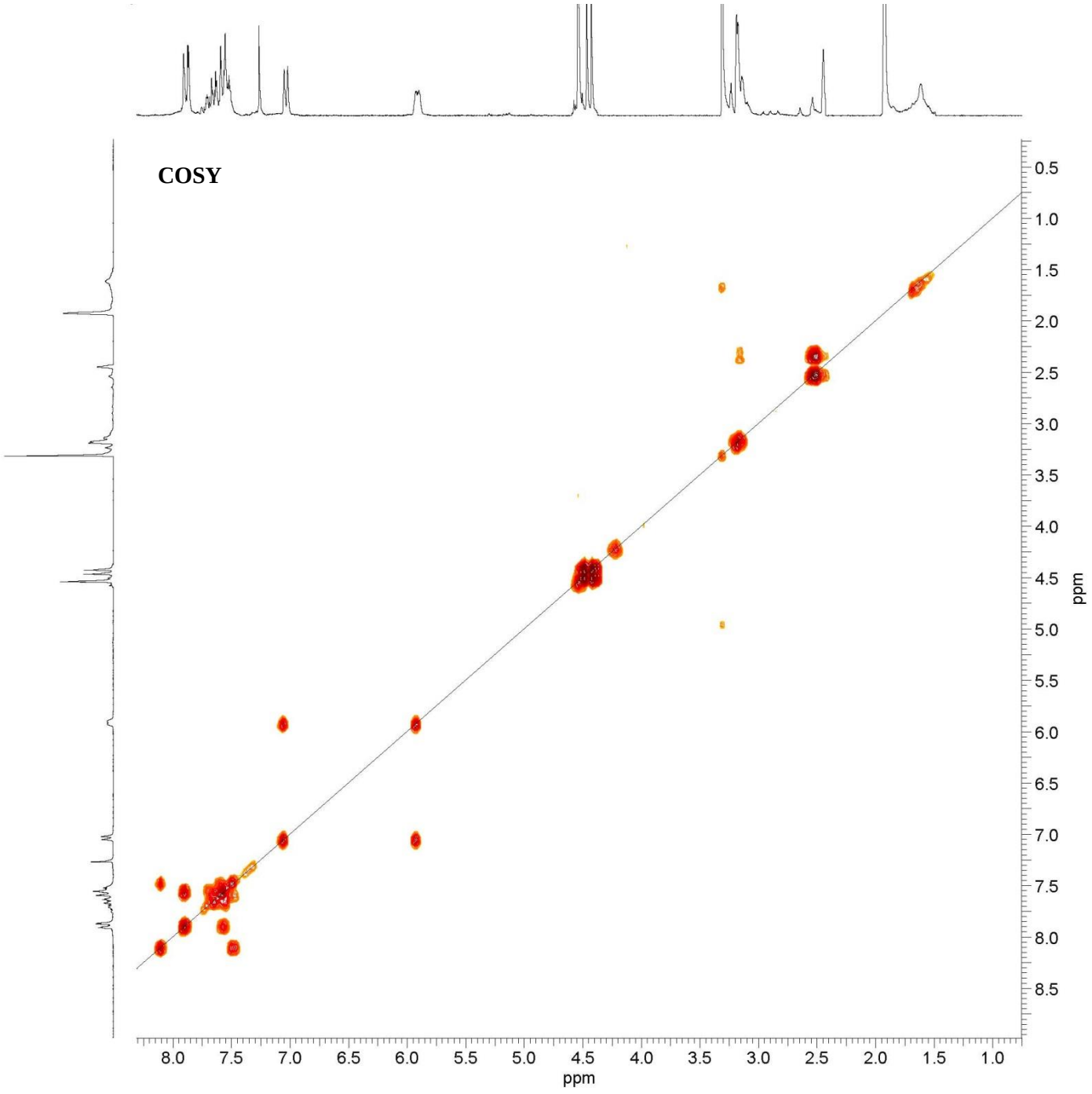
PeakTable

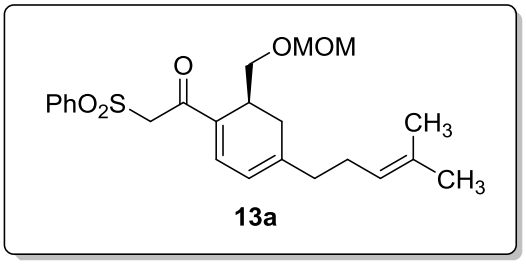
PDA Ch5 325nm 4nm

Peak#	Ret. Time	Area %
1	31.586	8.846
2	34.456	91.154
Total		100.000

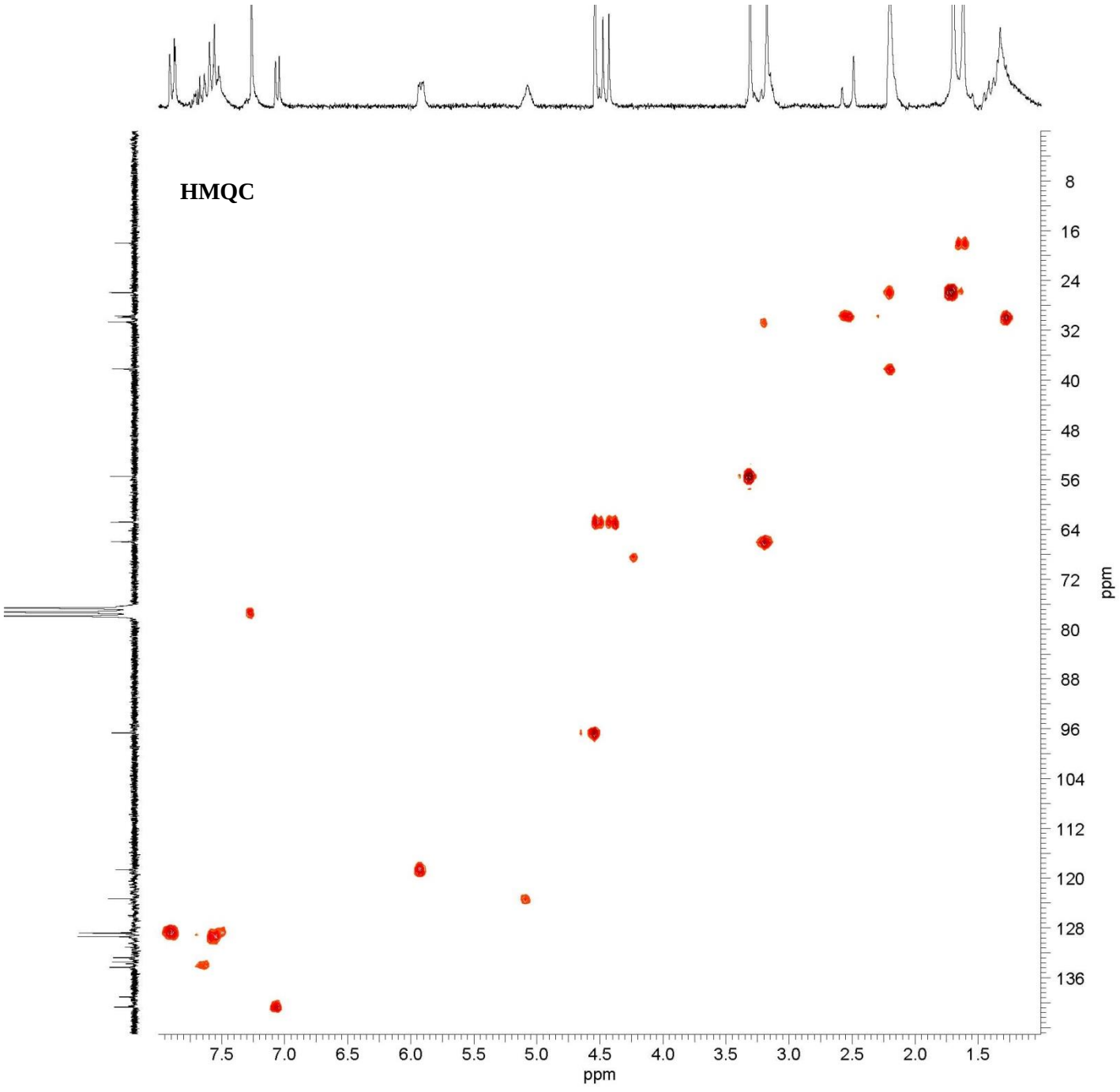


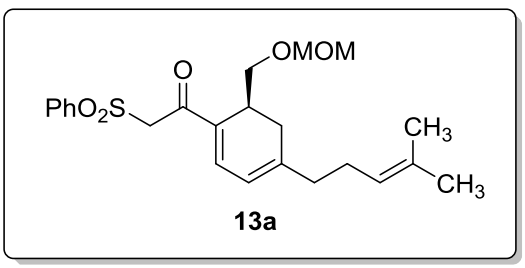
13a


COSY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm

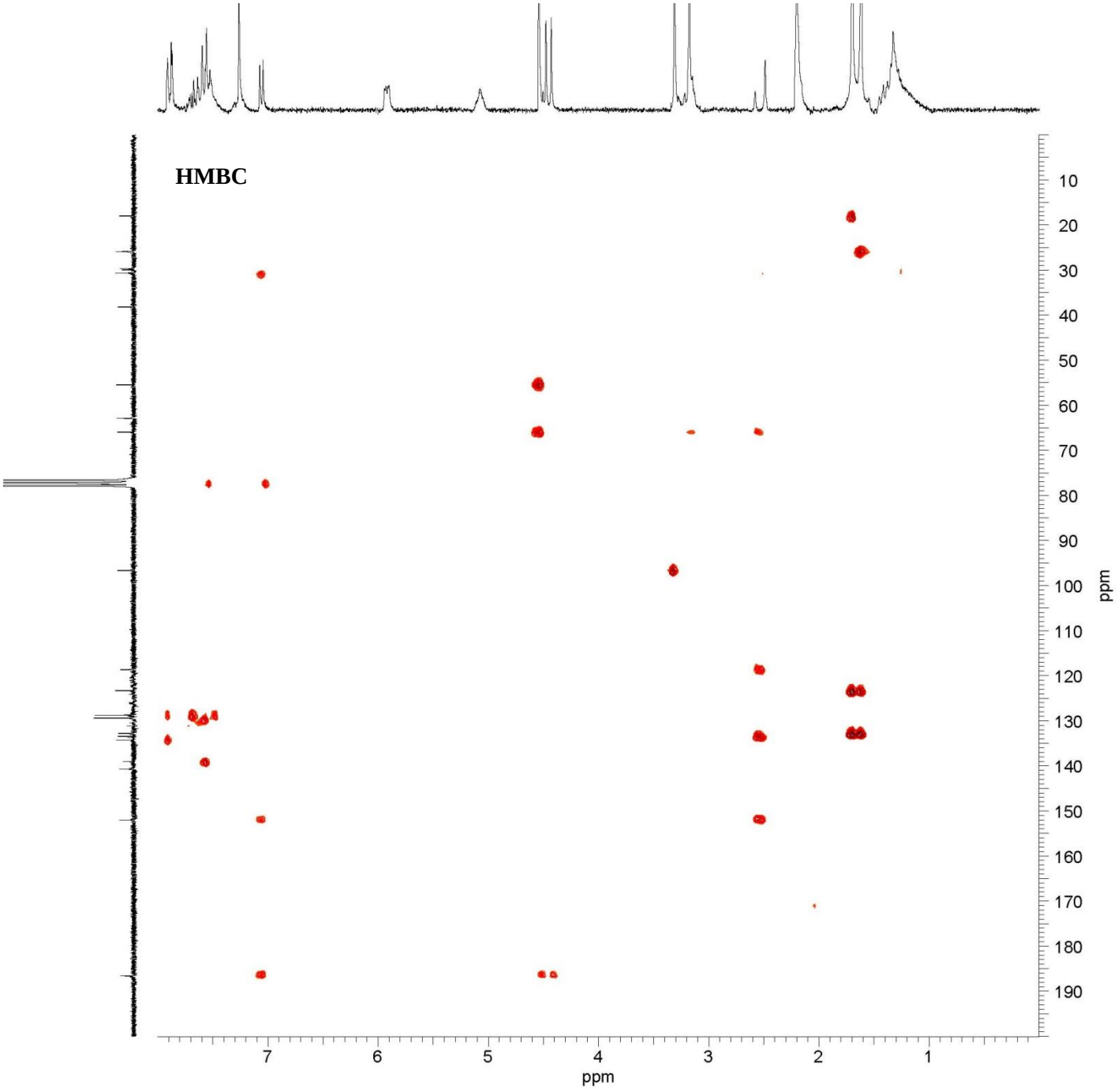

OMOM
O
PhO2S
CH3
CH3

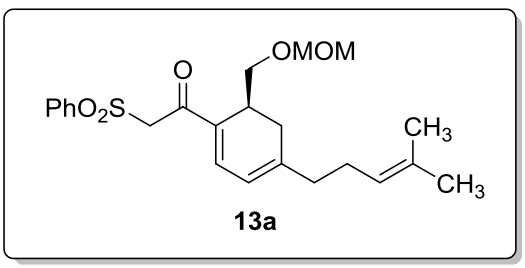
13a


HMQC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

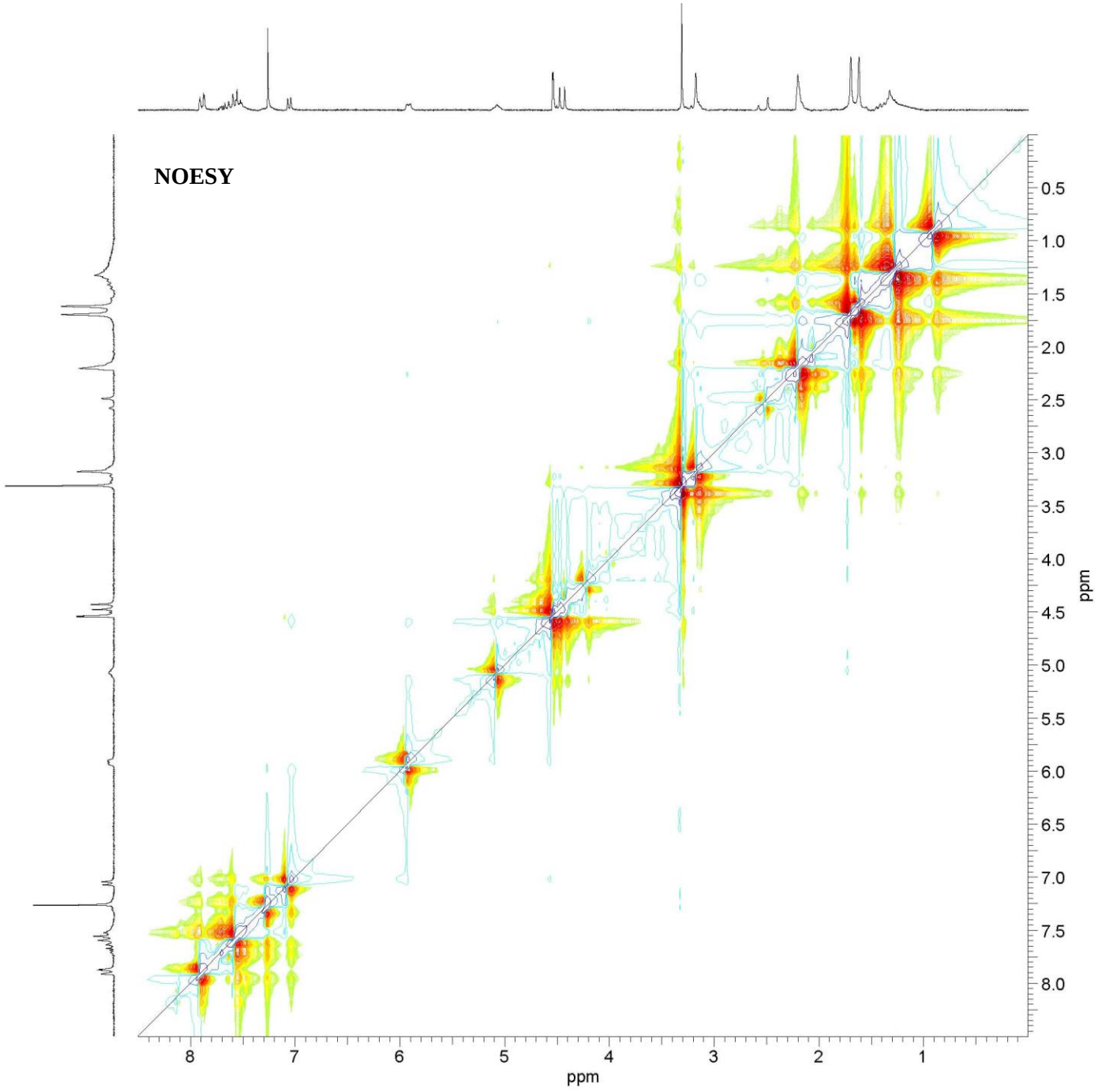

OMOM
O
PhO2S
CH3
CH3

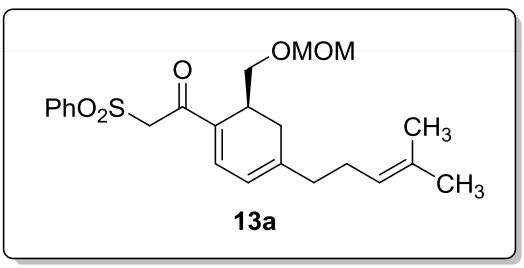
13a


HMBC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm
7
6
5
4
3
2
1
ppm

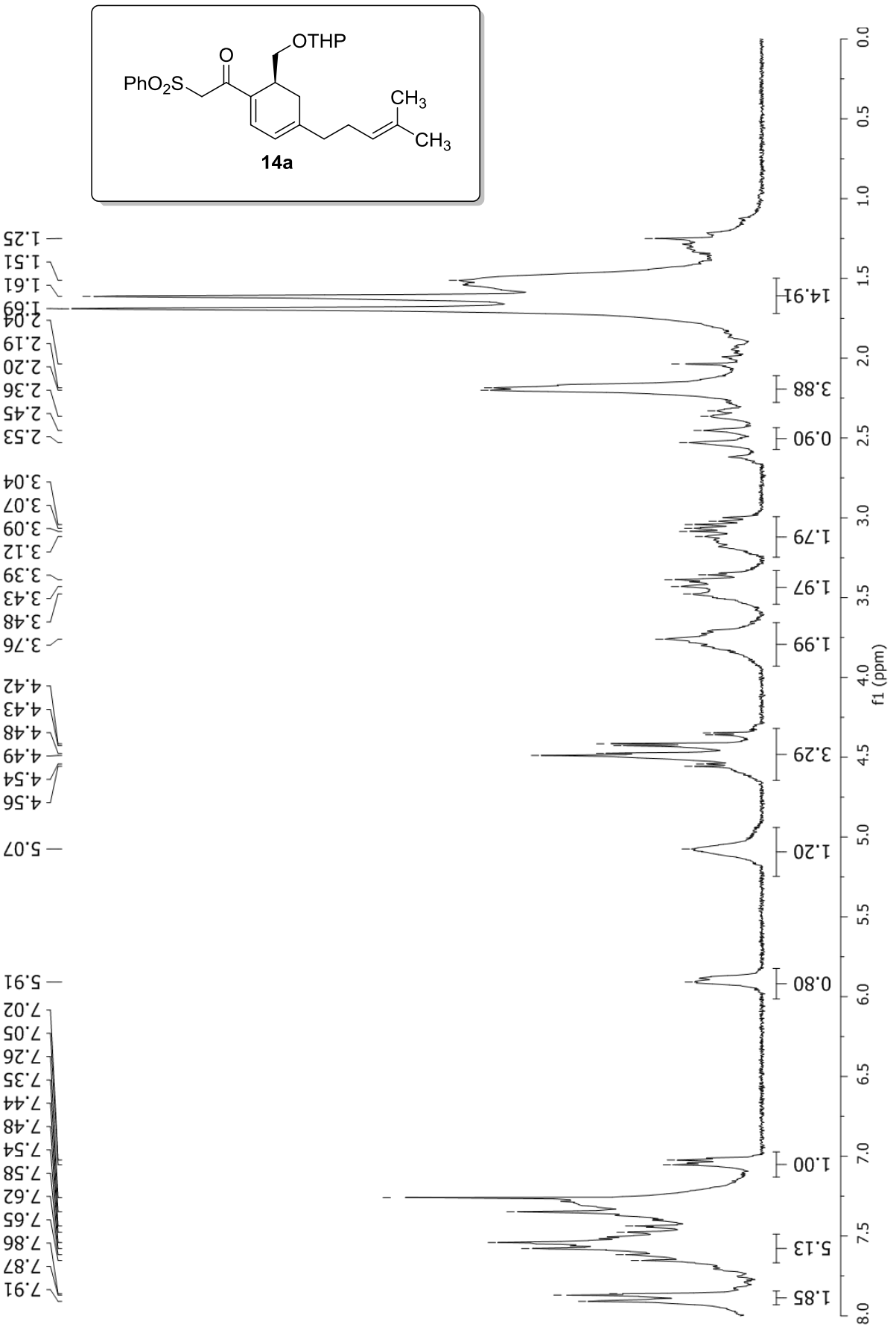

OMOM
O
PhO2S
CH3
CH3

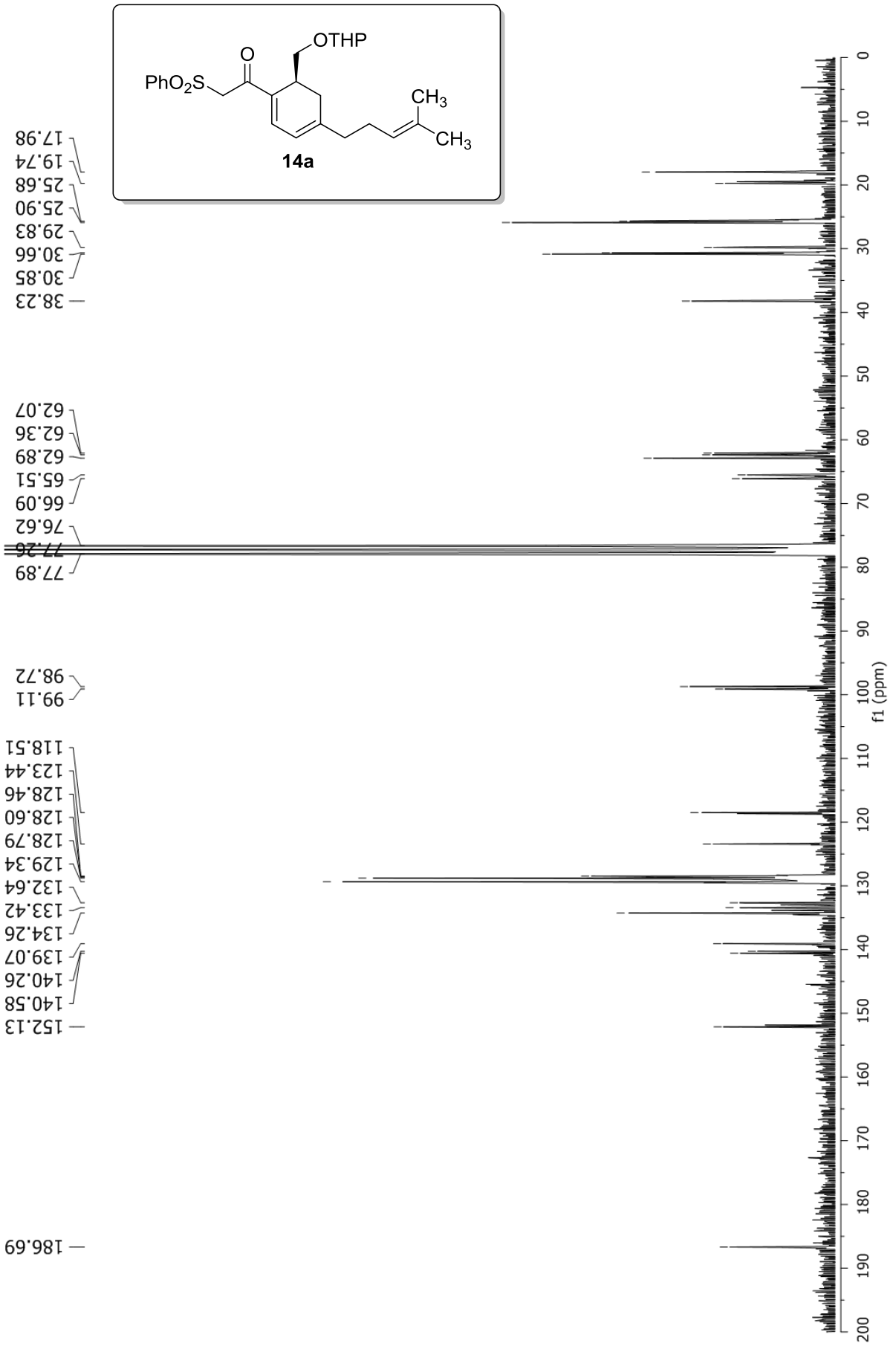
13a

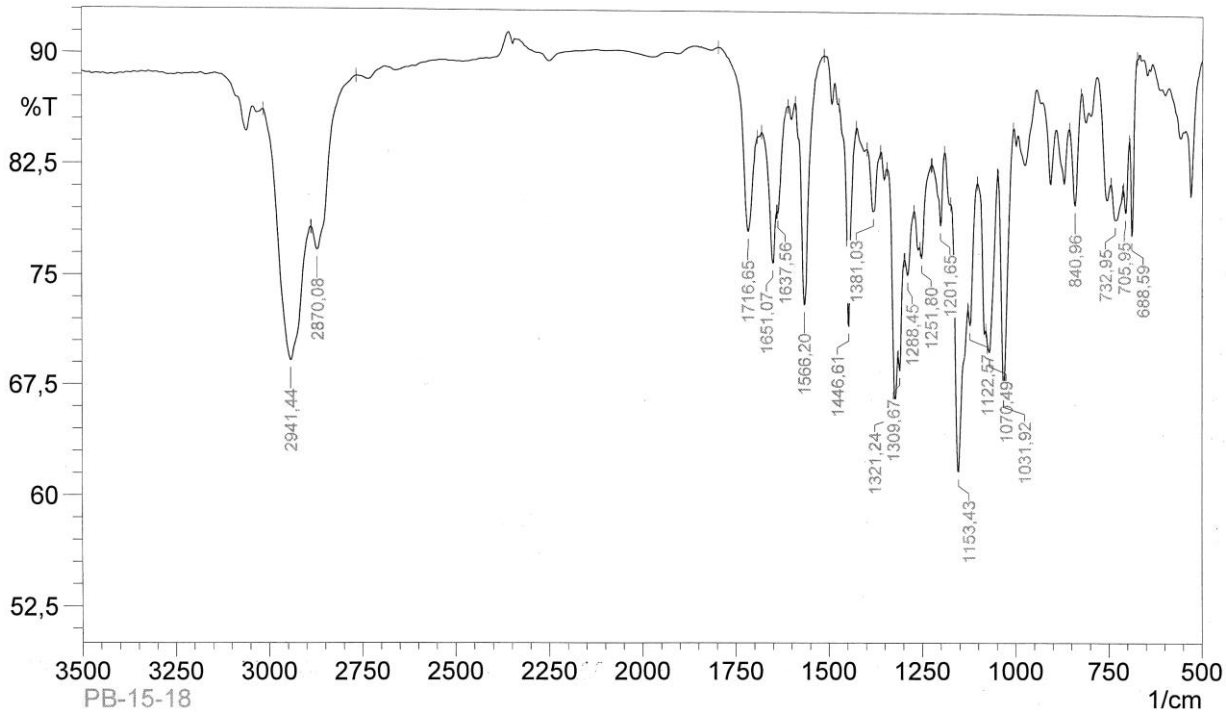

NOESY
8
7
6
5
4
3
2
1
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
ppm

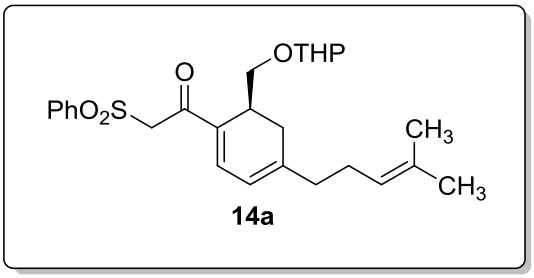

OMOM
O
PhO2S
CH3
CH3

13a

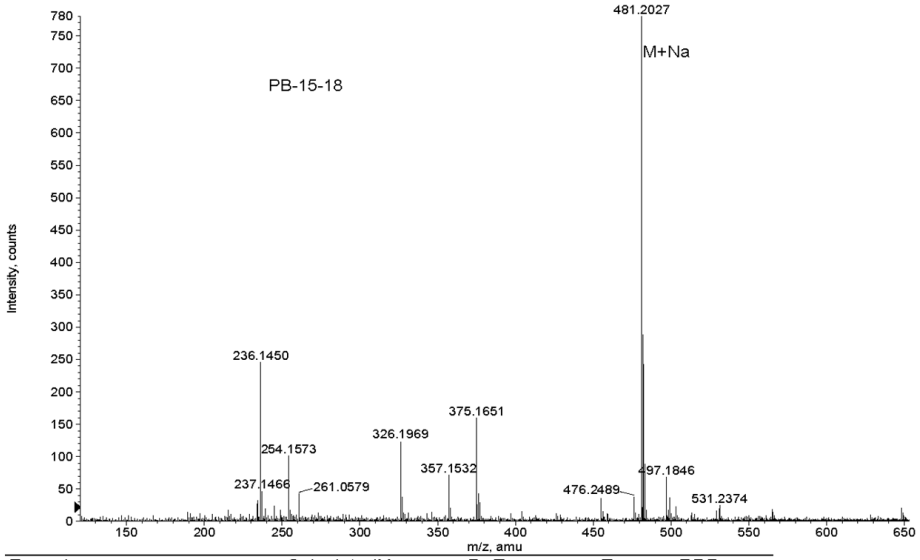

OTHP
O
PhO2S
CH3
CH3
14a
1.25
1.51
1.61
1.69
2.04
2.19
2.20
2.36
2.45
2.53
3.04
3.07
3.09
3.12
3.39
3.43
3.48
3.76
4.42
4.43
4.48
4.49
4.54
4.56
5.07
5.91
7.02
7.05
7.26
7.35
7.44
7.48
7.54
7.58
7.62
7.65
7.86
7.87
7.91
14.91
3.88
0.90
1.79
1.97
1.99
3.29
1.20
0.80
1.00
5.13
1.85
f1 (ppm)


OTHP
O
PhO2S
CH3
CH3
14a
17.98
19.74
25.68
25.90
29.83
30.66
30.85
38.23
62.07
62.36
62.89
65.51
66.09
76.62
77.26
77.89
98.72
99.11
118.51
123.44
128.46
128.60
128.79
129.34
132.64
133.42
134.26
139.07
140.26
140.58
152.13
186.69
f1 (ppm)

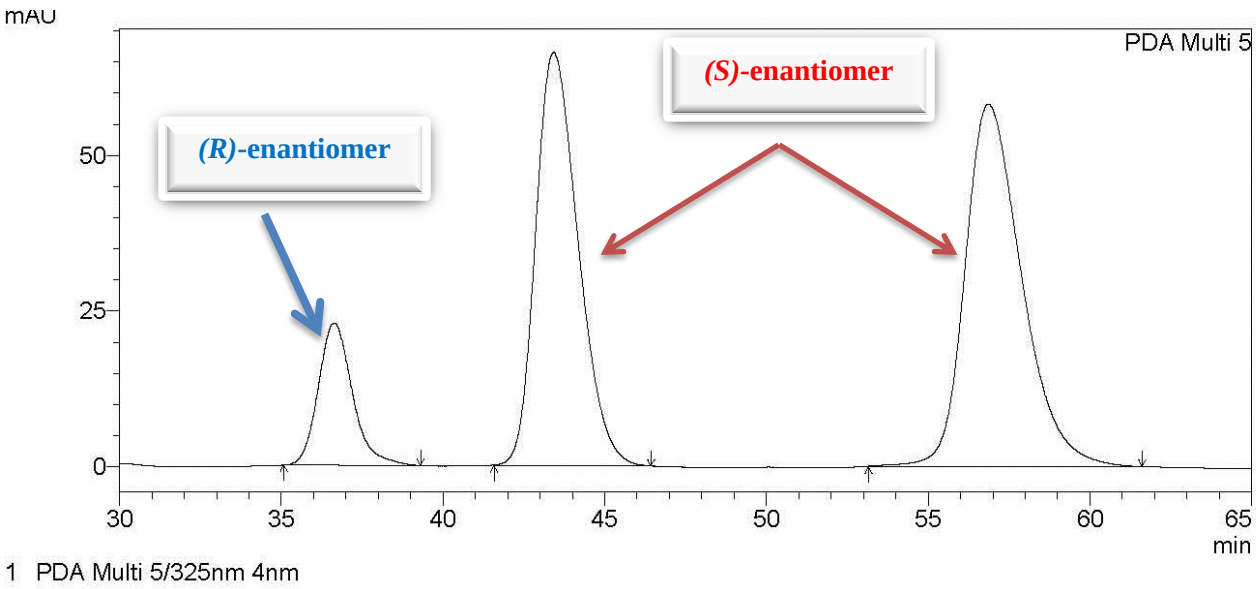




14a



Formula	CalculatedMass	mDaError	ppmError	RDB
C32 H25 N4 O	481.202288	0.411908	0.855996	22.5
C27 H30 N4 O Na S	481.203255	-0.554792	-1.152927	14.5
C26 H34 O5 Na S	481.201917	0.78252	1.626174	9.5

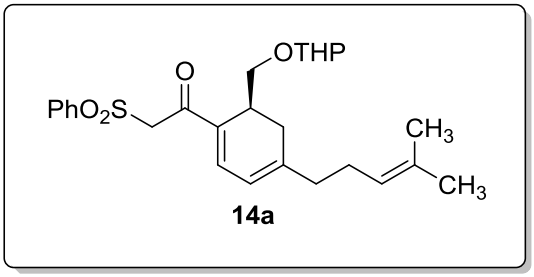


1 PDA Multi 5/325nm 4nm

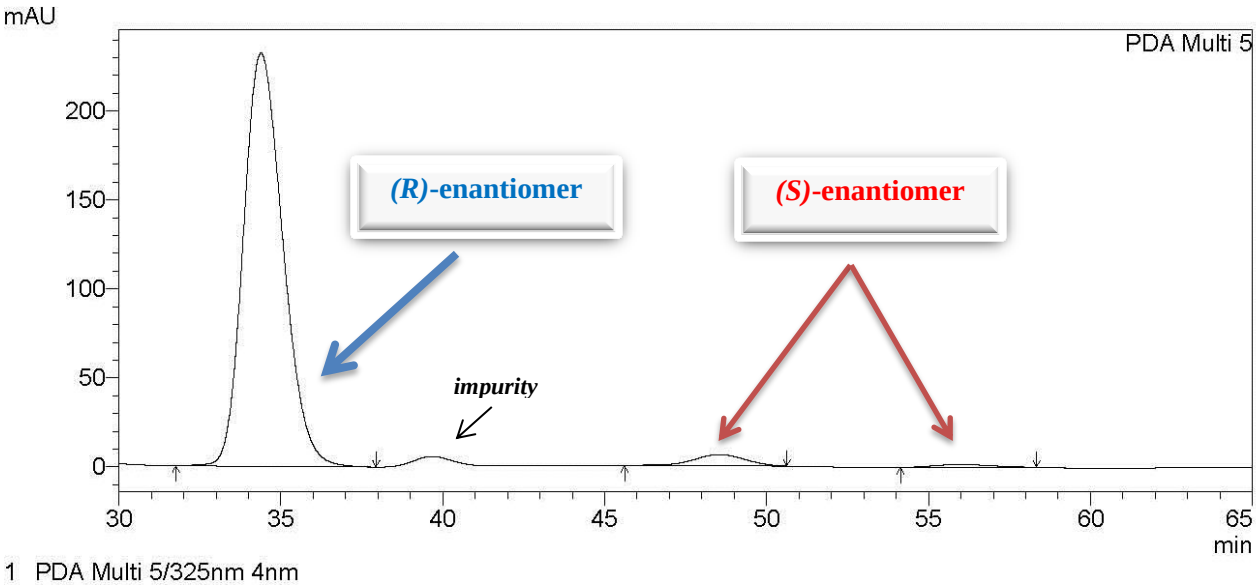
PeakTable

PDA Ch5 325nm 4nm

Peak#	Ret. Time	Area %
1	36.632	4.841
2	43.413	43.792
3	56.852	51.366
Total		100.000



14a

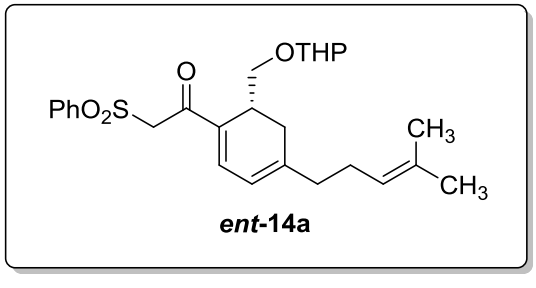


1 PDA Multi 5/325nm 4nm

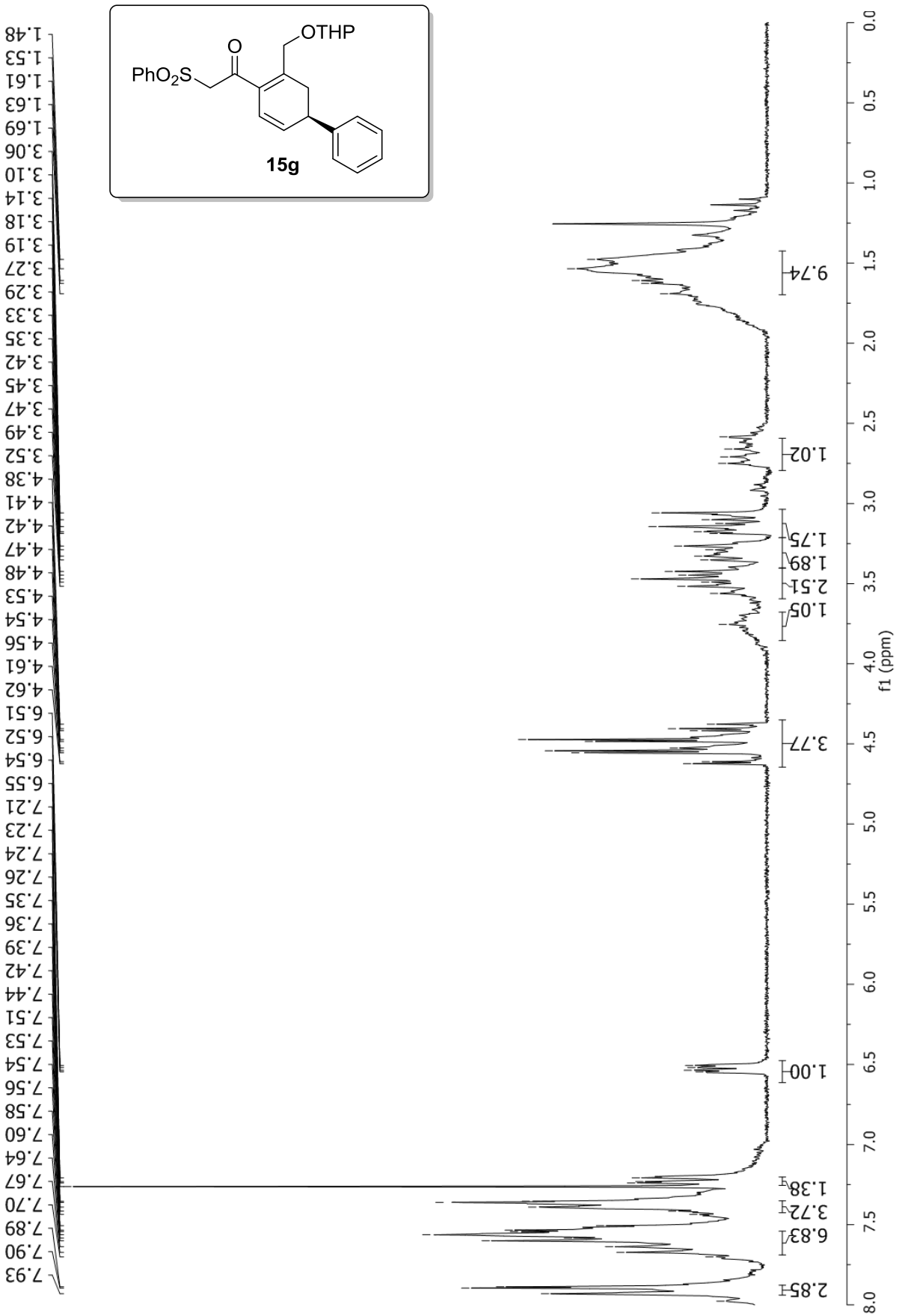
PeakTable

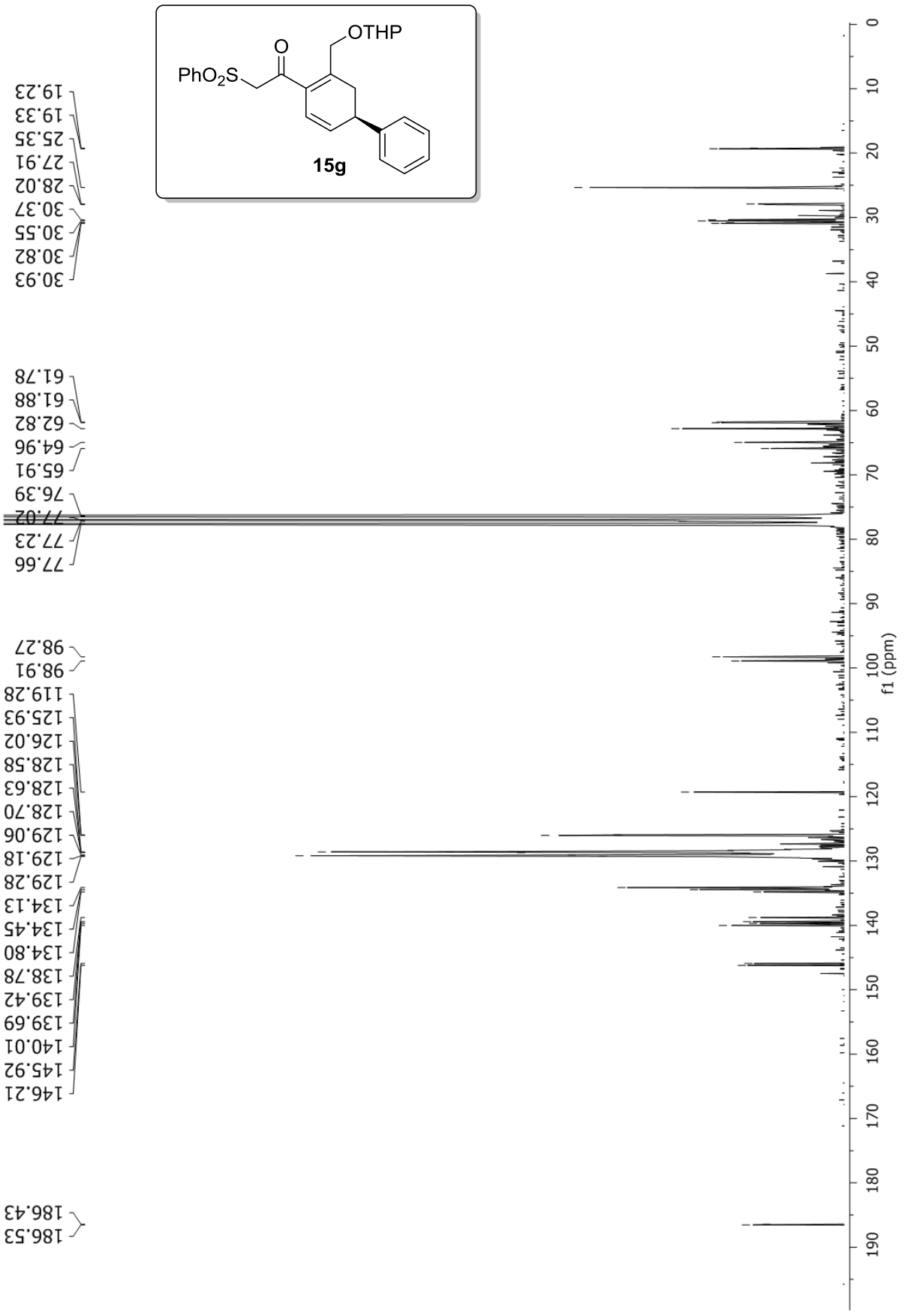
PDA Ch5 325nm 4nm

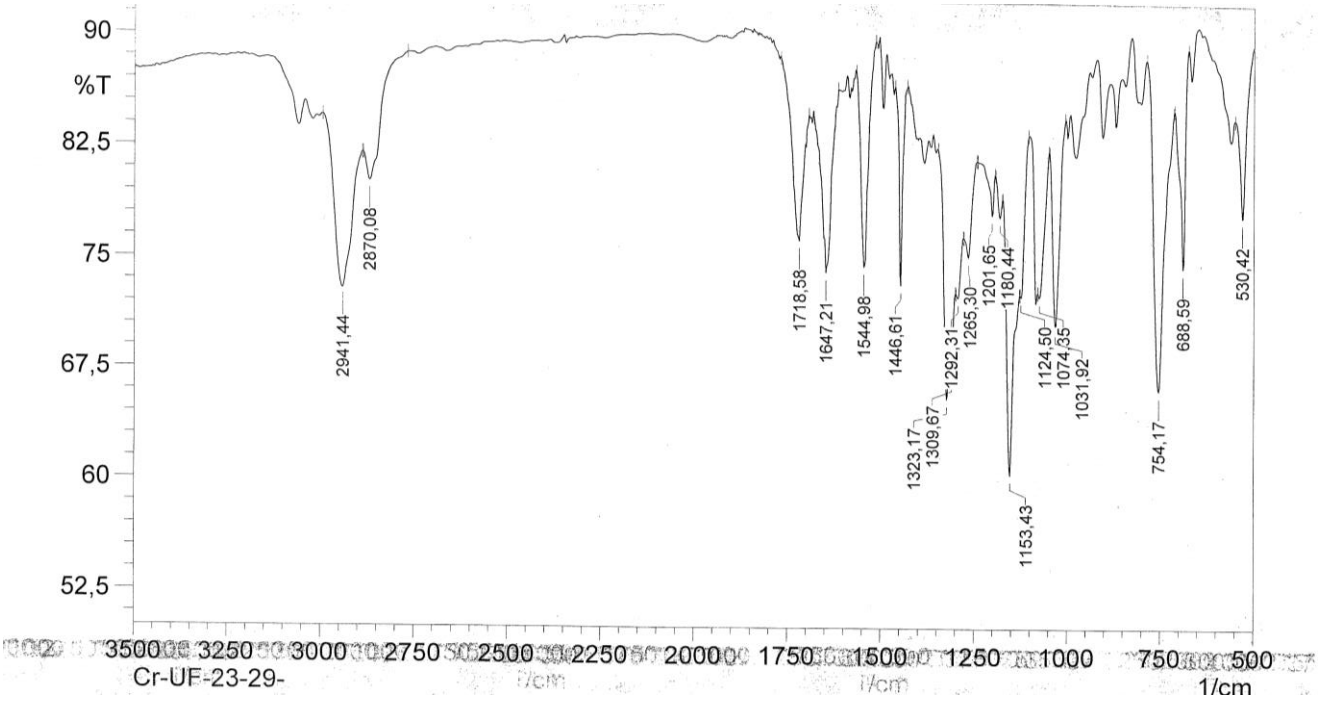
Peak#	Ret. Time	Area %
1	34.384	95.616
2	48.558	3.427
3	55.995	0.957
Total		100.000

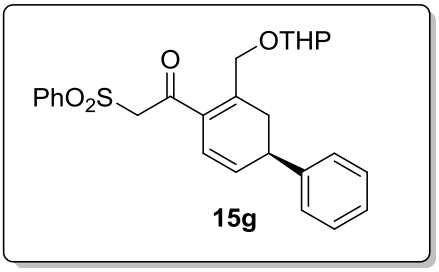


***ent*-14a**

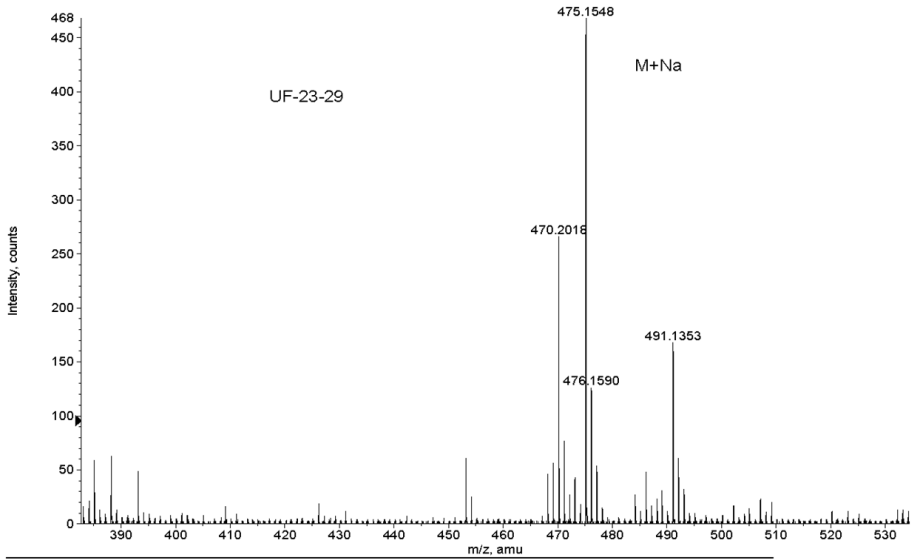

OTHP
O
PhO2S
15g
f1 (ppm)


OTHP
O
PhO2S
15g
19.23
19.33
25.35
27.91
28.02
30.37
30.55
30.82
30.93
61.78
61.88
62.82
64.96
65.91
76.39
77.02
77.23
77.66
98.27
98.91
119.28
125.93
126.02
128.58
128.63
128.70
129.06
129.18
129.28
134.13
134.45
134.80
138.78
139.42
139.69
140.01
145.92
146.21
186.43
186.53
f1 (ppm)

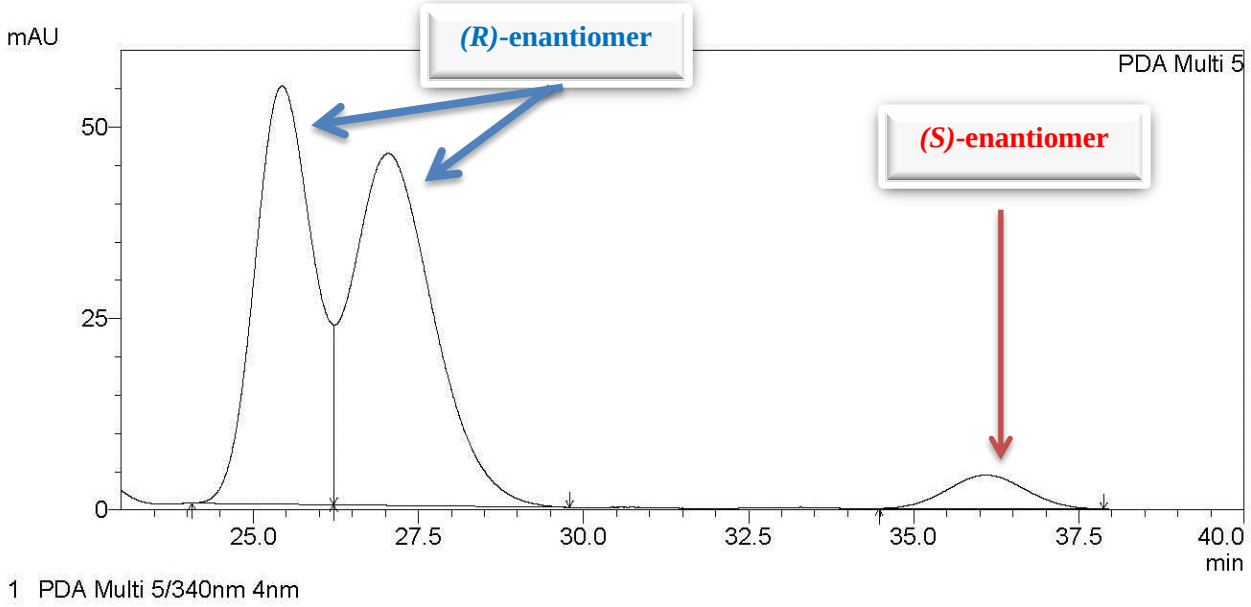




15g



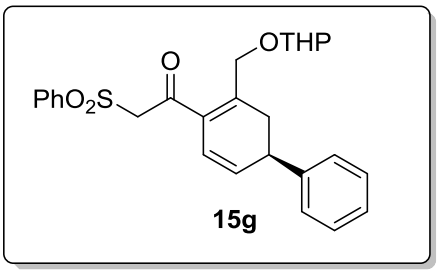
Formula	CalculatedMass	mDaError	ppmError	RDB
C26 H28 O5 Na S	475.154967	-0.16724	-0.351969	12.5



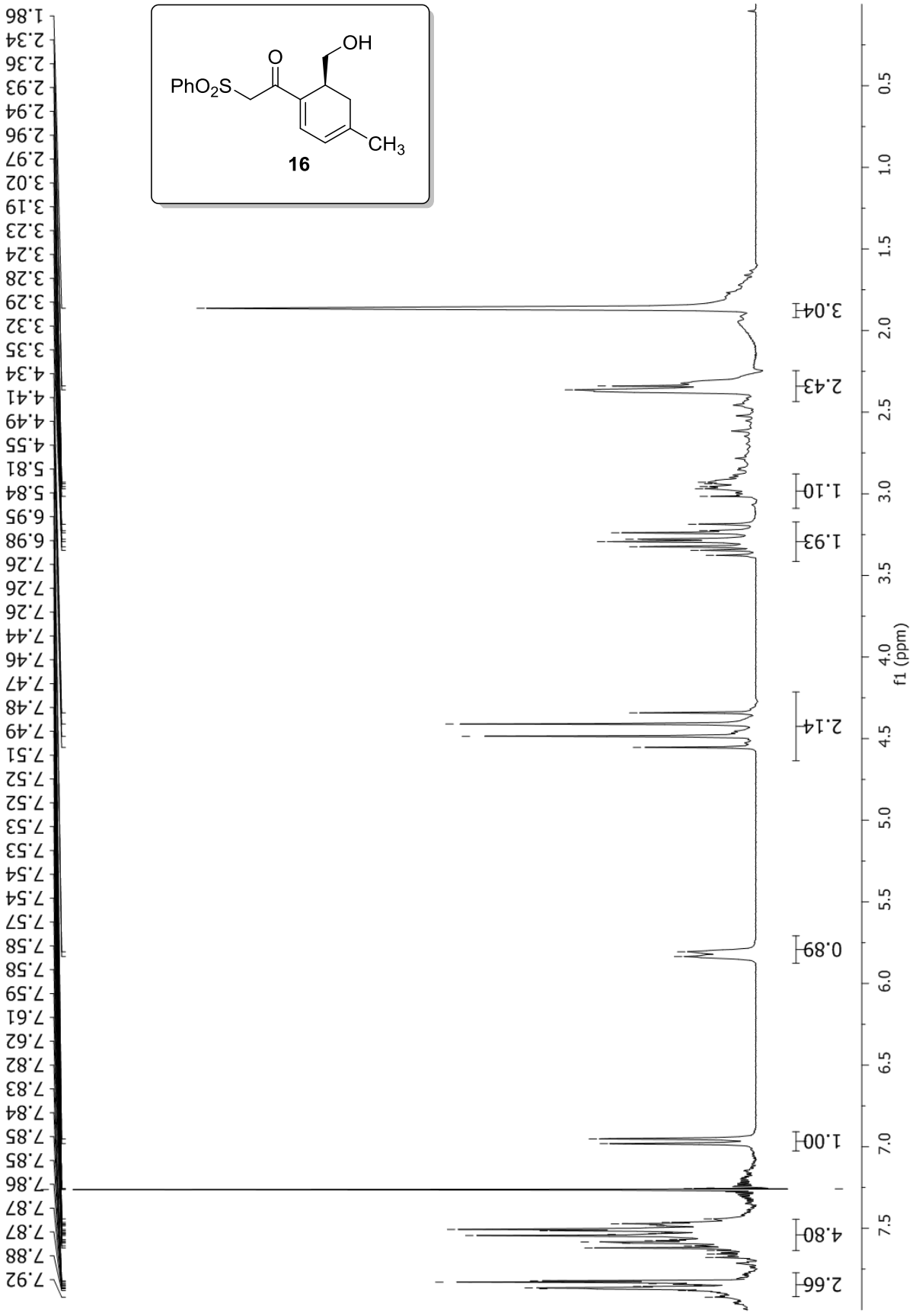
PeakTable

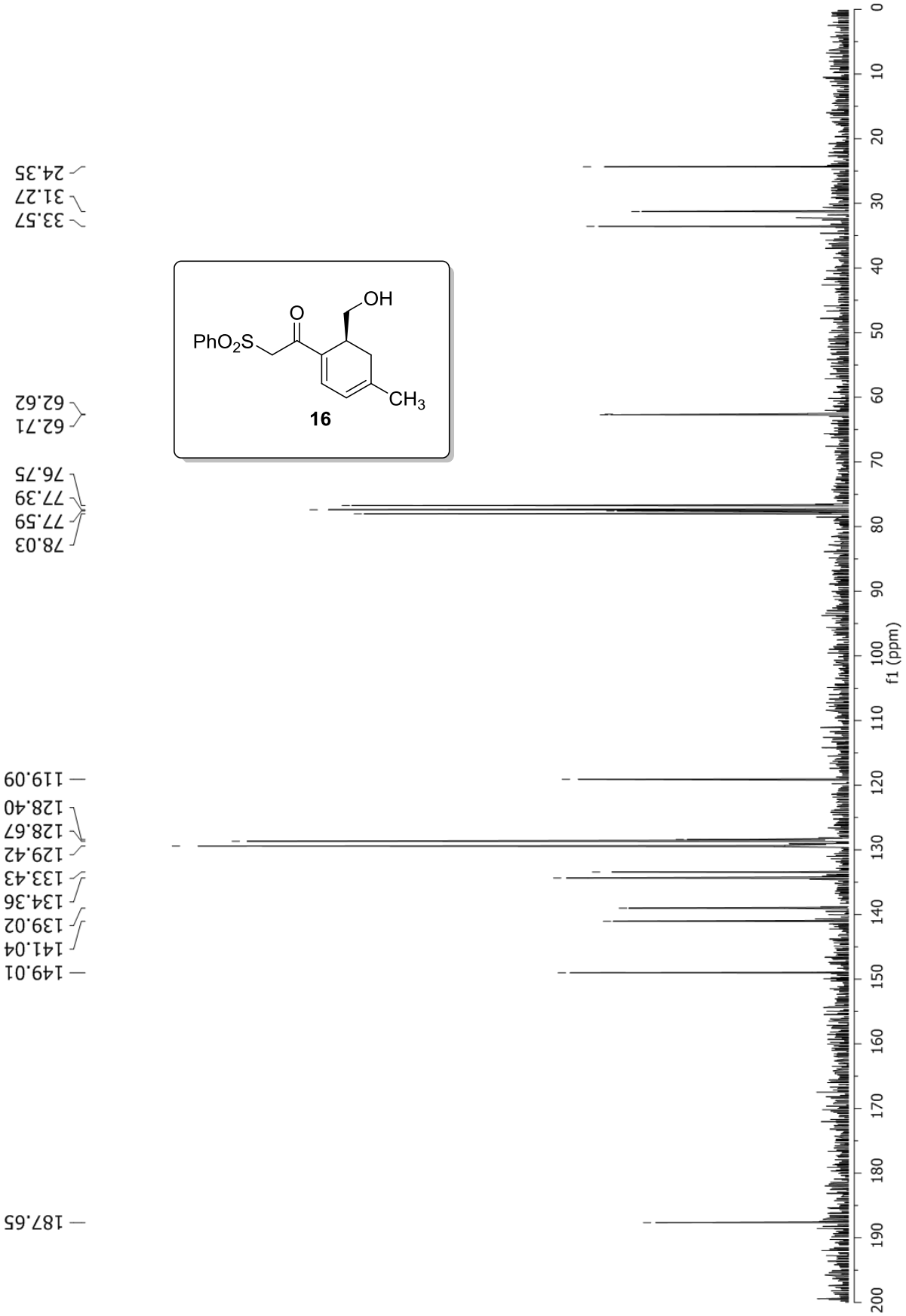
PDA Ch5 340nm 4nm

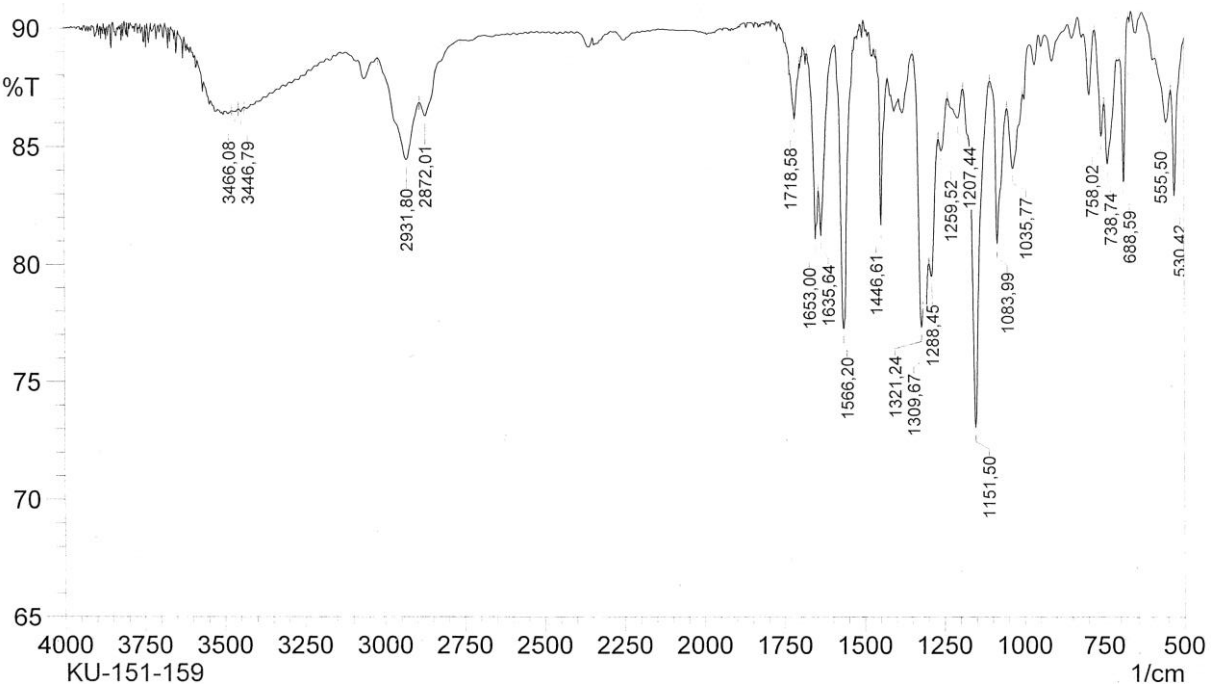
Peak#	Ret. Time	Area %
1	25.431	43.750
2	27.042	51.512
3	36.072	4.739
Total		100.000

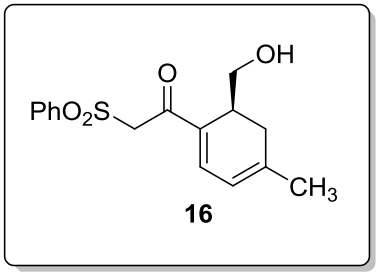


15g

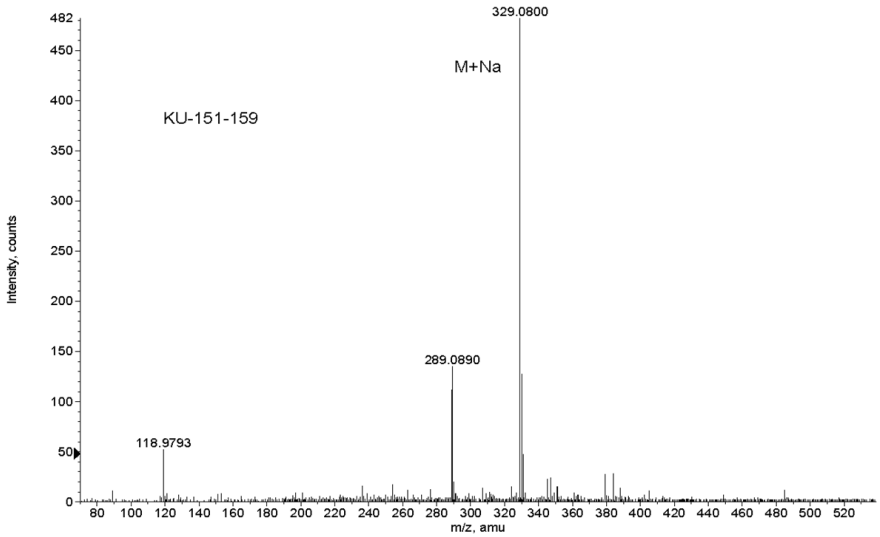

OH
O
PhO2S
CH3
16
f1 (ppm)


24.35
31.27
33.57
62.62
62.71
76.75
77.39
77.59
78.03
119.09
128.40
128.67
129.42
133.43
134.36
139.02
141.04
149.01
187.65
PhO2S
O
OH
CH3
16
f1 (ppm)

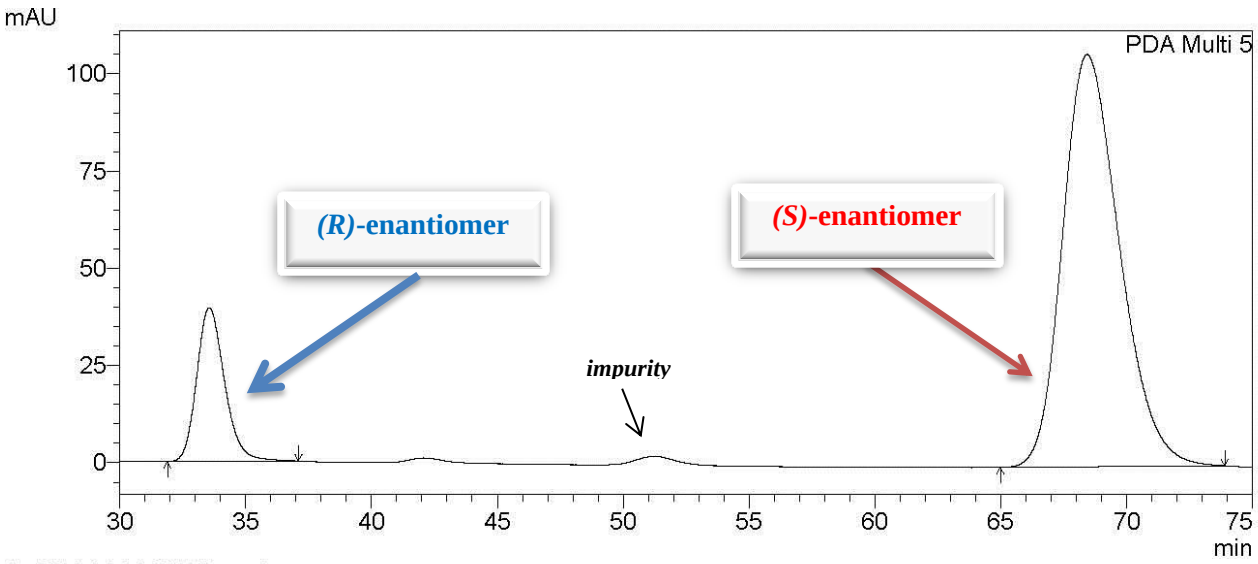




16



Formula	CalculatedMass	mDaError	ppmError	RDB
C21 H13 O4	329.080836	-0.8355	-2.538892	15.5
C19 H14 O4 Na	329.07843	1.56976	4.770139	12.5
C16 H18 O4 Na S	329.081802	-1.8022	-5.476471	7.5

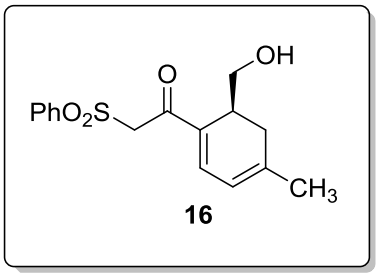


1 PDA Multi 5/325nm 4nm

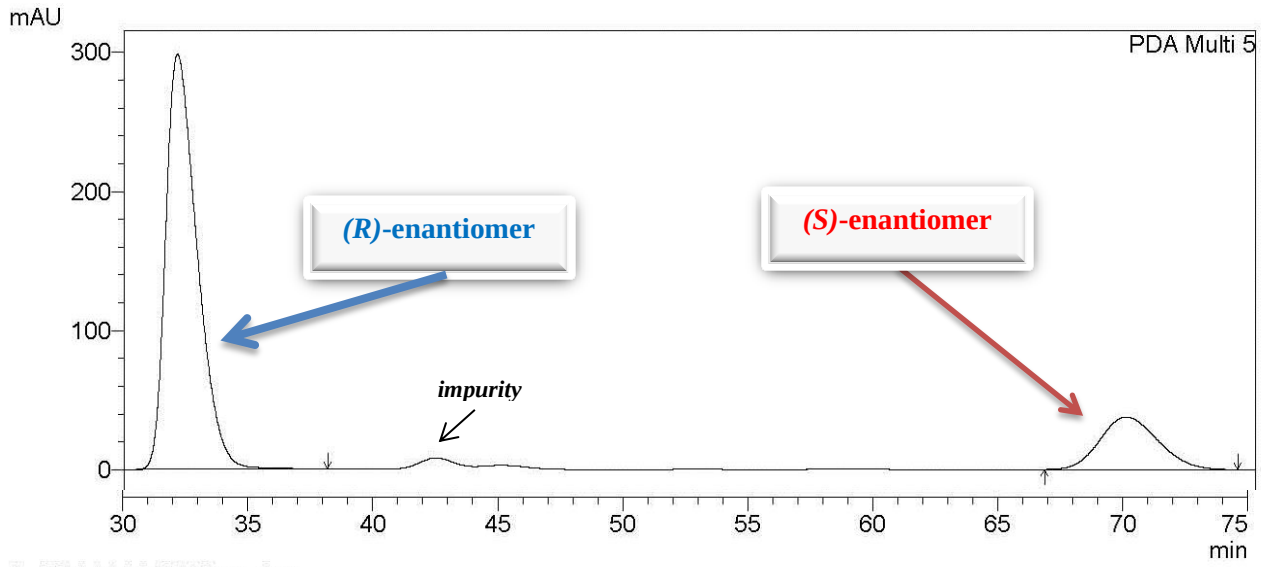
PeakTable

PDA Ch5 325nm 4nm

Peak#	Ret. Time	Area %
1	33.553	15.411
2	68.425	84.589
Total		100.000



16

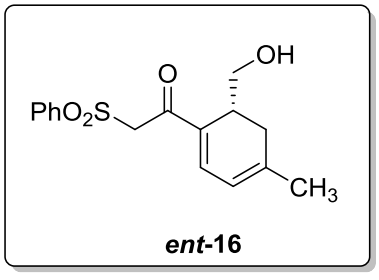


1 PDA Multi 5/325nm 4nm

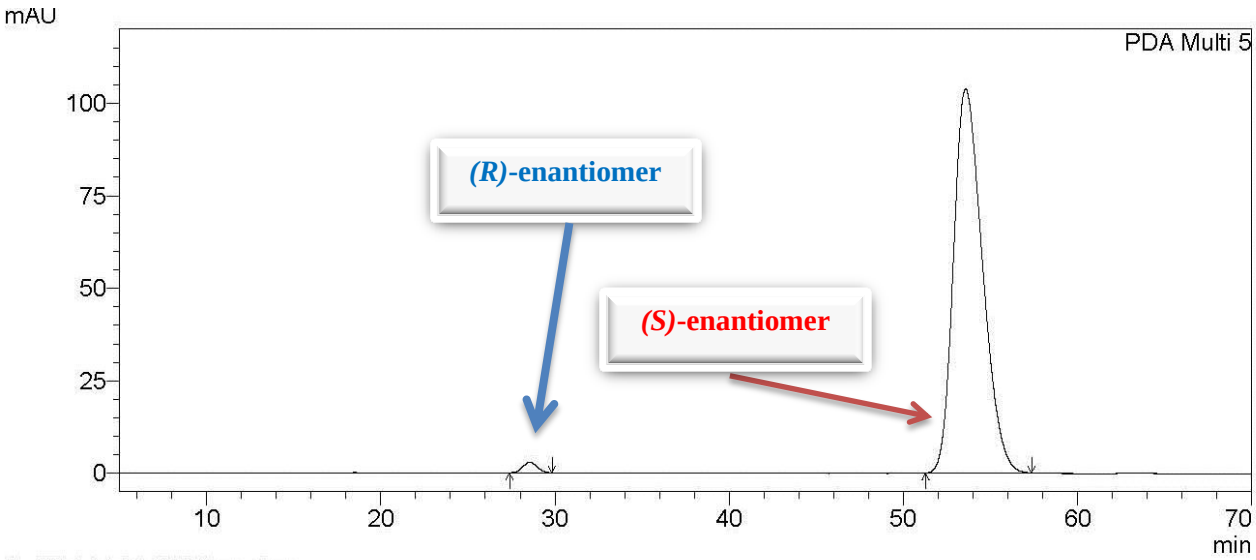
PeakTable

PDA Ch5 325nm 4nm

Peak#	Ret. Time	Area %
1	31.819	81.094
2	69.774	18.906
Total		100.000



***ent*-16**

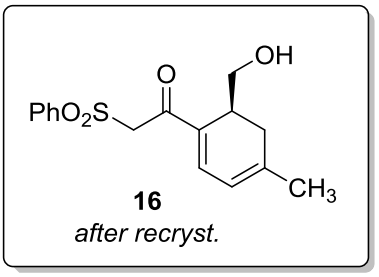


1 PDA Multi 5/360nm 4nm

PeakTable

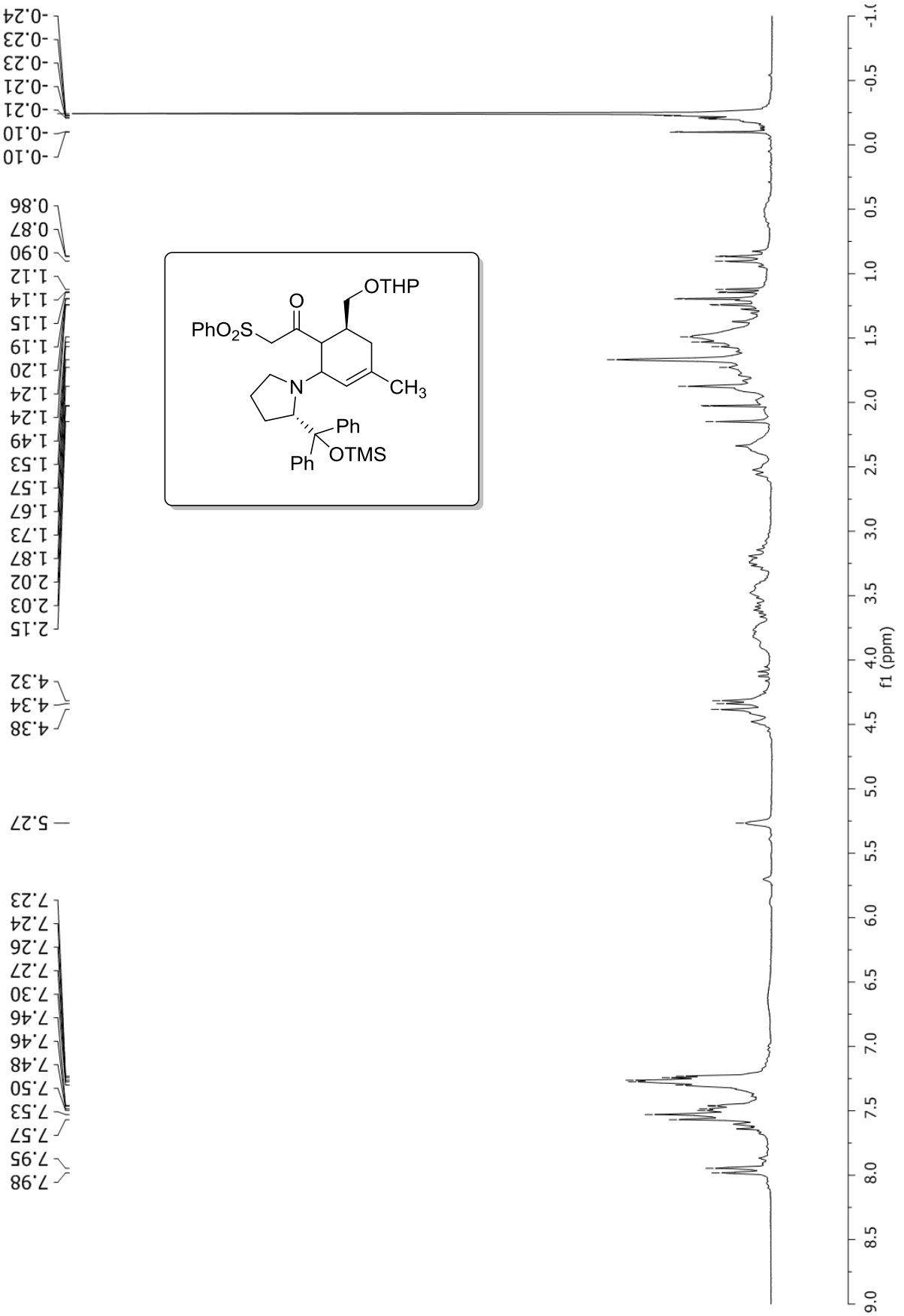
PDA Ch5 360nm 4nm

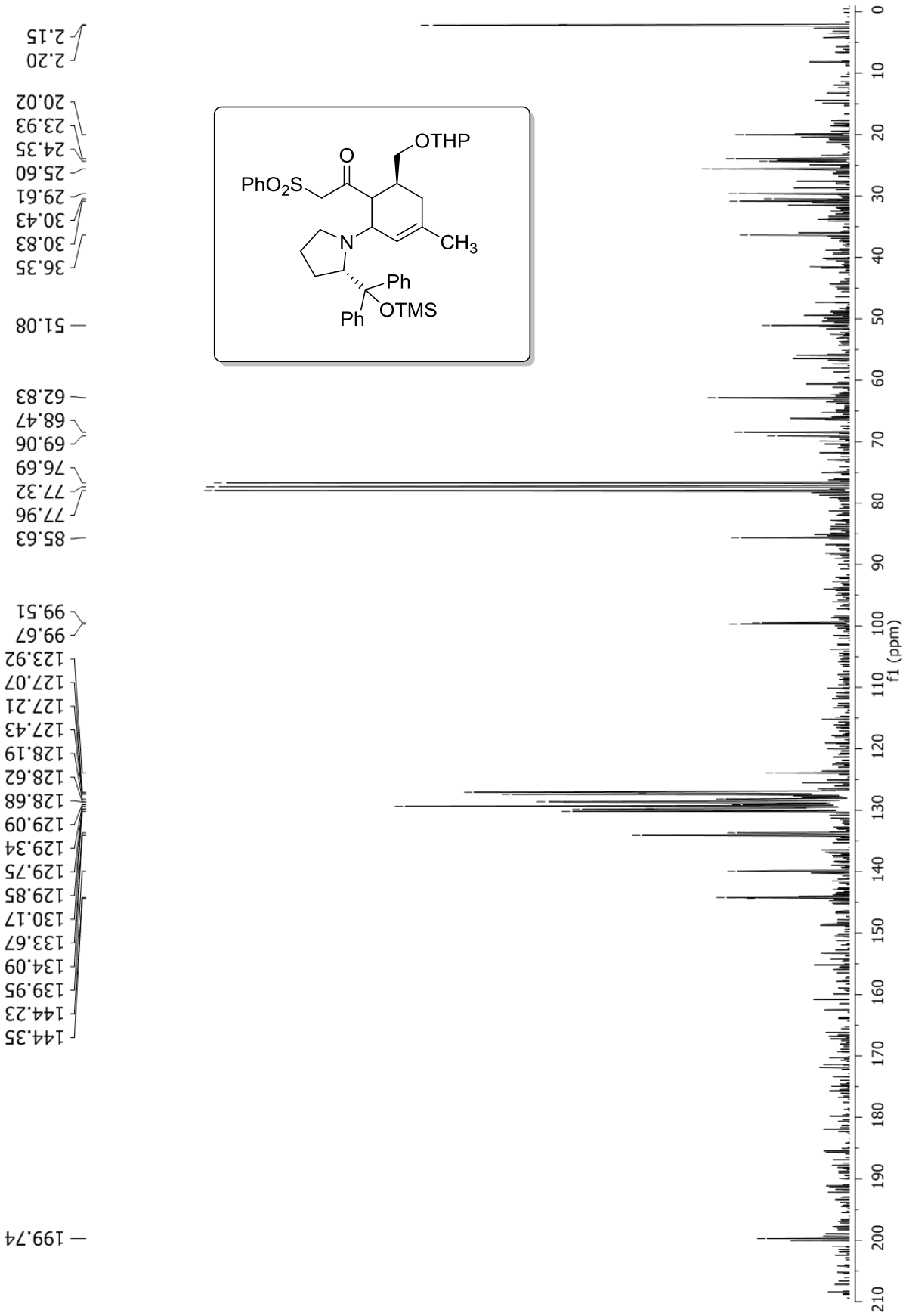
Peak#	Ret. Time	Area %
1	28.539	1.367
2	53.573	98.633
Total		100.000

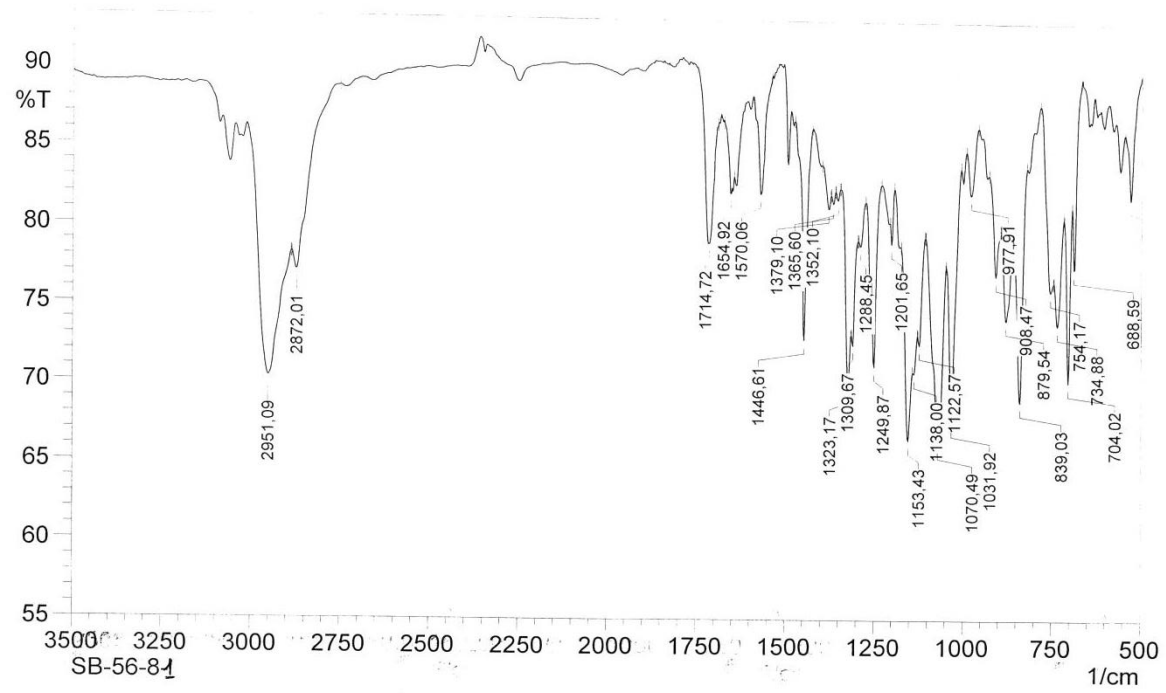


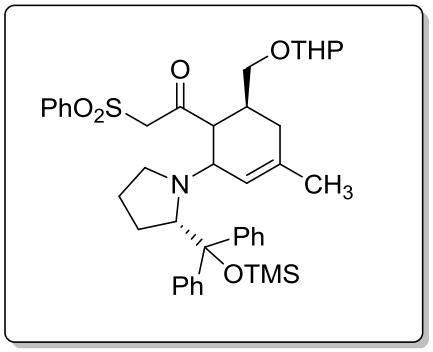
16

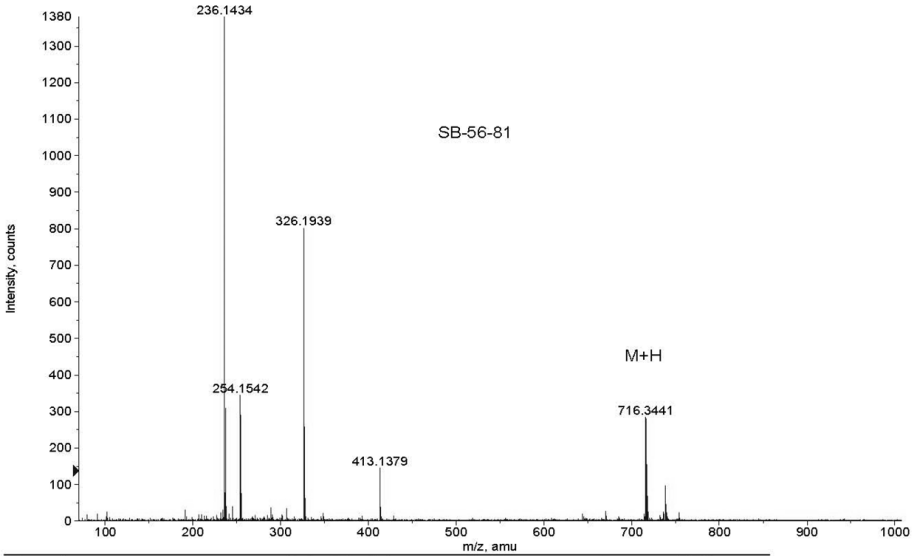
after recryst.


-0.24
-0.23
-0.23
-0.21
-0.21
-0.10
-0.10
0.86
0.87
0.90
1.12
1.14
1.15
1.19
1.20
1.24
1.24
1.49
1.53
1.57
1.67
1.73
1.87
2.02
2.03
2.15
4.32
4.34
4.38
5.27
7.23
7.24
7.26
7.27
7.30
7.46
7.46
7.48
7.50
7.53
7.57
7.95
7.98
OTHP
O
PhO2S
N
CH3
Ph
Ph
OTMS
f1 (ppm)

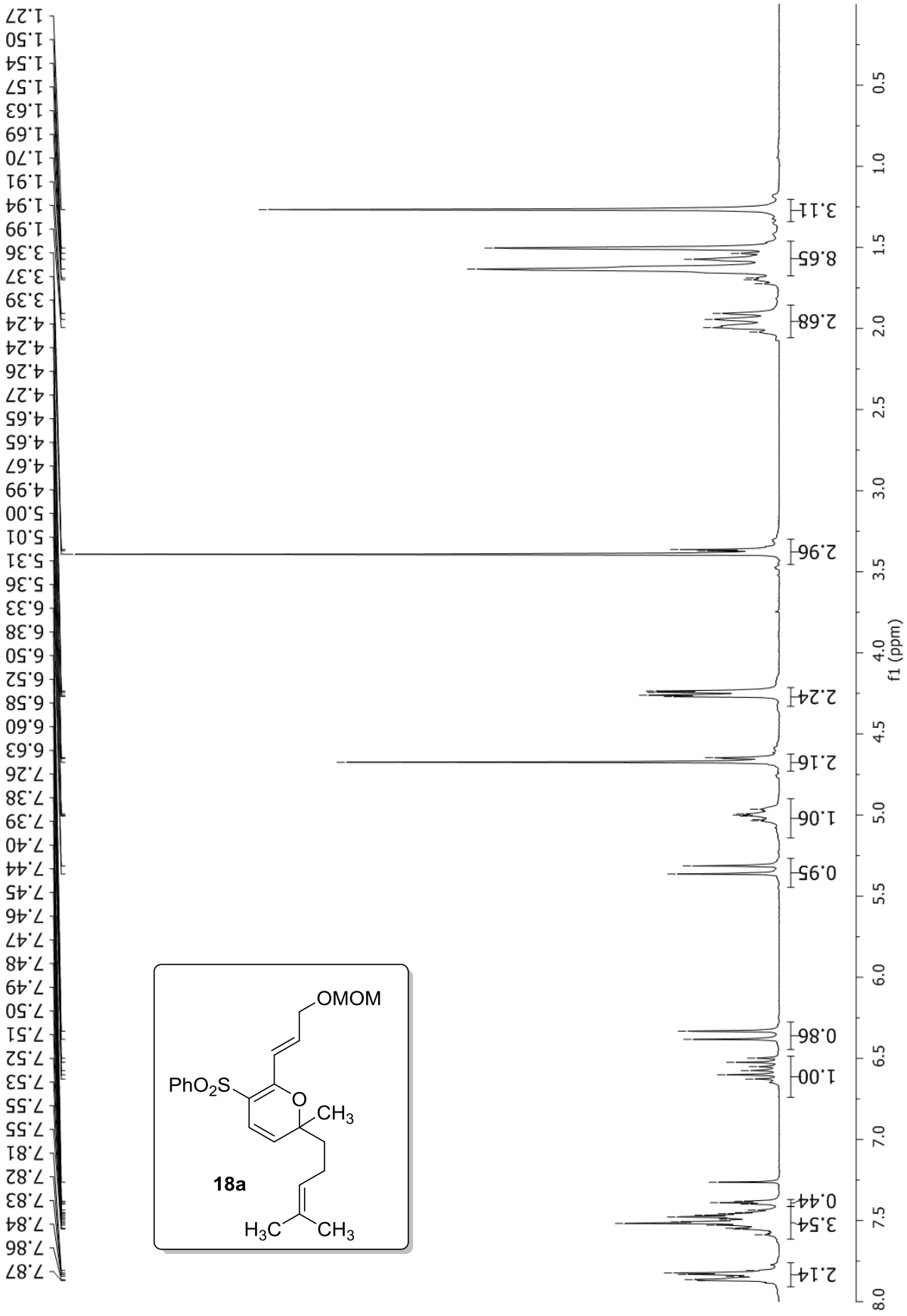

OTHP
O
PhO2S
N
CH3
Ph
OTMS
Ph
f1 (ppm)

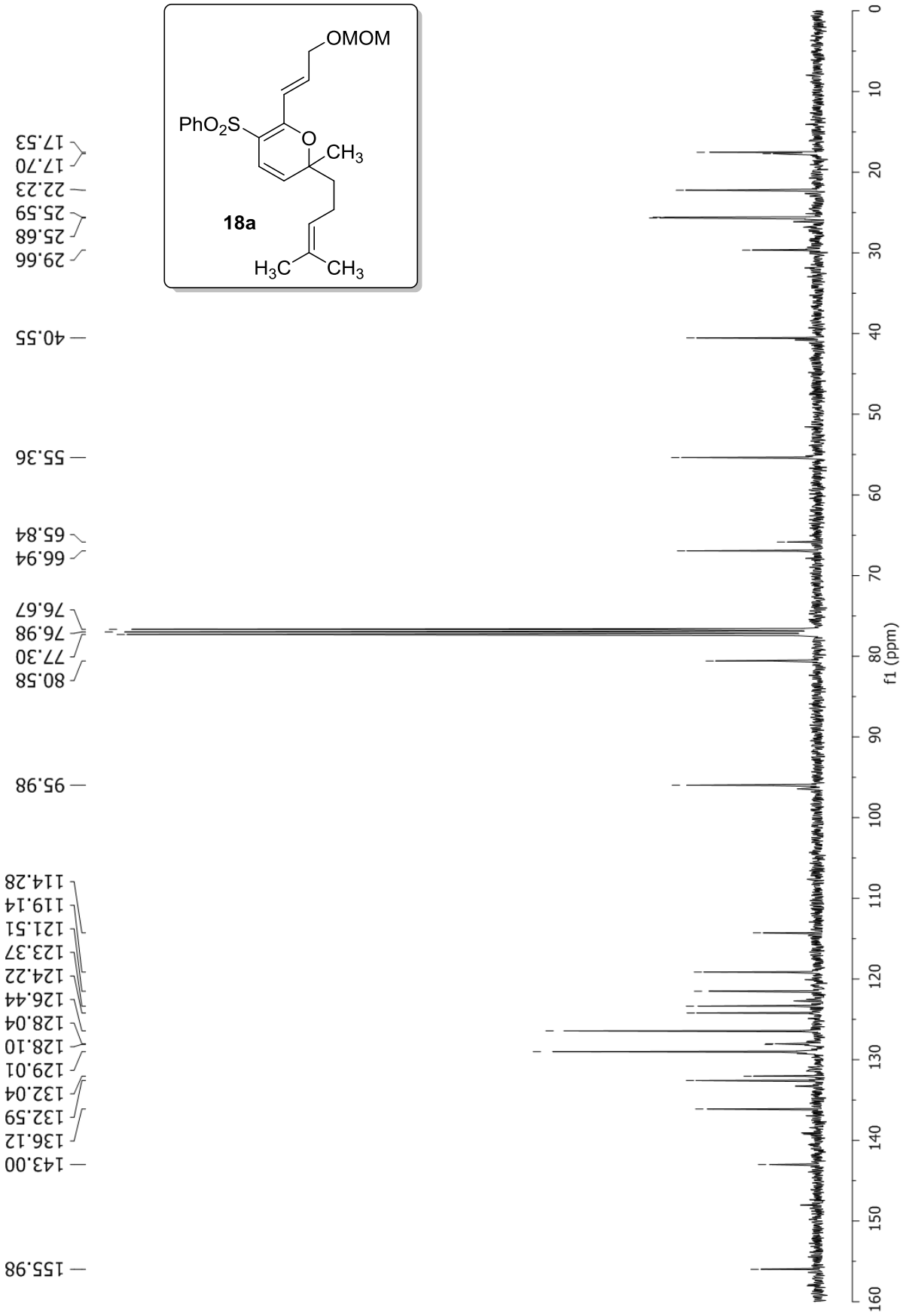






Formula	CalculatedMass	mDaError	ppmError	RDB
C41 H54 N O6 Si S	716.343566	0.534372	0.745971	16.5
C42 H50 N5 O2 Si S	716.344903	-0.80294	-1.120885	21.5
C40 H51 N5 O2 Na Si S	716.342498	1.60232	2.2368	18.5
C45 H51 N3 Na Si S	716.34652	-2.420384	-3.378798	22.5


OMOM
PhO2S
O
CH3
18a
H3C
CH3
f1 (ppm)


OMOM
PhO2S
O
CH3
18a
H3C
CH3
17.53
17.70
22.23
25.59
25.68
29.66
40.55
55.36
65.84
66.94
76.67
76.98
77.30
80.58
95.98
114.28
119.14
121.51
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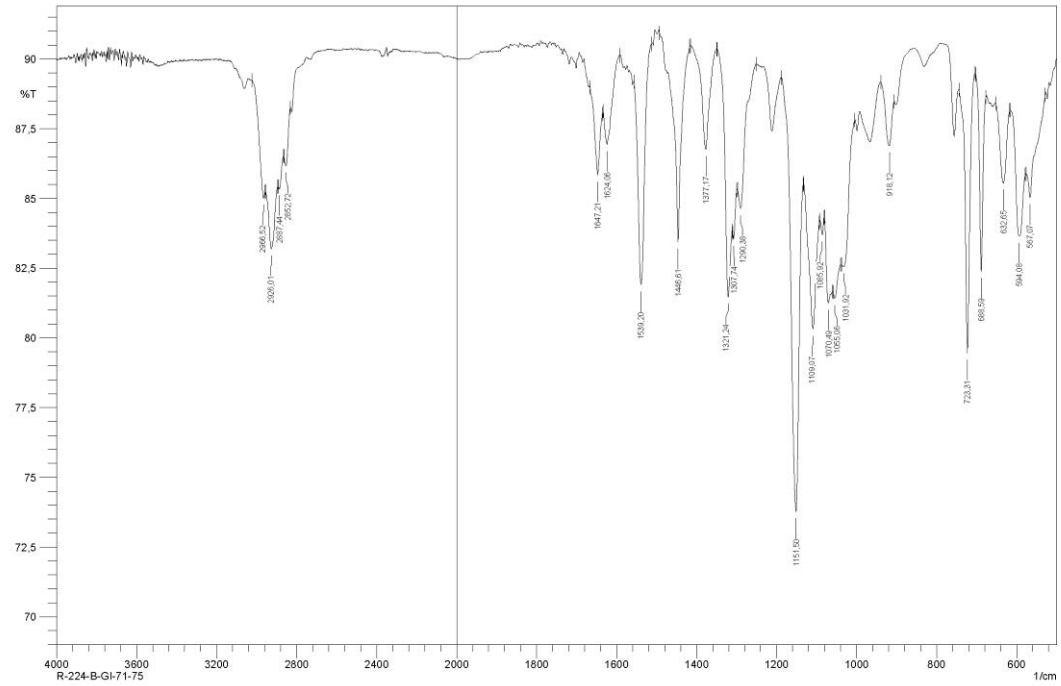
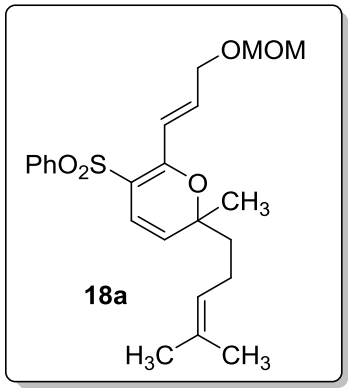
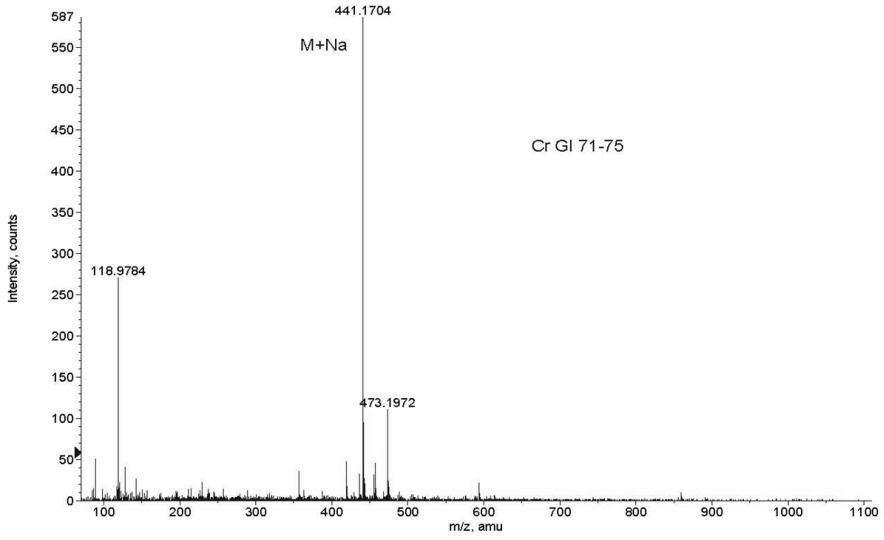
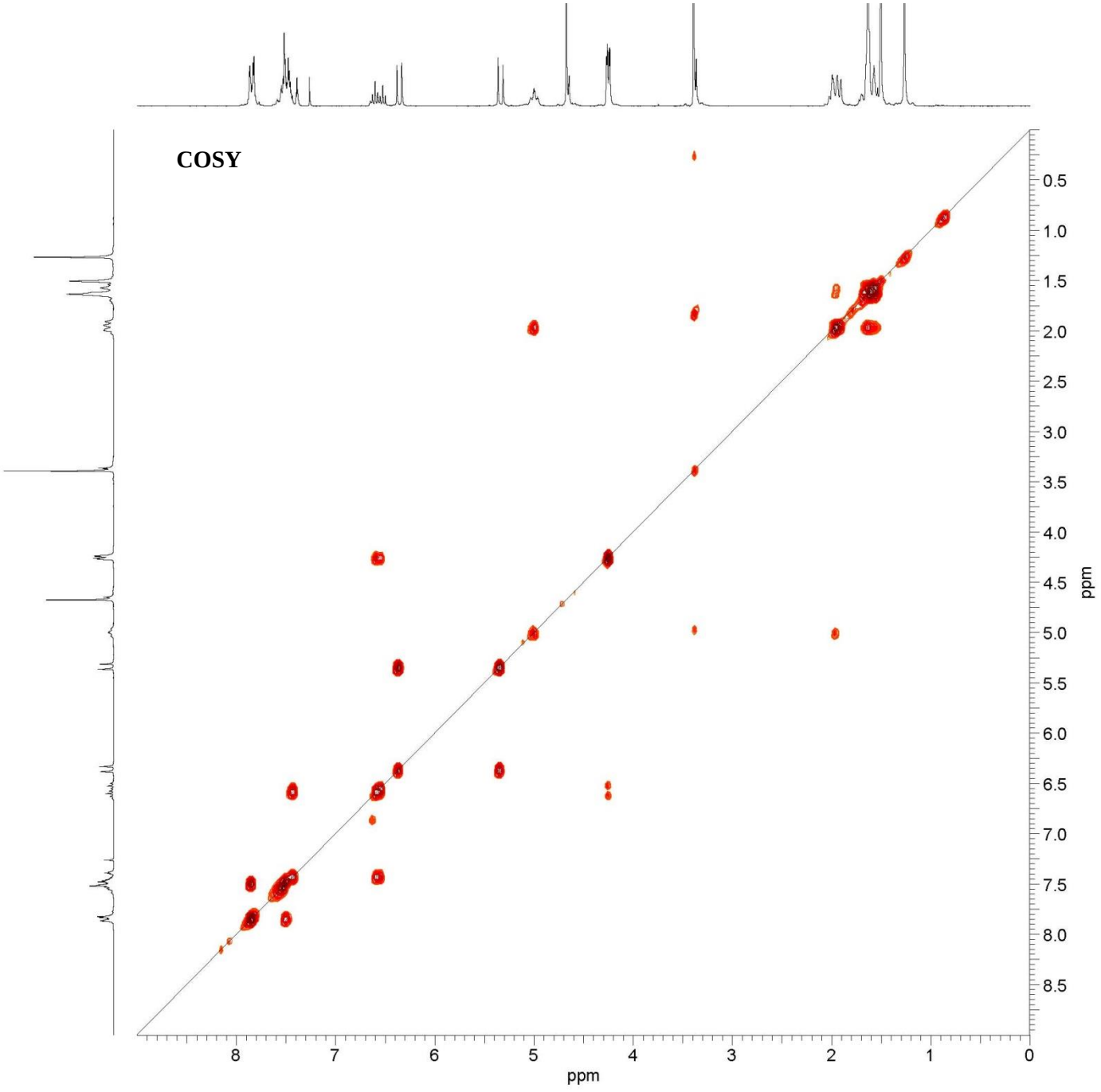
132.59
136.12
143.00
155.98
f1 (ppm)

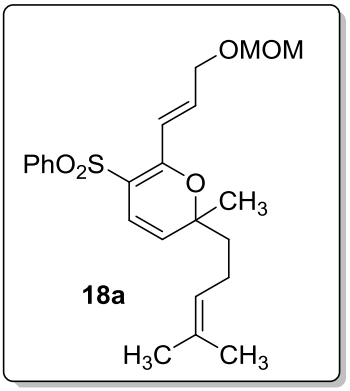




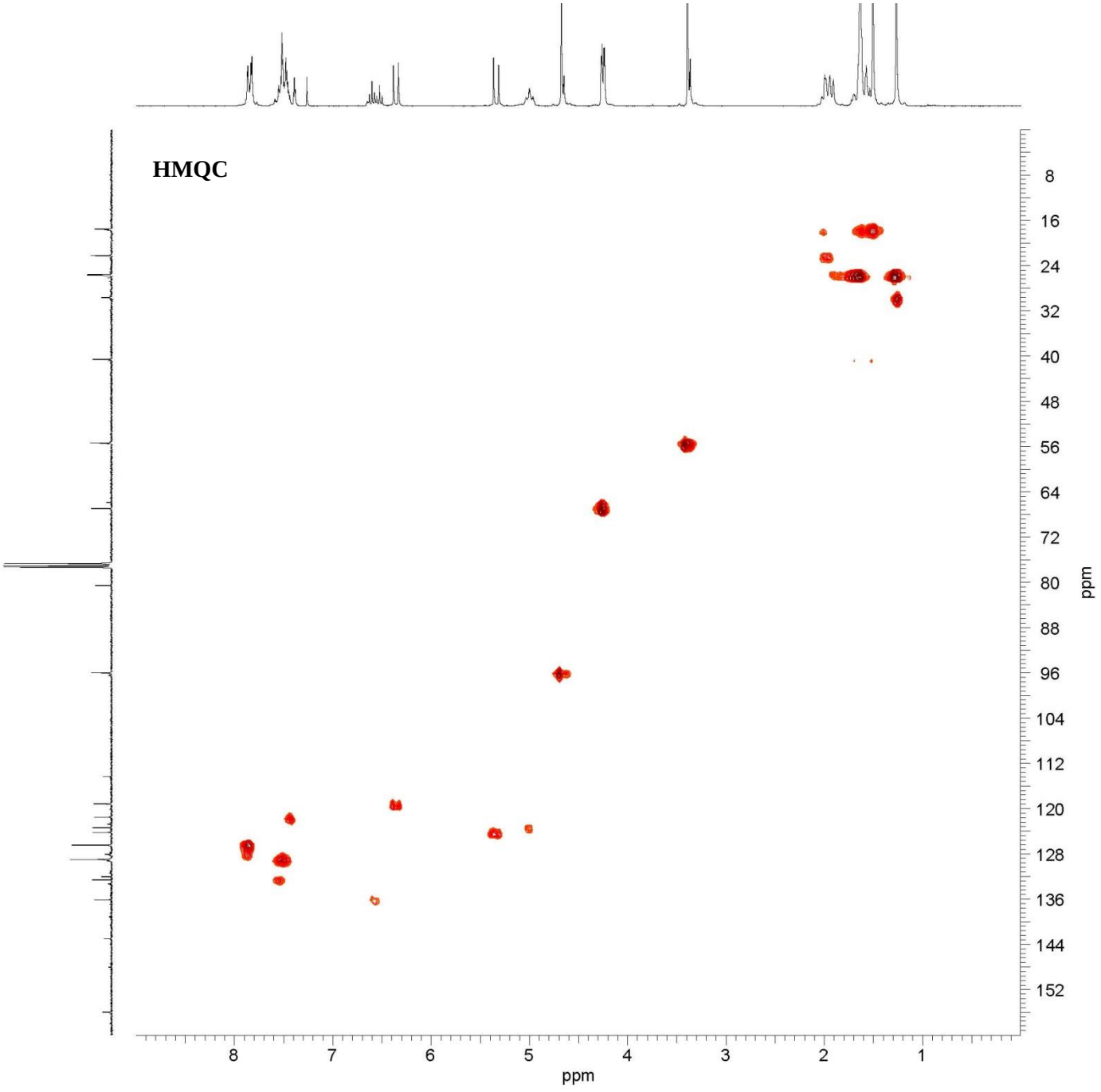


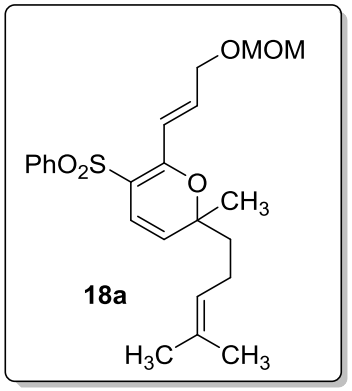
Formula	CalculatedMass	mDaError	ppmError	RDB
C21 H25 N6 O3 S	441.170337	0.062812	0.142376	12.5
C23 H30 O5 Na S	441.170617	-0.21732	-0.492598	8.5

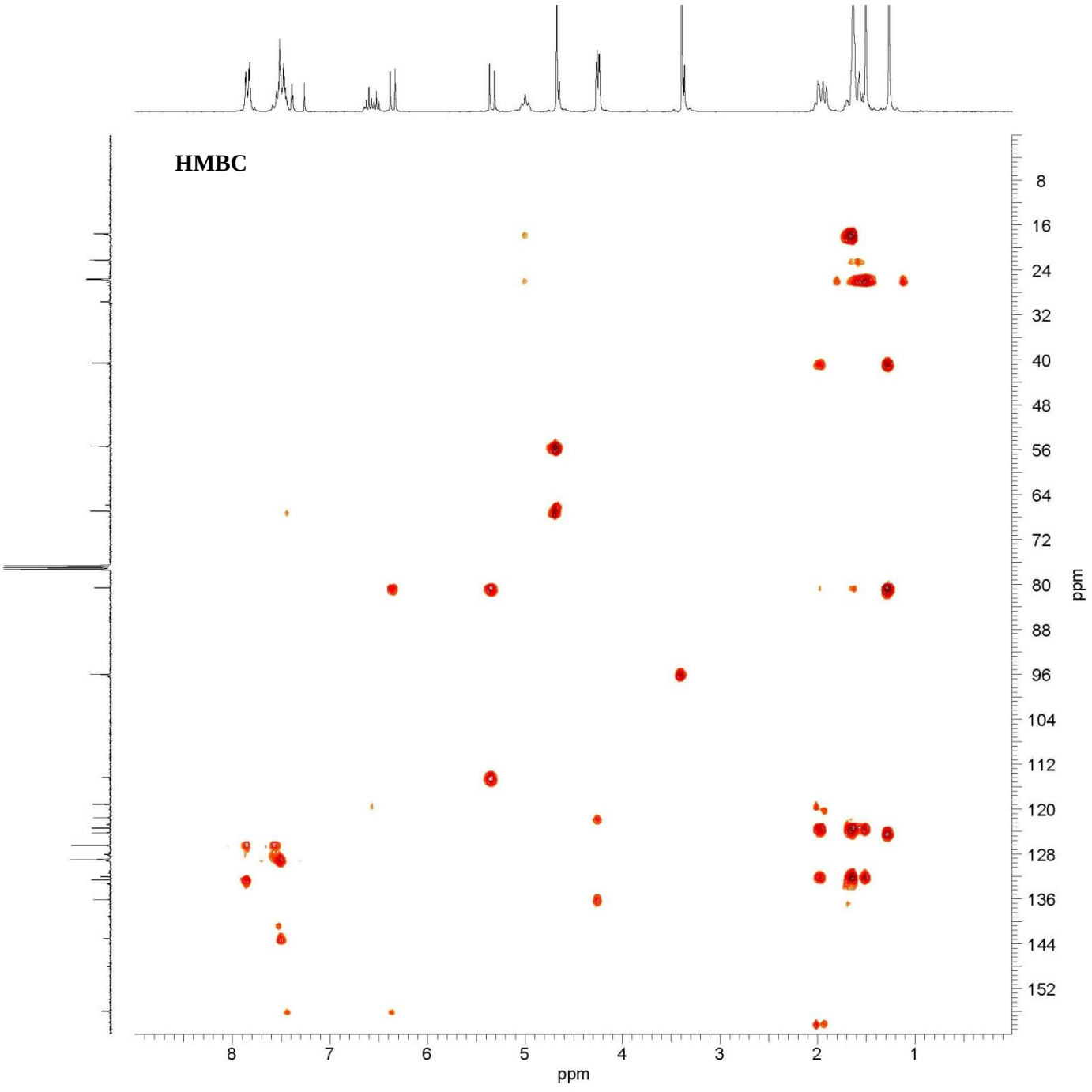


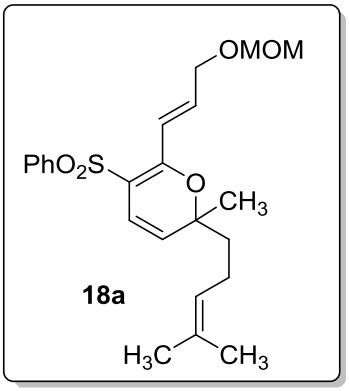


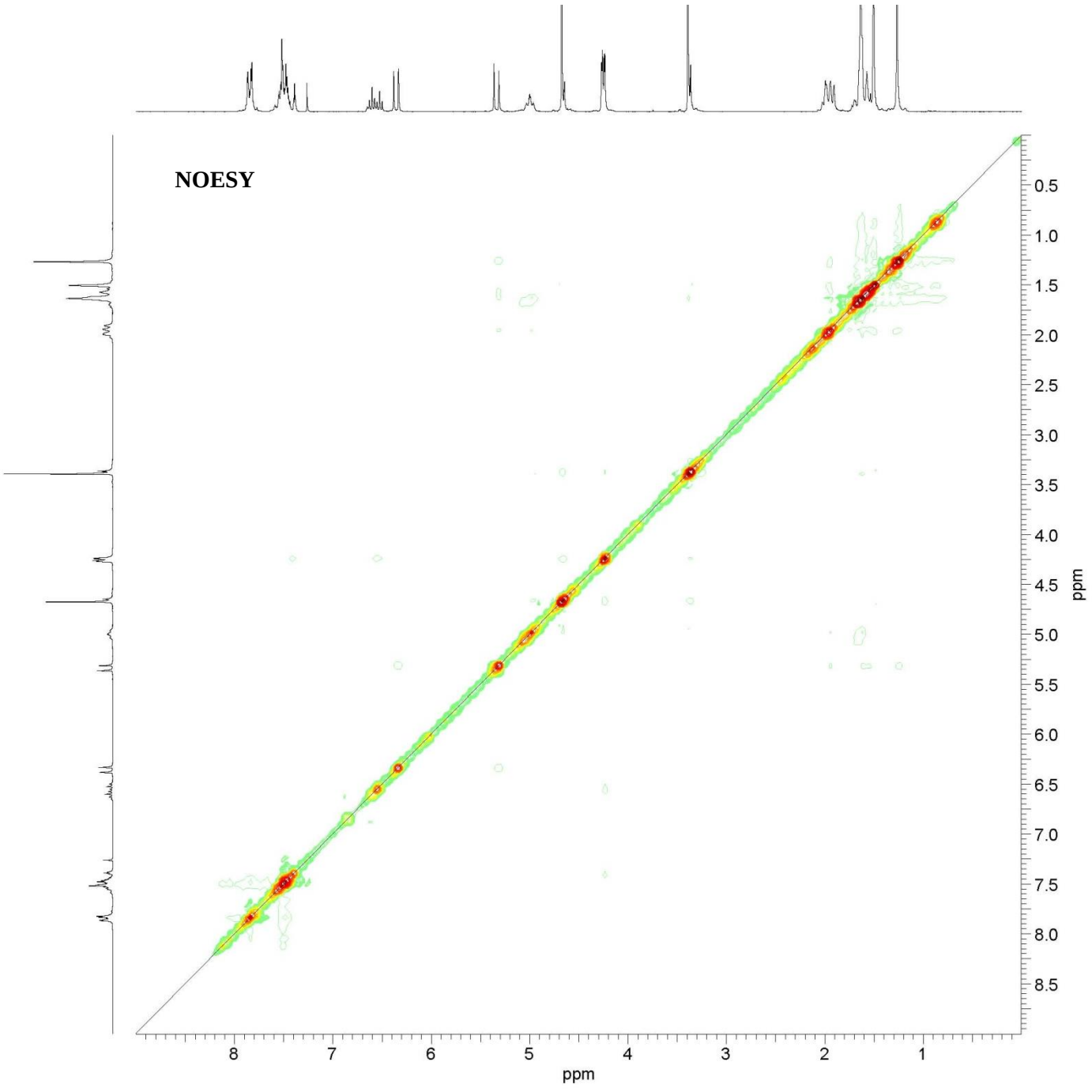
18a


HMQC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
ppm
8
7
6
5
4
3
2
1
ppm


OMOM
PhO2S
O
CH3
18a
H3C
CH3


HMBC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
ppm
8
7
6
5
4
3
2
1
ppm


OMOM
PhO2S
O
CH3
18a
H3C
CH3


NOESY
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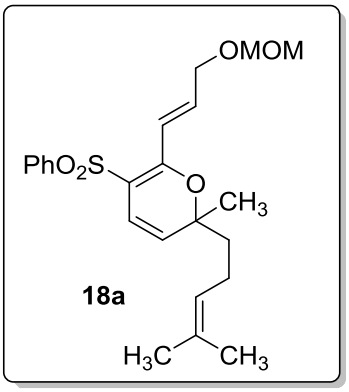
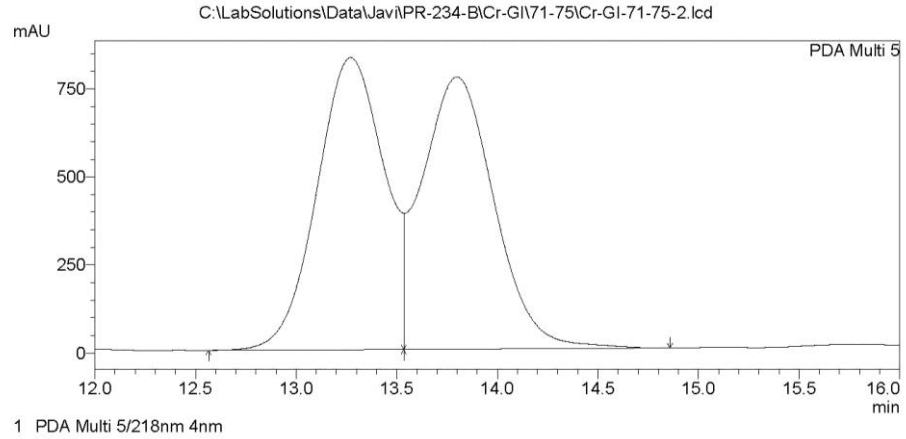
7
6
5
4
3
2
1
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm


OMOM
PhO2S
O
CH3
H3C
CH3

18a

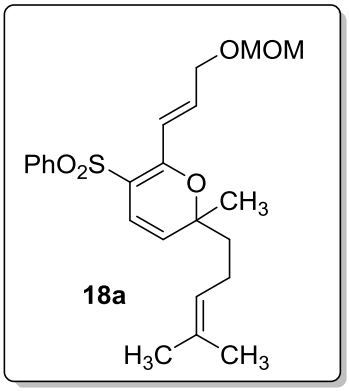
<Chromatogram>



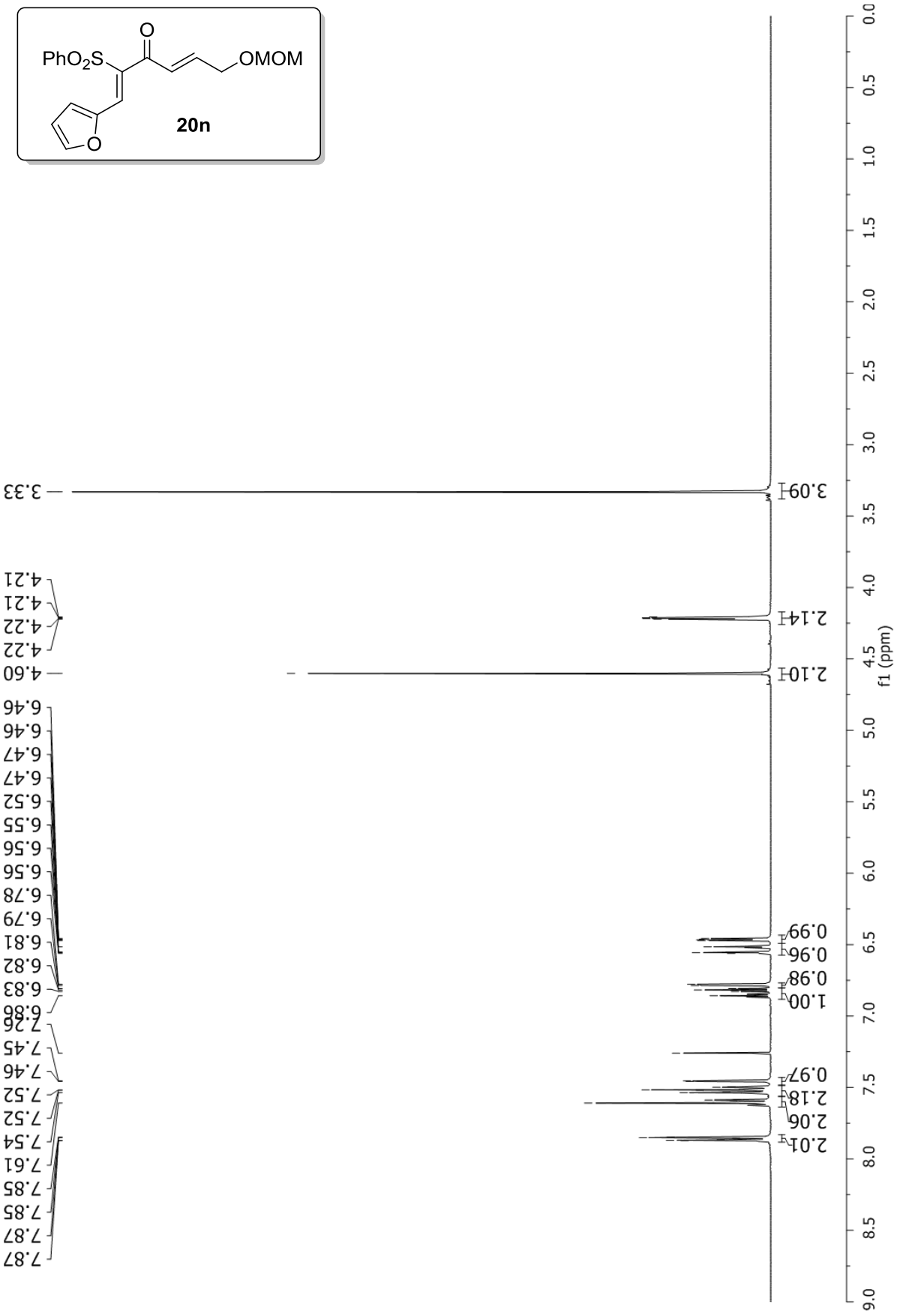
PeakTable

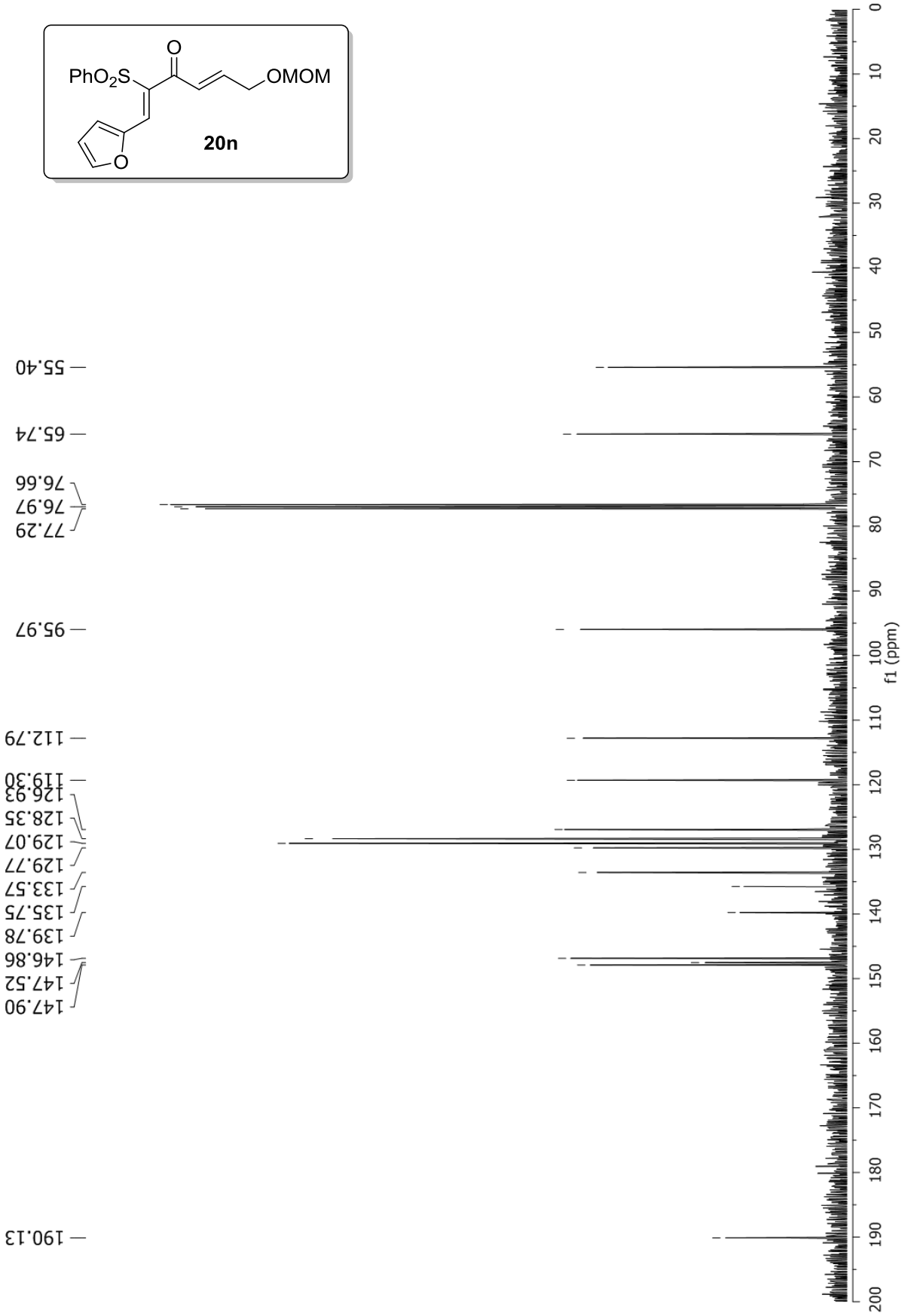
PDA Ch5 218nm 4nm

Peak#	Ret. Time	Area %
1	13.265	50.162
2	13.794	49.838
Total		100.000



18a


PhO2S
O
OMOM
O
20n
f1 (ppm)


PhO2S
O
OMOM
O
20n
55.40
65.74
76.66
76.97
77.29
95.97
112.79
119.30
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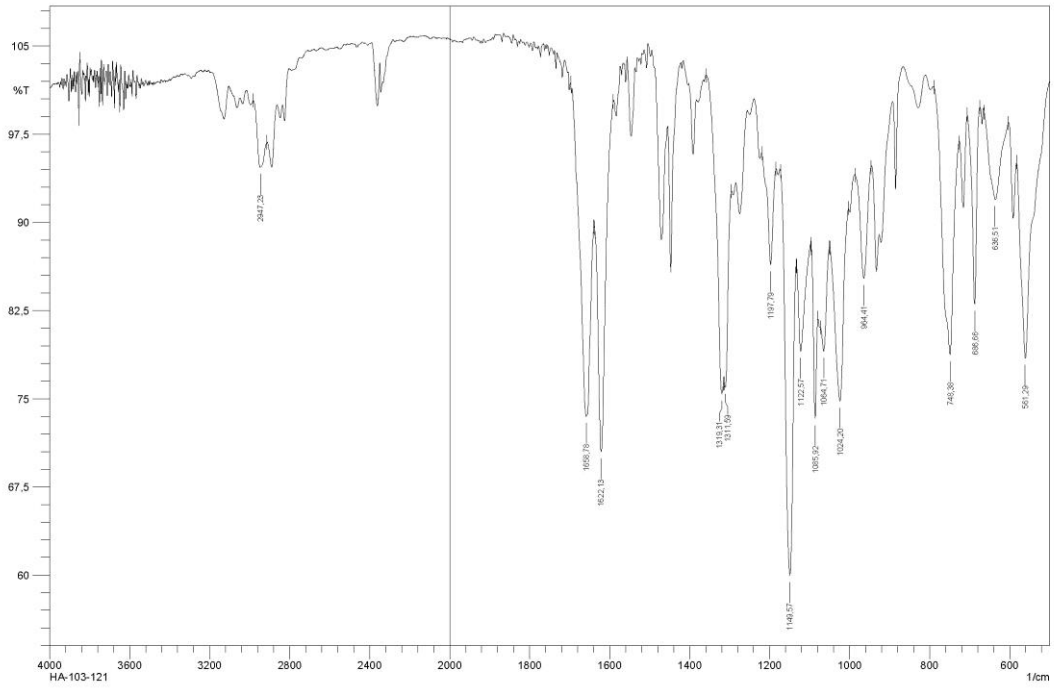
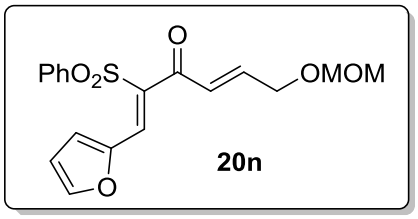
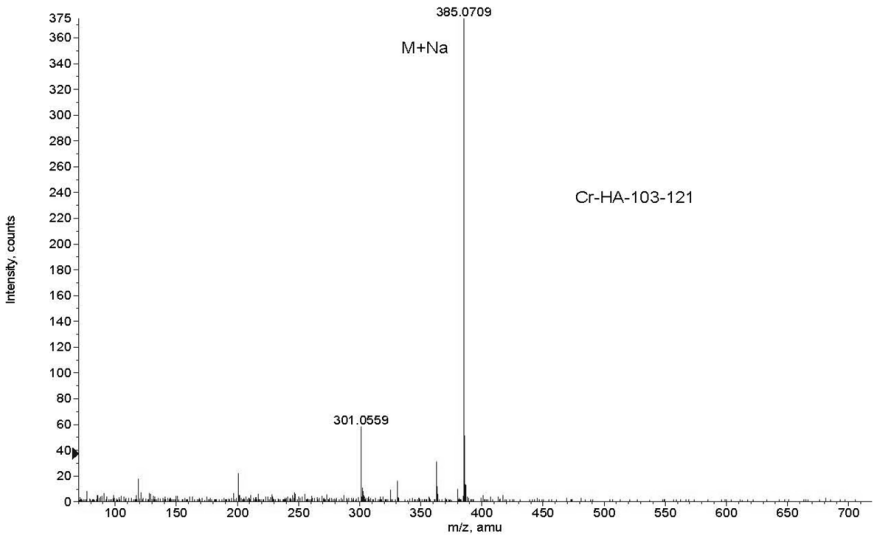
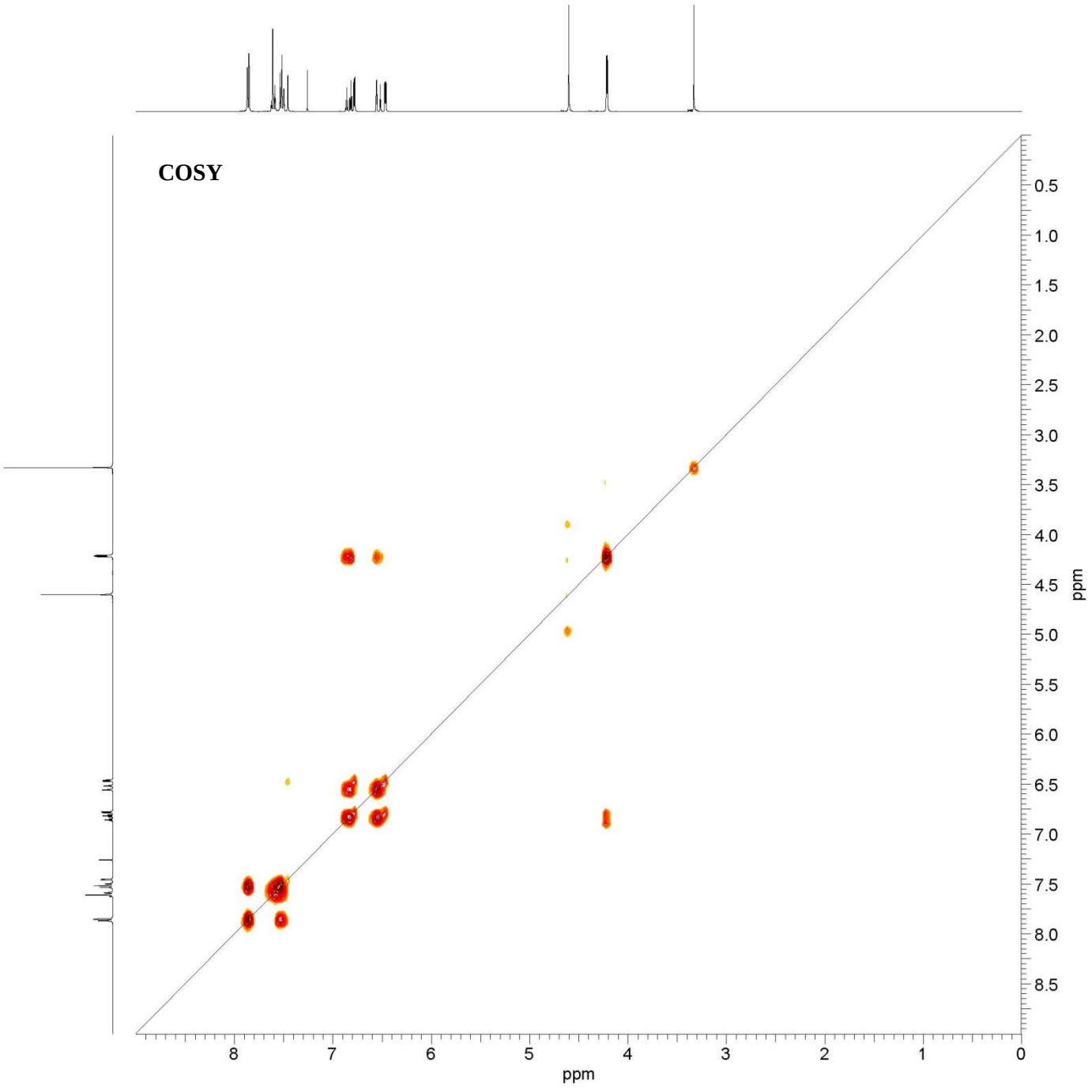
146.86
147.52
147.90
190.13
f1 (ppm)







Formula	CalculatedMass	mDaError	ppmError	RDB
H13 N14 O9 S	385.070517	0.383388	0.995628	1.5
C16 H13 N6 O4 S	385.071351	-0.451348	-1.172115	13.5
C15 H10 N10 Na S	385.070283	0.6166	1.601261	15.5
C18 H18 O6 Na S	385.071631	-0.73148	-1.899596	9.5
C15 H17 N2 O8 S	385.070014	0.885964	2.300778	8.5
C3 H14 N12 O7 Na S	385.072134	-1.234056	-3.204746	2.5


COSY
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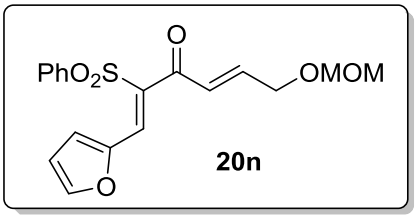
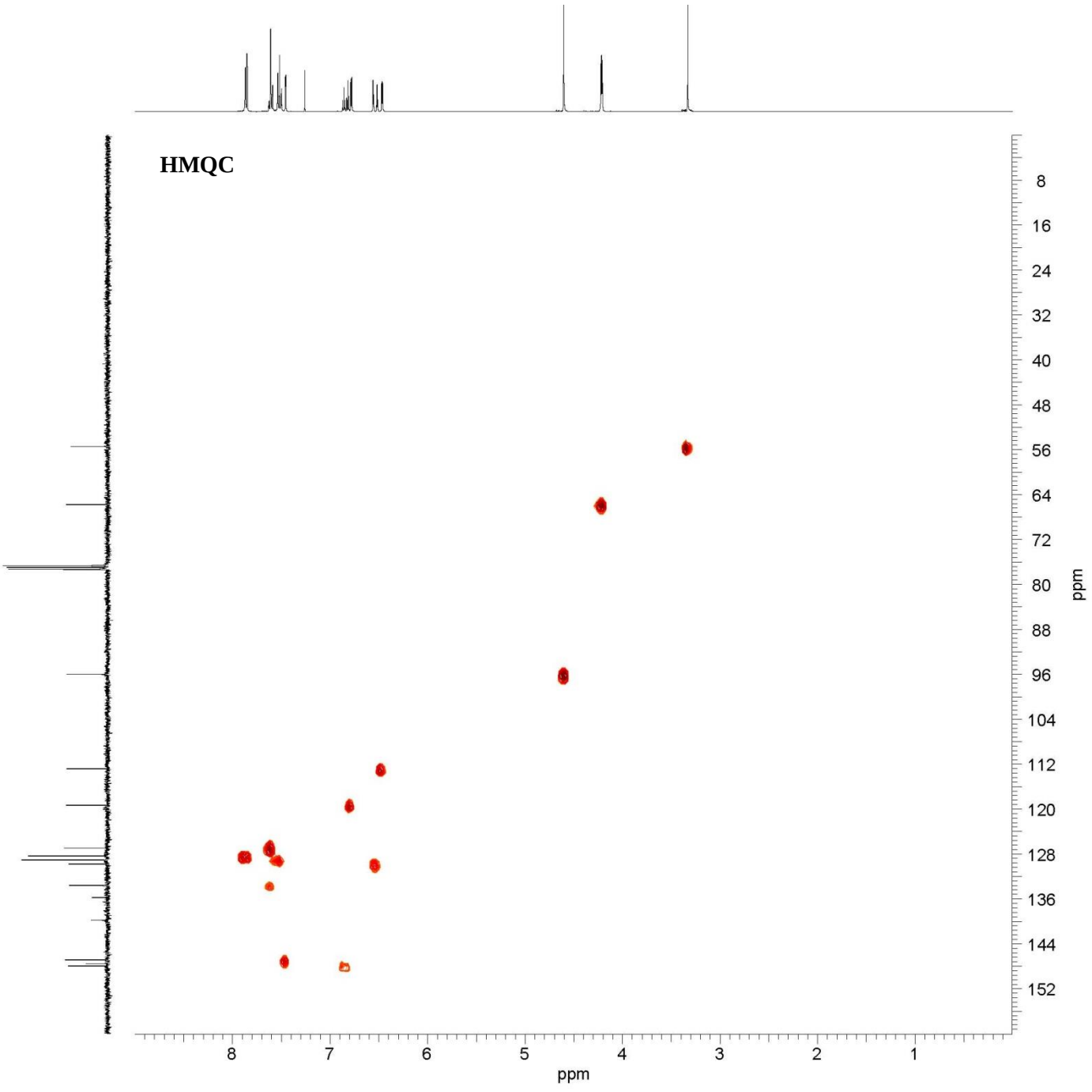
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm
8
7
6
5
4
3
2
1
0
ppm


PhO2S
O
OMOM
O

20n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ppm
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6
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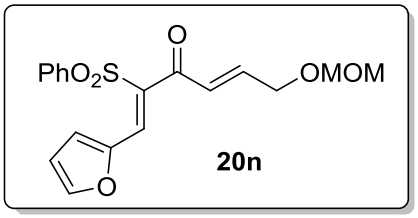
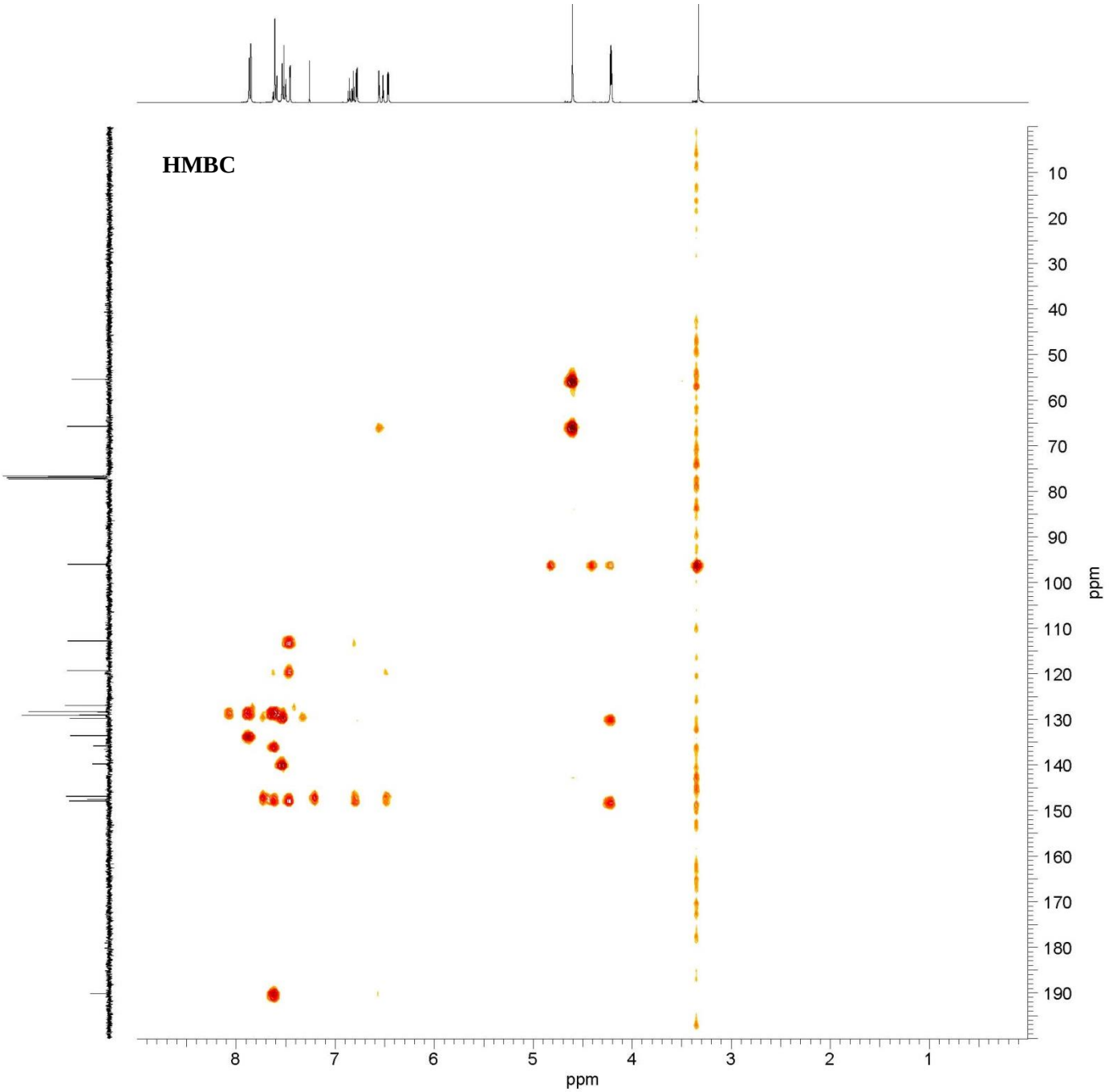
4
3
2
1
ppm


O
PhO2S
OMOM
O

20n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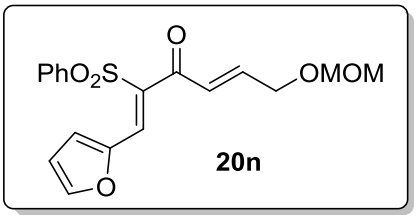
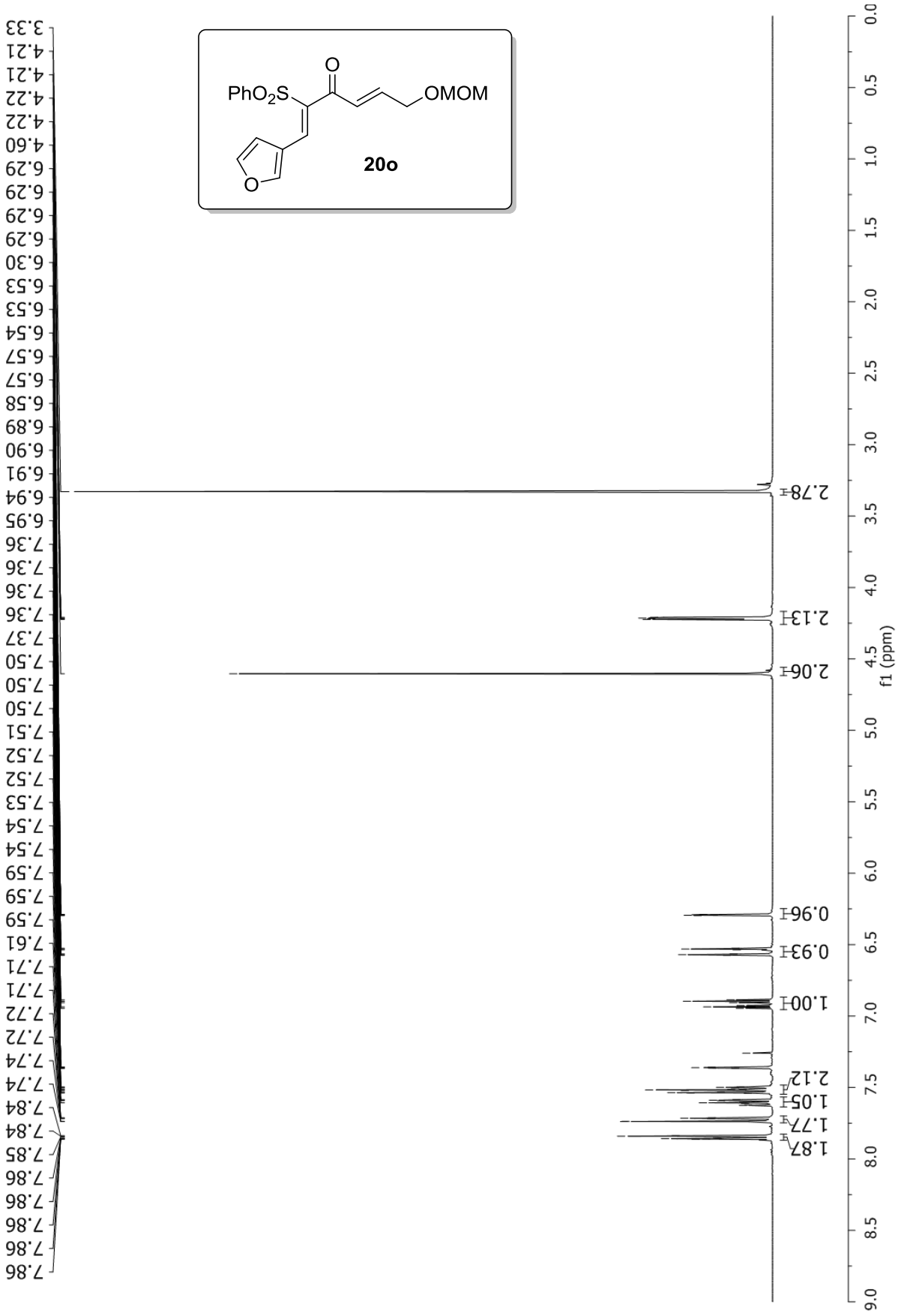
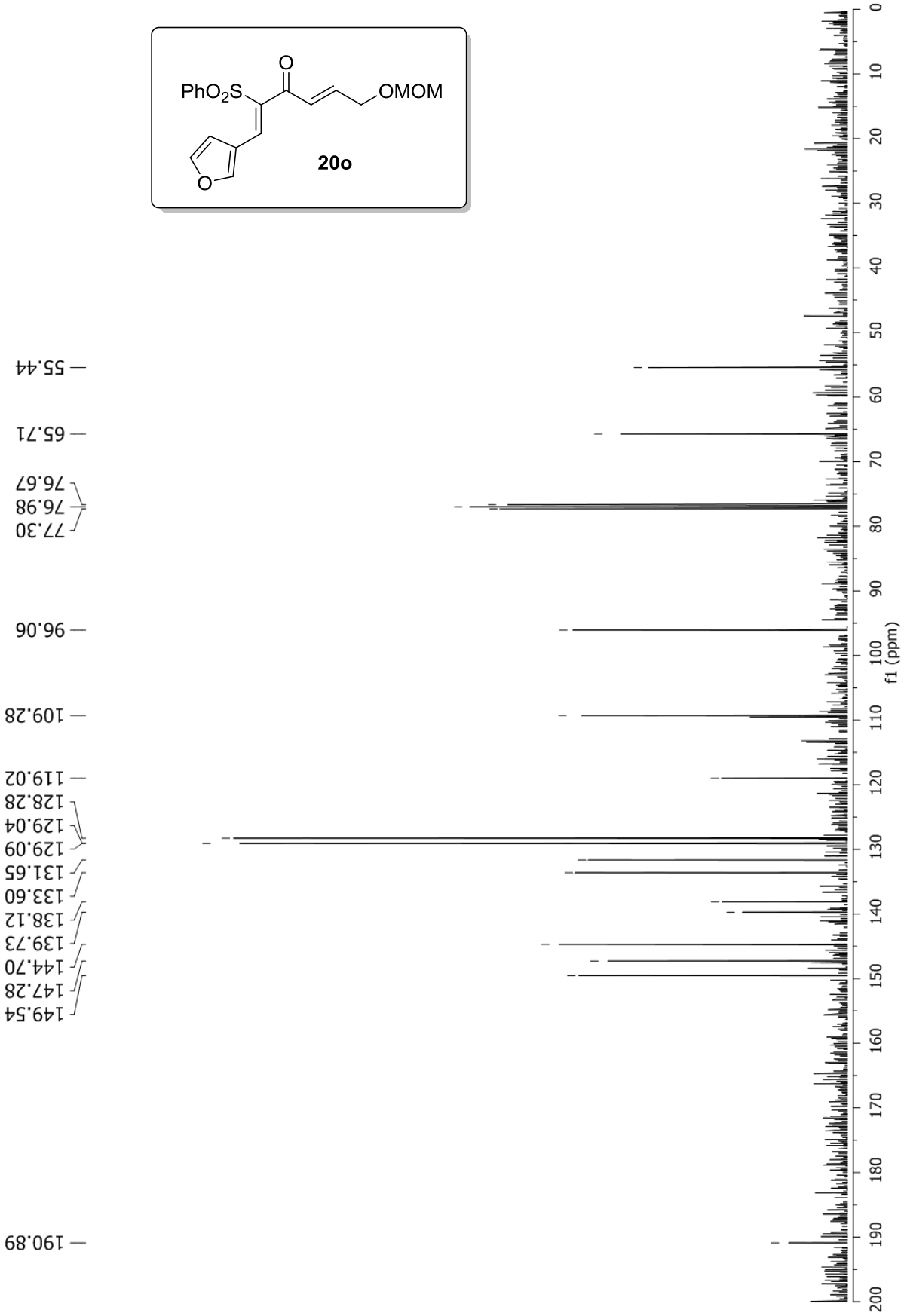
ppm


O
PhO2S
OMOM
O

20n


PhO2S
O
OMOM
O
20o
f1 (ppm)


PhO2S
O
OMOM
O
20o
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109.28
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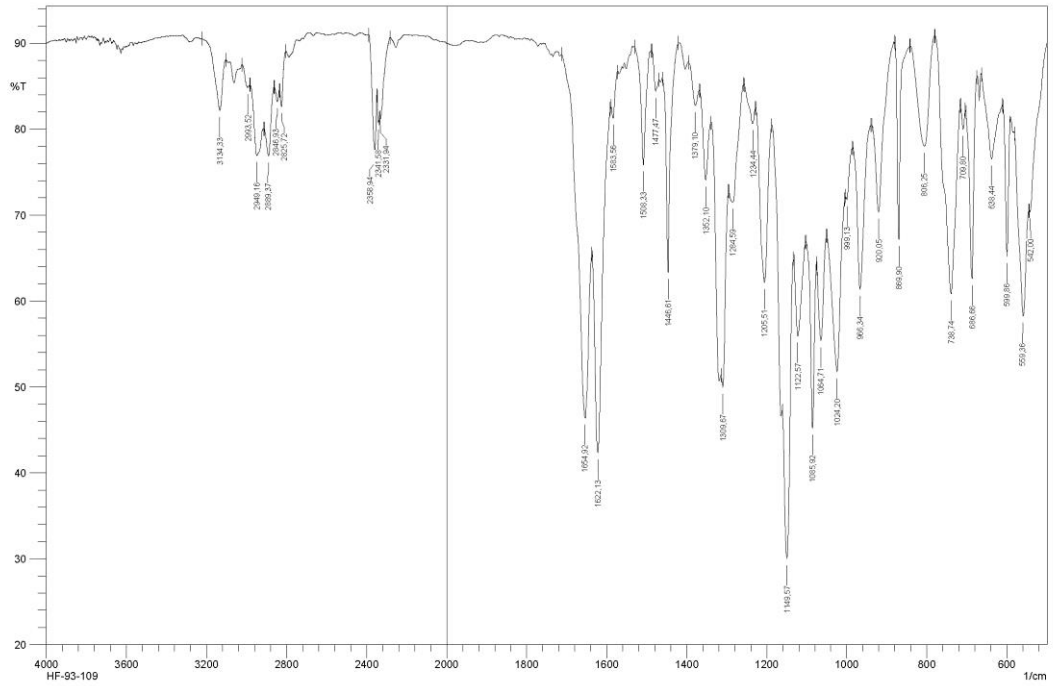
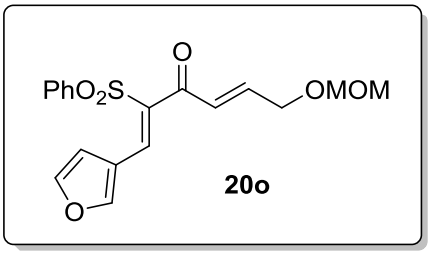
f1 (ppm)





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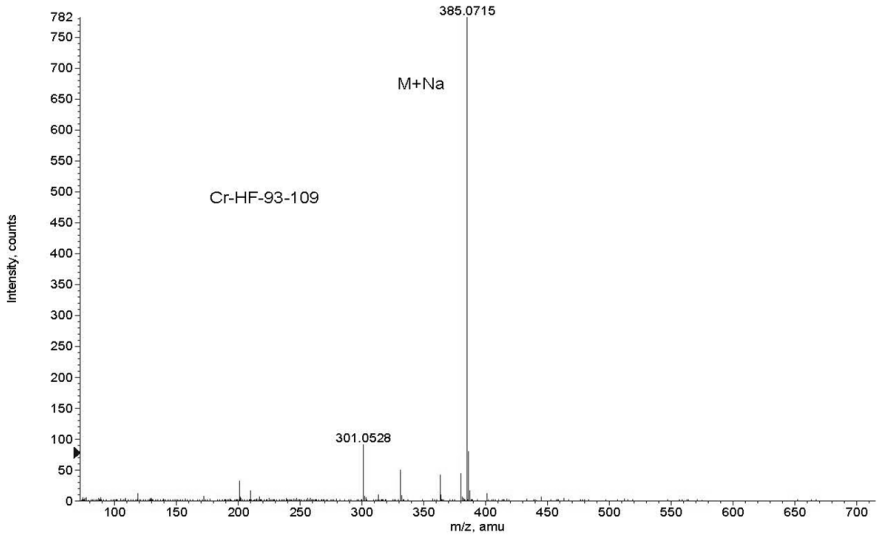
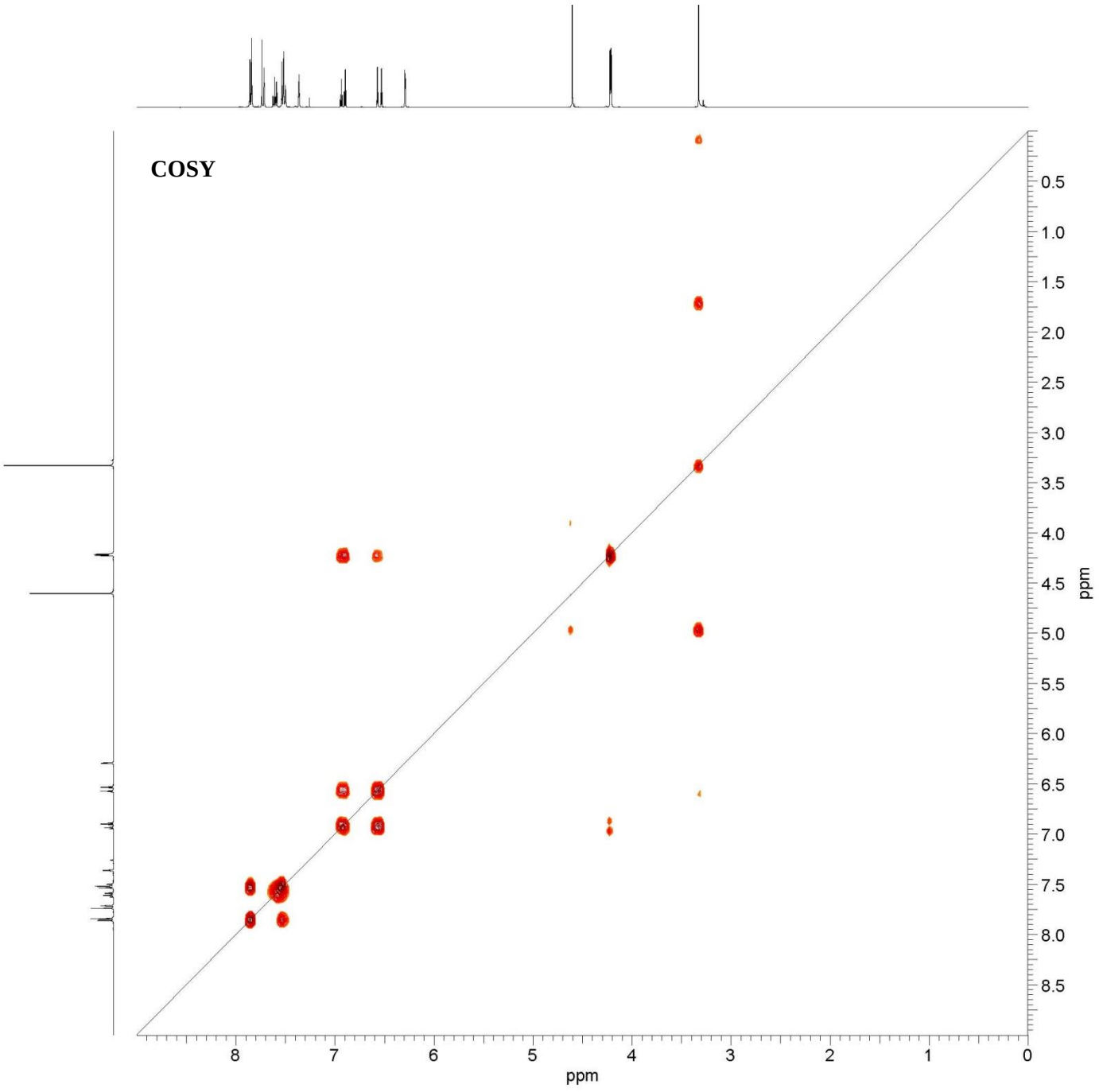
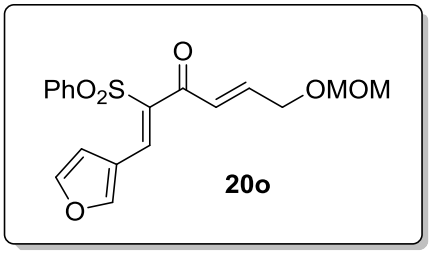


Formula	CalculatedMass	mDaError	ppmError	RDB
C18 H18 O6 Na S	385.071631	-0.13148	-0.341443	9.5
C16 H13 N6 O4 S	385.071351	0.148652	0.386037	13.5
C3 H14 N12 O7 Na S	385.072134	-0.634056	-1.646591	2.5
H13 N14 O9 S	385.070517	0.983388	2.553777	1.5
C17 H9 N10 S	385.072689	-1.18866	-3.086851	18.5





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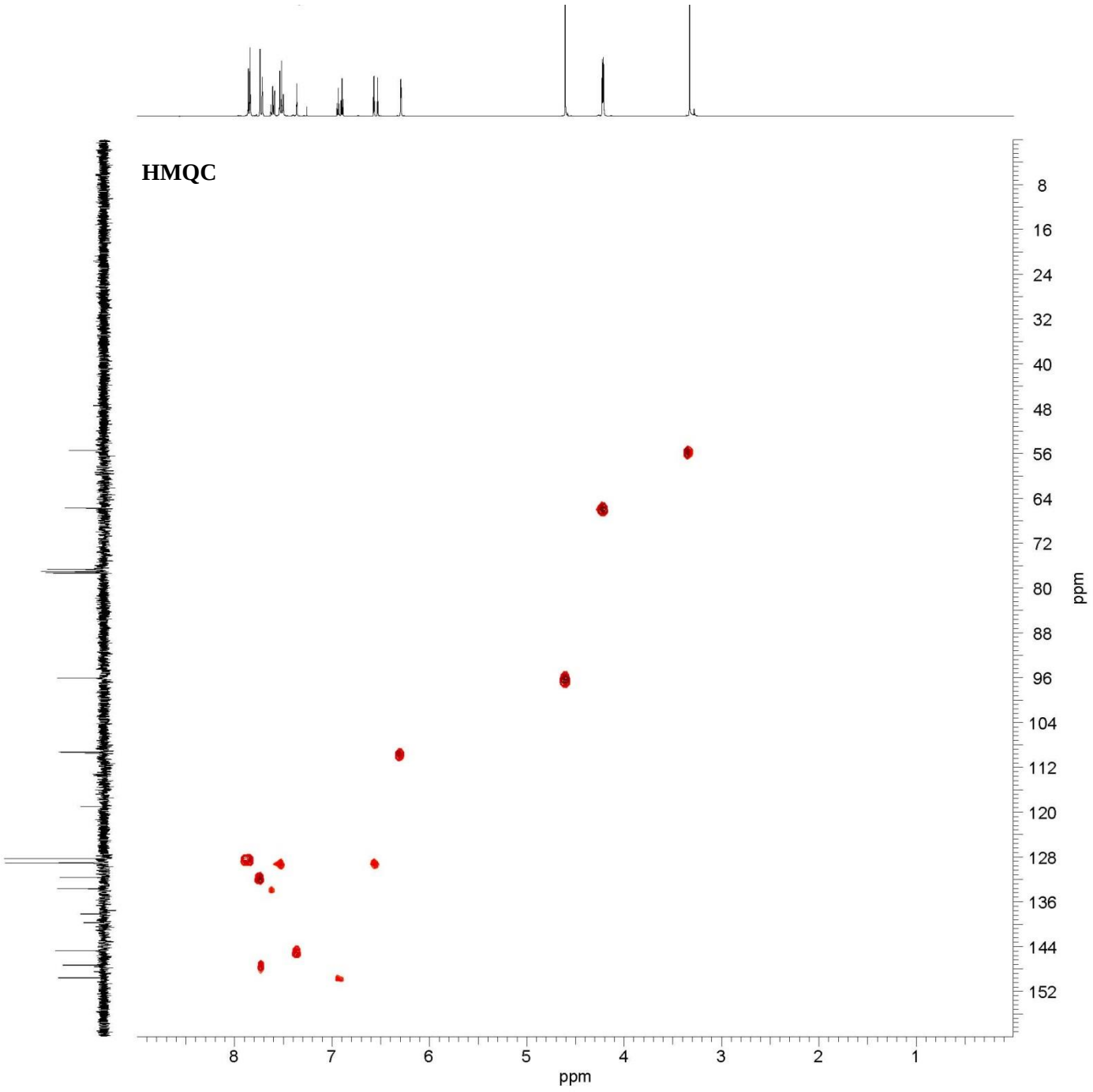
HMQC
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24
32
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ppm
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7
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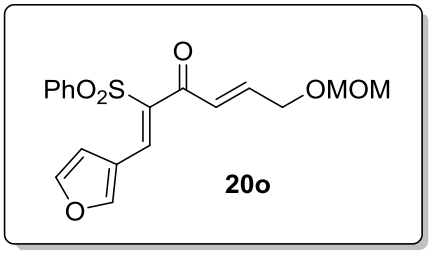
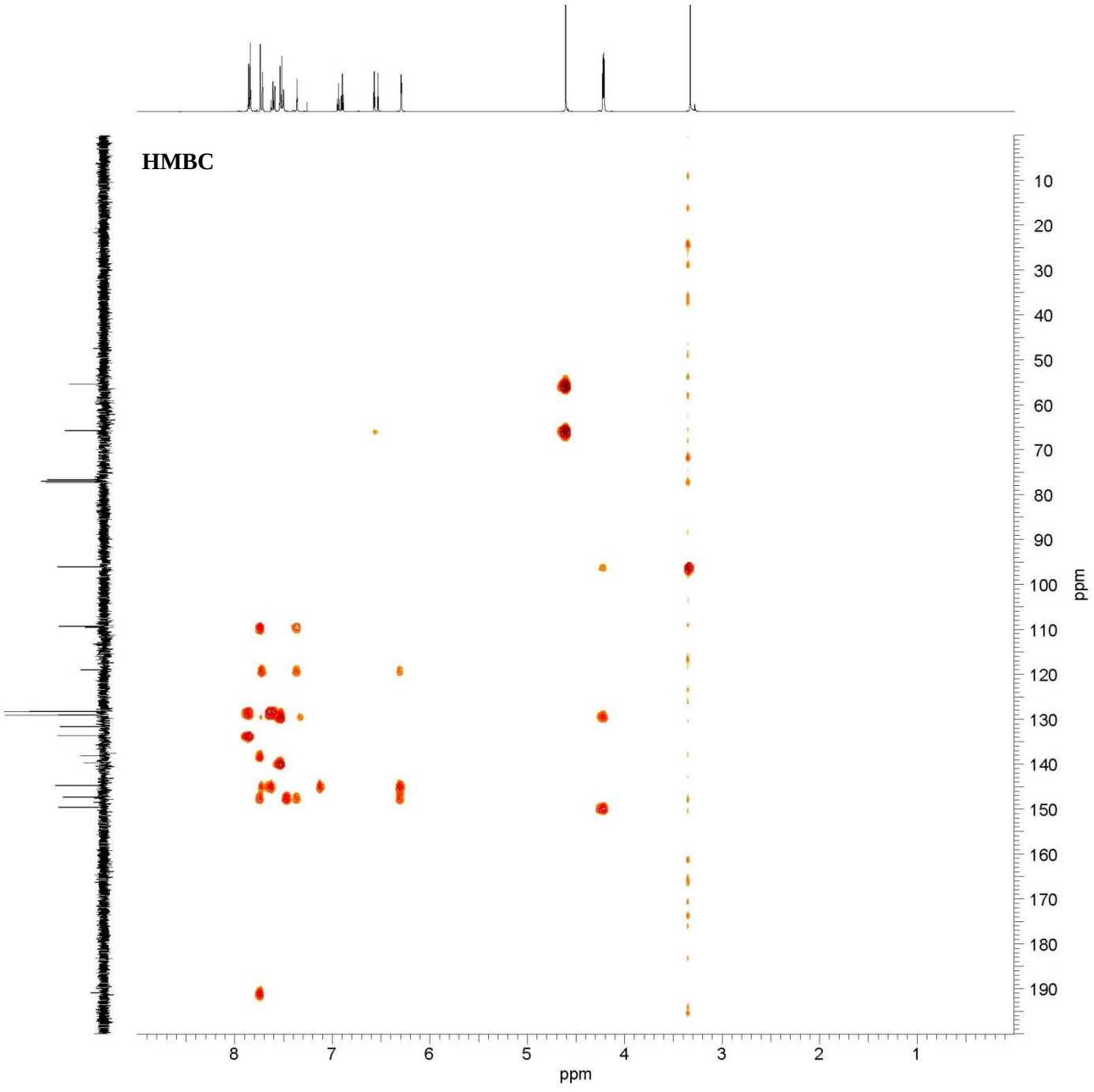
4
3
2
1
ppm


PhO2S
O
OMOM
O

20o


HMBC
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150
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170
180
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ppm
8
7
6
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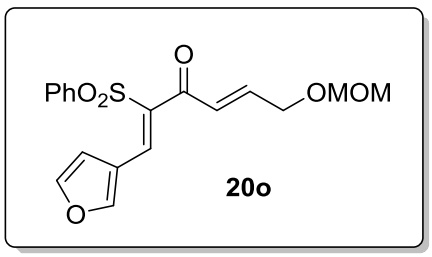
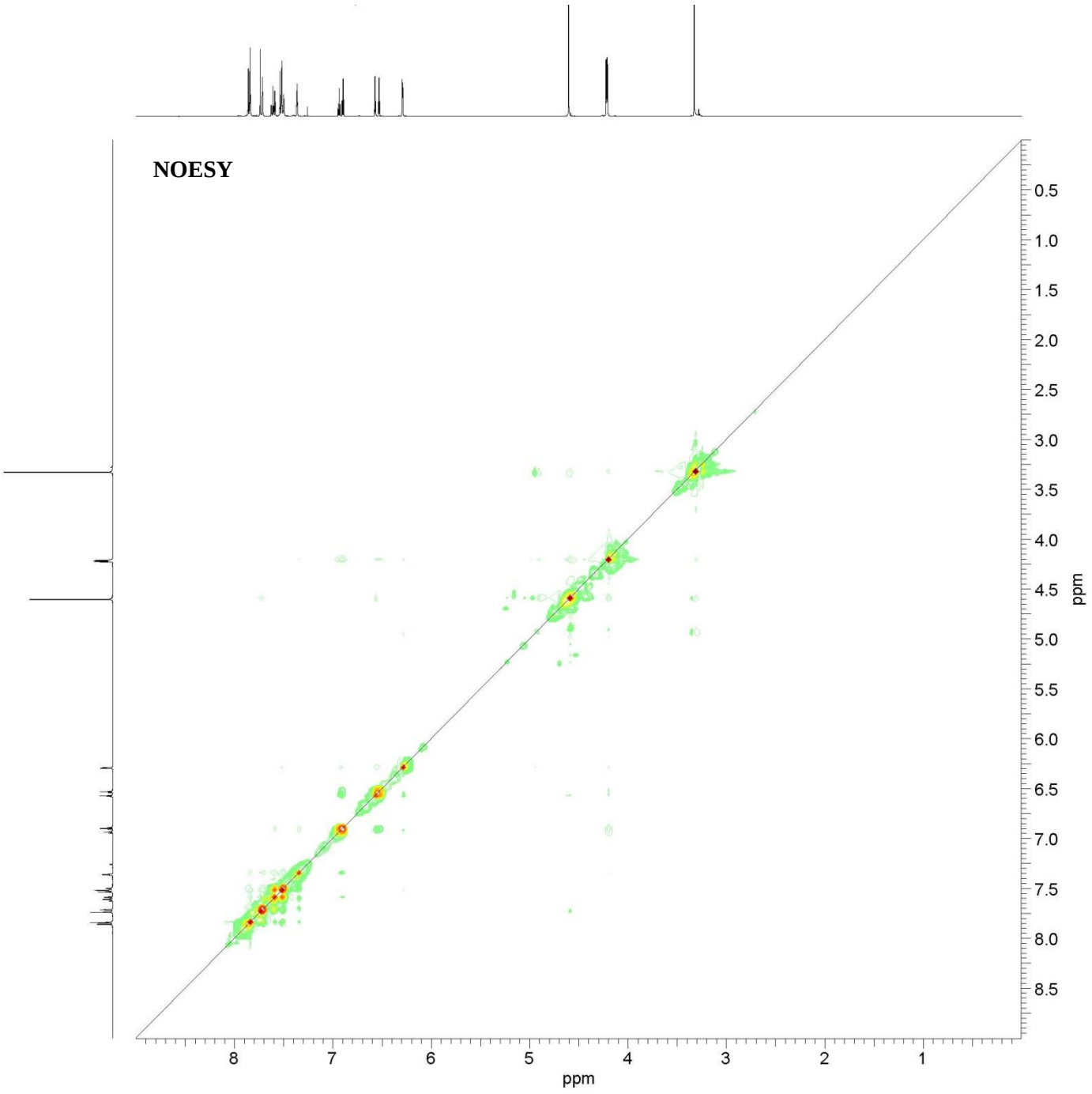
4
3
2
1
ppm


PhO2S
O
OMOM
O

20o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7
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5
4
3
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1
ppm
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2.5
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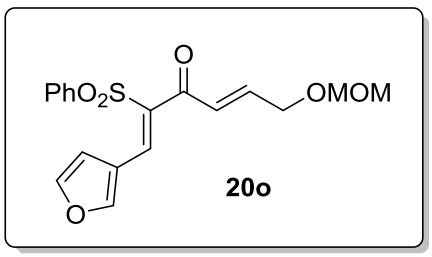
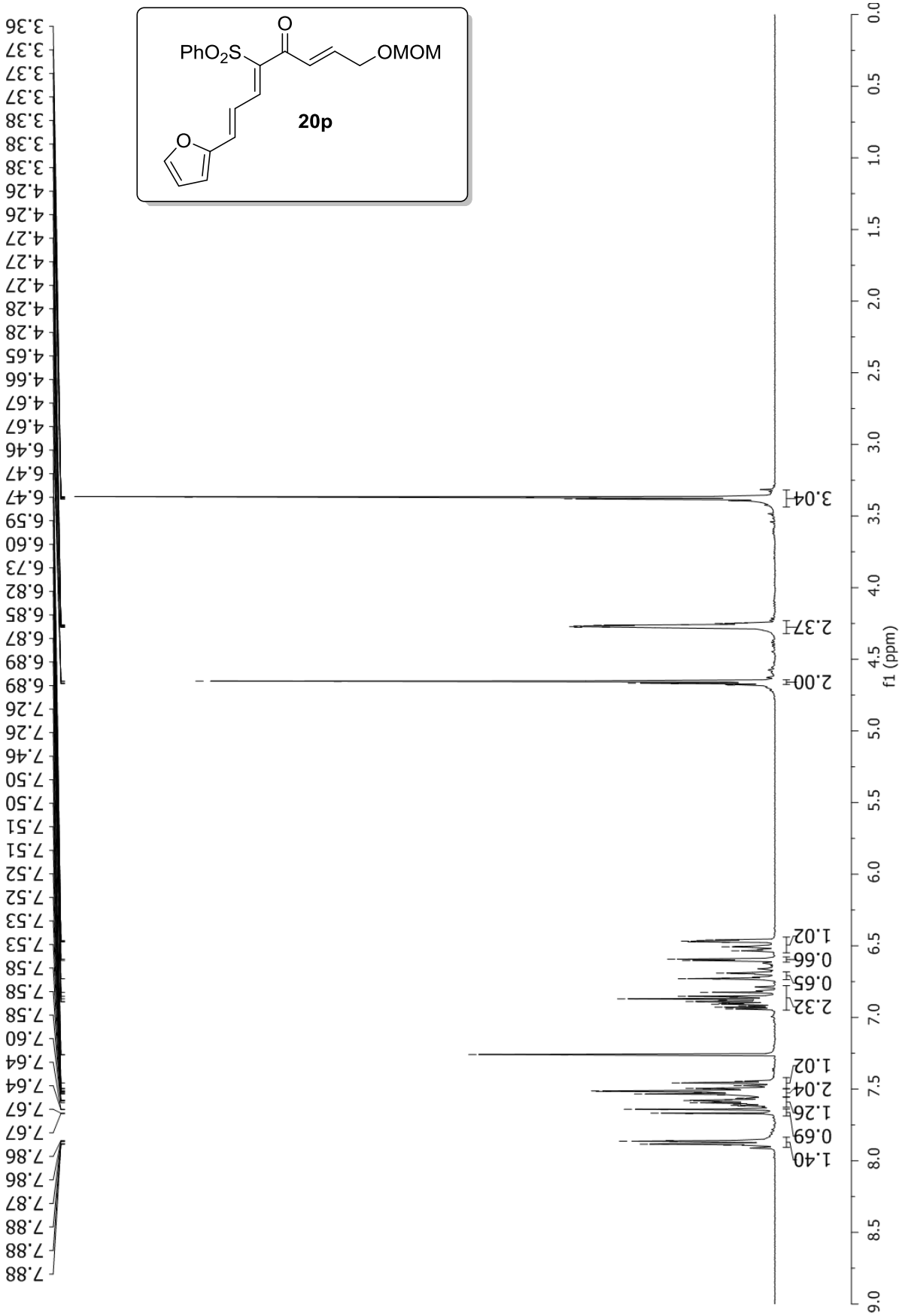
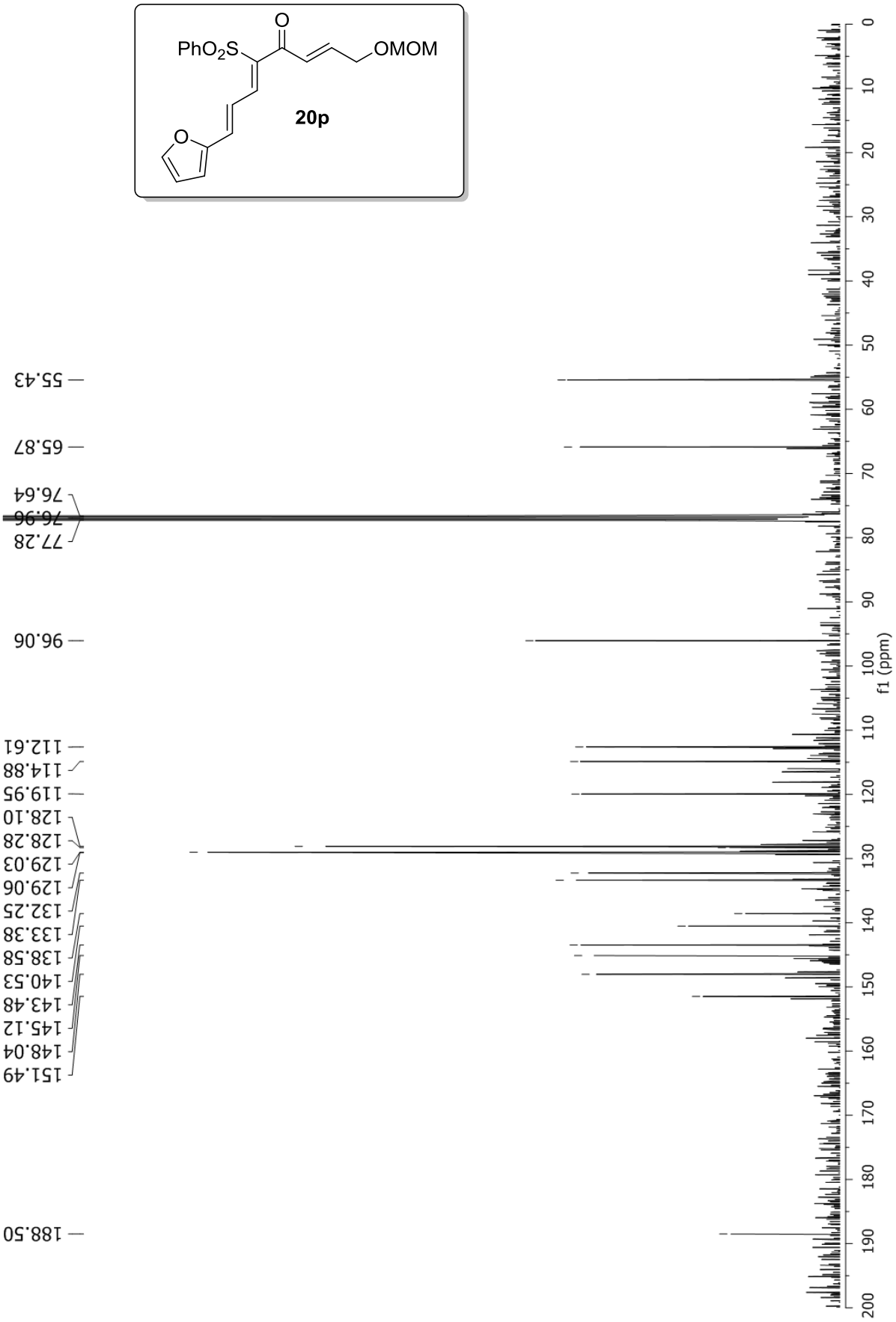
8.0
8.5
ppm


O
PhO2S
OMOM
O

20o


PhO2S
O
OMOM
O
20p
f1 (ppm)


O
PhO2S
OMOM
20p
O
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96.06
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119.95
128.10
128.28
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145.12
148.04
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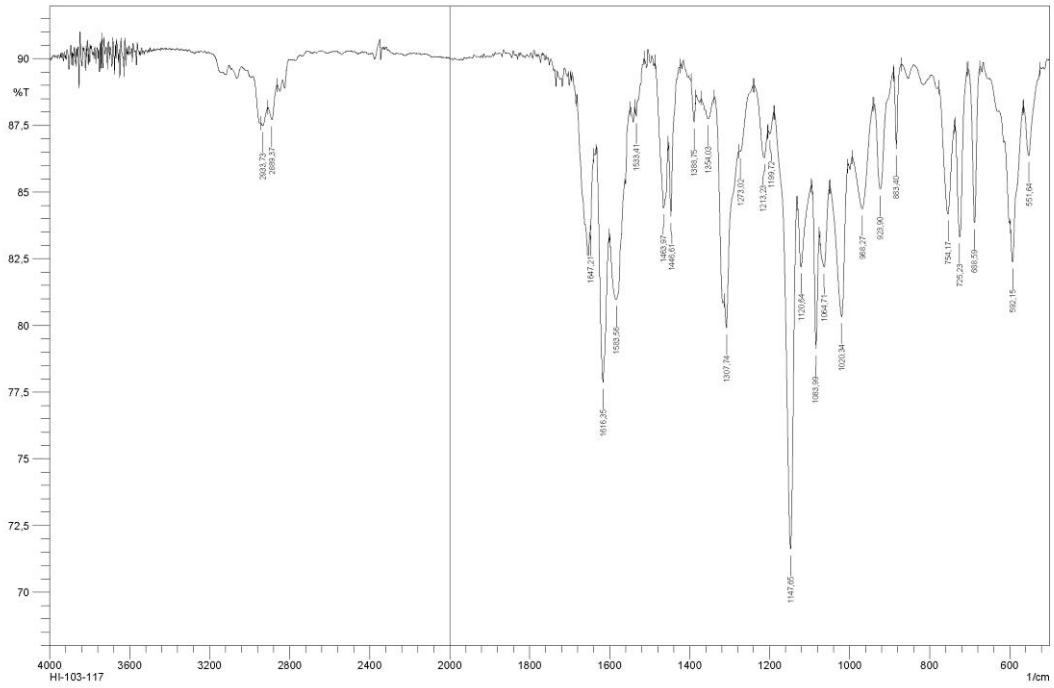
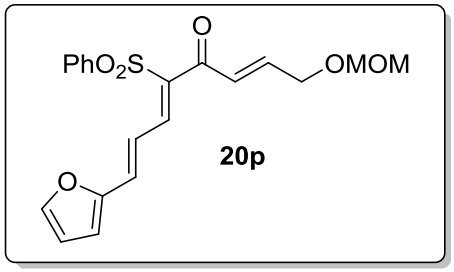
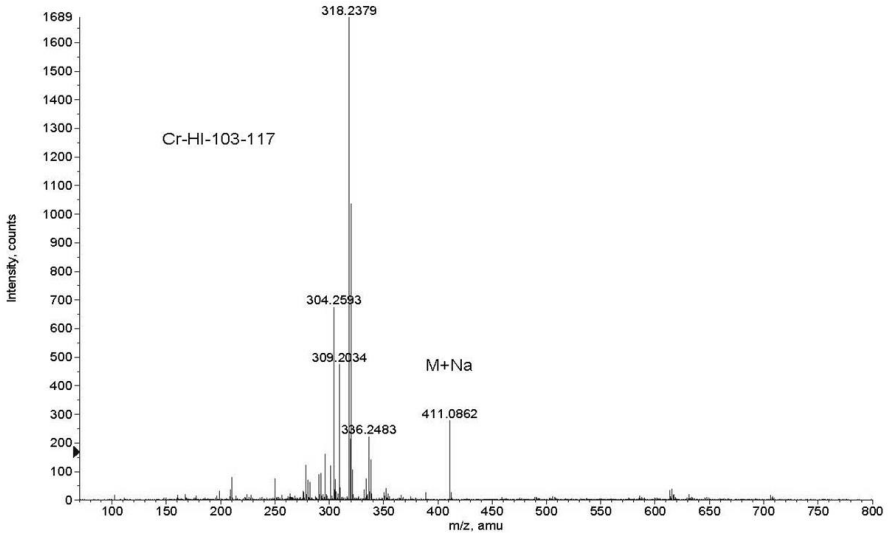
188.50
f1 (ppm)

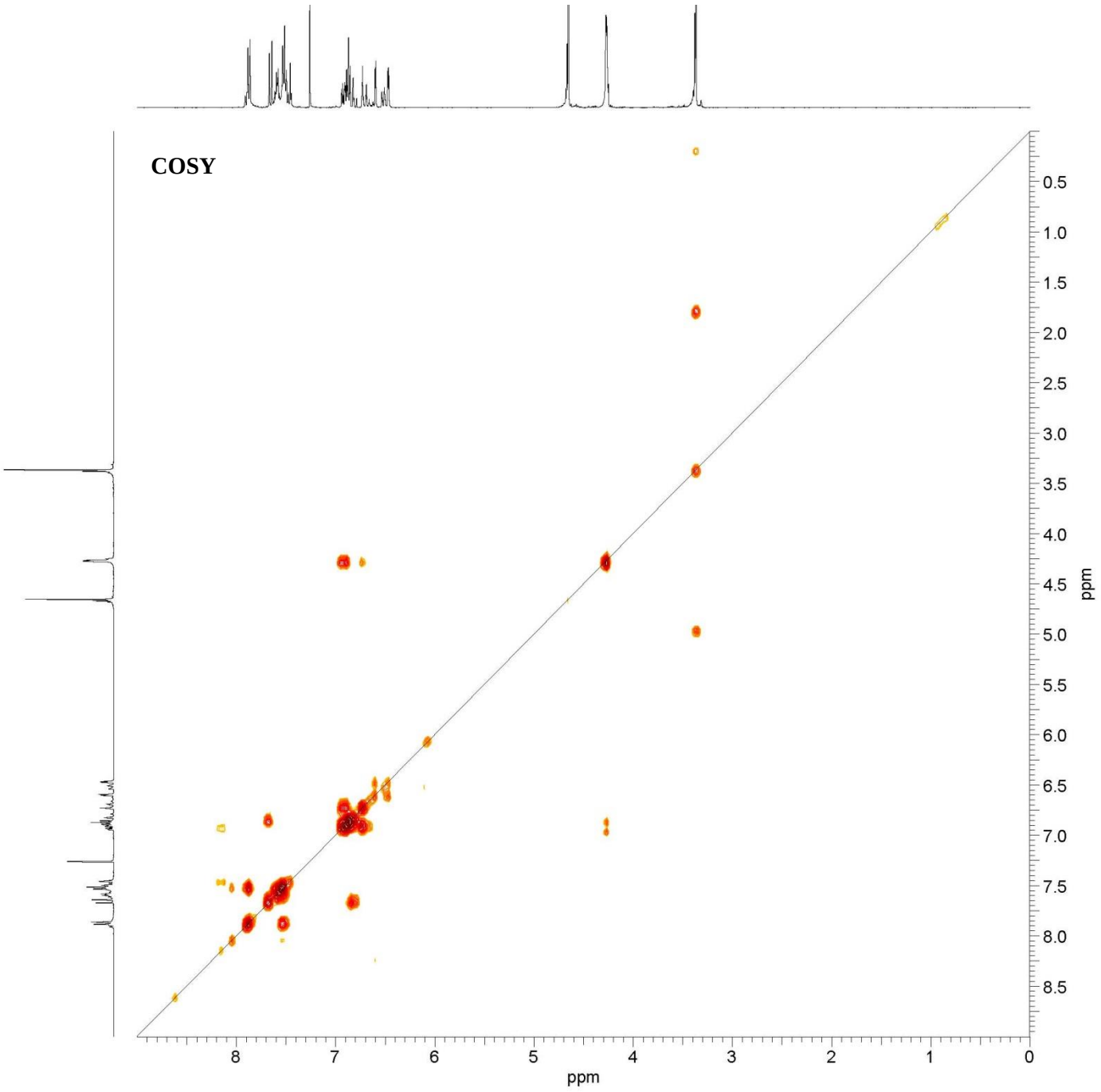


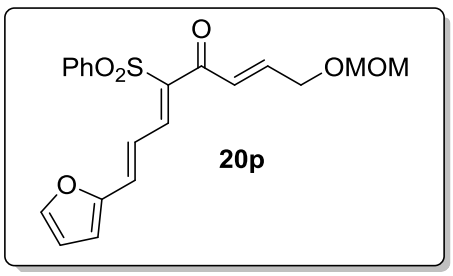


20p



Formula	CalculatedMass	mDaError	ppmError	RDB
C2 H15 N14 O9 S	411.086167	0.033308	0.081024	2.5
C17 H12 N10 Na S	411.085933	0.26652	0.64833	16.5
C17 H19 N2 O8 S	411.085664	0.535884	1.303579	9.5
C18 H15 N6 O4 S	411.087001	-0.801428	-1.949535	14.5
C20 H20 O6 Na S	411.087282	-1.08156	-2.630978	10.5
C5 H16 N12 O7 Na S	411.087784	-1.584136	-3.853532	3.5





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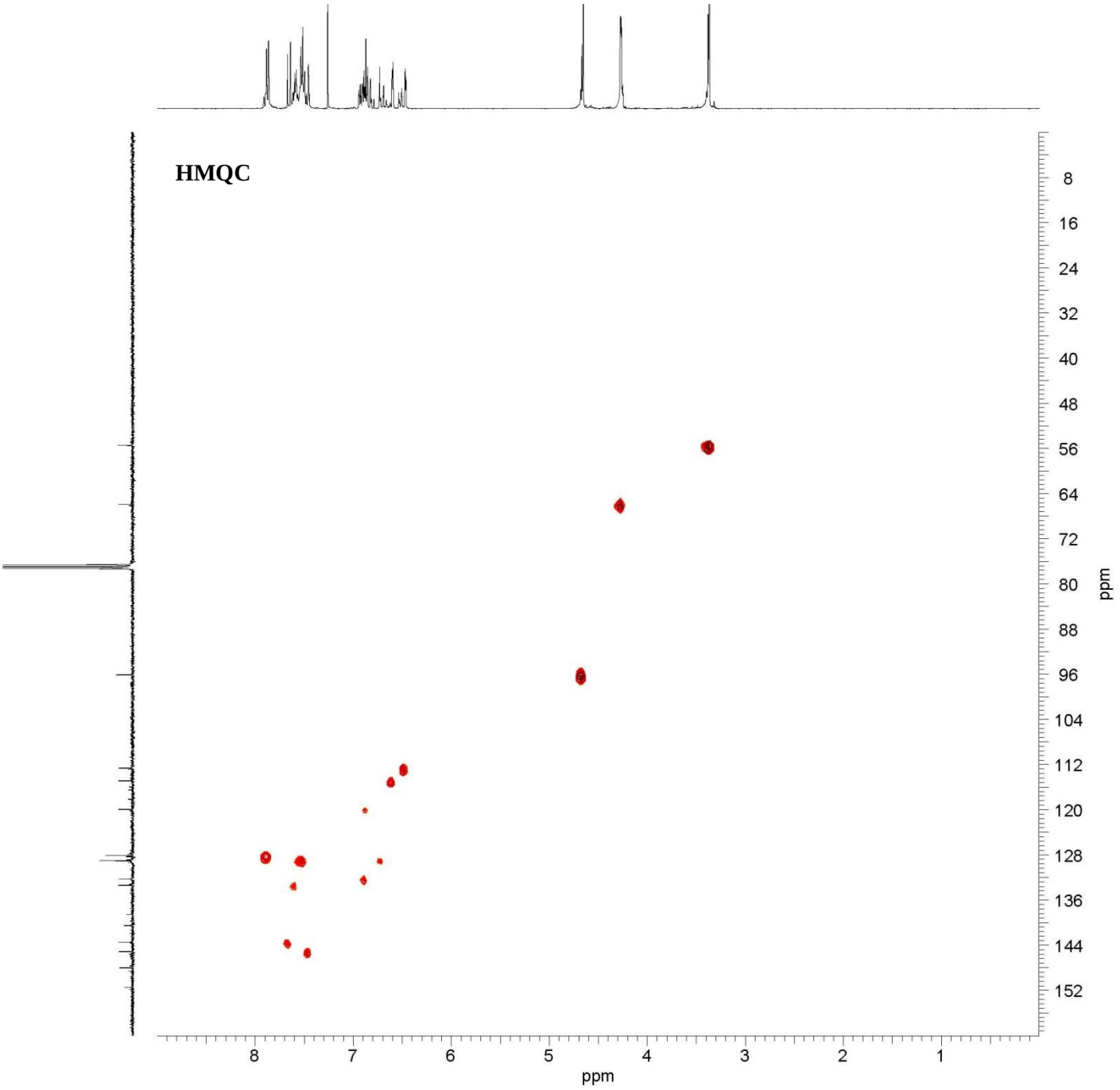
HMQC
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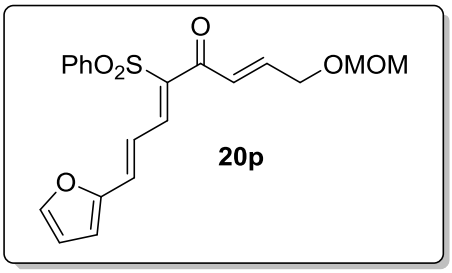
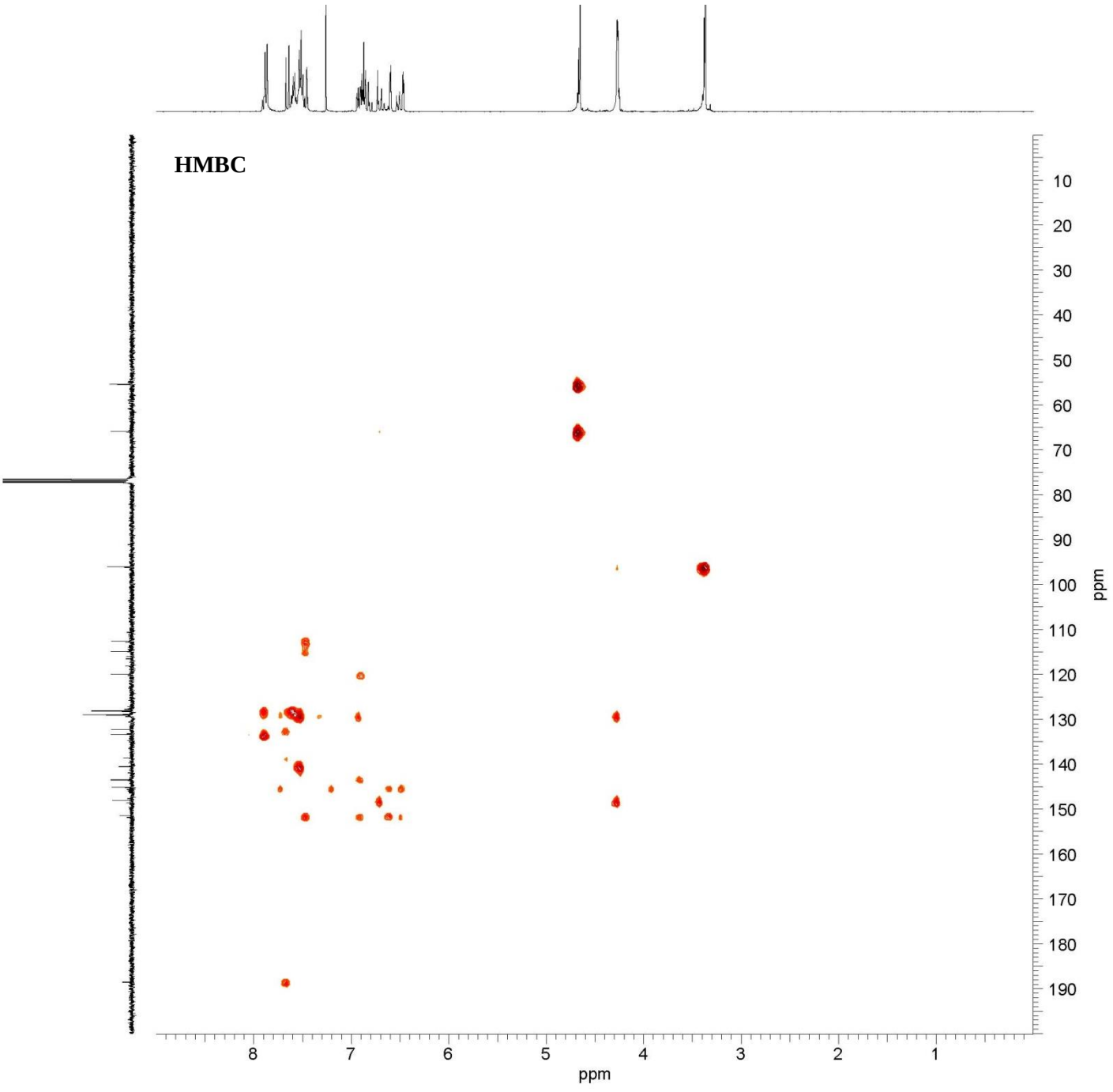
ppm


O
PhO2S
OMOM
O

20p


HMBC
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ppm
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7
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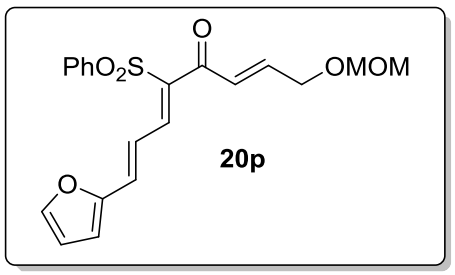
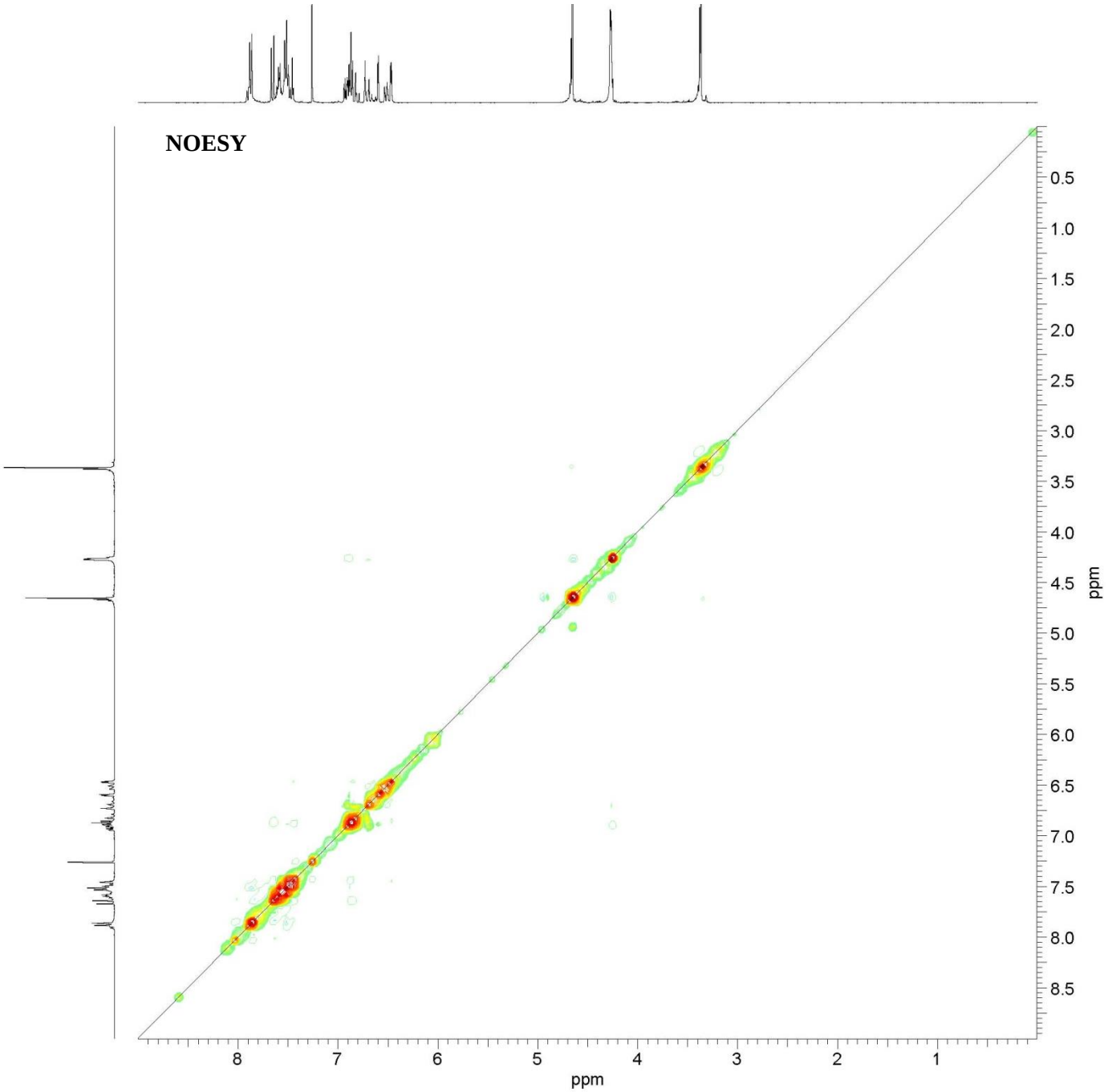
3
2
1
ppm


O
PhO2S
OMOM
O

20p


NOESY
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7
6
5
4
3
2
1
ppm
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1.5
2.0
2.5
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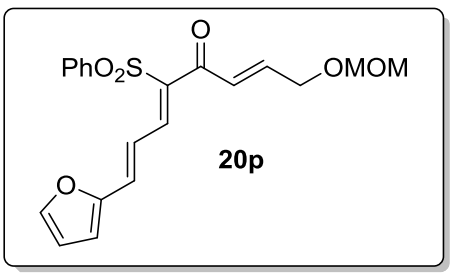
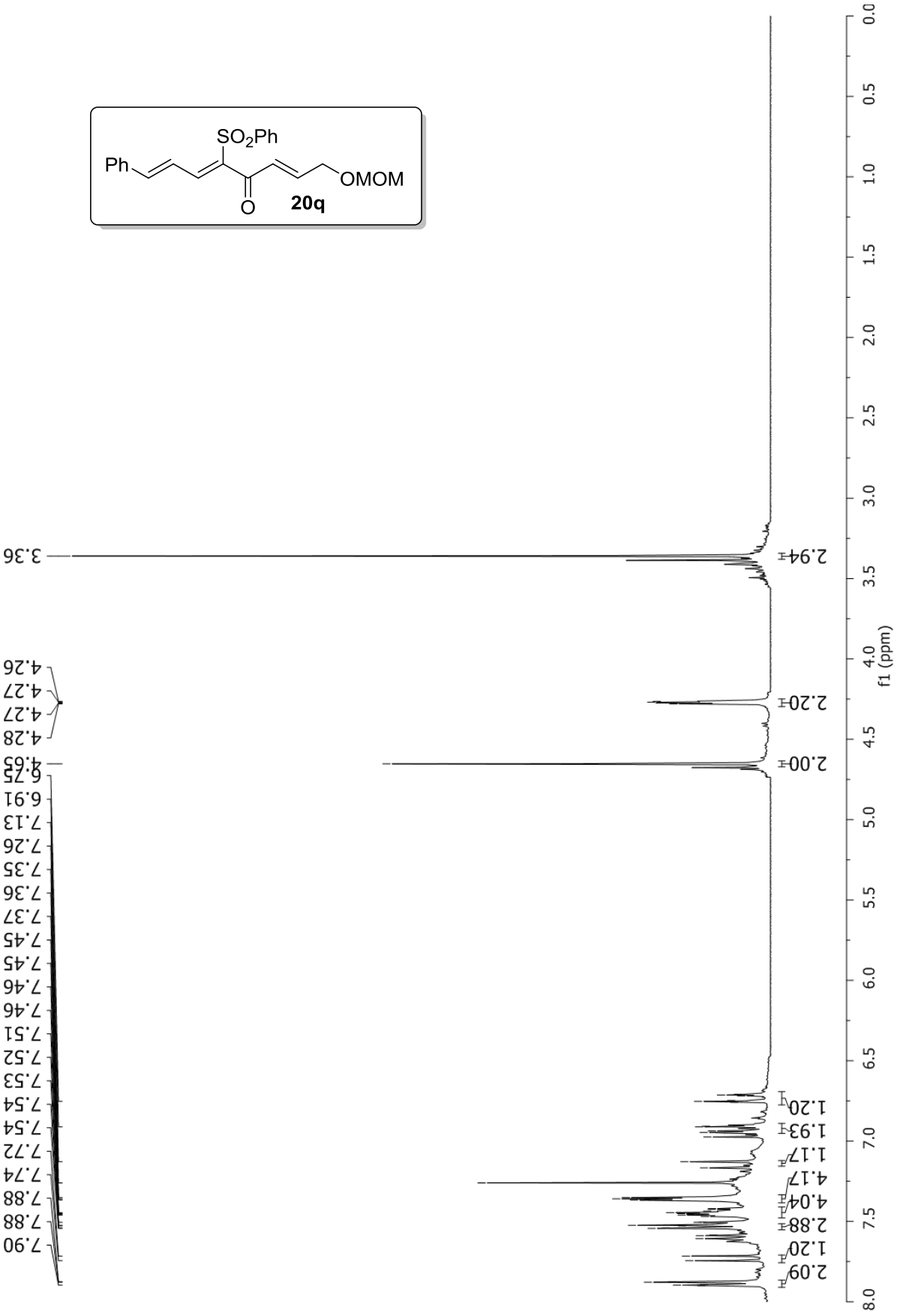
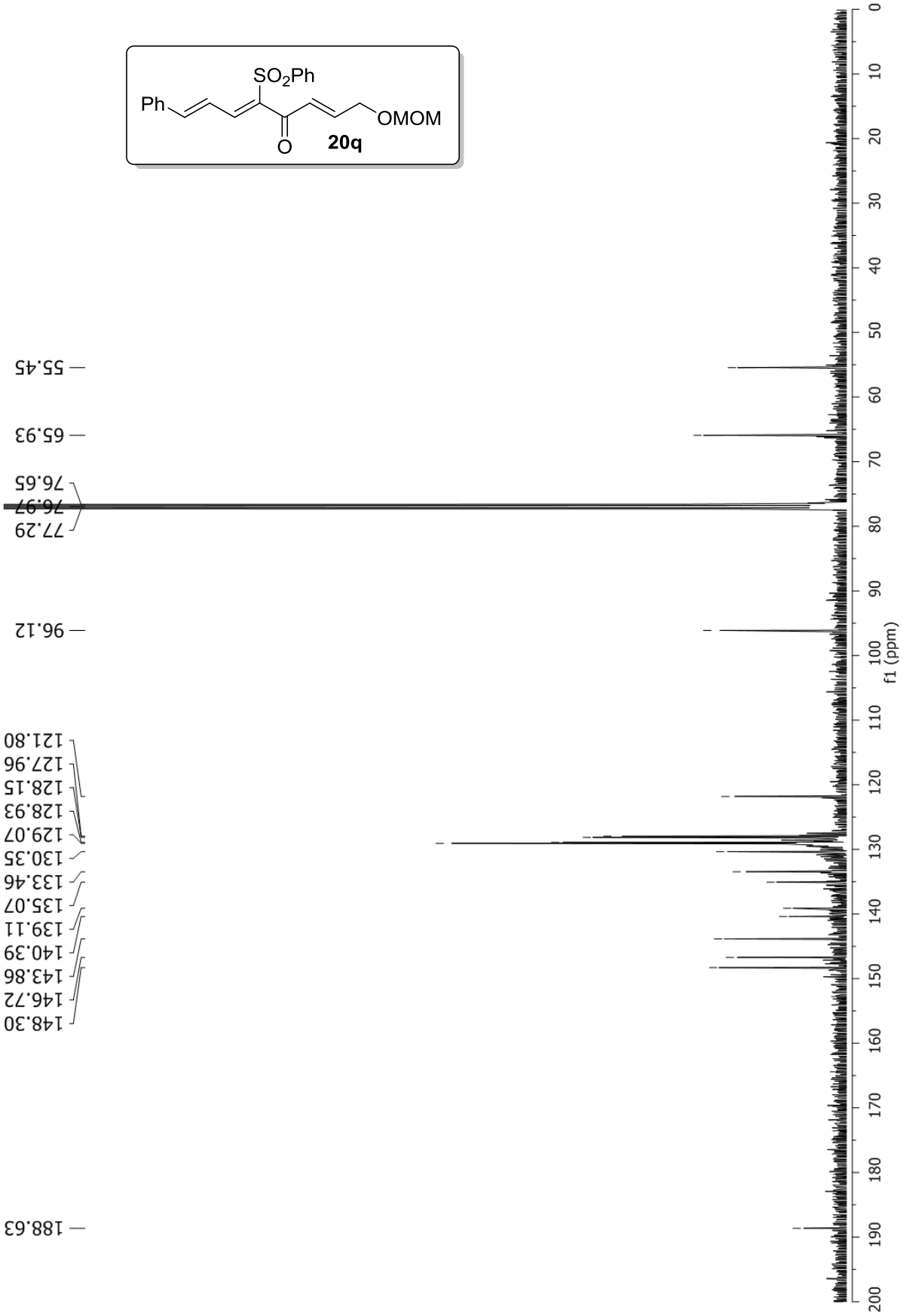

O
PhO2S
OMOM
O

20p


SO2Ph
Ph
OMOM
O
20q
f1 (ppm)


SO2Ph
Ph
OMOM
O
20q
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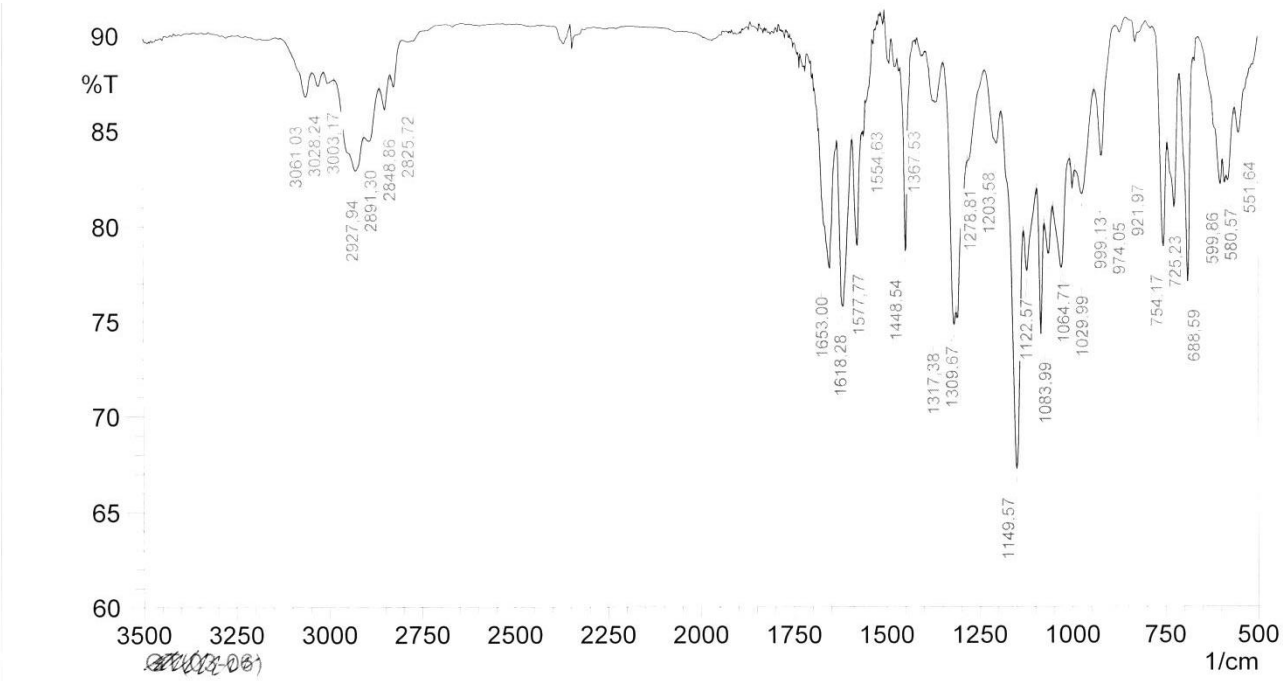
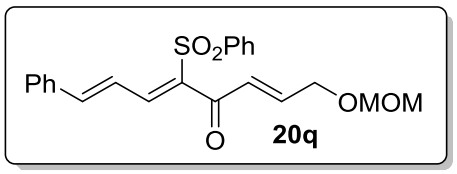
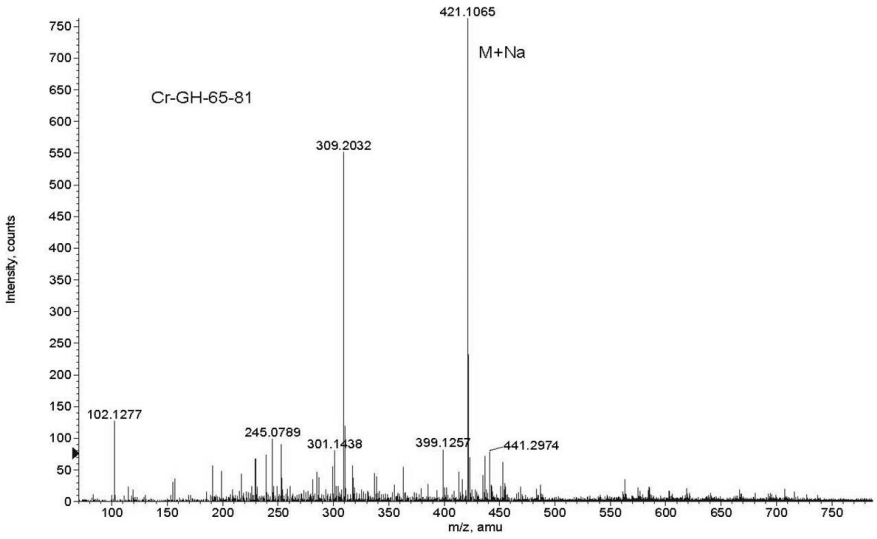
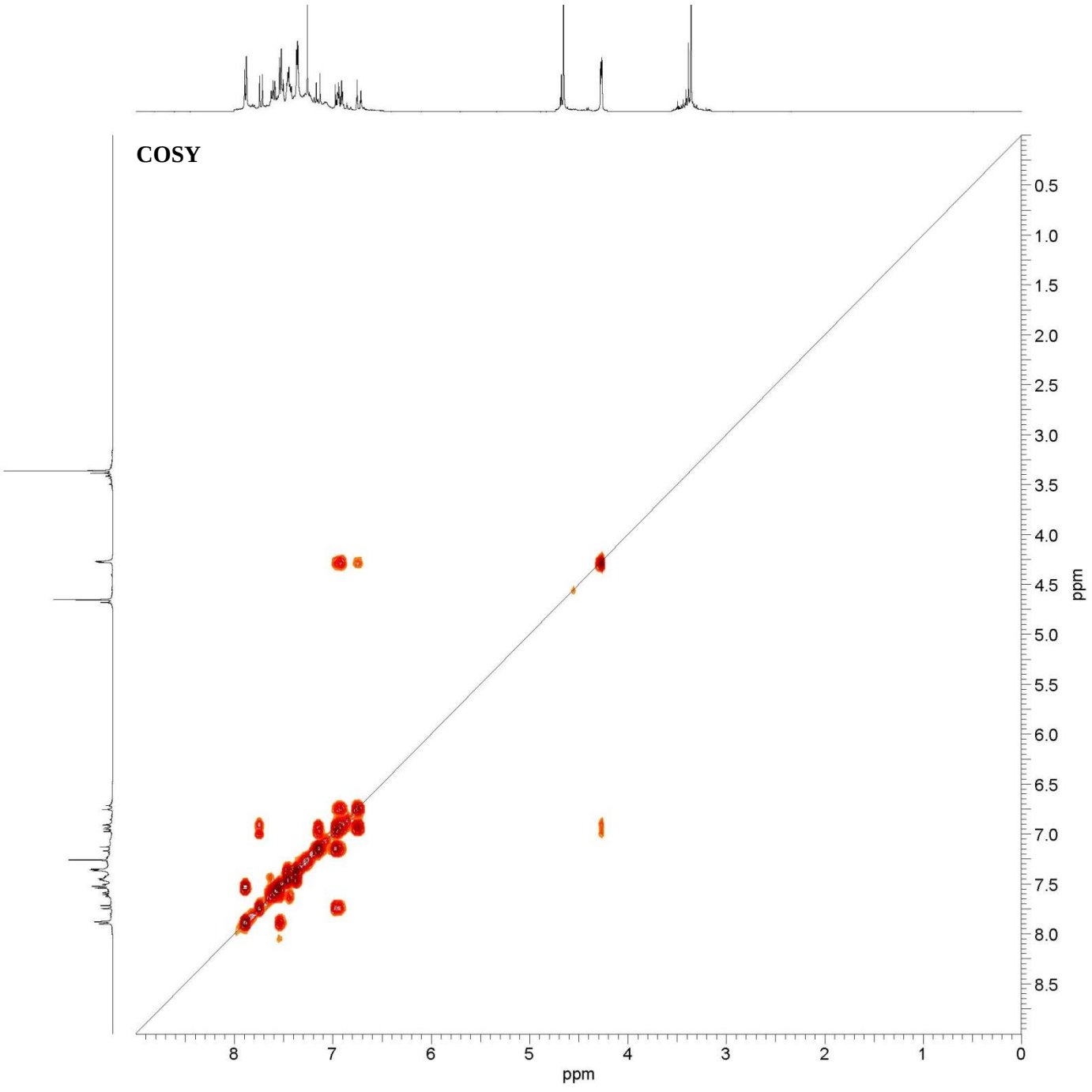
f1 (ppm)







Formula	CalculatedMass	mDaError	ppmError	RDB
C13 H22 N2 O12 Na	421.106496	0.004304	0.010221	3.5
C19 H21 N2 O7 S	421.1064	0.100444	0.238524	10.5
C11 H17 N8 O10	421.106216	0.284436	0.675448	7.5
C4 H17 N14 O8 S	421.106902	-0.402132	-0.95494	3.5
C26 H14 N4 O Na	421.105982	0.517648	1.229255	21.5
C27 H17 O5	421.10705	-0.5503	-1.306794	19.5
C6 H22 N8 O10 Na S	421.107182	-0.682264	-1.620168	-0.5
C12 H13 N12 O6	421.107553	-1.052876	-2.500257	12.5
C18 H18 N6 O3 Na S	421.105332	1.168392	2.774572	12.5
C20 H17 N6 O3 S	421.107737	-1.236868	-2.937182	15.5
C14 H18 N6 O8 Na	421.107833	-1.333008	-3.165485	8.5
C10 H14 N12 O6 Na	421.105148	1.352384	3.211497	9.5
C16 H13 N12 O S	421.105051	1.448524	3.4398	16.5
C22 H22 O5 Na S	421.108017	-1.517	-3.602409	11.5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5.0
5.5
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6.5
7.0
7.5
8.0
8.5
ppm
8
7
6
5
4
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2
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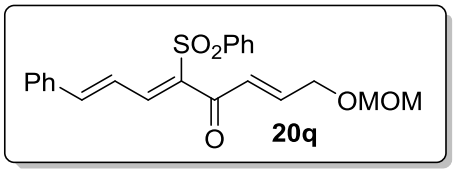
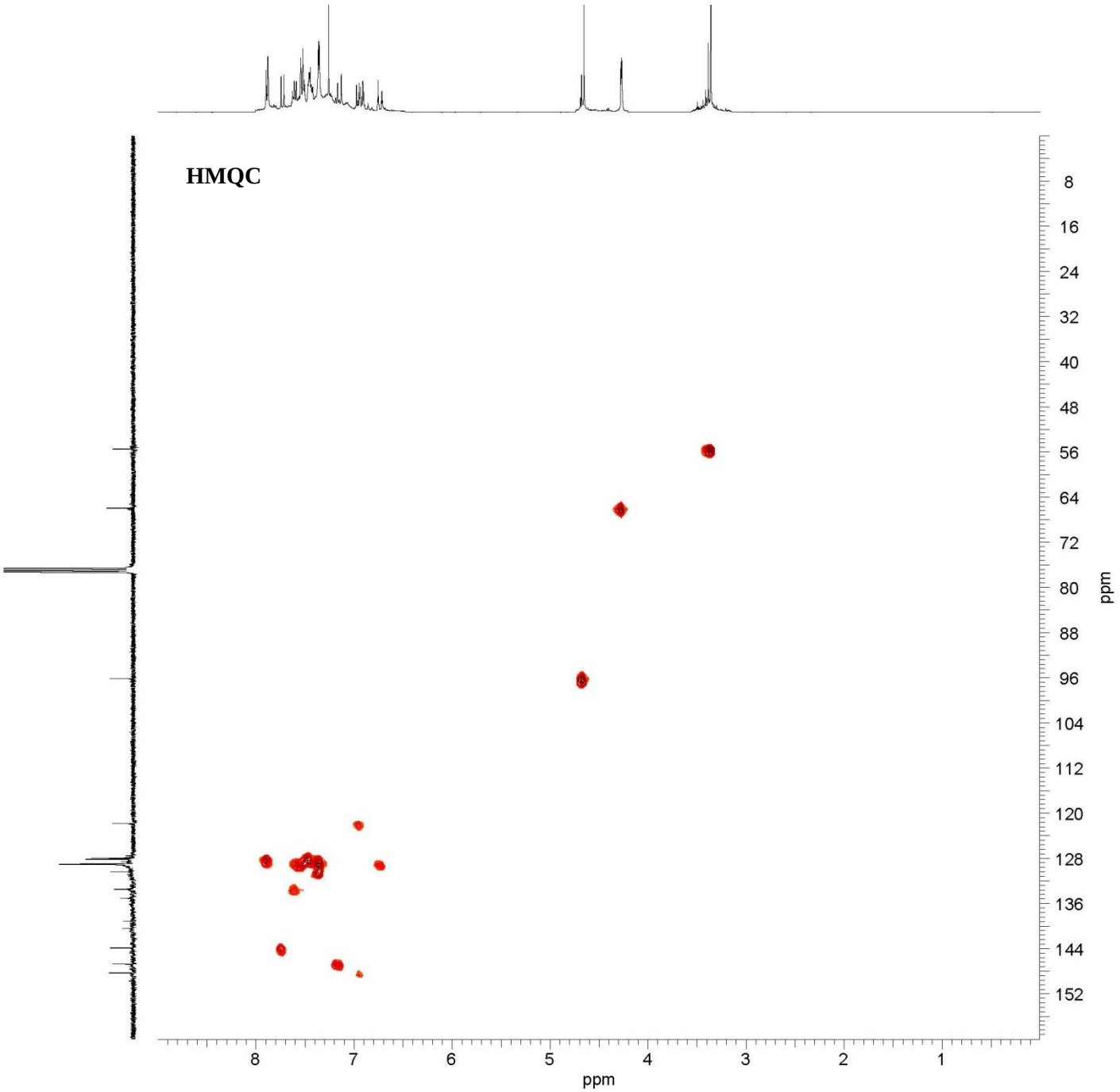
0
ppm


SO2Ph
Ph
OMOM
O
20q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48
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112
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128
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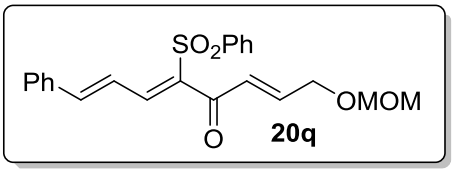
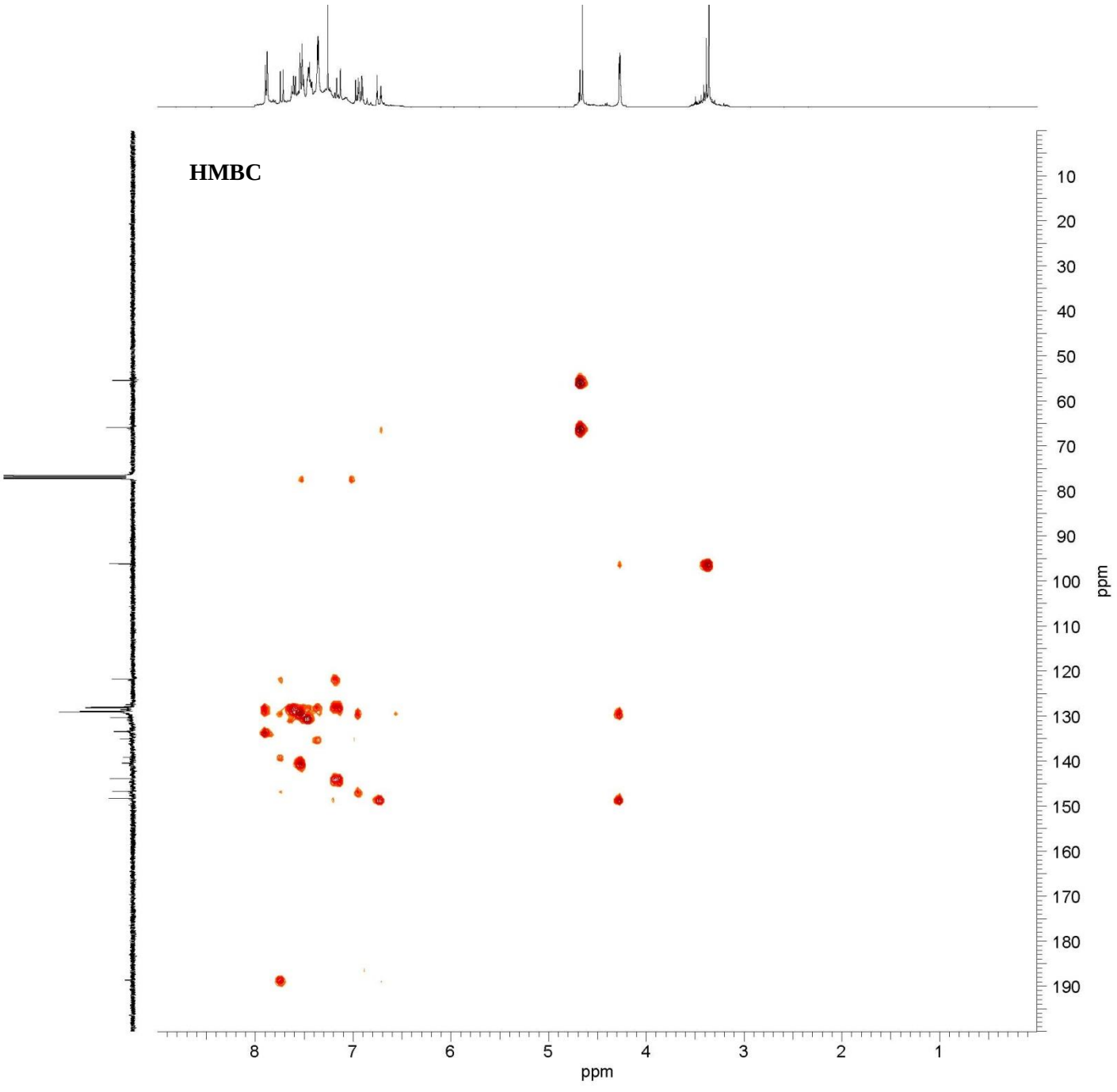
144
152
ppm
8
7
6
5
4
3
2
1
ppm


SO2Ph
Ph
OMOM
O
20q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110
120
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140
150
160
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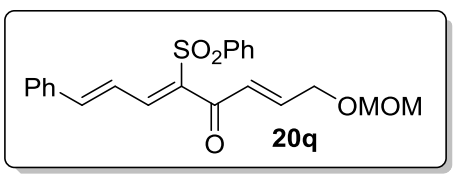
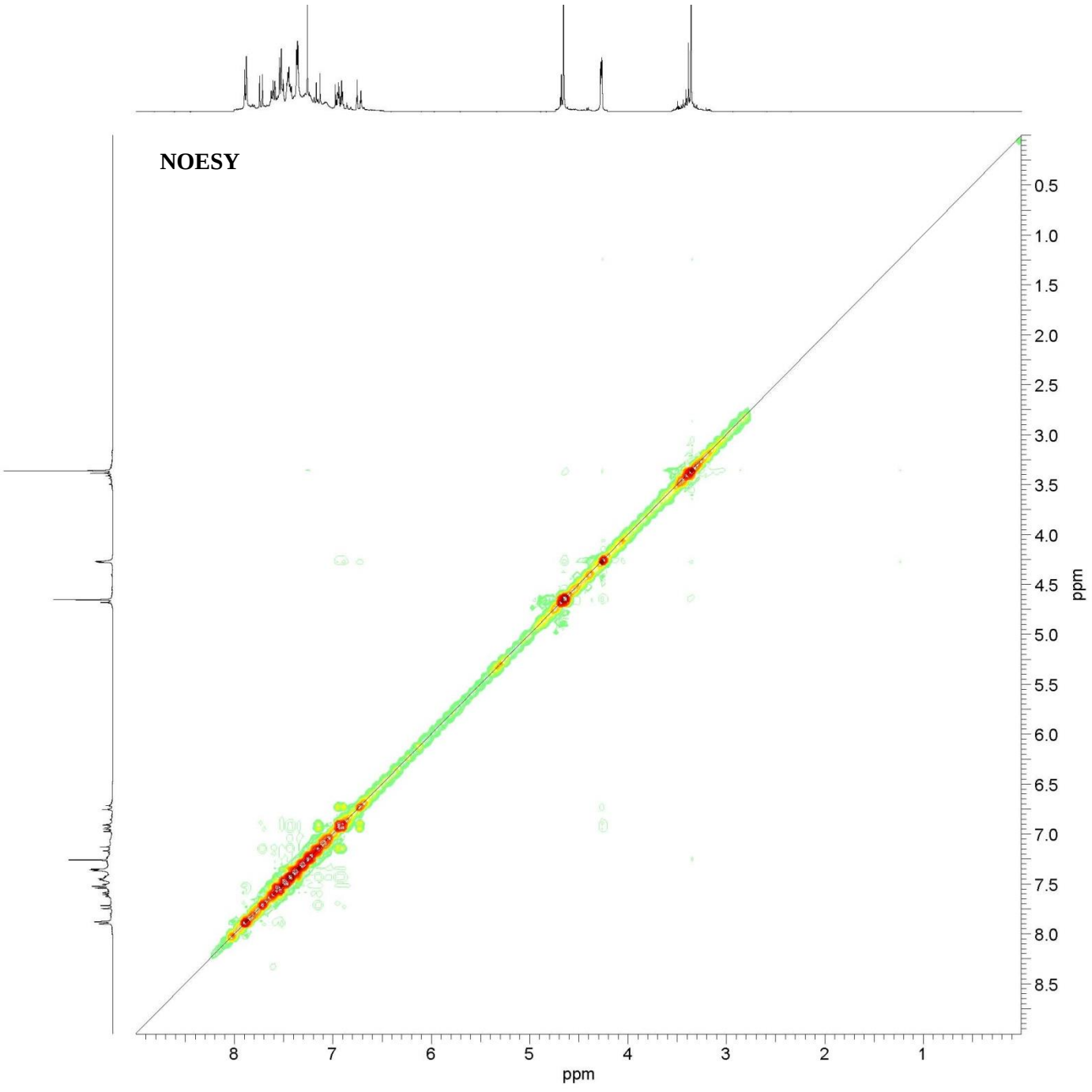
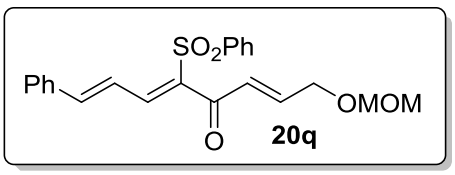
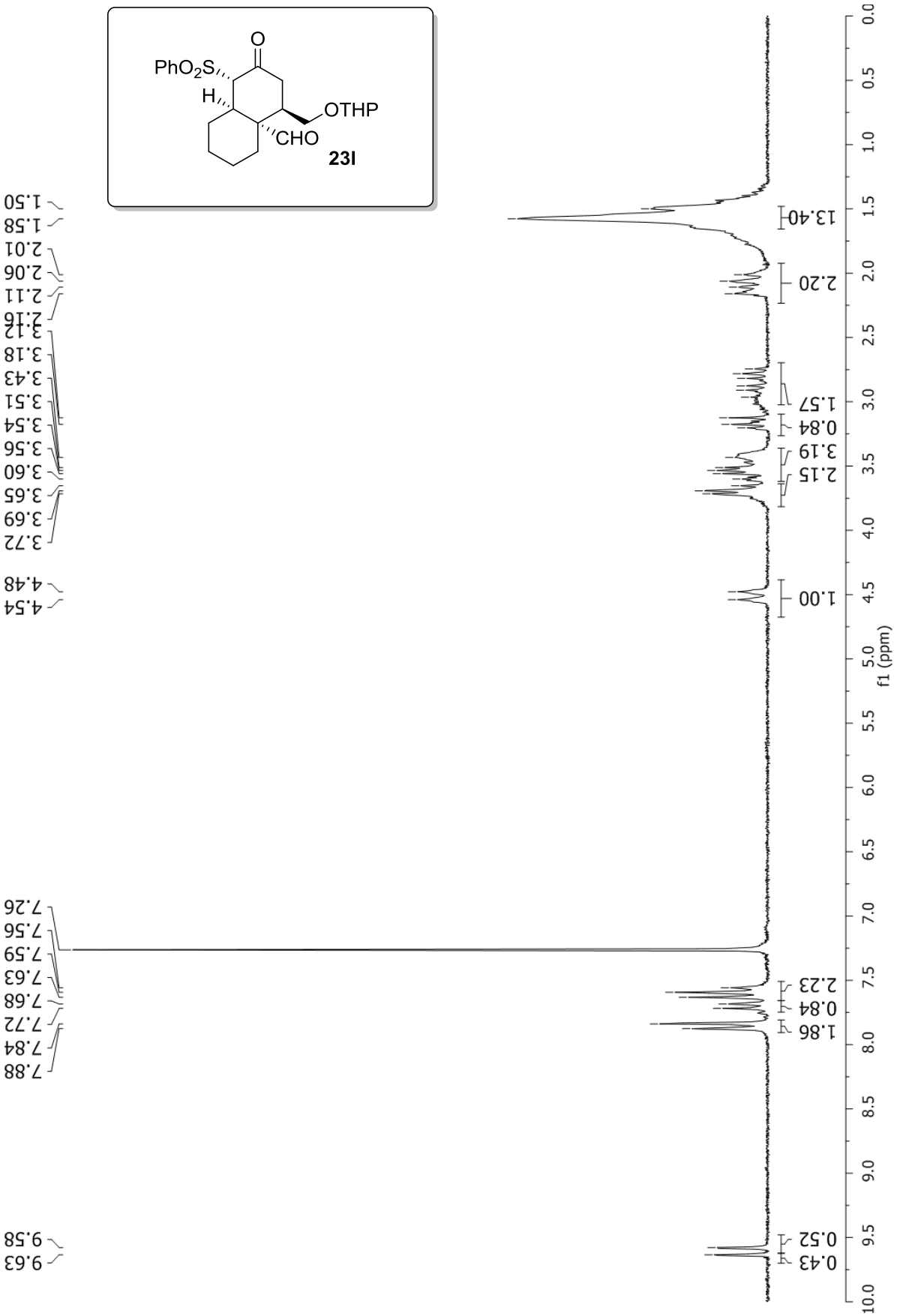
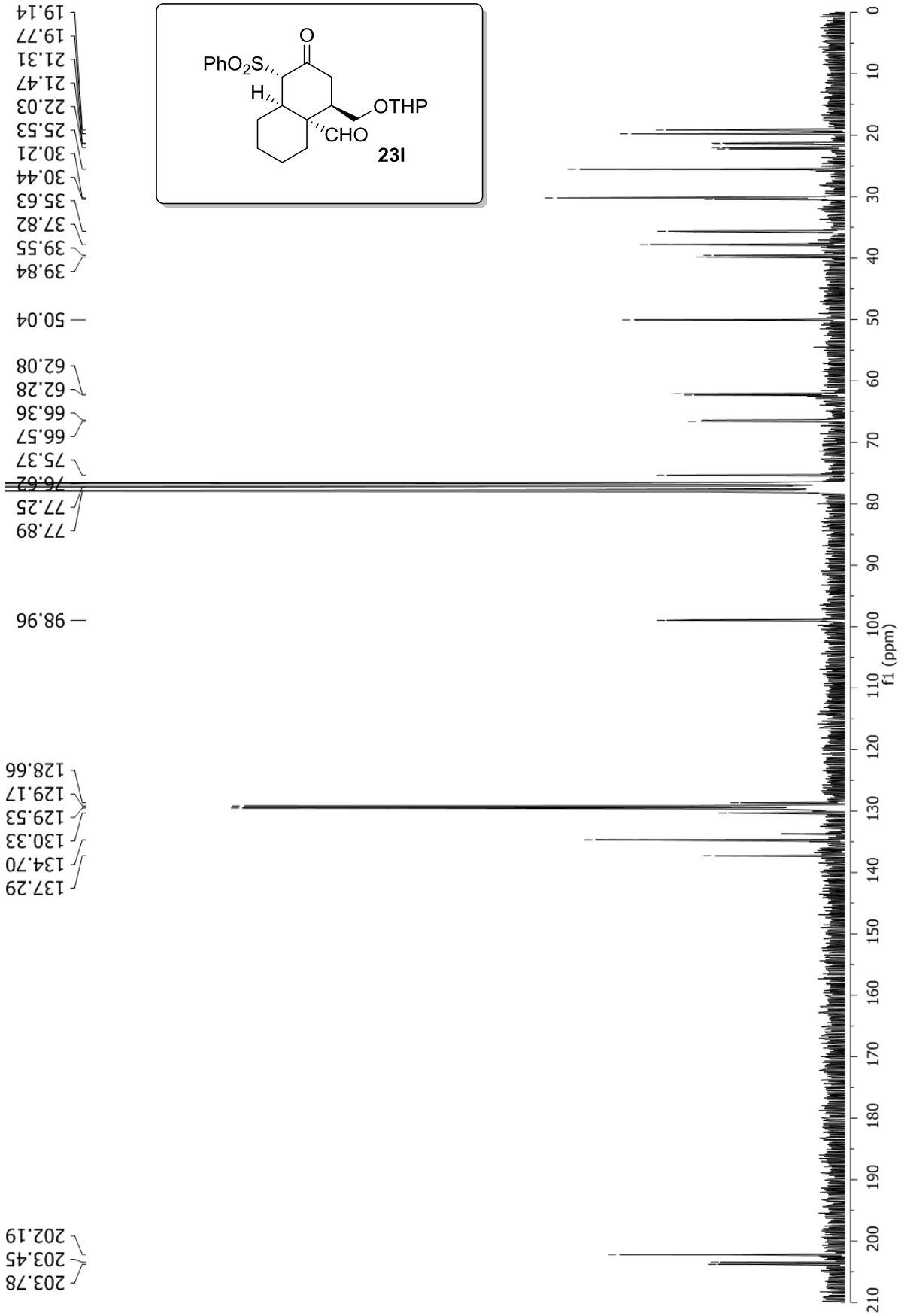
180
190
ppm
8
7
6
5
4
3
2
1
ppm

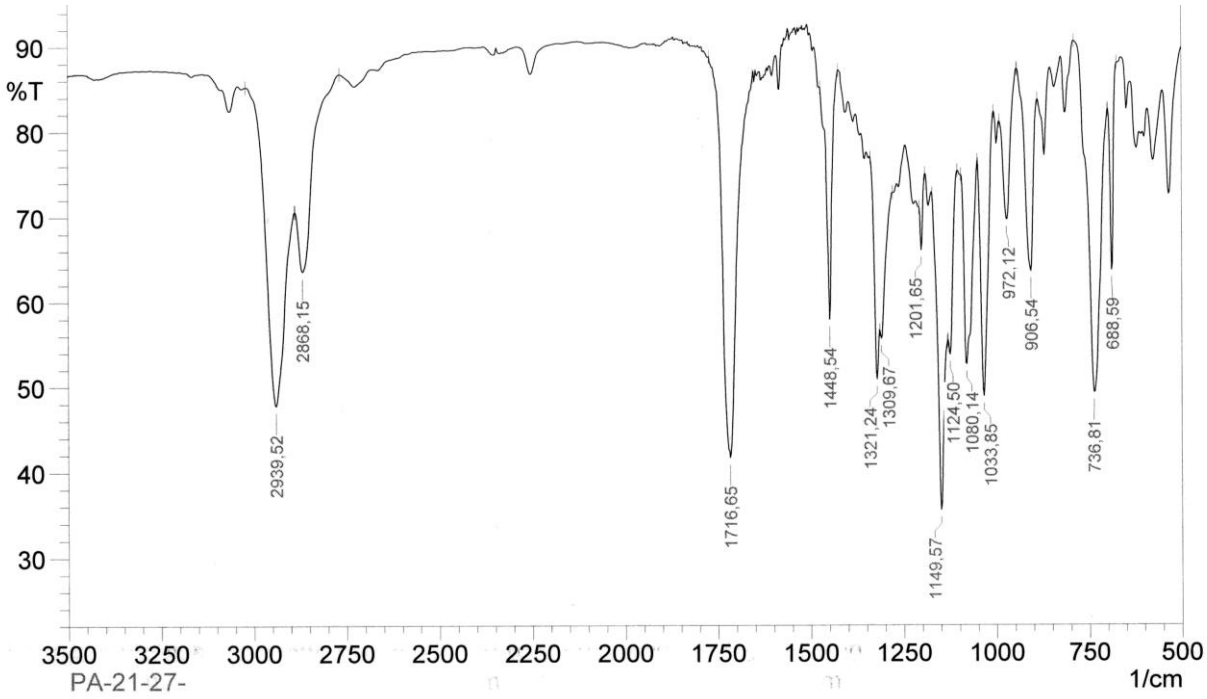

SO2Ph
Ph
OMOM
O
20q

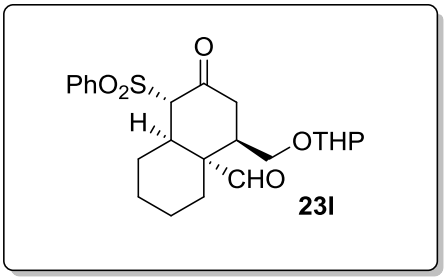

NOESY
8
7
6
5
4
3
2
1
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm

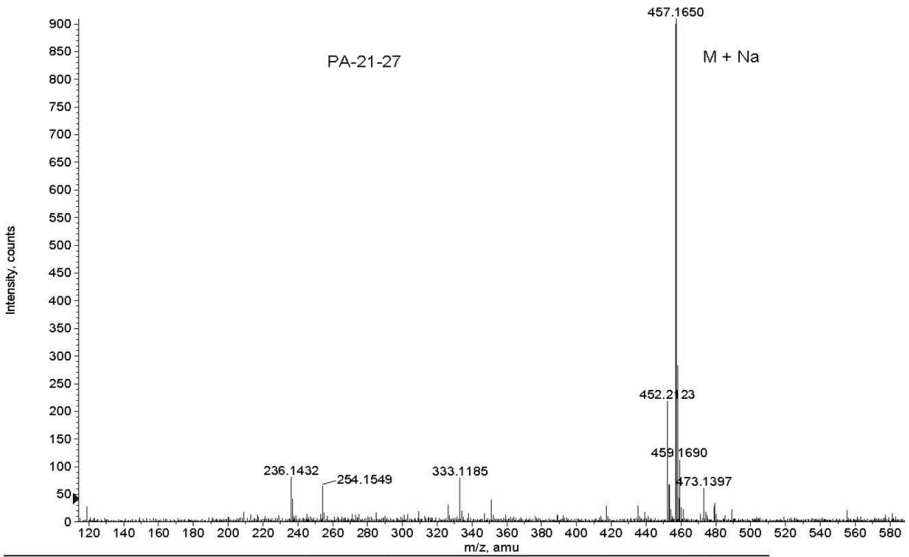

SO2Ph
Ph
OMOM
O
20q


O
PhO2S
H
OTHP
CHO
23l
f1 (ppm)

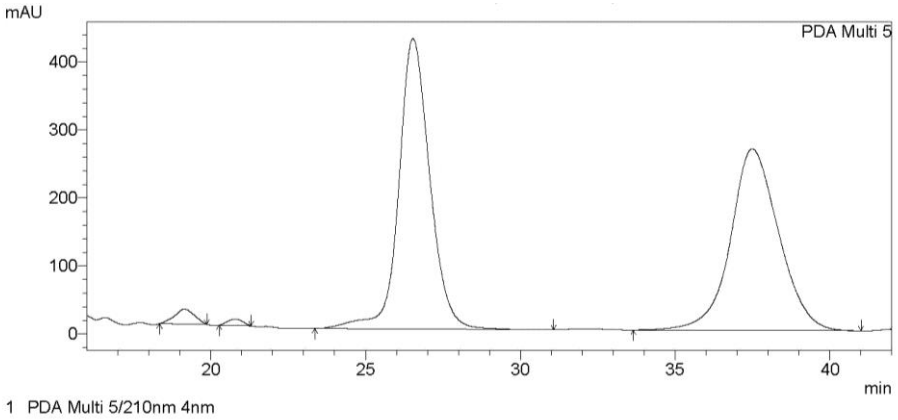

PhO2S
H
O
OTHP
CHO
23l
19.14
19.77
21.31
21.47
22.03
25.53
30.21
30.44
35.63
37.82
39.55
39.84
50.04
62.08
62.28
66.36
66.57
75.37
76.62
77.25
77.89
98.96
128.66
129.17
129.53
130.33
134.70
137.29
202.19
203.45
203.78
f1 (ppm)







Formula	CalculatedMass	mDaError	ppmError	RDB
C21 H25 N6 O4 S	457.165252	-0.251828	-0.550846	12.5
C15 H26 N6 O9 Na	457.165348	-0.347968	-0.761142	5.5
C28 H25 O6	457.164565	0.43474	0.950947	16.5
C23 H30 O6 Na S	457.165532	-0.53196	-1.163605	8.5

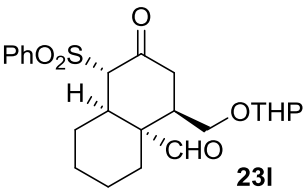


1 PDA Multi 5/210nm 4nm

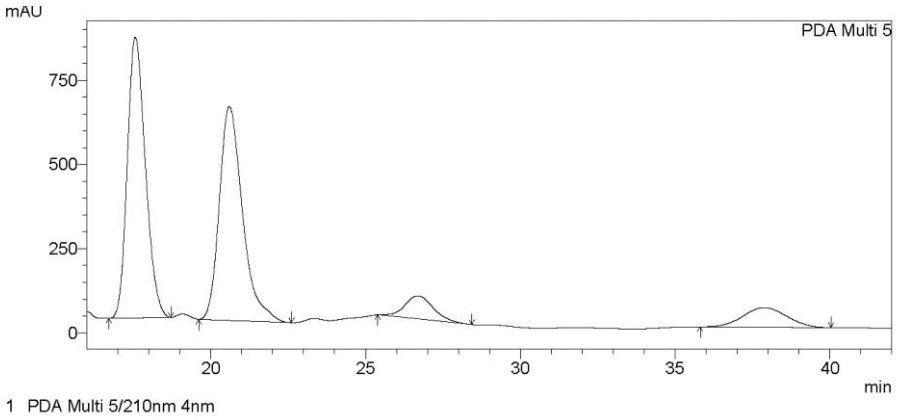
PeakTable

PDA Ch5 210nm 4nm

Peak#	Ret. Time	Area %
1	19.141	1.612
2	20.775	0.527
3	26.527	49.707
4	37.486	48.154
Total		100.000



23l

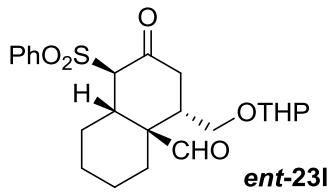


1 PDA Multi 5/210nm 4nm

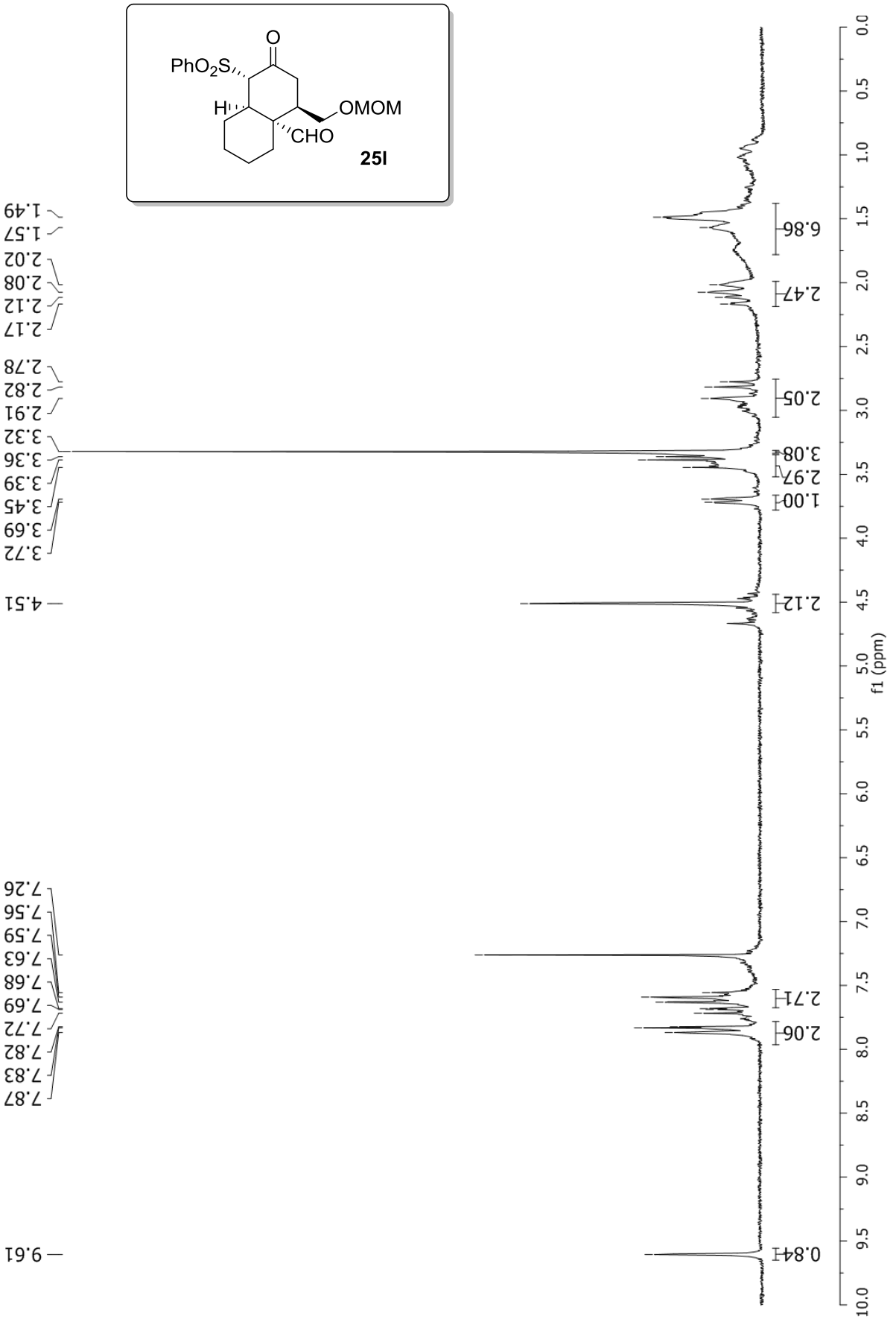
PeakTable

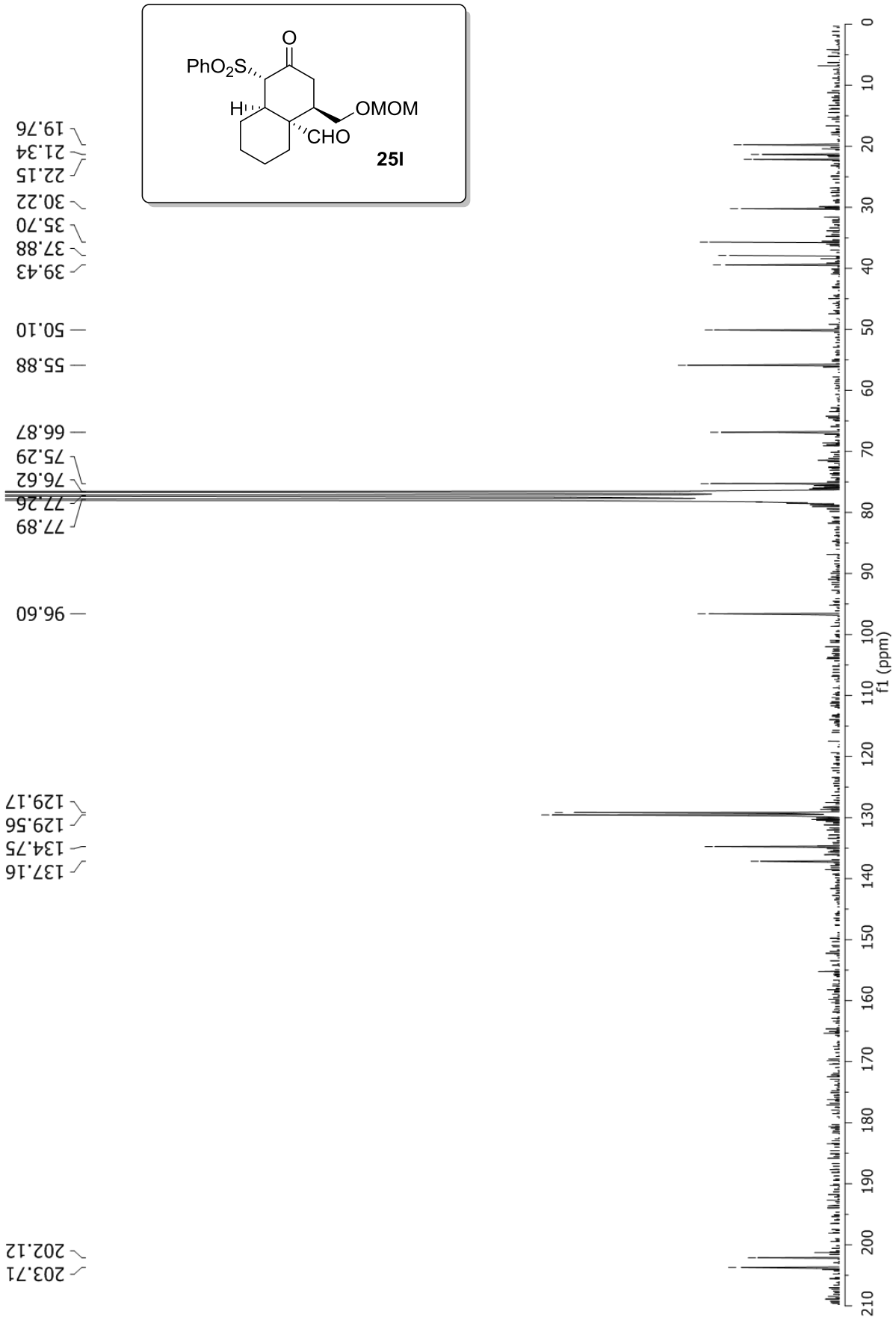
PDA Ch5 210nm 4nm

Peak#	Ret. Time	Area %
1	17.557	43.999
2	20.595	42.994
3	26.682	5.655
4	37.883	7.351
Total		100.000



***ent*-23l**


O
PhO2S
H
OMOM
CHO
25l
1.49
1.57
2.02
2.08
2.12
2.17
2.78
2.82
2.91
3.32
3.36
3.39
3.45
3.69
3.72
4.51
7.26
7.56
7.59
7.63
7.68
7.69
7.72
7.82
7.83
7.87
9.61
6.86
2.47
2.05
3.08
2.97
1.00
2.12
2.71
2.06
0.84
f1 (ppm)


O
PhO2S
H
OMOM
CHO
25l
19.76
21.34
22.15
30.22
35.70
37.88
39.43
50.10
55.88
66.87
75.29
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77.89
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129.17
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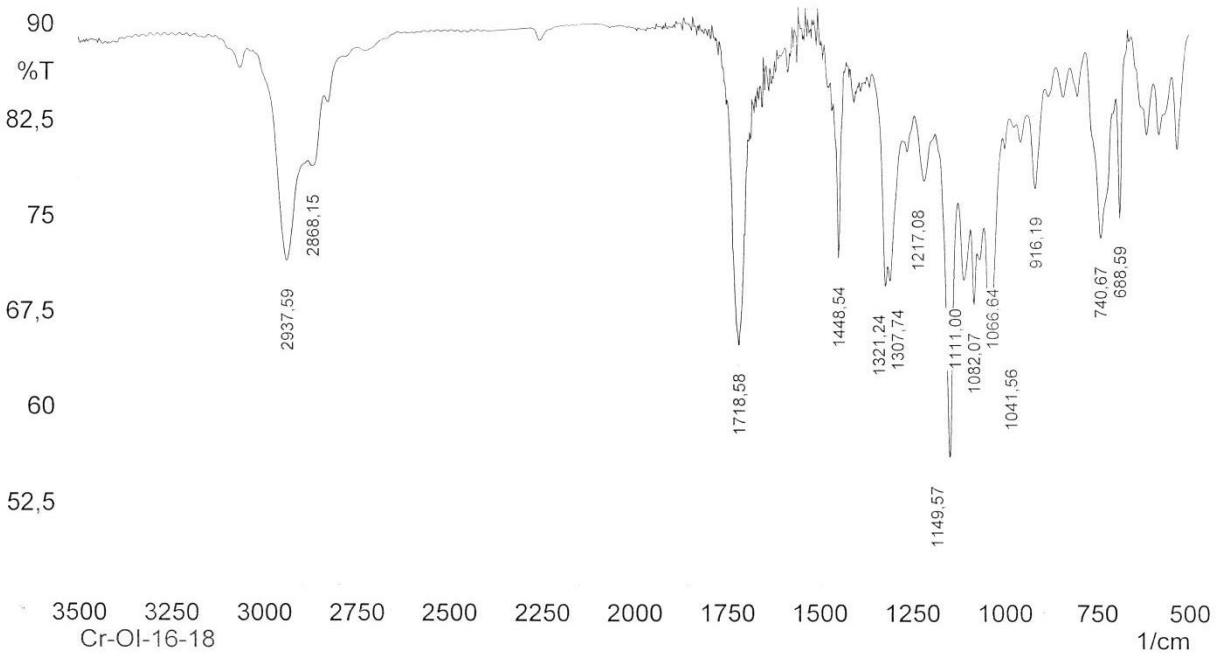
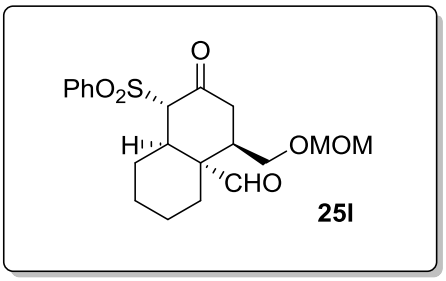
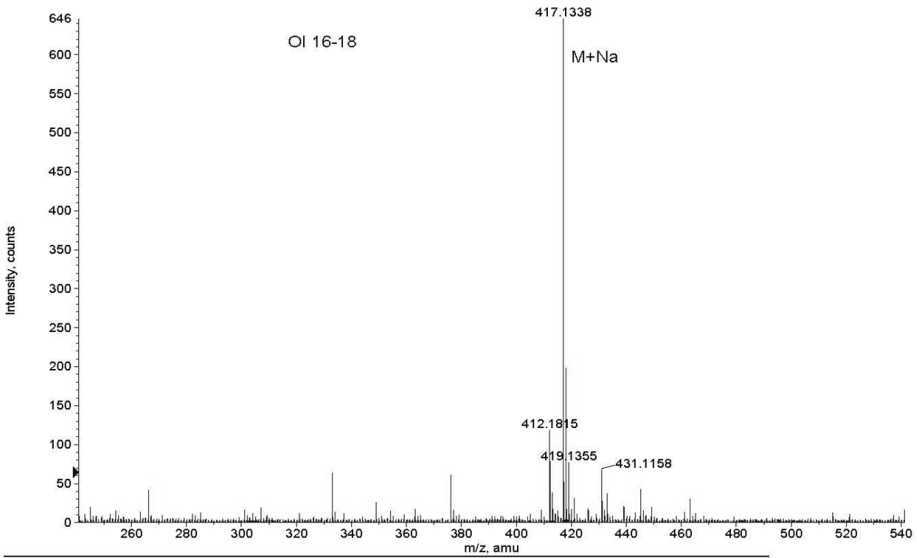
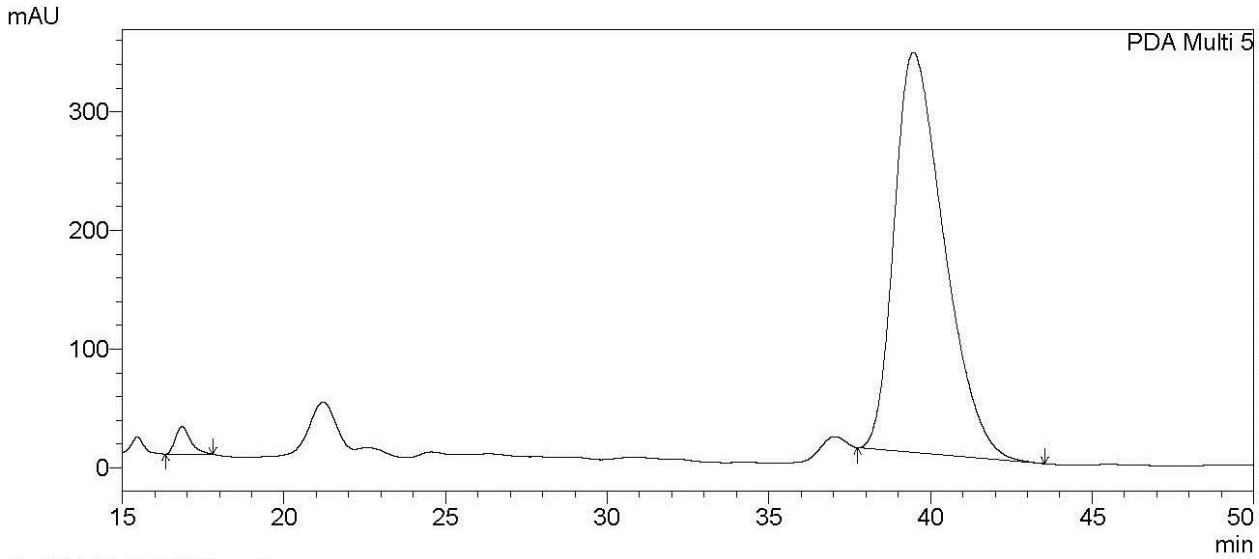
134.75
137.16
202.12
203.71
f1 (ppm)







Formula	CalculatedMass	mDaError	ppmError	RDB
C20 H26 O6 Na S	417.134232	-0.4318	-1.035158	7.5

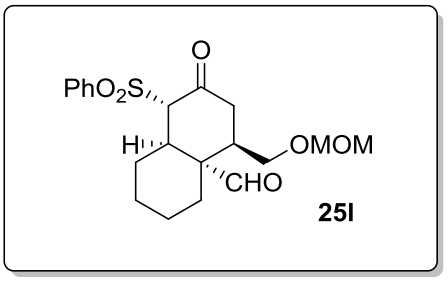


1 PDA Multi 5/210nm 4nm

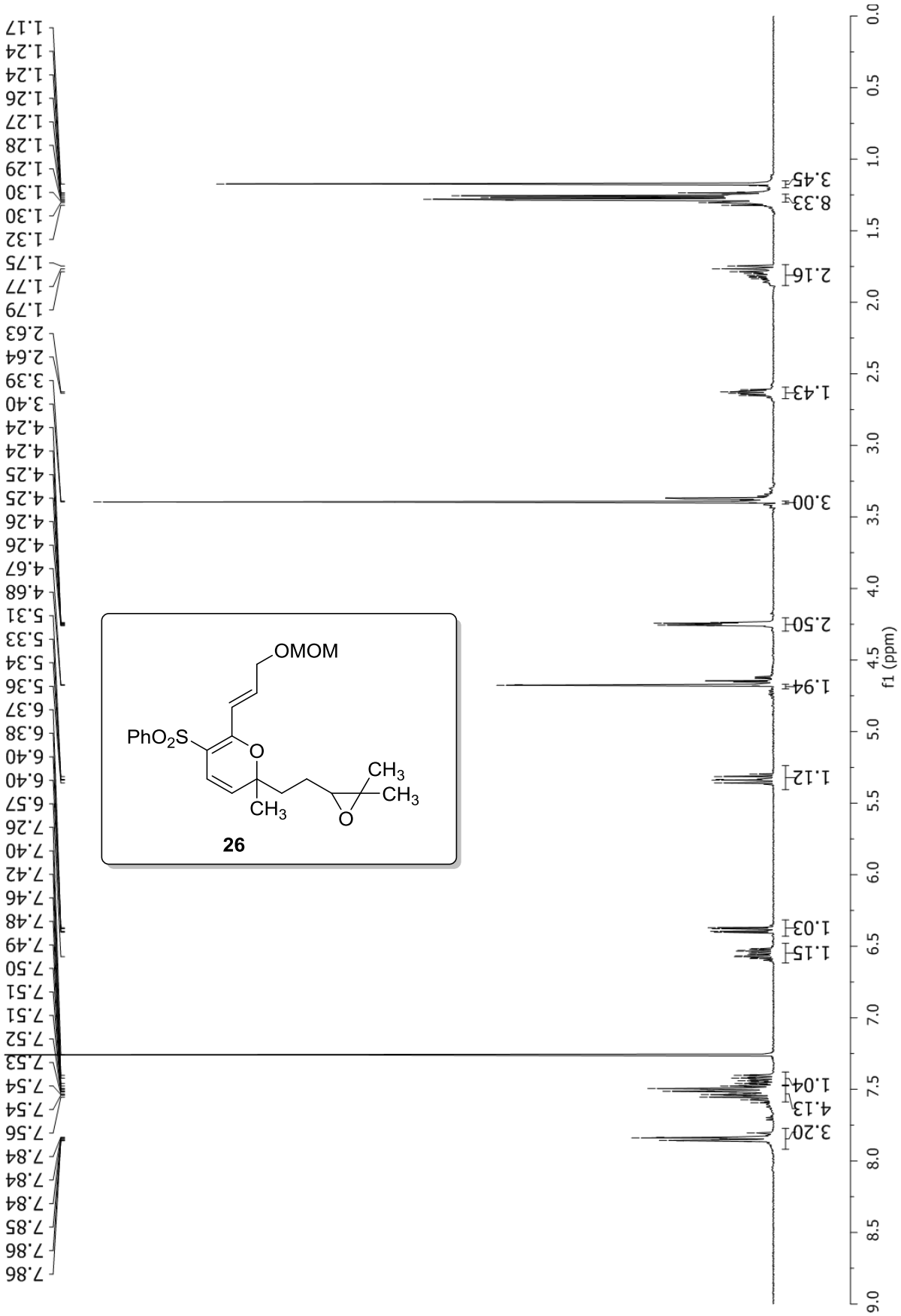
PeakTable

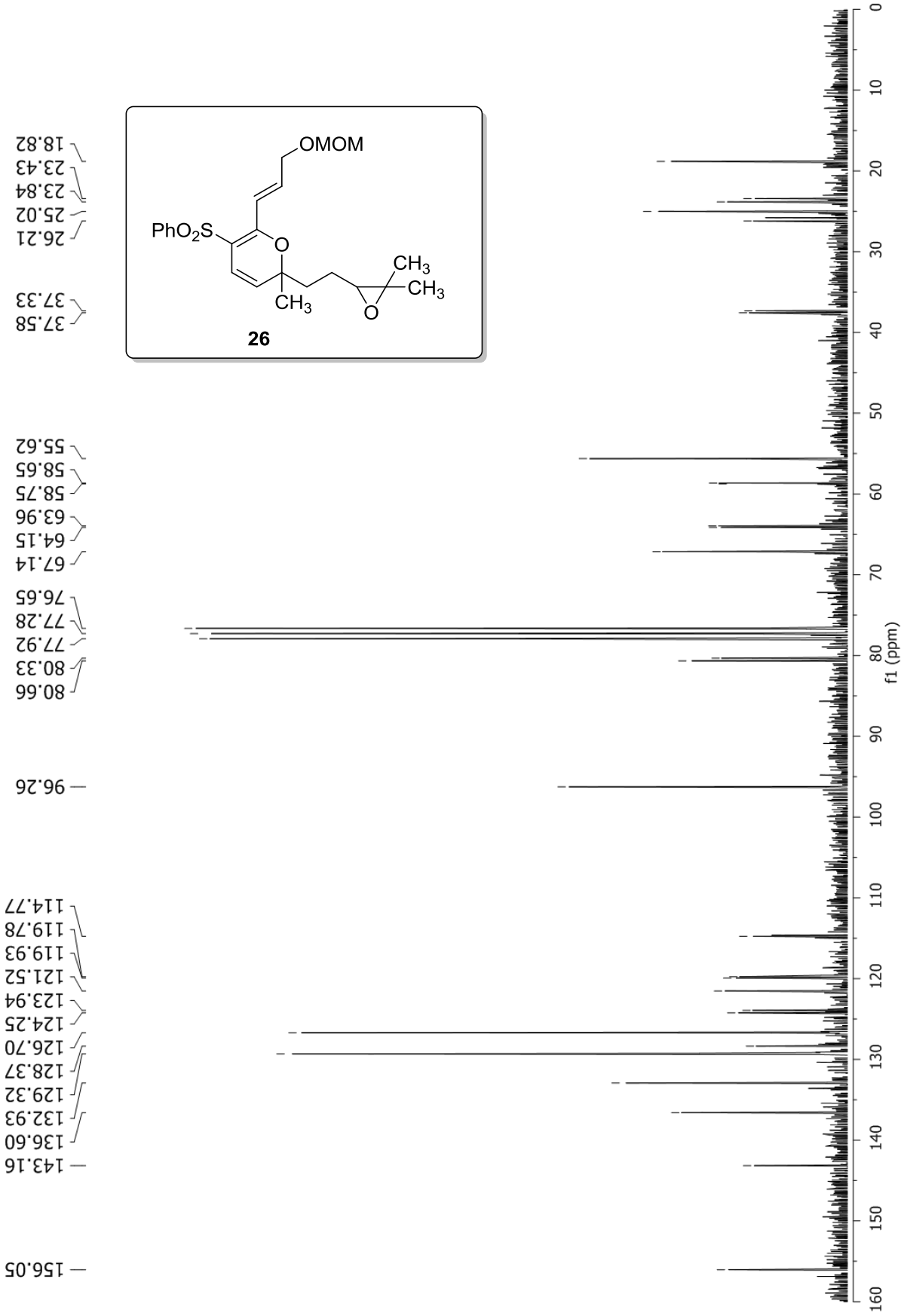
PDA Ch5 210nm 4nm

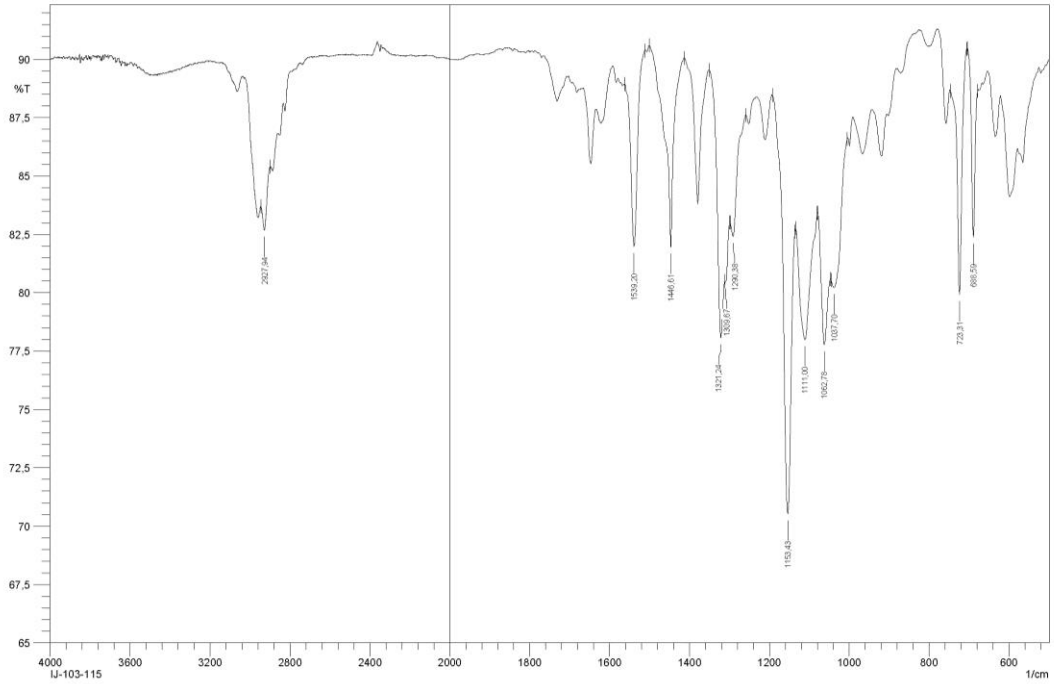
Peak#	Ret. Time	Area %
1	16.837	2.056
2	39.465	97.944
Total		100.000

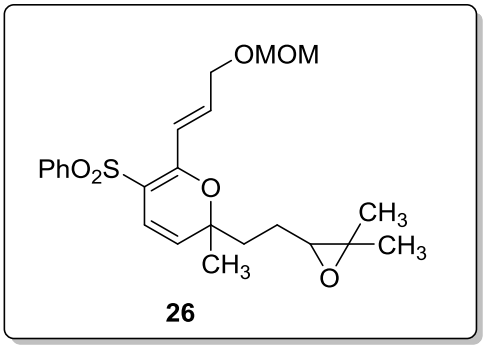


25l

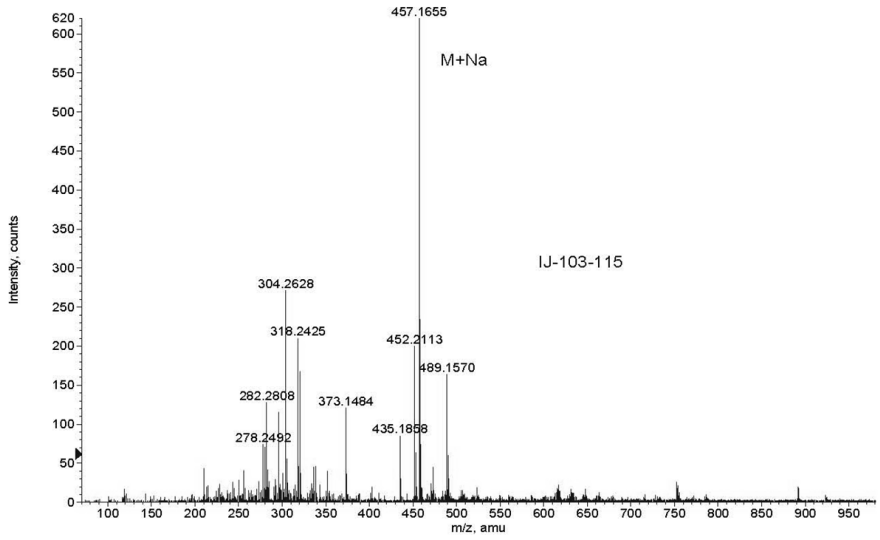

OMOM
PhO2S
O
CH3
CH3
CH3
O
26
f1 (ppm)

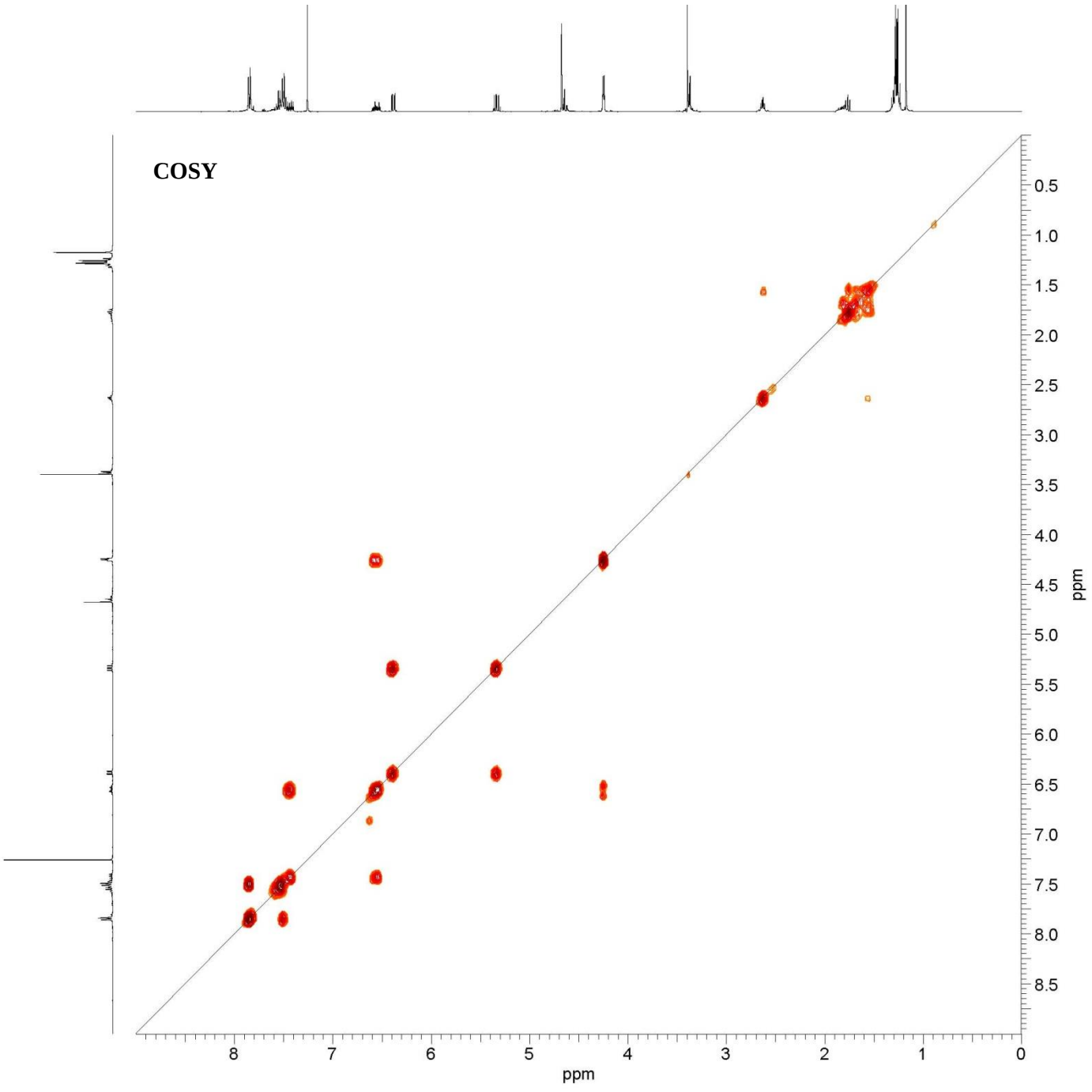

OMOM
PhO2S
O
CH3
CH3
CH3
O
26
18.82
23.43
23.84
25.02
26.21
37.33
37.58
55.62
58.65
58.75
63.96
64.15
67.14
76.65
77.28
77.92
80.33
80.66
96.26
114.77
119.78
119.93
121.52
123.94
124.25
126.70
128.37
129.32
132.93
136.60
143.16
156.05
f1 (ppm)


%T
IJ-103-115
1/cm
2927.94
1539.20
1446.61
1331.24
1305.67
1290.38
1153.43
1111.00
1062.75
1037.70
720.91
686.59


OMOM
PhO2S
O
CH3
CH3
CH3
O

26


457.1655
M+Na
IJ-103-115
304.2628
318.2425
452.2113
489.1570
282.2808
373.1484
435.1858
278.2492
Intensity, counts
m/z, amu


COSY
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1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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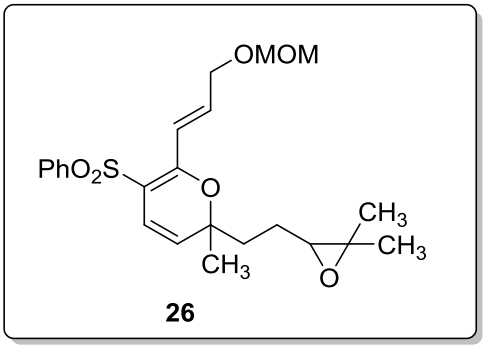
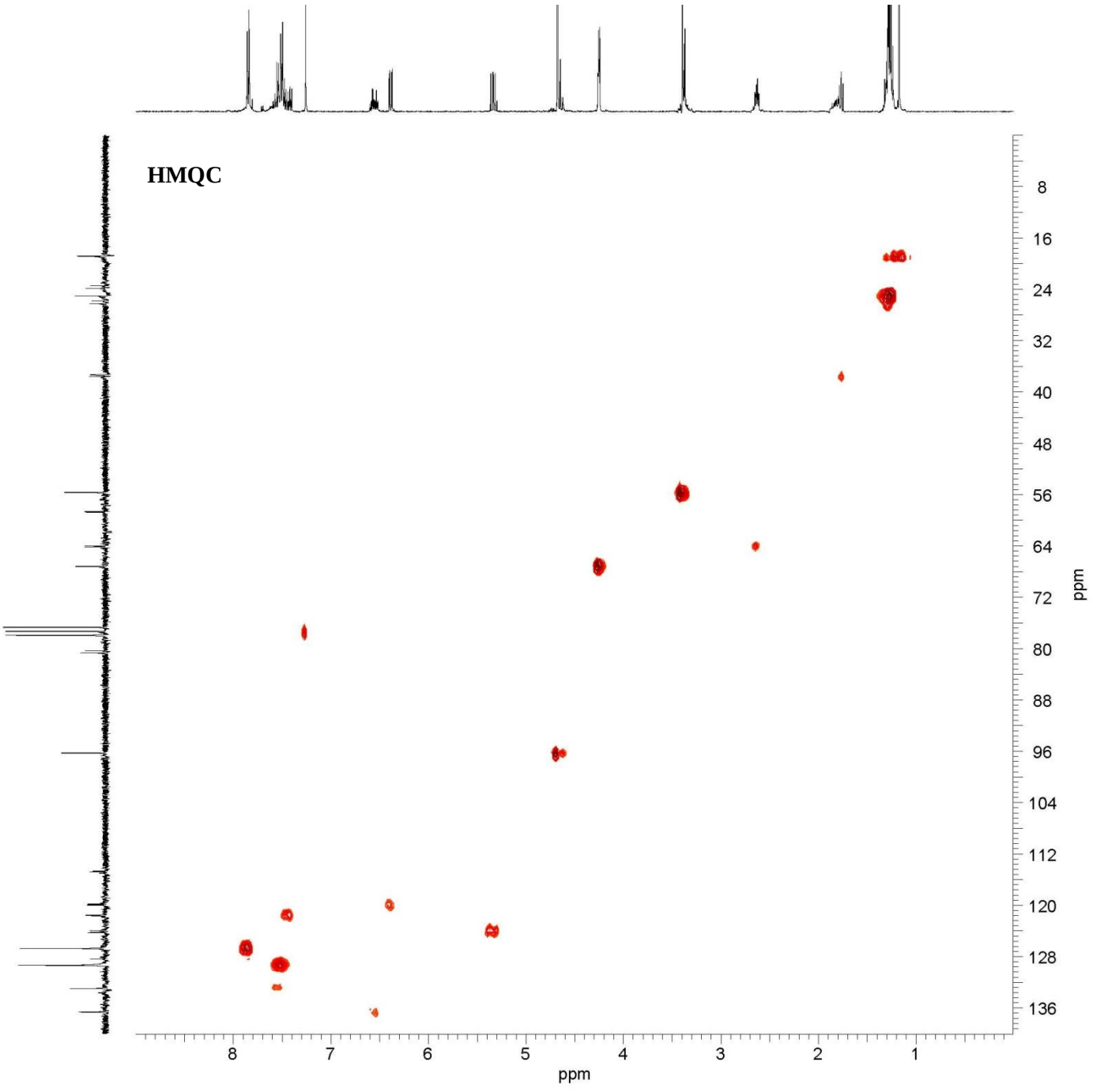
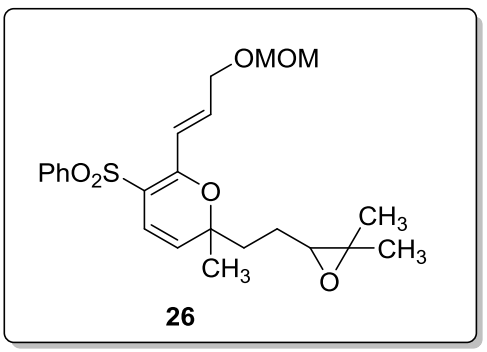
7.5
8.0
8.5
ppm
8
7
6
5
4
3
2
1
0
ppm

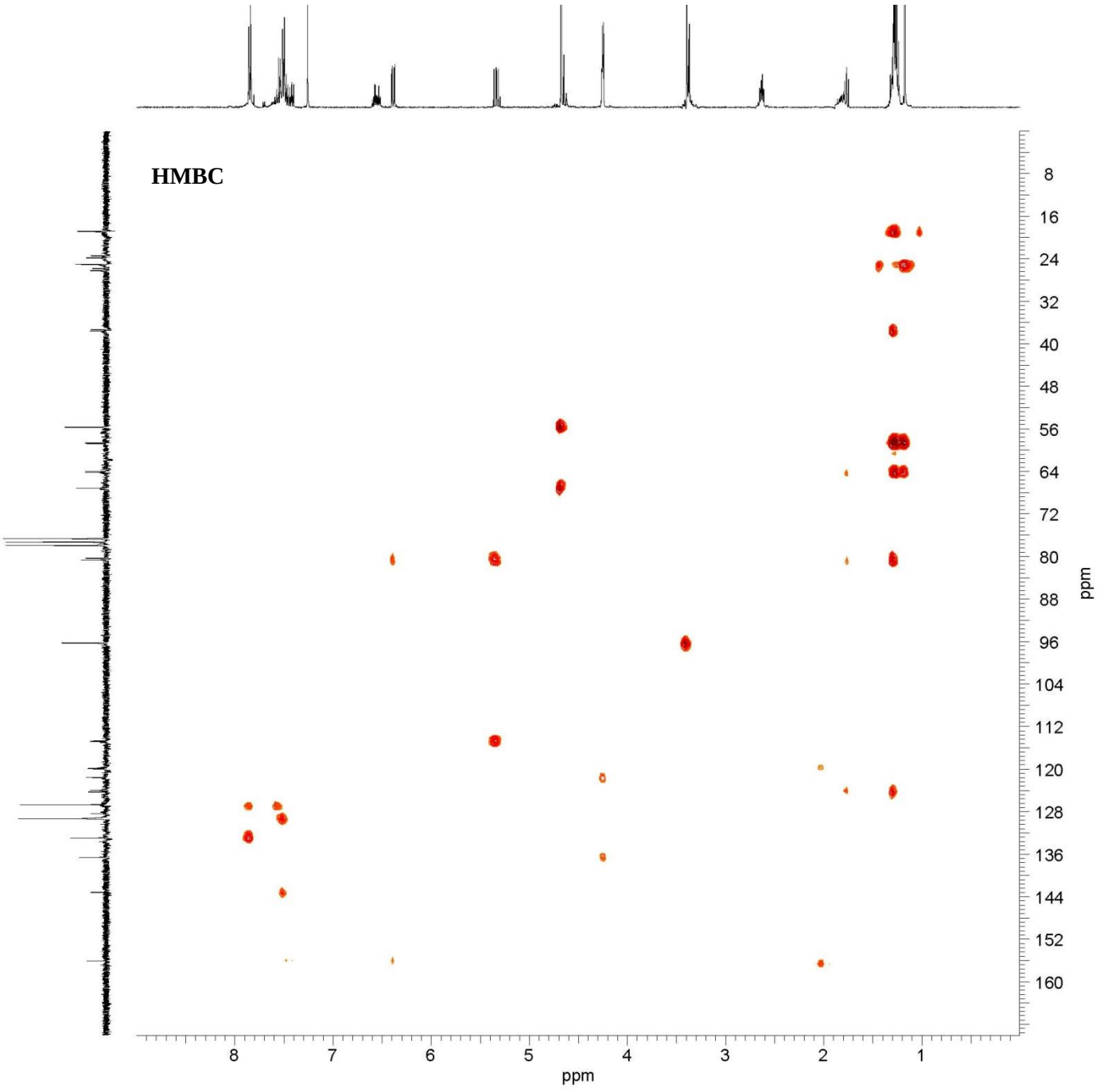

OMOM
PhO2S
O
CH3
CH3
CH3
O

26


HMQC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
ppm
8
7
6
5
4
3
2
1
ppm


OMOM
PhO2S
O
CH3
CH3
CH3
O

26


HMBC
8
16
24
32
40
48
56
64
72
80
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96
104
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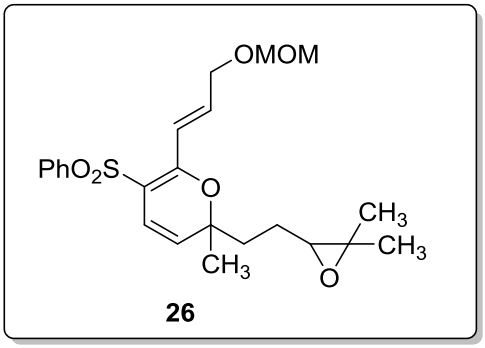
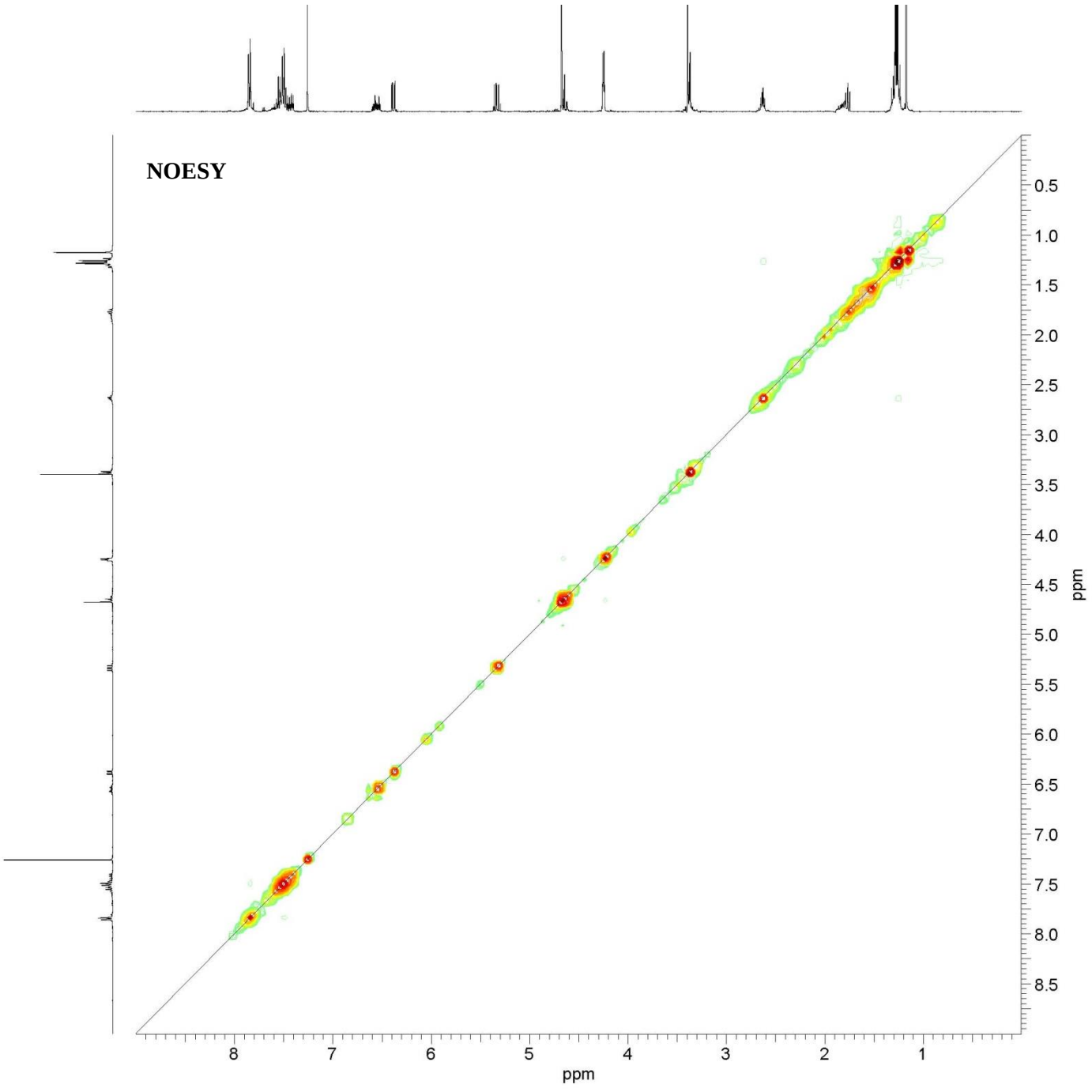
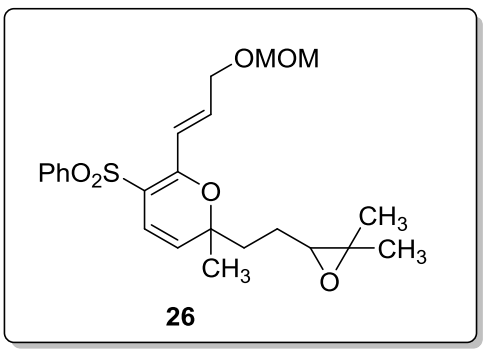
120
128
136
144
152
160
ppm
8
7
6
5
4
3
2
1
ppm

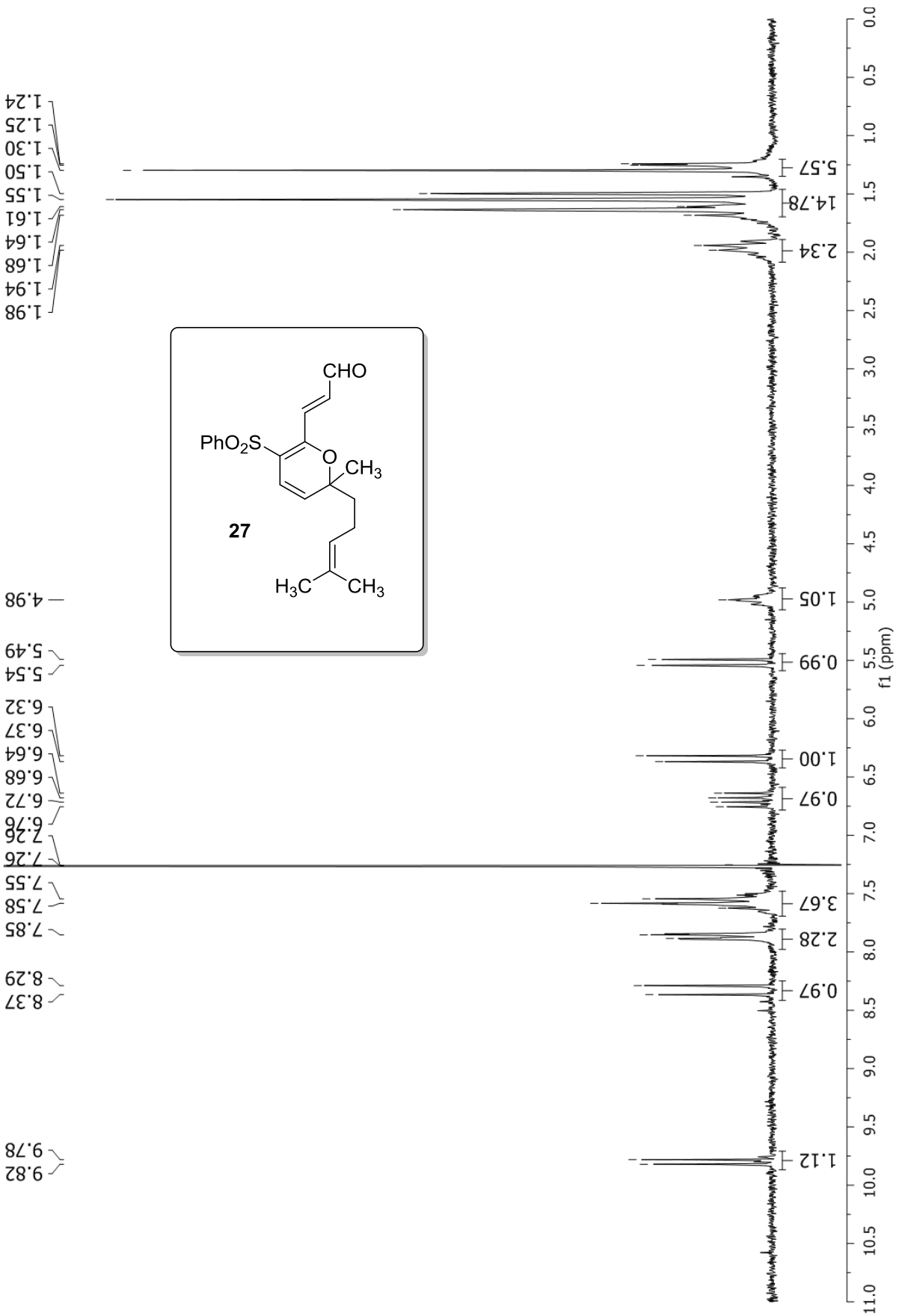

OMOM
PhO2S
O
CH3
CH3
CH3
O

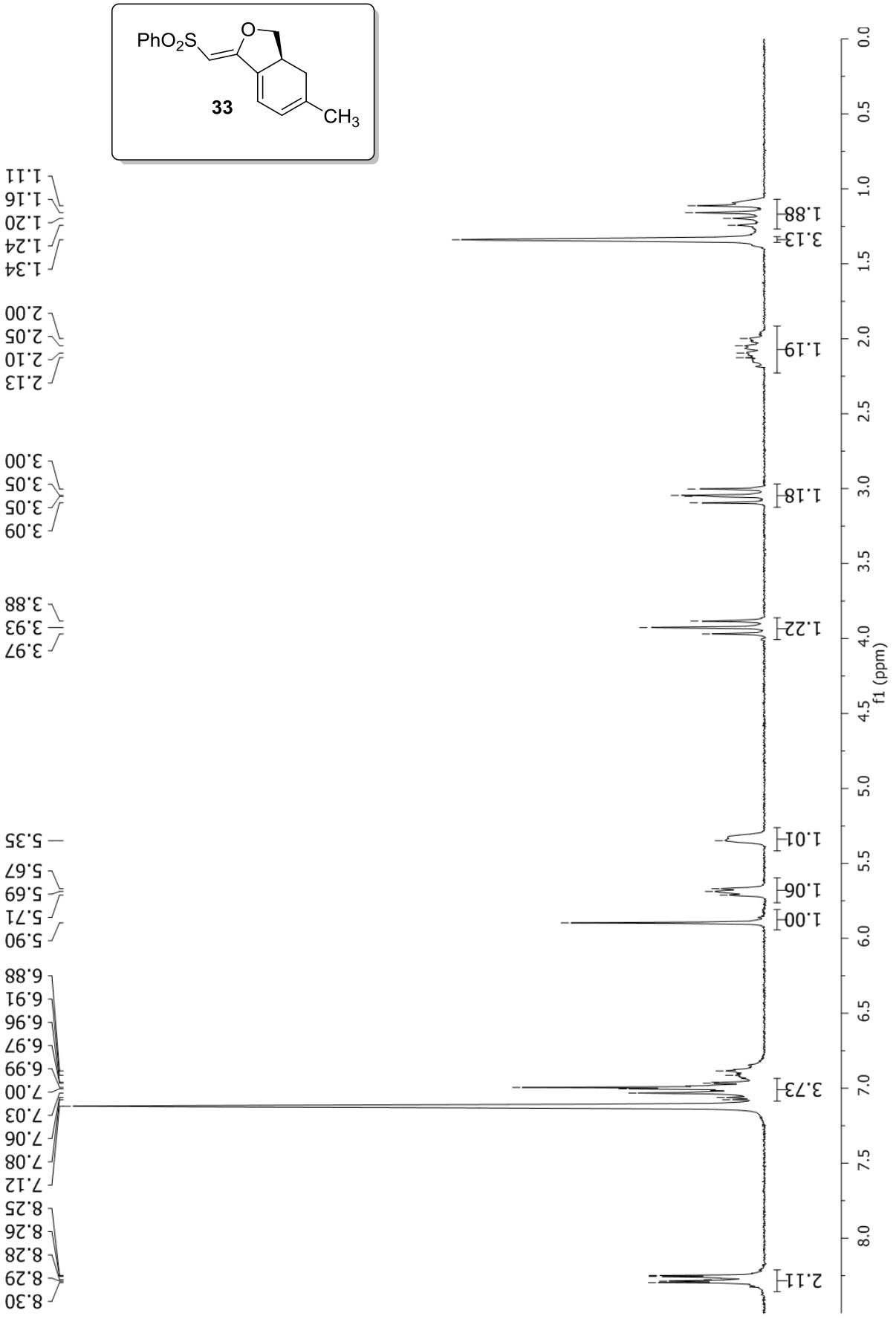
26

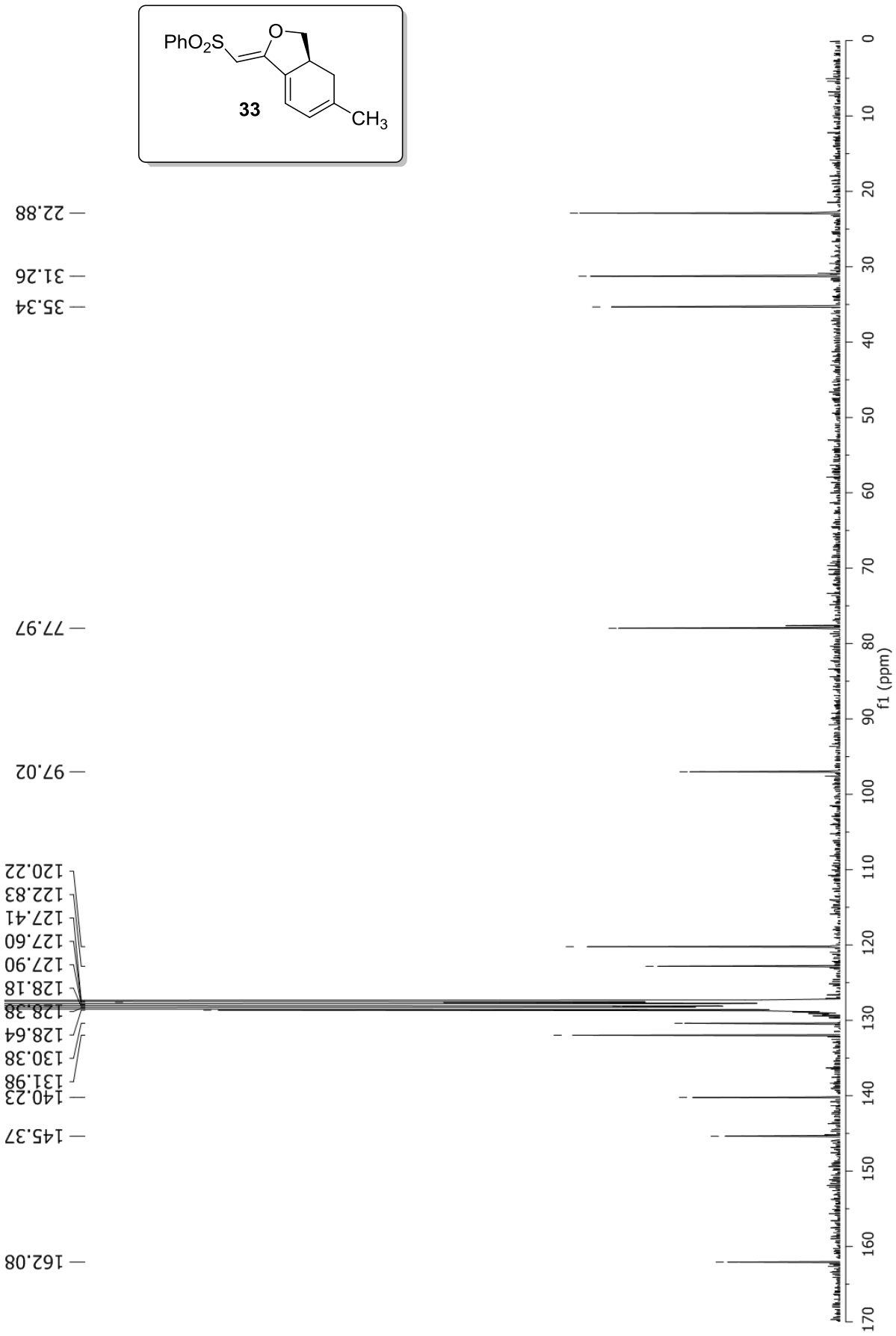

NOESY
8
7
6
5
4
3
2
1
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm

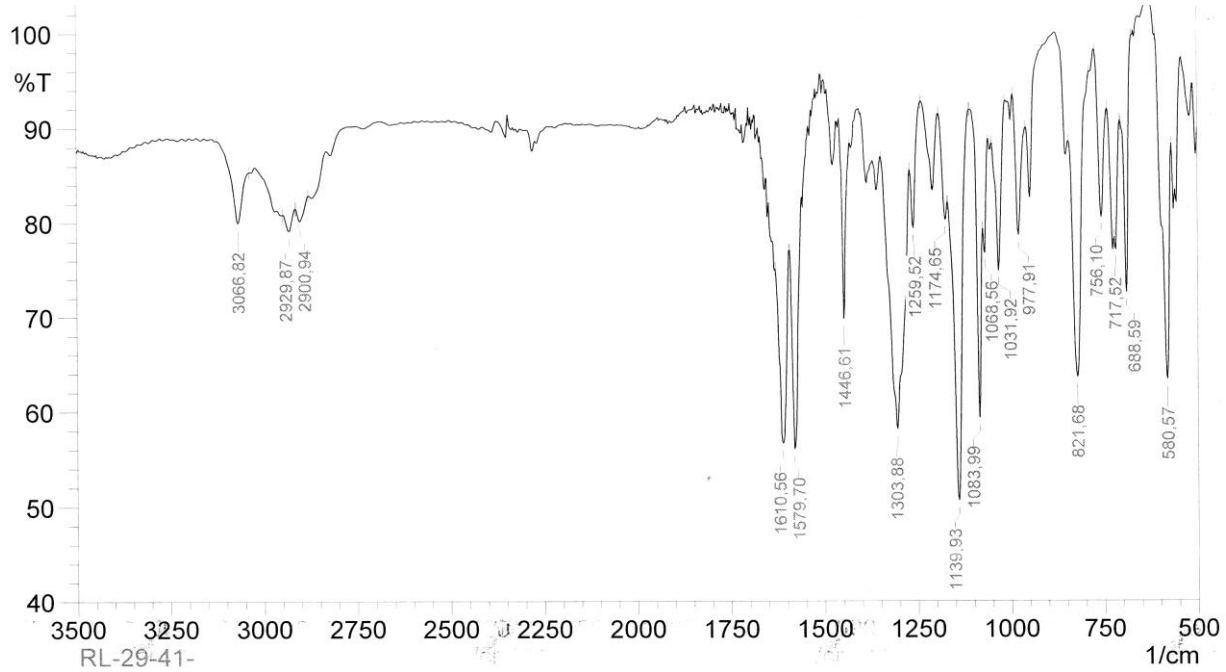

OMOM
PhO2S
O
CH3
CH3
CH3
O

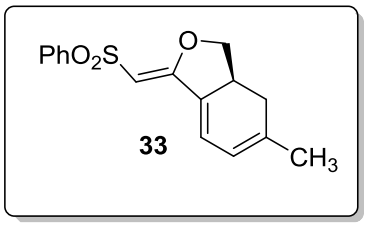
26


CHO
PhO2S
O
CH3
H3C
CH3
27
f1 (ppm)

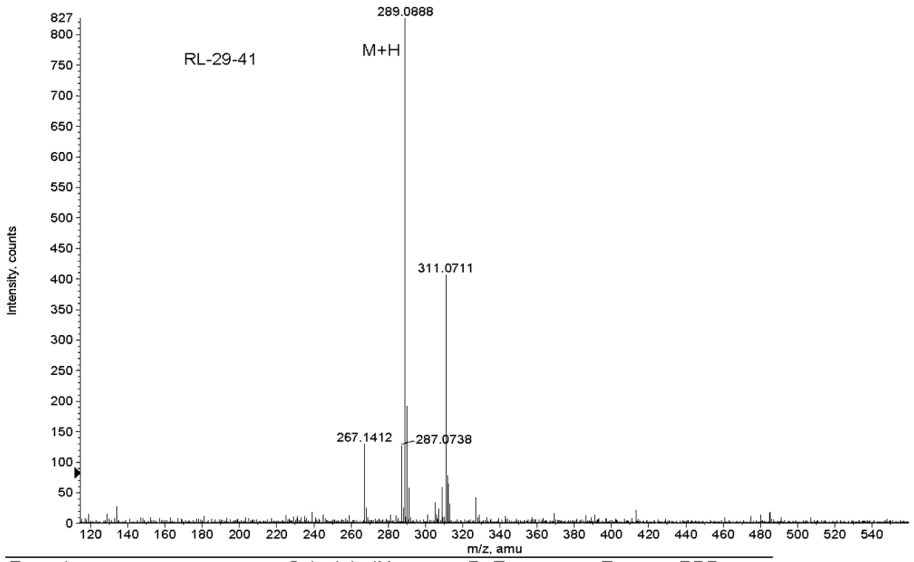

PhO2S
O
33
CH3
f1 (ppm)


PhO2S
O
33
CH3
22.88
31.26
35.34
77.97
97.02
120.22
122.83
127.41
127.60
127.90
128.18
128.38
128.64
130.38
131.98
140.23
145.37
162.08
f1 (ppm)

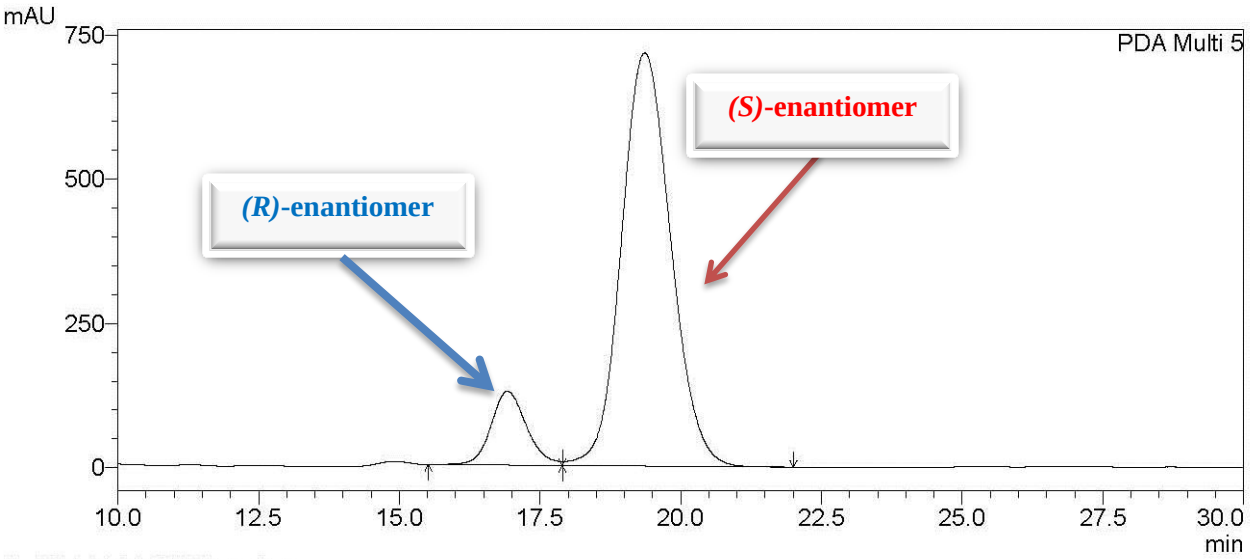




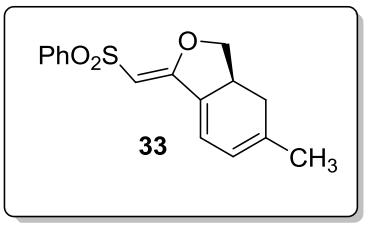
33



Formula	CalculatedMass	mDaError	ppmError	RDB
C8 H13 N6 O6	289.089109	-0.308828	-1.068279	5.5
C16 H17 O3 S	289.089293	-0.49282	-1.704732	8.5



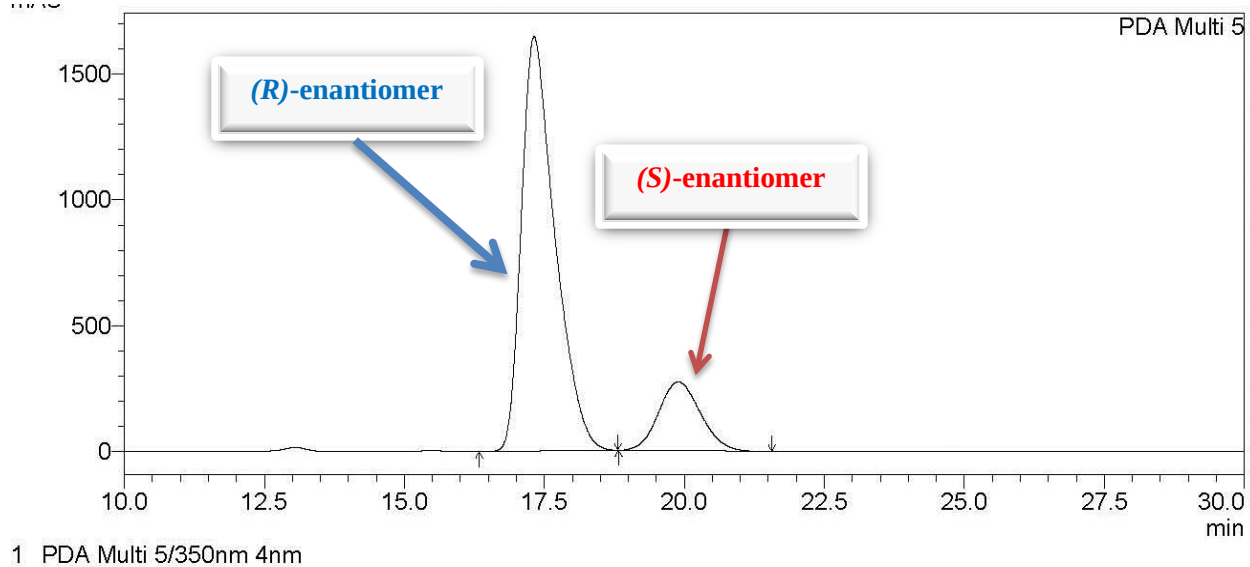
1 PDA Multi 5/350nm 4nm



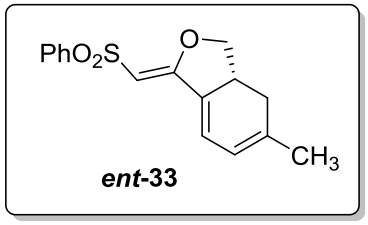
PeakTable

PDA Ch5 350nm 4nm

Peak#	Ret. Time	Area %
1	16.917	11.406
2	19.354	88.594
Total		100.000



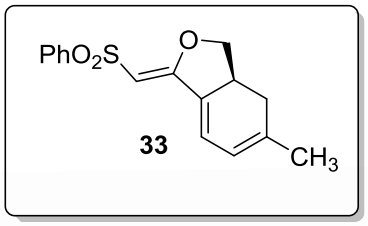
1 PDA Multi 5/350nm 4nm



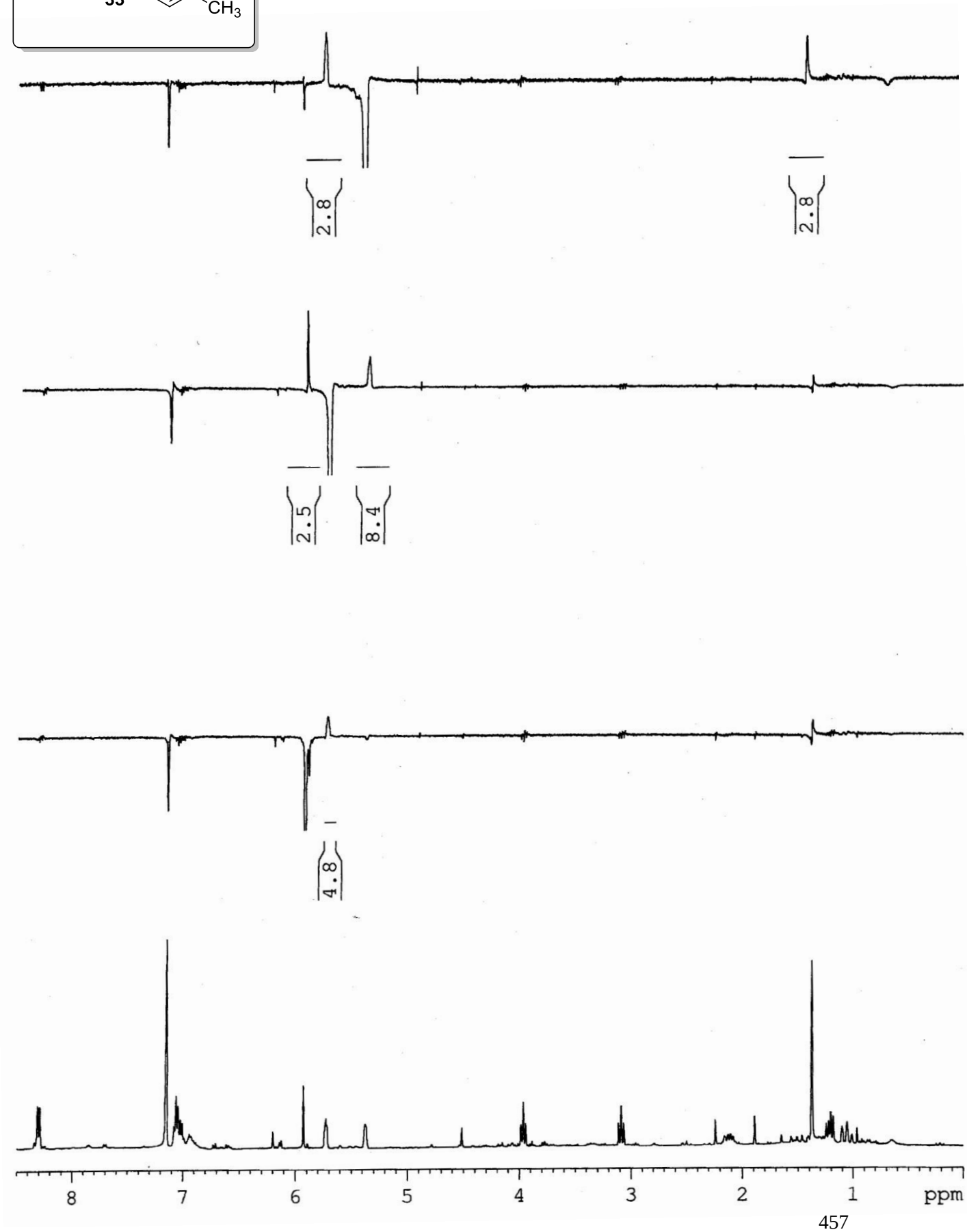
PeakTable

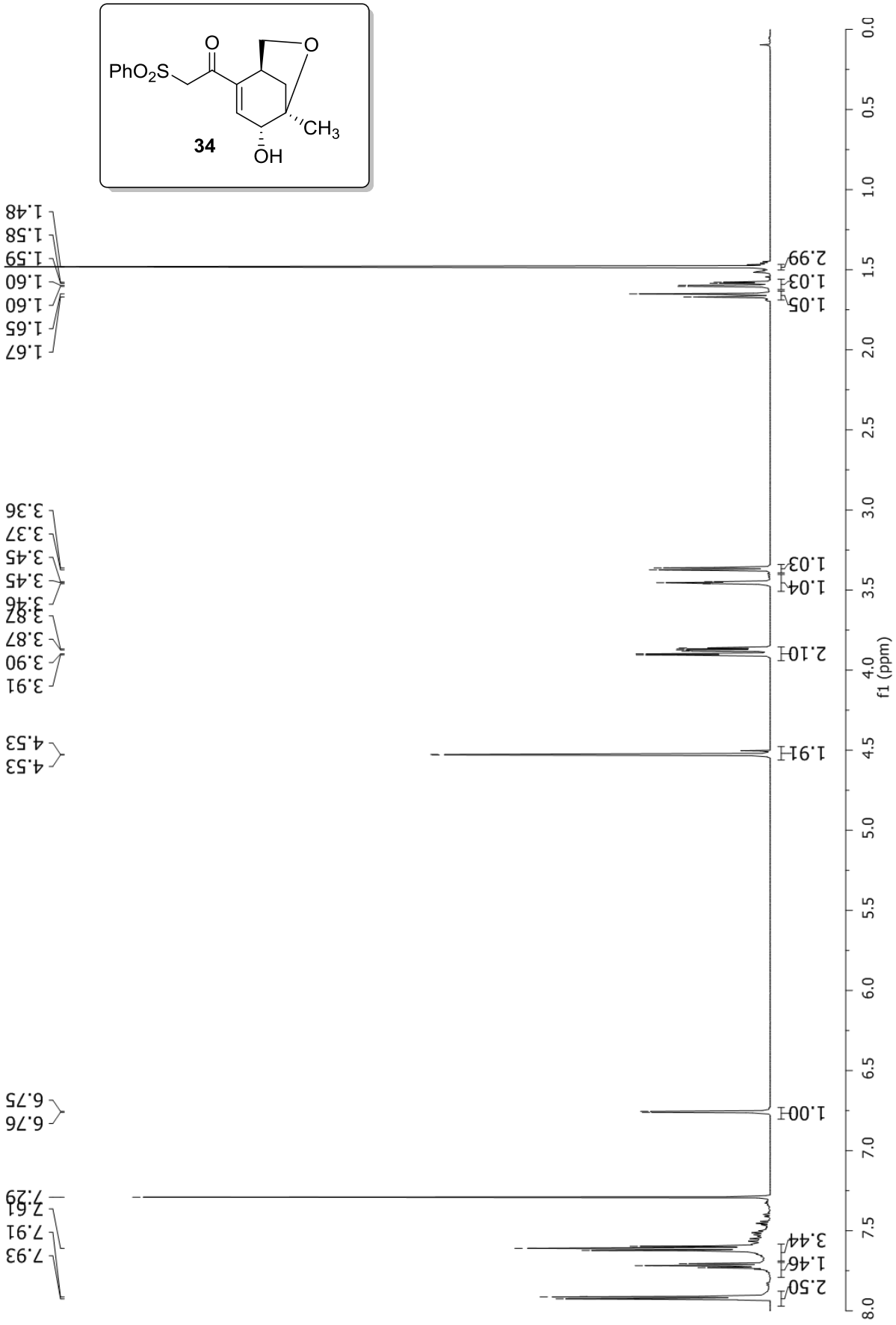
PDA Ch5 350nm 4nm

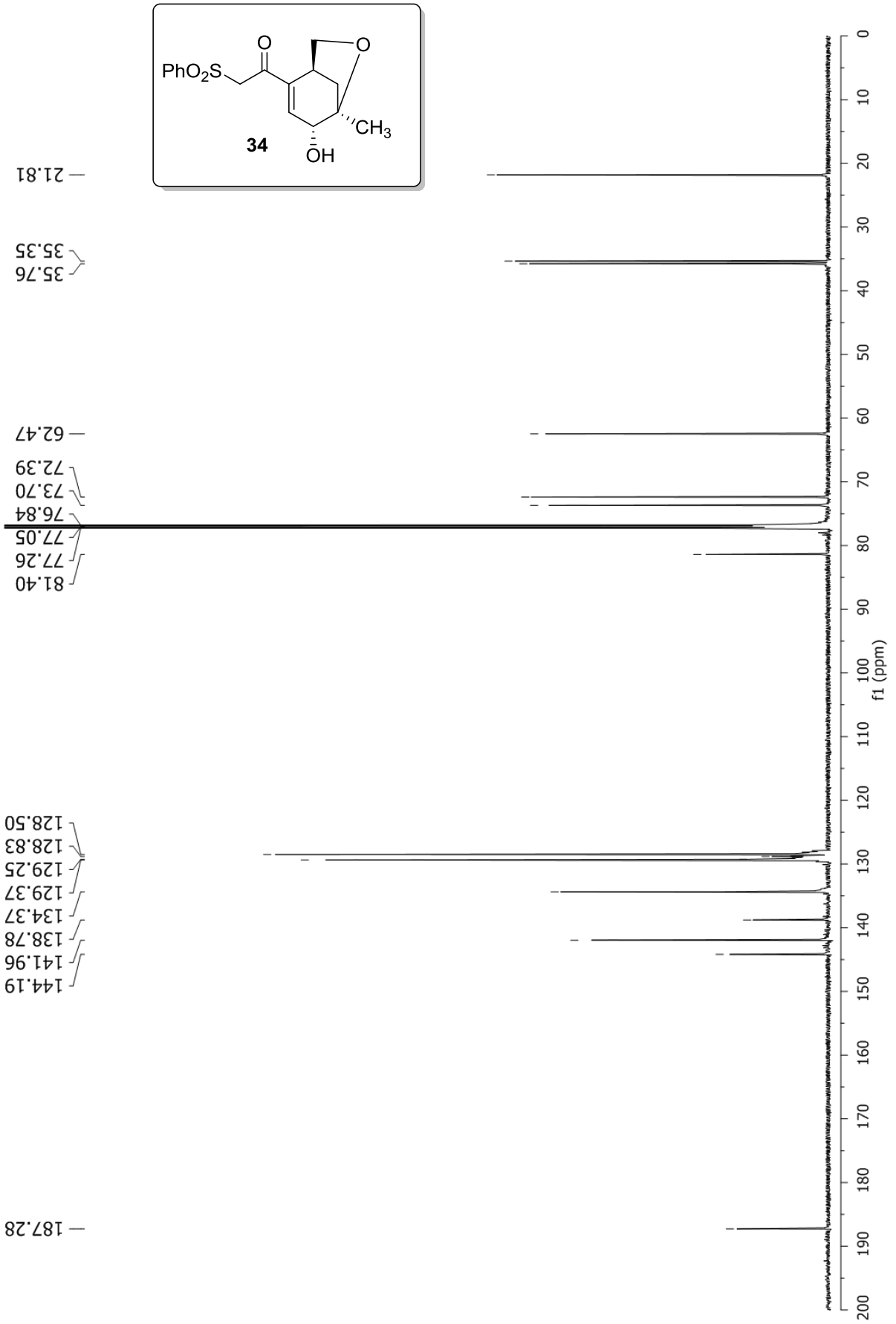
Peak#	Ret. Time	Area %
1	17.313	82.913
2	19.885	17.087
Total		100.000

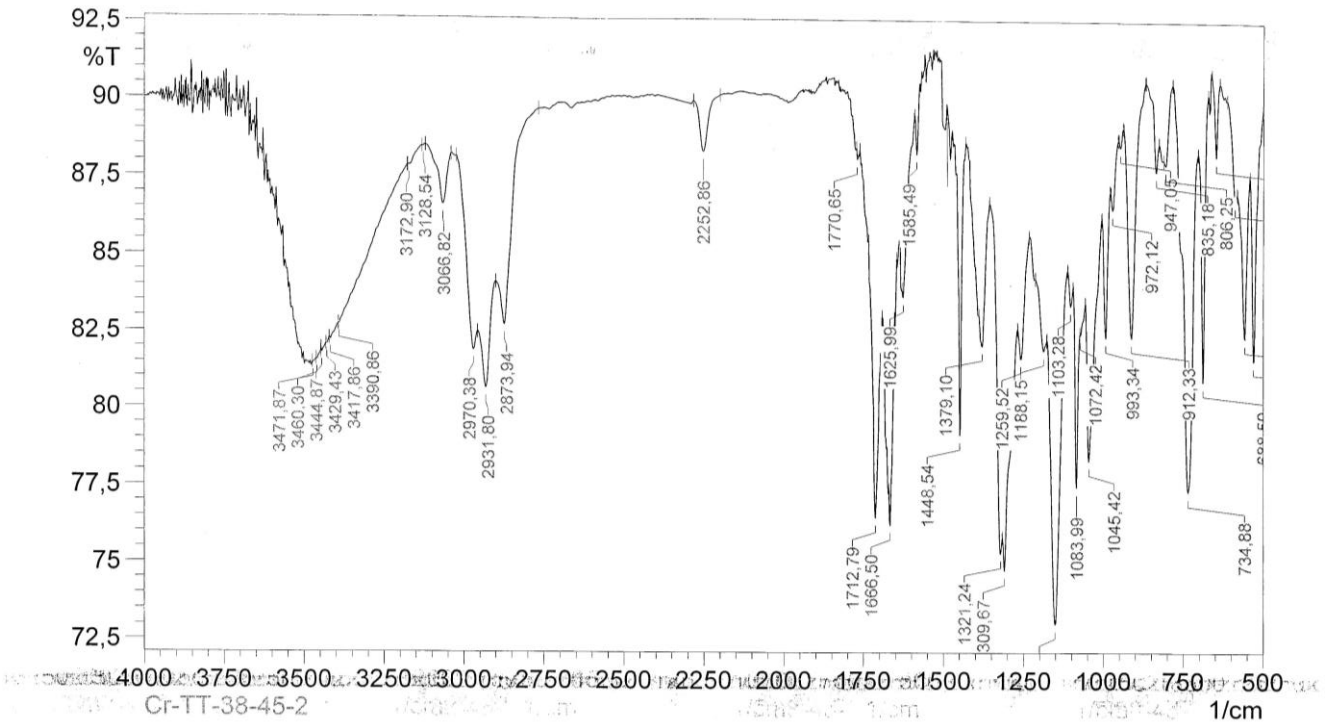


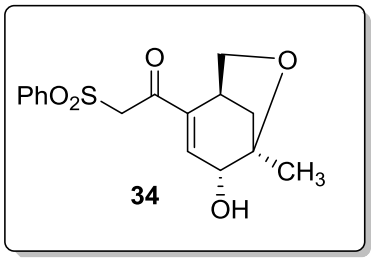
NOE

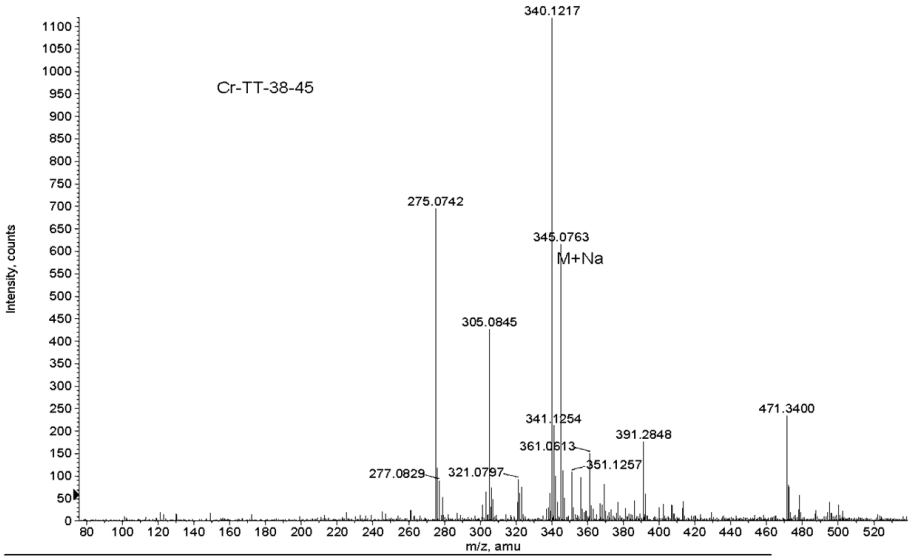



PhO2S
O
O
CH3
OH
34
f1 (ppm)

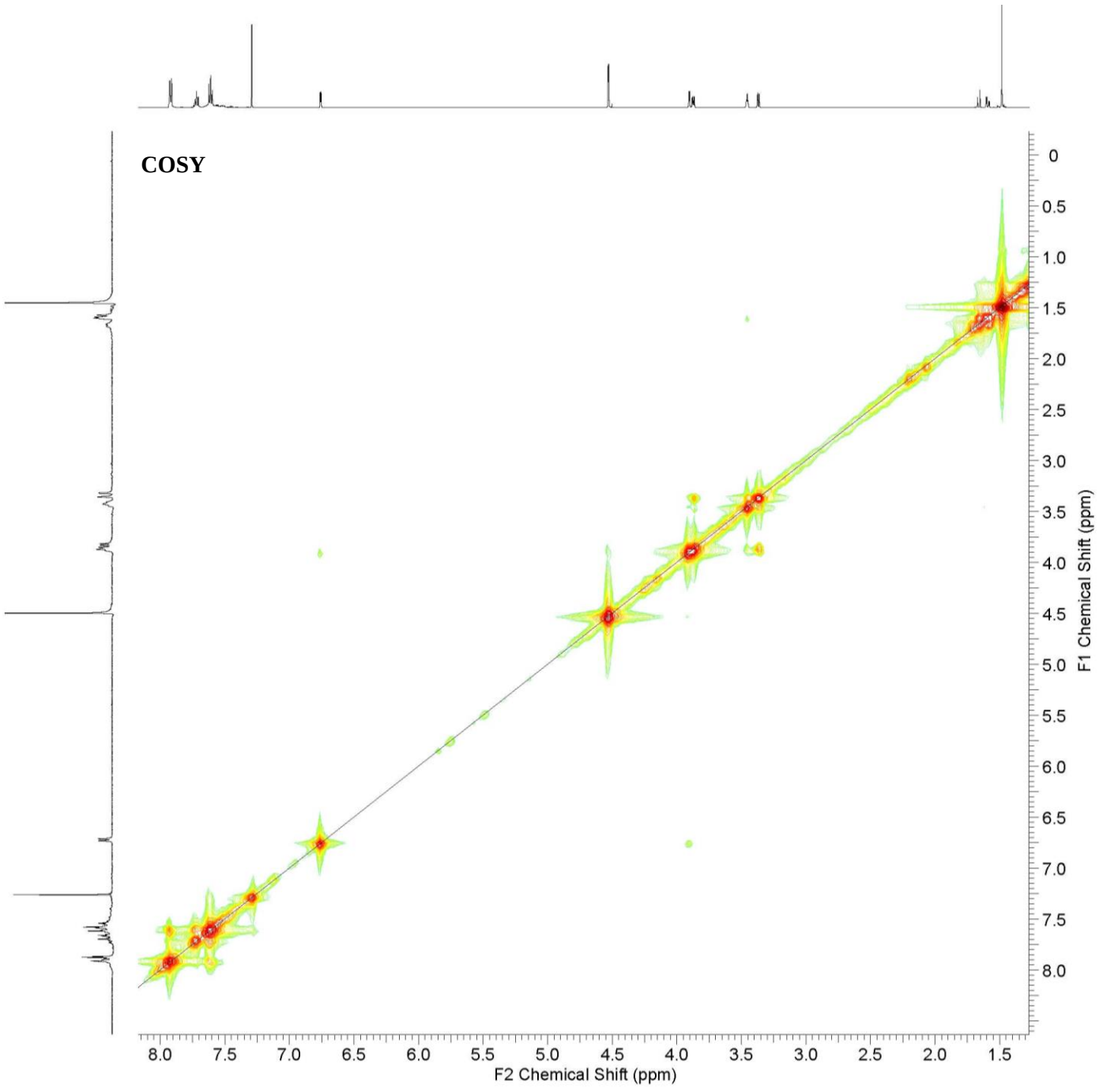

PhO2S
O
O
CH3
OH
34
21.81
35.35
35.76
62.47
72.39
73.70
76.84
77.05
77.26
81.40
128.50
128.83
129.25
129.37
134.37
138.78
141.96
144.19
187.28
f1 (ppm)

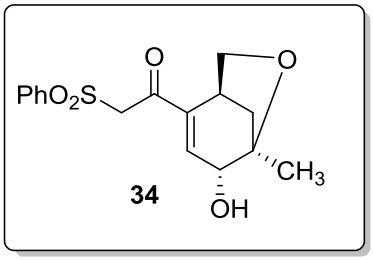




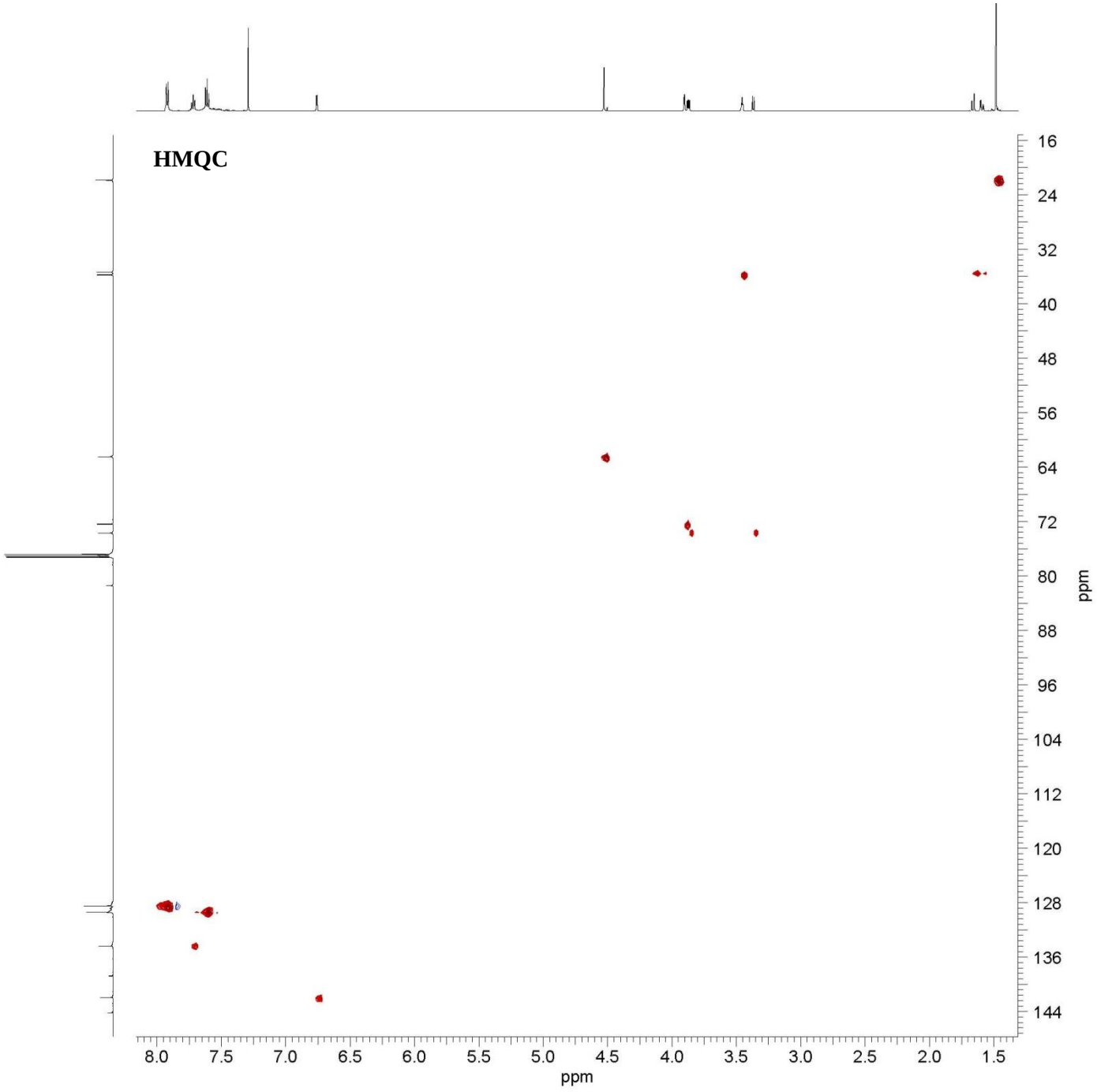


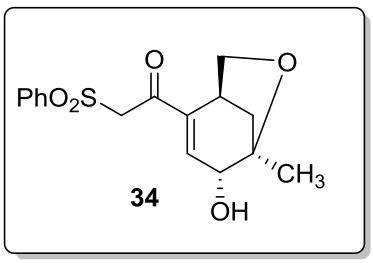
Formula	CalculatedMass	mDaError	ppmError	RDB
C16 H18 O5 Na S	345.076717	-0.41684	-1.207963	7.5


COSY
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

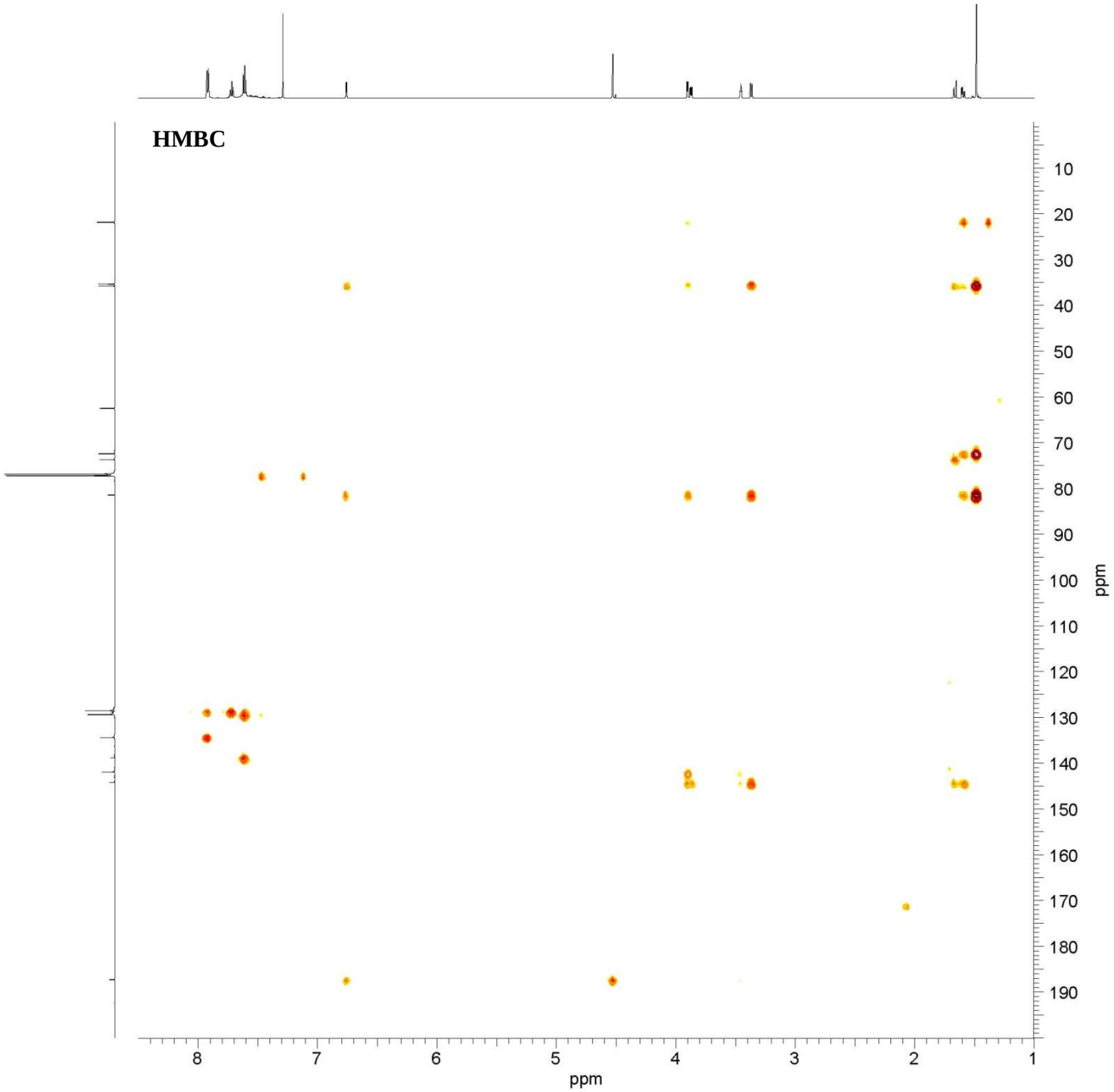

PhO2S
O
O
CH3
OH

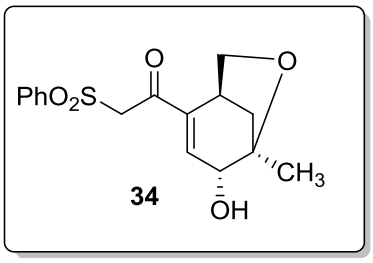
34


HMQC
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

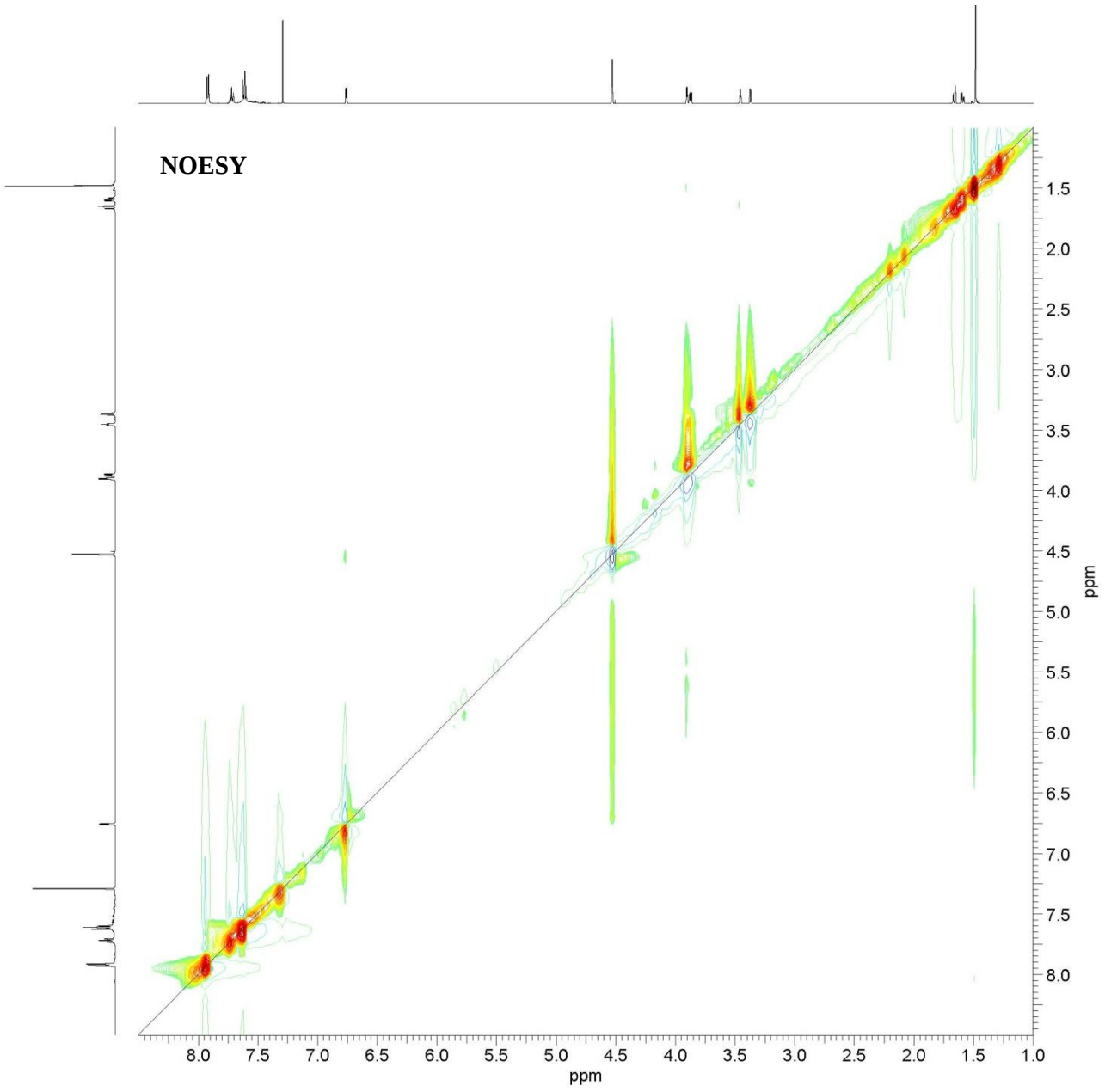

PhO2S
O
O
CH3
OH

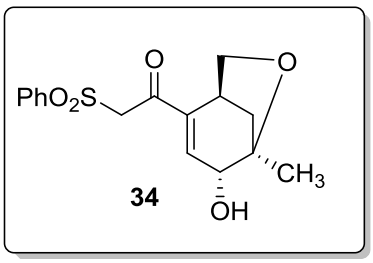
34


HMBC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm
8
7
6
5
4
3
2
1
ppm

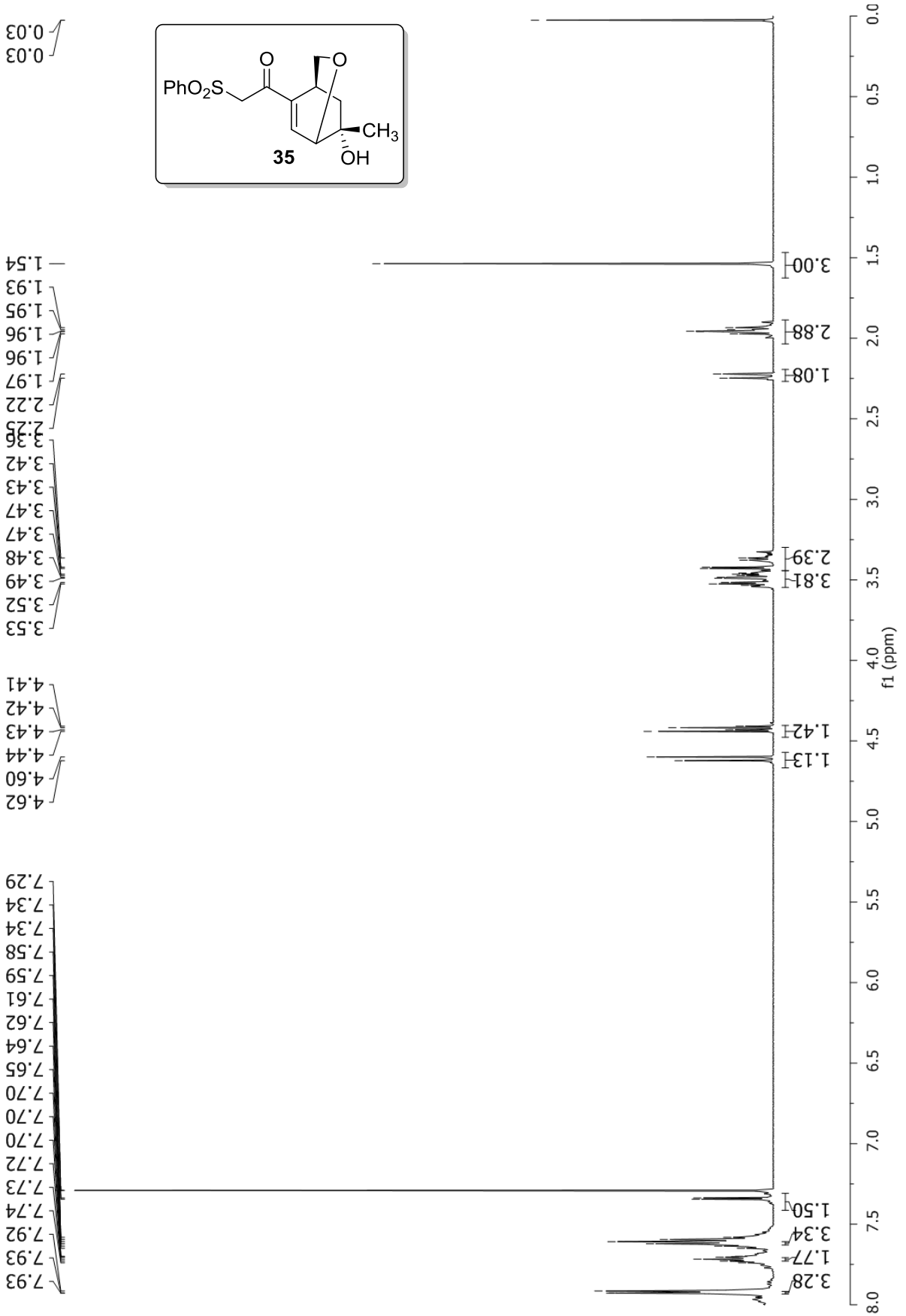

O
O
PhO2S
CH3
OH

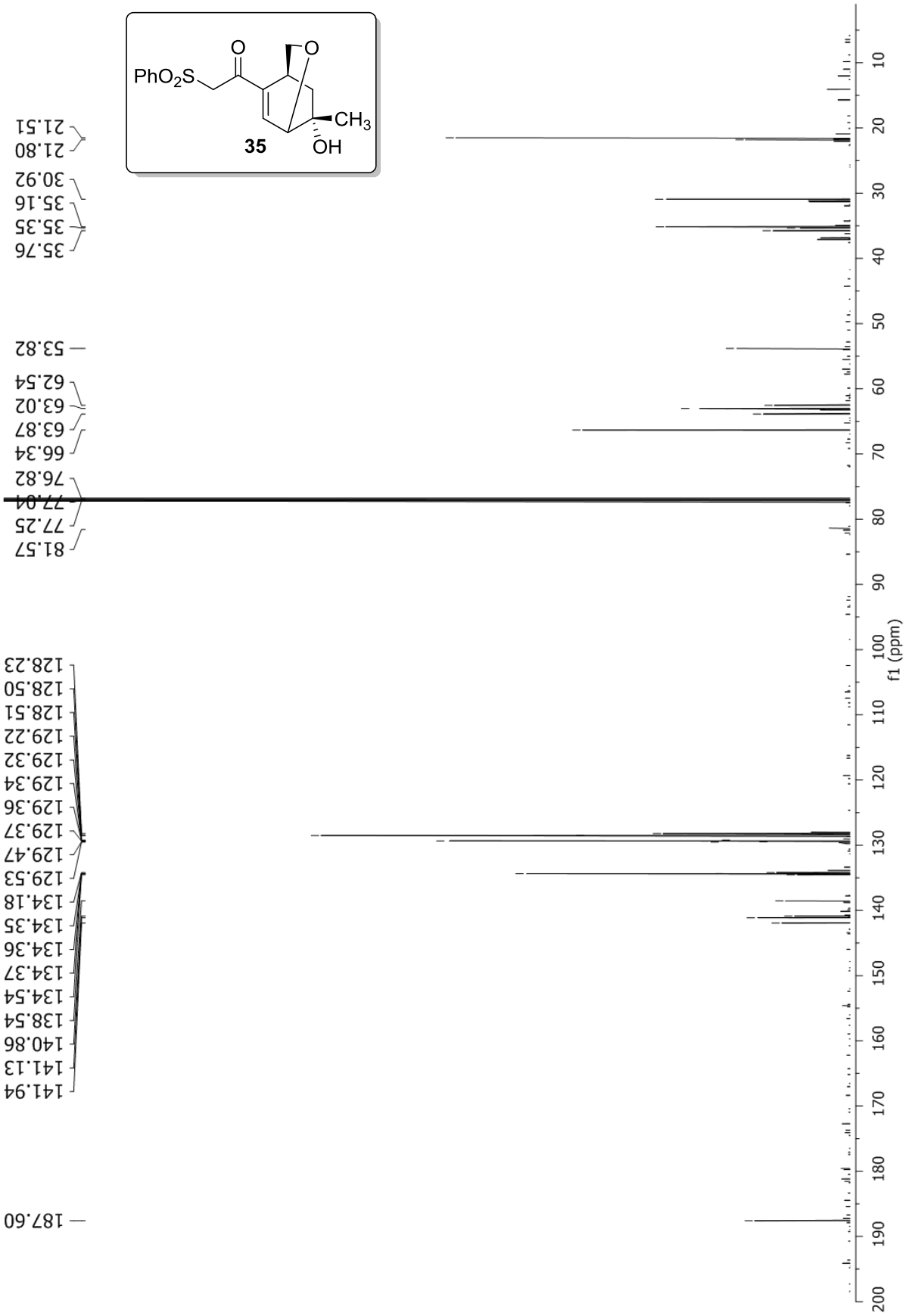
34

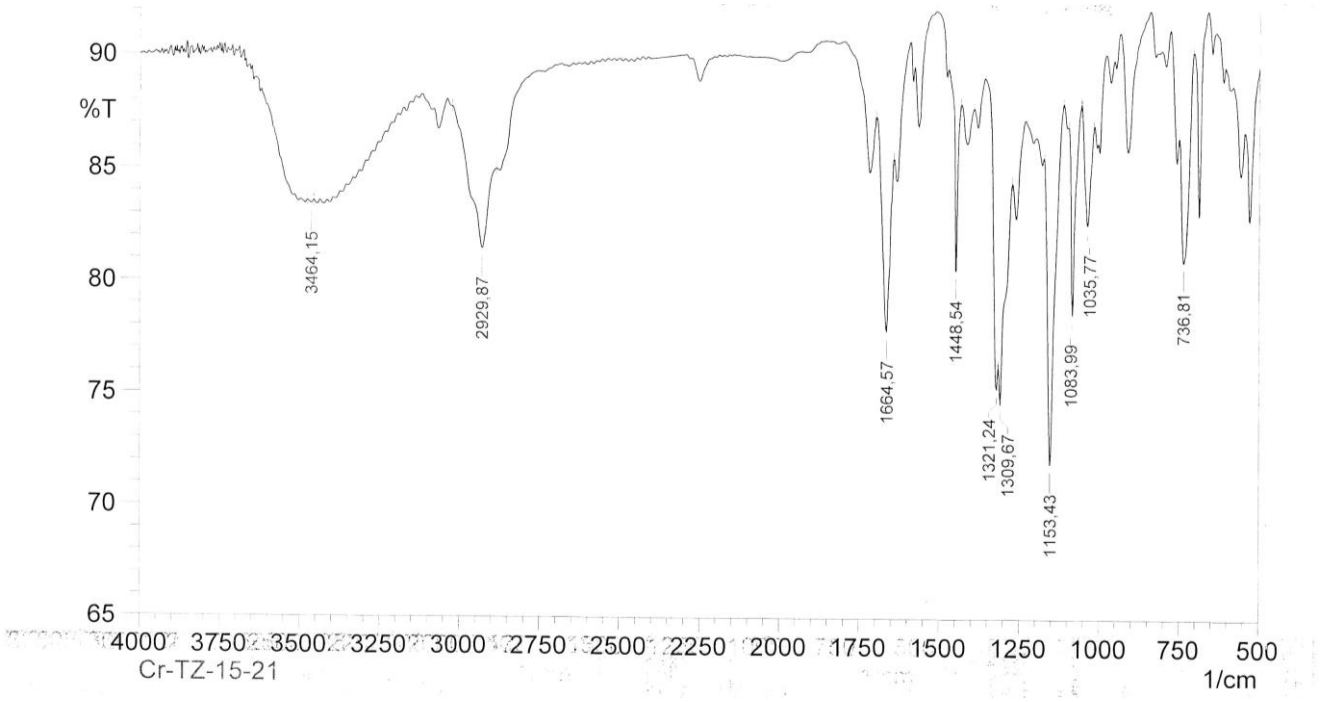

NOESY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
ppm

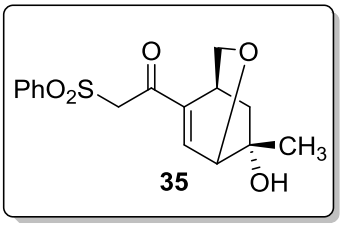

PhO2S
O
O
CH3
OH

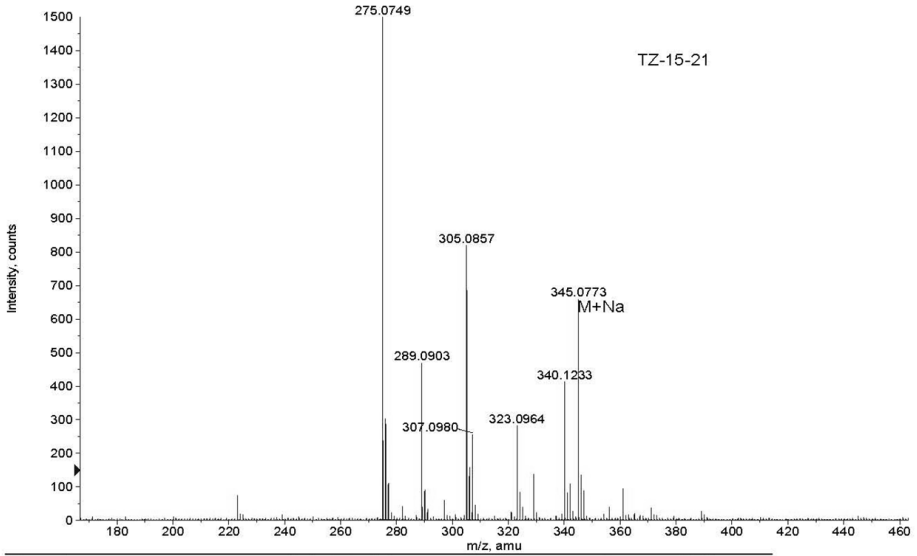
34


PhO2S
O
O
CH3
OH
35
f1 (ppm)

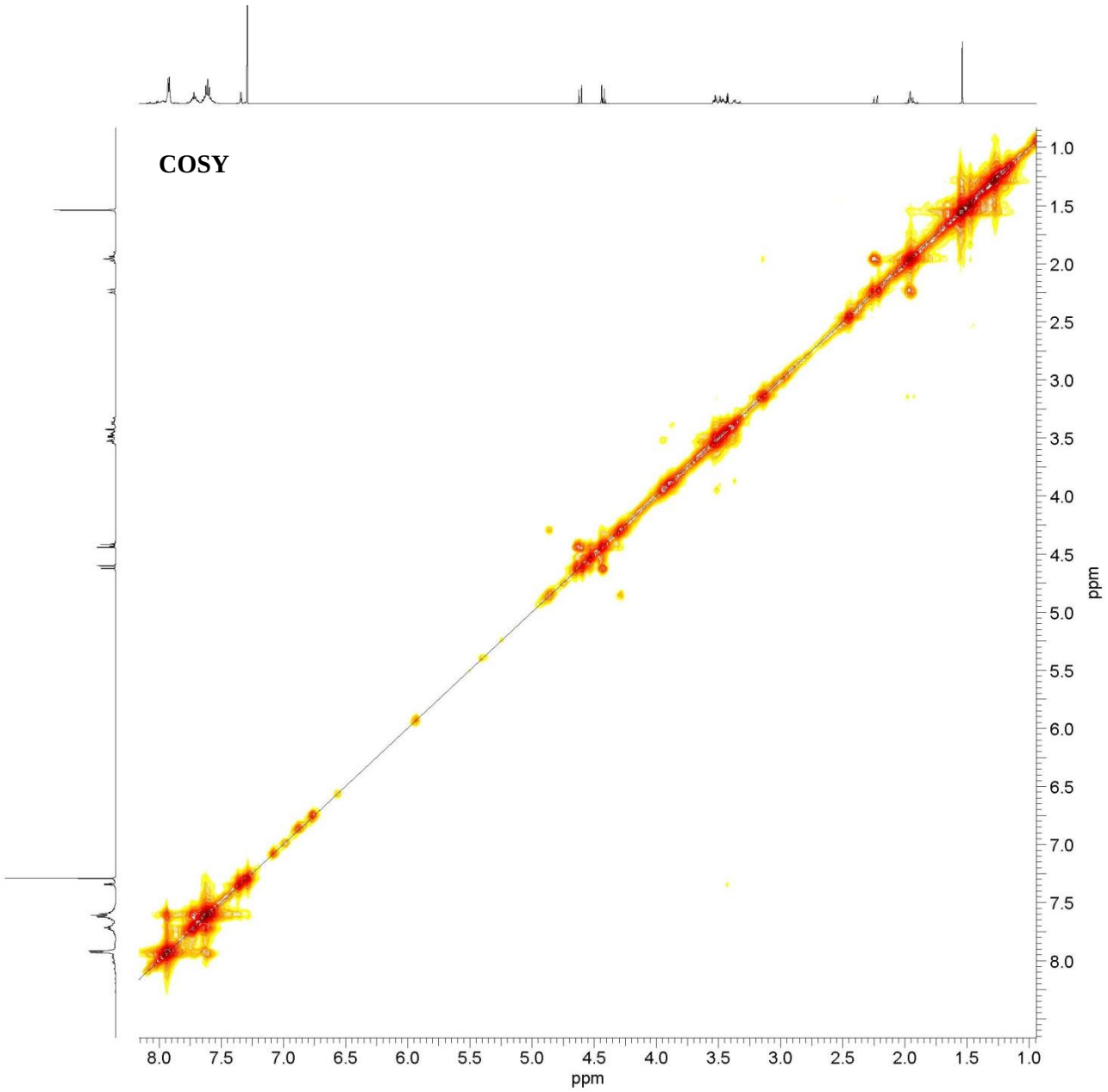

PhO2S
O
O
CH3
OH
35
21.51
21.80
30.92
35.16
35.35
35.76
53.82
62.54
63.02
63.87
66.34
76.82
77.04
77.25
81.57
128.23
128.50
128.51
129.22
129.32
129.34
129.36
129.37
129.47
129.53
134.18
134.35
134.36
134.37
134.54
138.54
140.86
141.13
141.94
187.60
f1 (ppm)

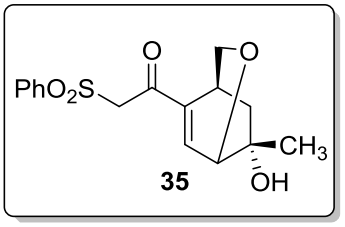




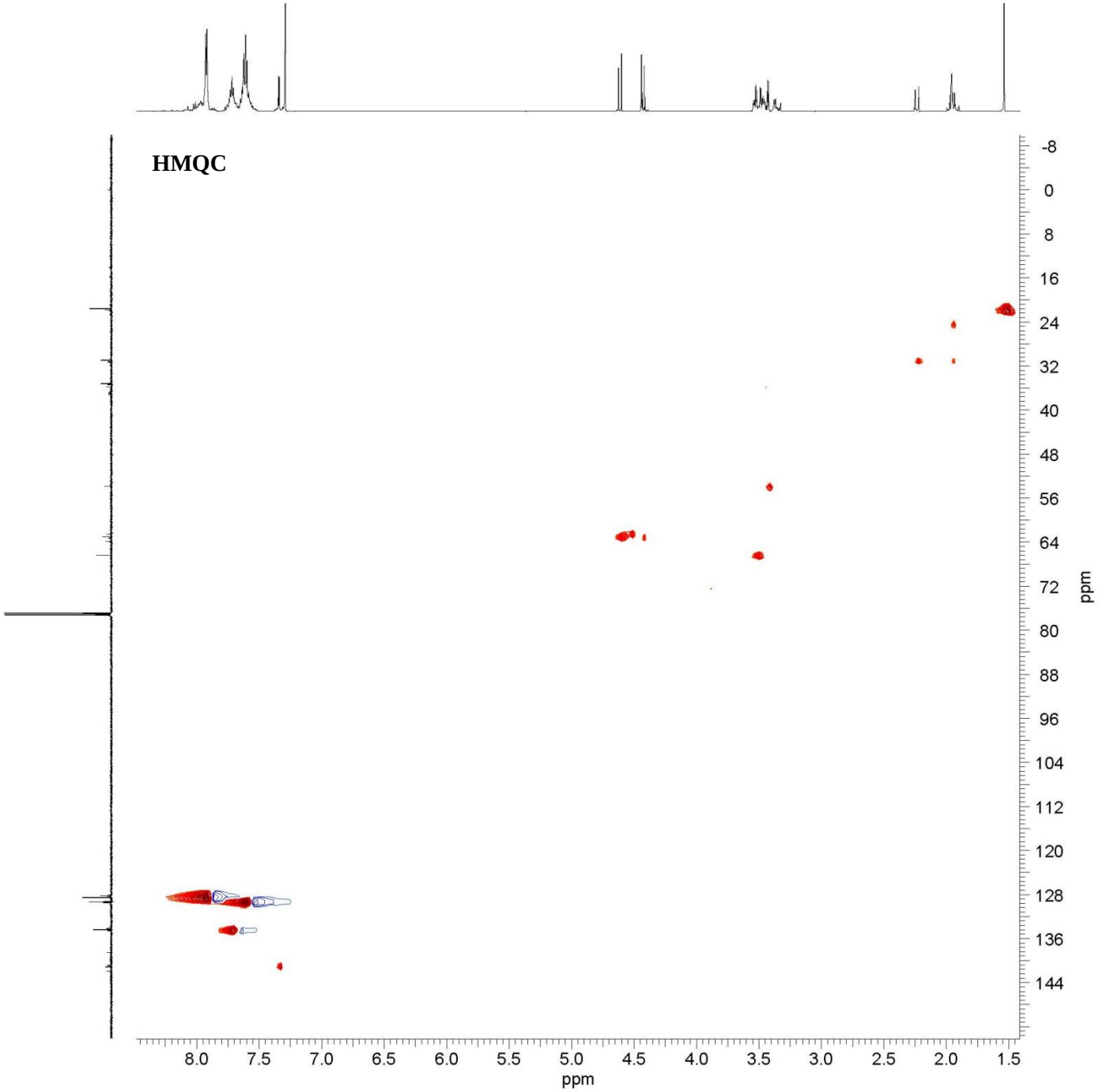


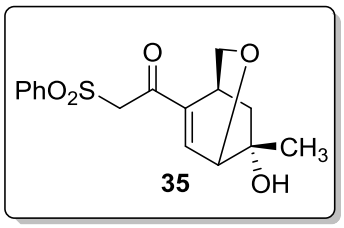
Formula	CalculatedMass	mDaError	ppmError	RDB
C22 H9 N4 O	345.077087	0.212548	0.615942	20.5
C16 H18 O5 Na S	345.076717	0.58316	1.689938	7.5



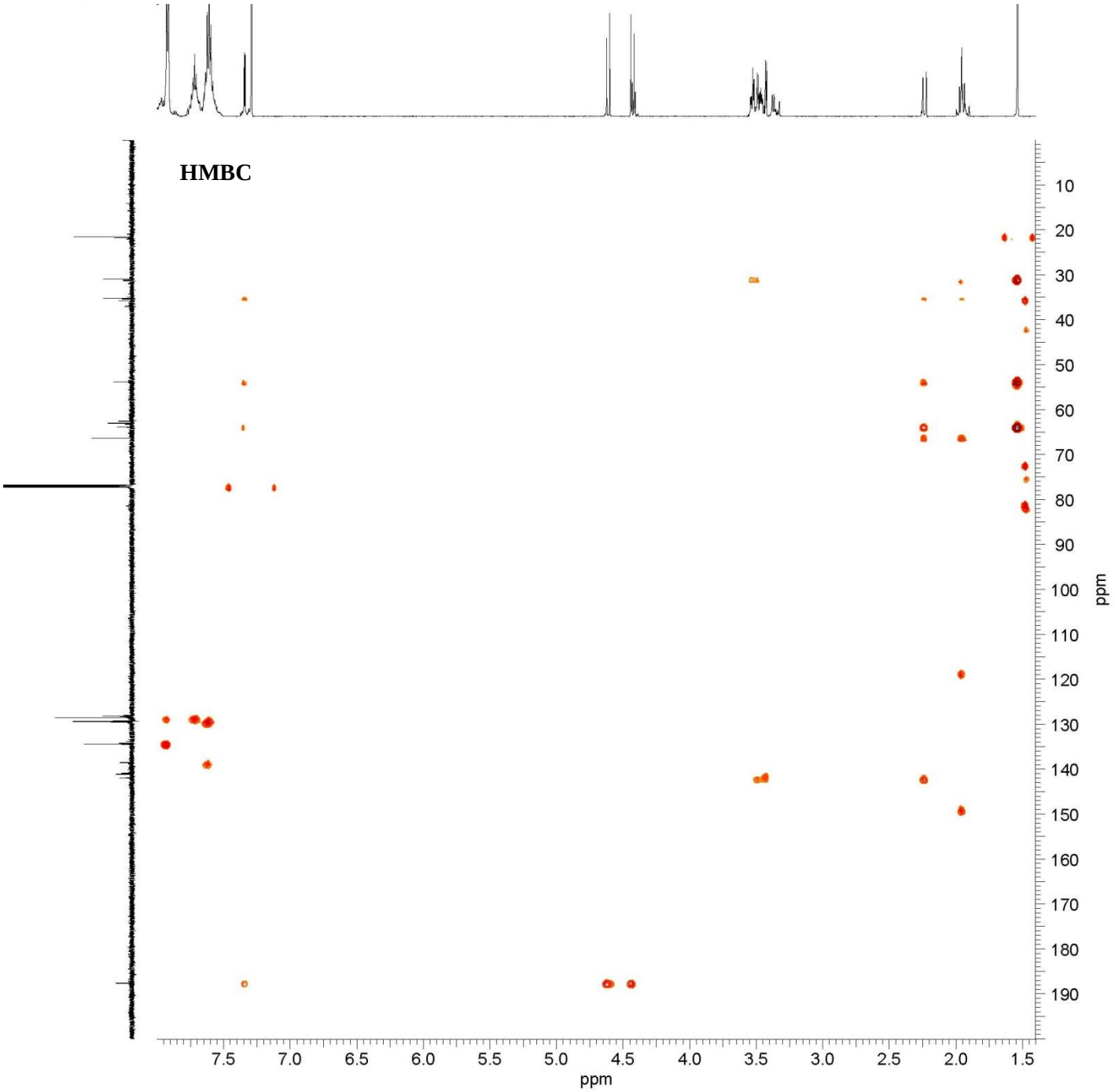


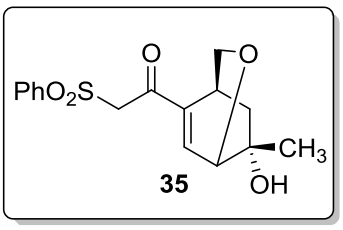
35


HMQC
-8
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

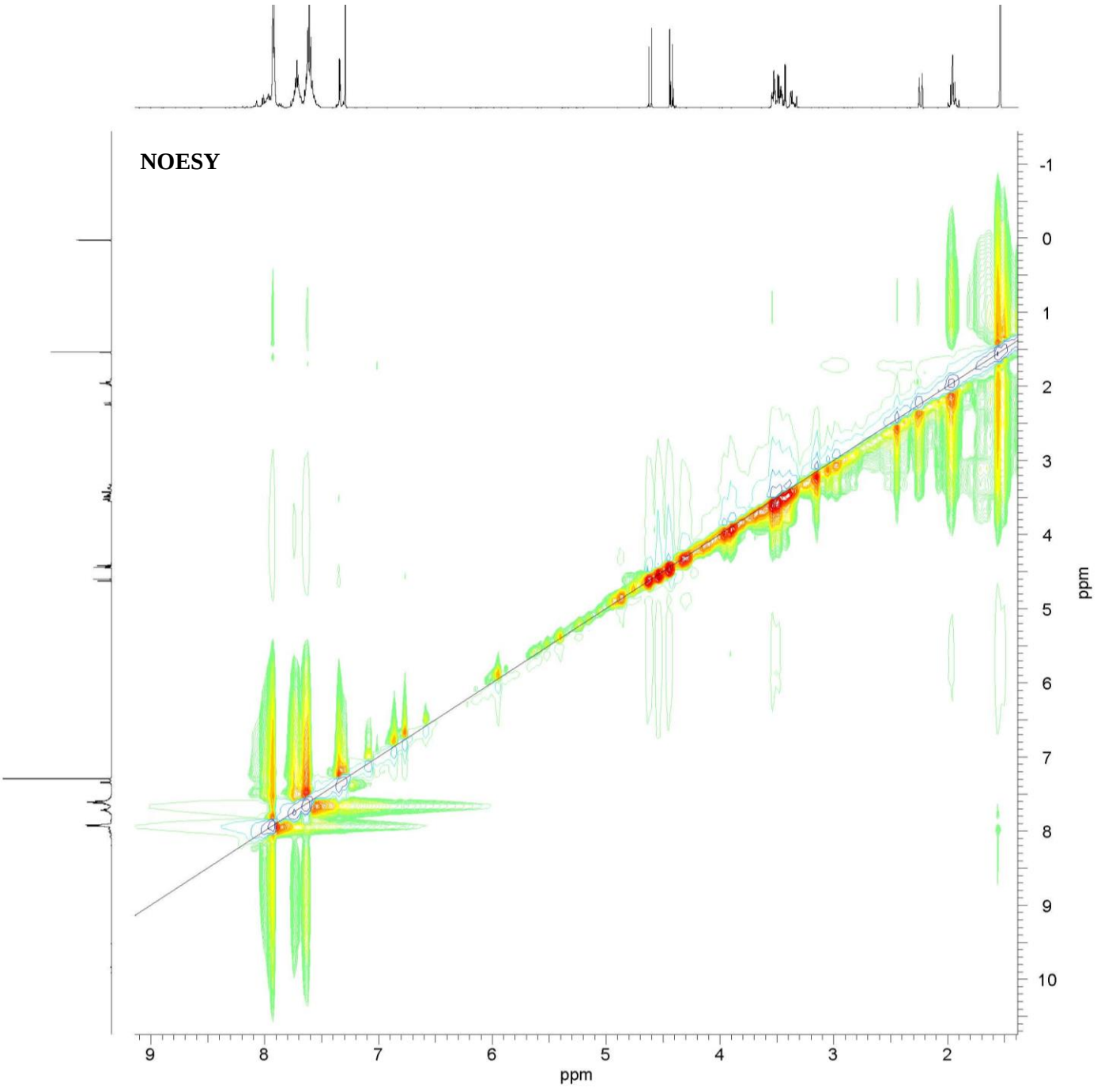

O
O
PhO2S
CH3
OH

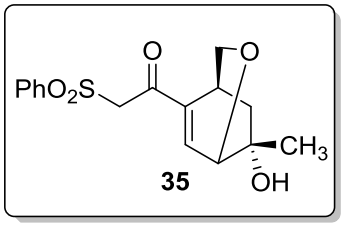
35

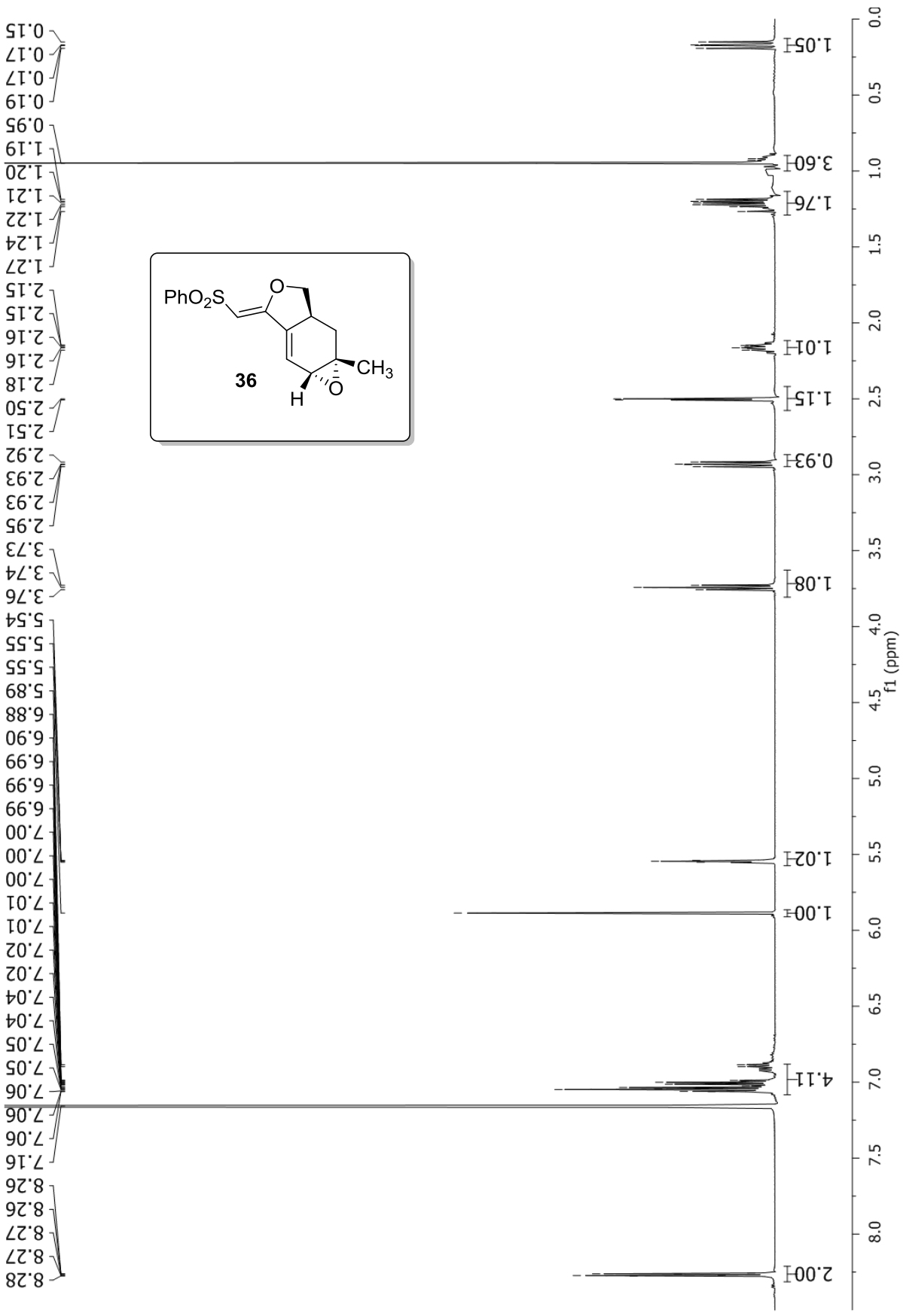

HMBC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

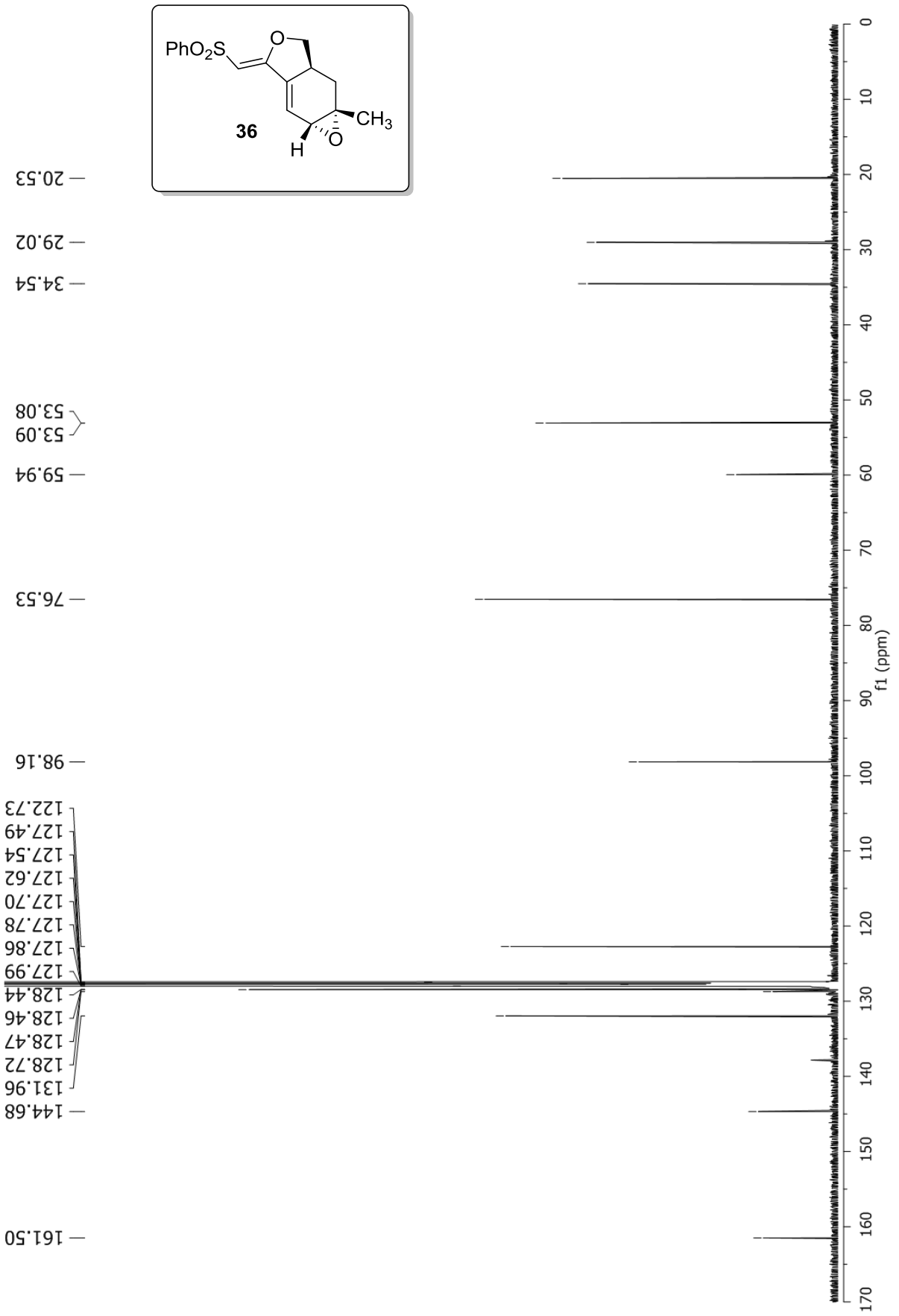

PhO2S
O
O
CH3
OH

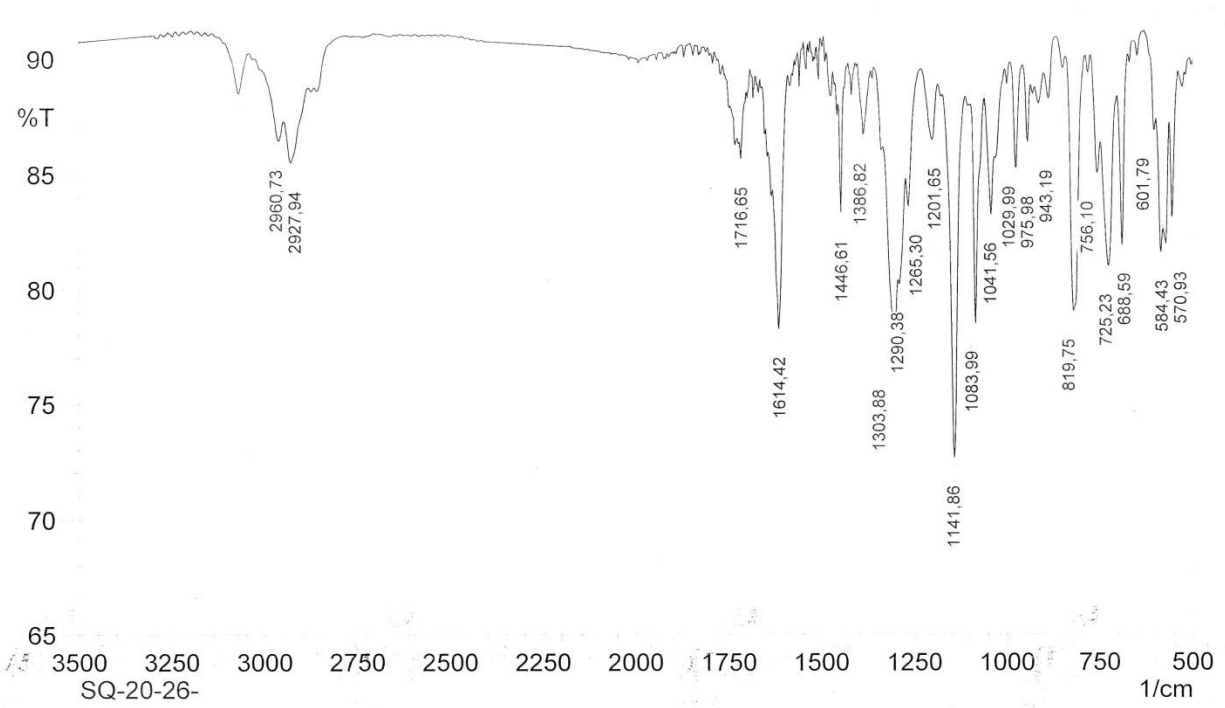
35

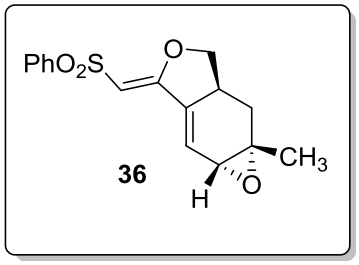

NOESY
9
8
7
6
5
4
3
2
ppm
-1
0
1
2
3
4
5
6
7
8
9
10
ppm

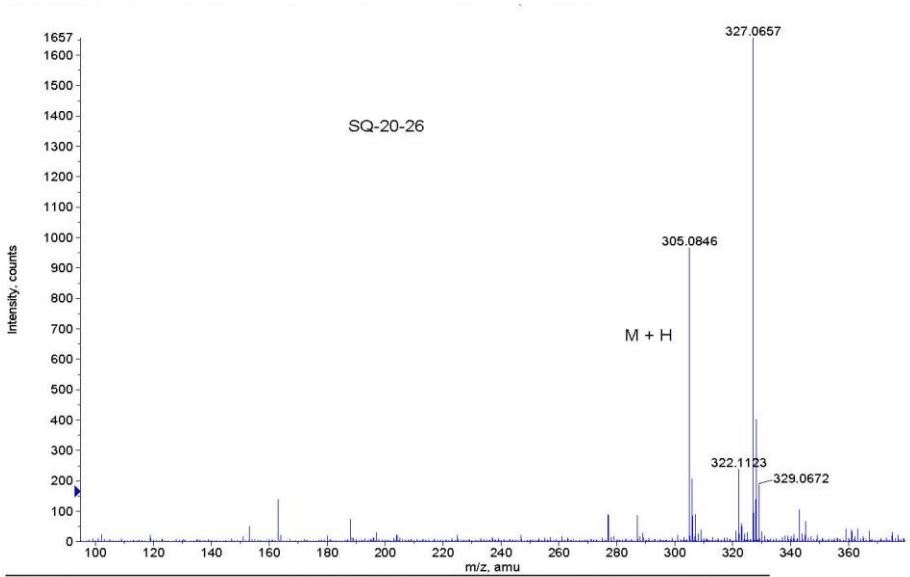

PhO2S
O
O
CH3
OH
35


PhO2S
O
CH3
H
O
36
f1 (ppm)

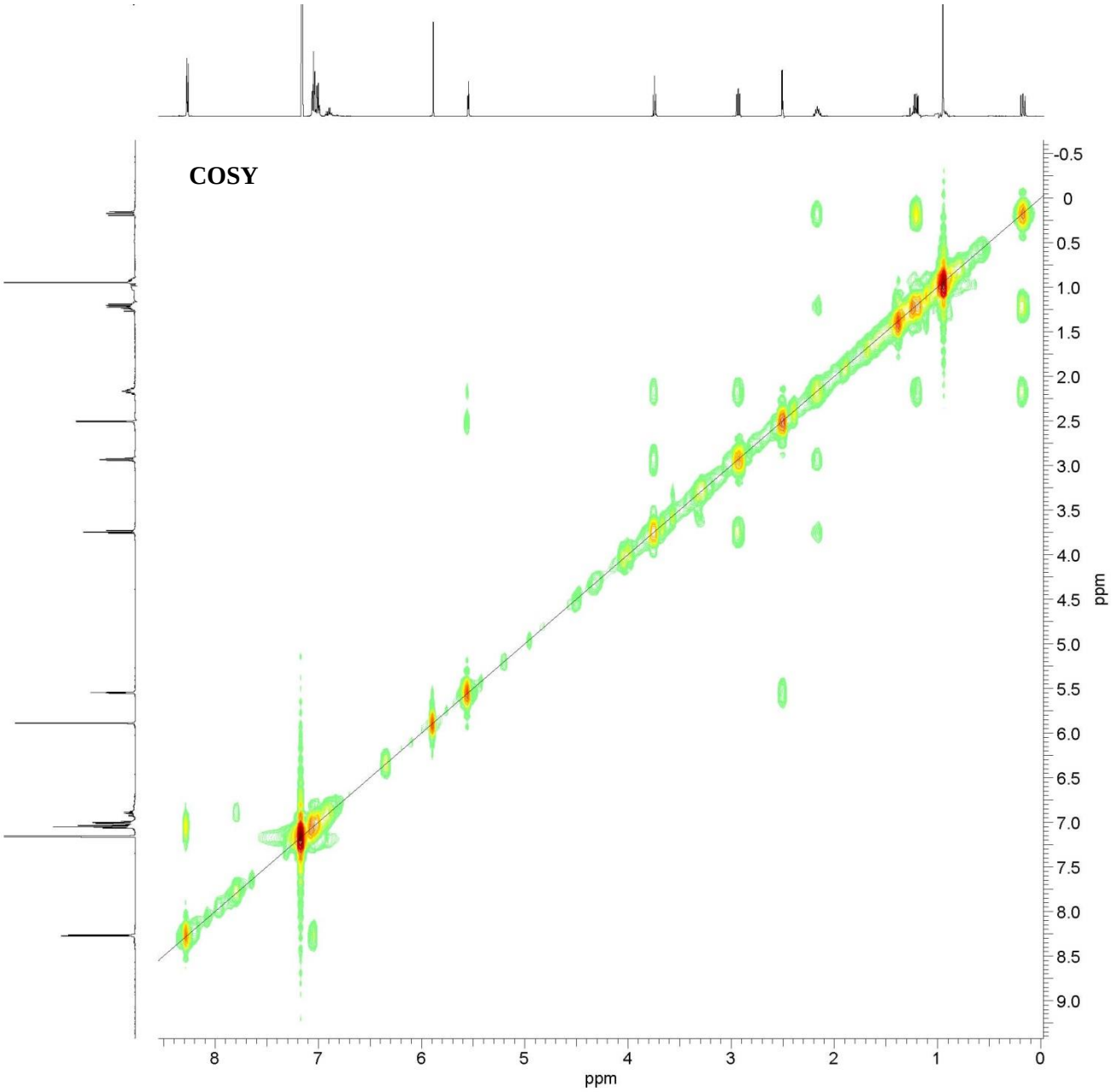

PhO2S
O
CH3
36
H
O
20.53
29.02
34.54
53.08
53.09
59.94
76.53
98.16
122.73
127.49
127.54
127.62
127.70
127.78
127.86
127.99
128.44
128.46
128.47
128.72
131.96
144.68
161.50
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

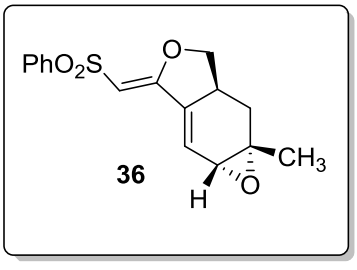




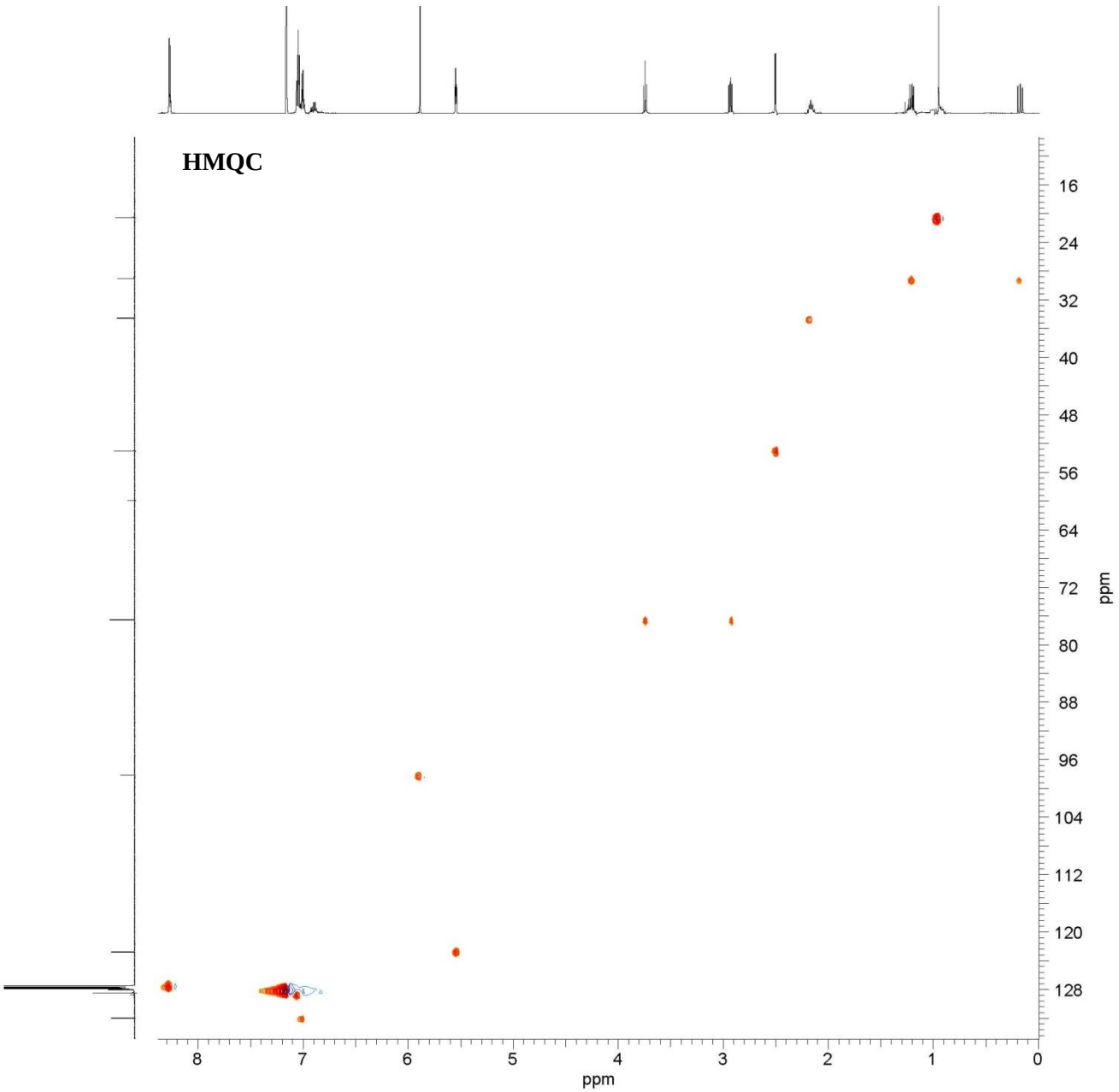


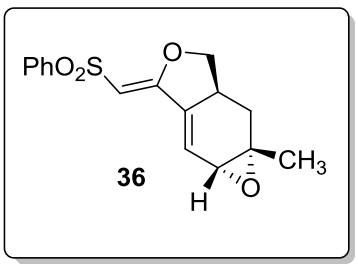
Formula	CalculatedMass	mDaError	ppmError	RDB
C10 H18 O9 Na	305.084304	0.2964	0.971532	1.5
C16 H17 O4 S	305.084207	0.39254	1.286657	8.5


COSY
-0.5
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
ppm
8
7
6
5
4
3
2
1
0
ppm

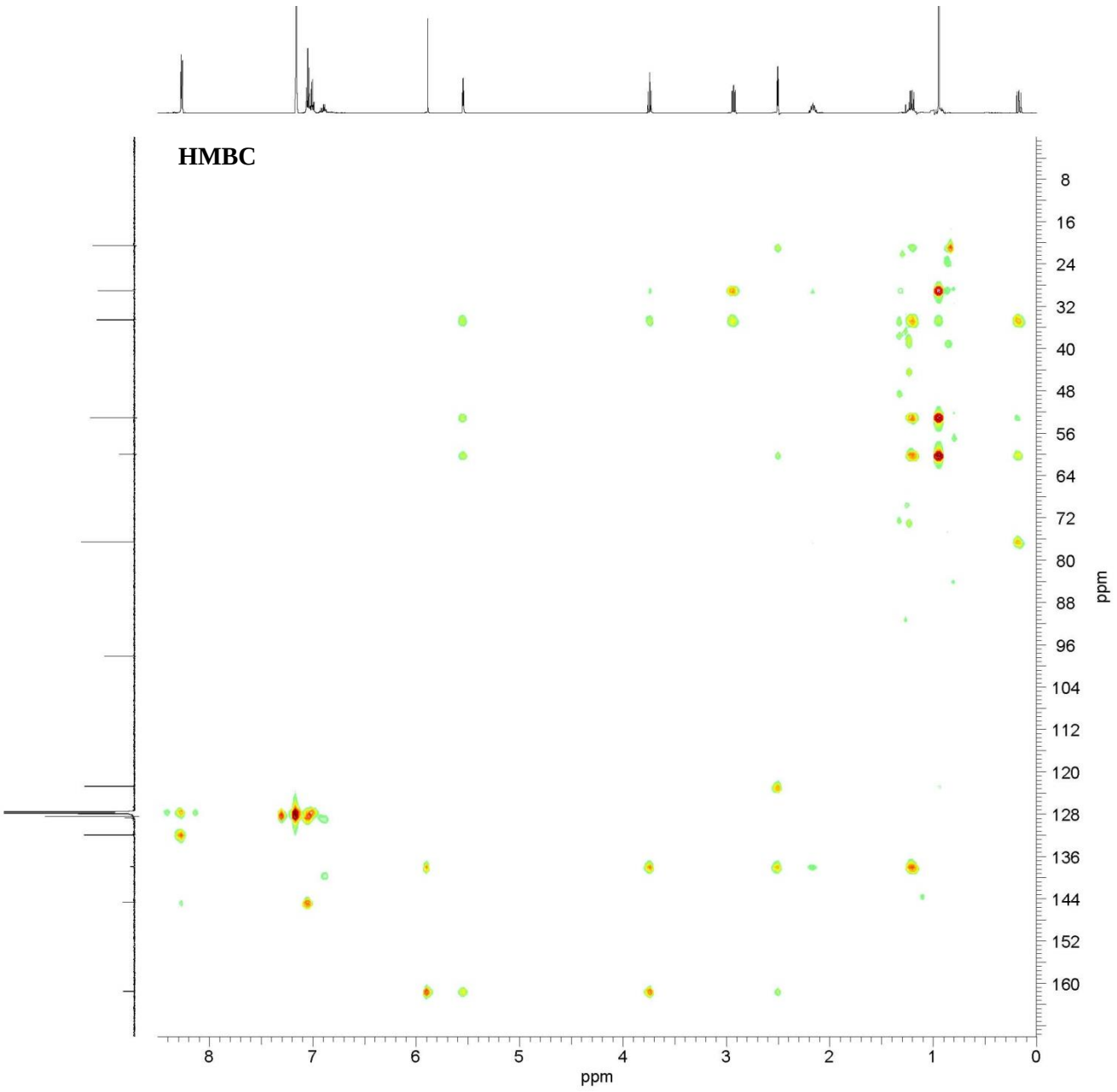

PhO2S
O
CH3
H
O

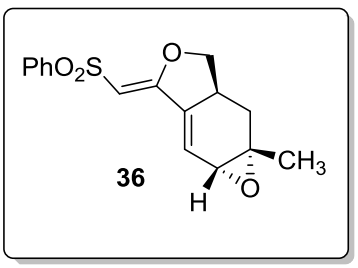
36


HMQC
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
ppm
8
7
6
5
4
3
2
1
0
ppm

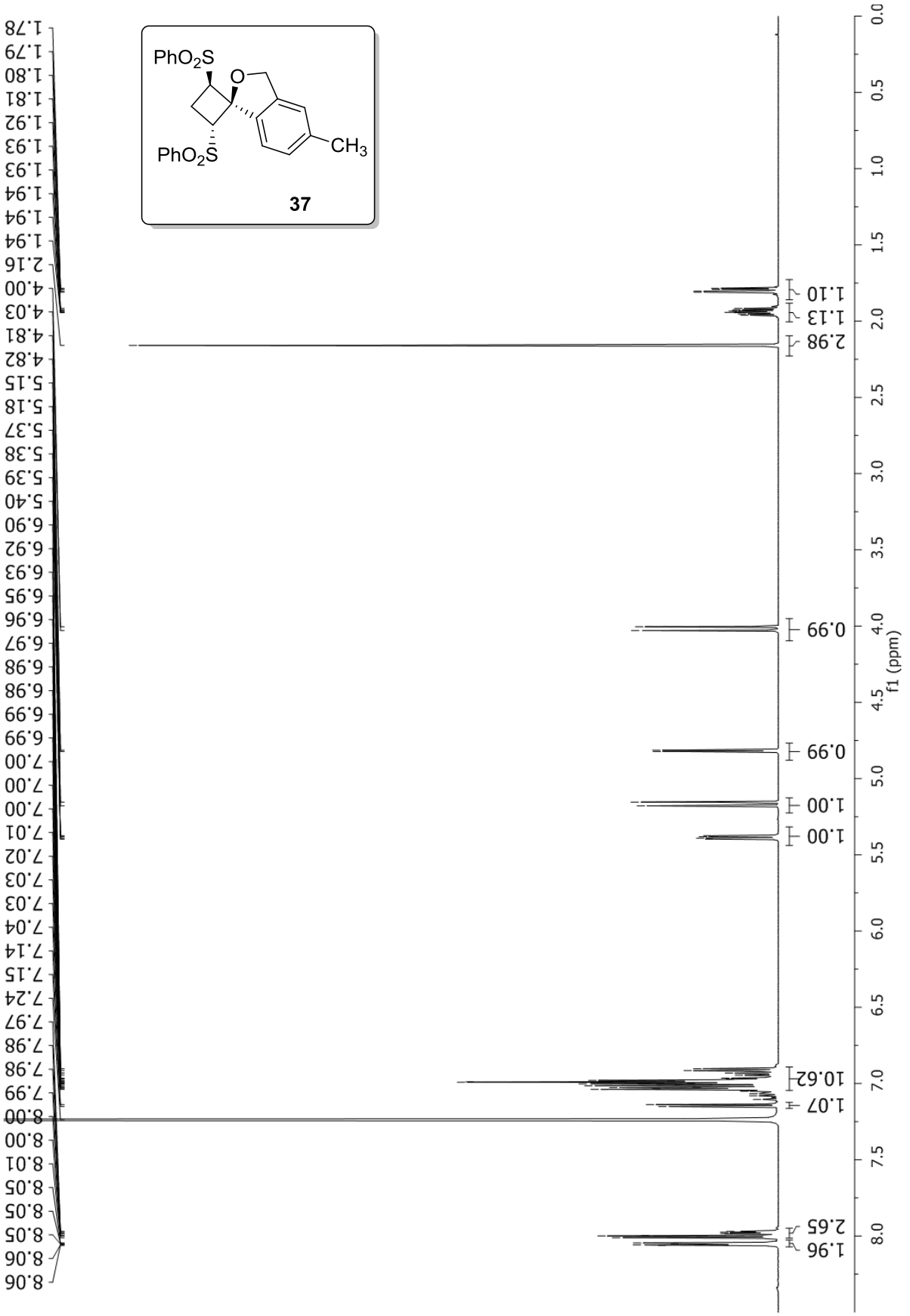

PhO2S
O
CH3
O
H

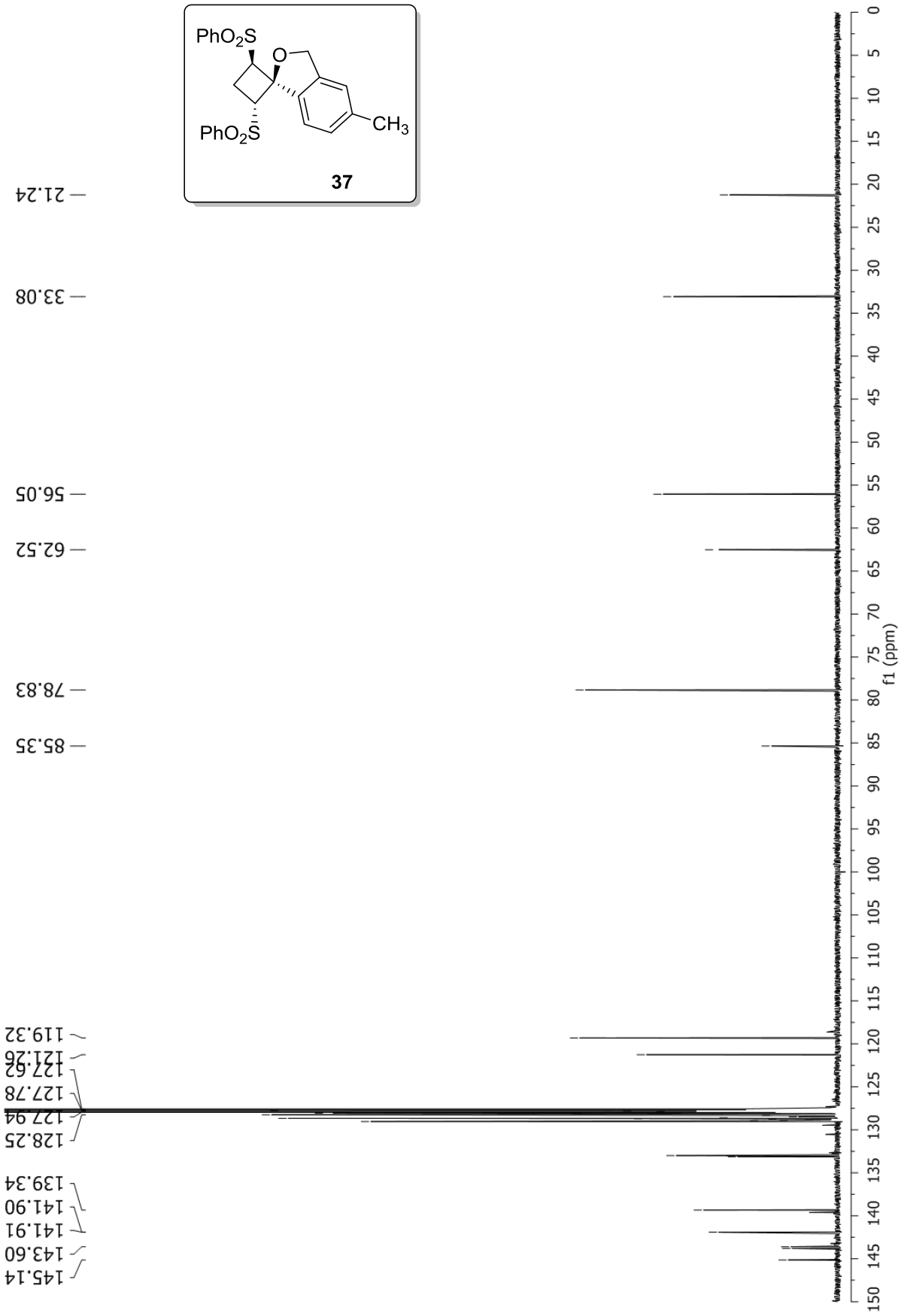
36

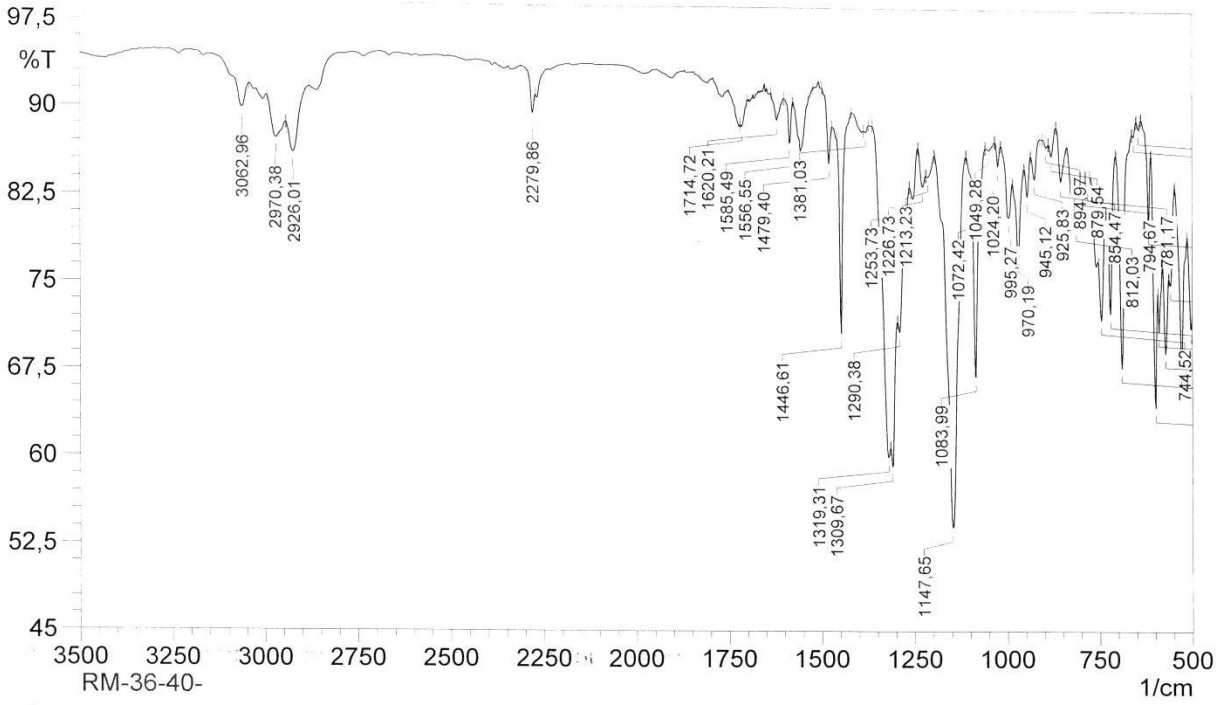

HMBC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
160
ppm
8
7
6
5
4
3
2
1
0
ppm

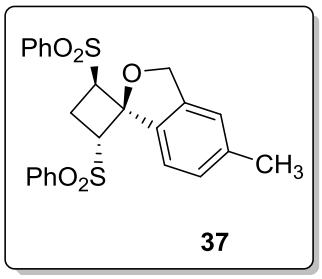

PhO2S
O
CH3
O
H

36

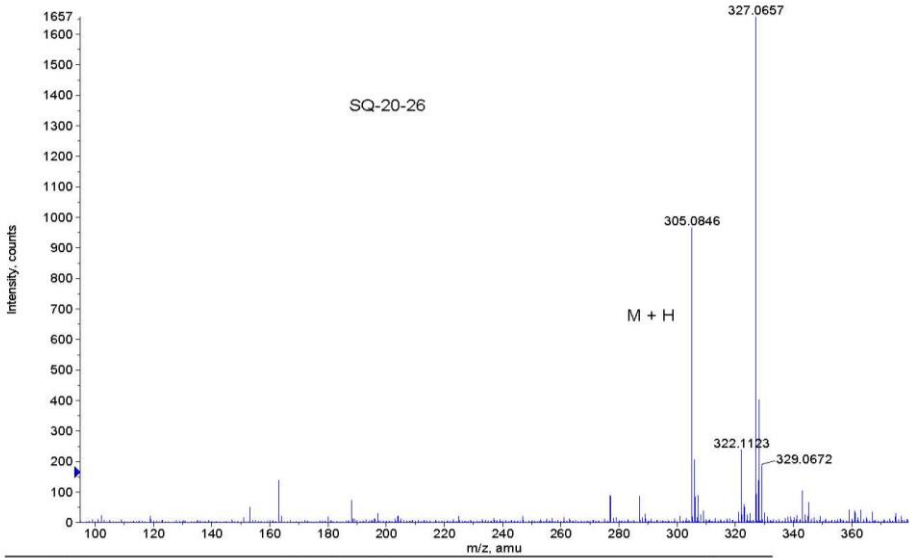

PhO2S
O
PhO2S
CH3
37
f1 (ppm)
1.10
1.13
2.98
0.99
0.99
1.00
1.00
10.62
1.07
2.65
1.96


PhO2S
O
PhO2S
CH3
37
21.24
33.08
56.05
62.52
78.83
85.35
119.32
121.26
127.62
127.78
127.94
128.25
139.34
141.90
141.91
143.60
145.14
f1 (ppm)

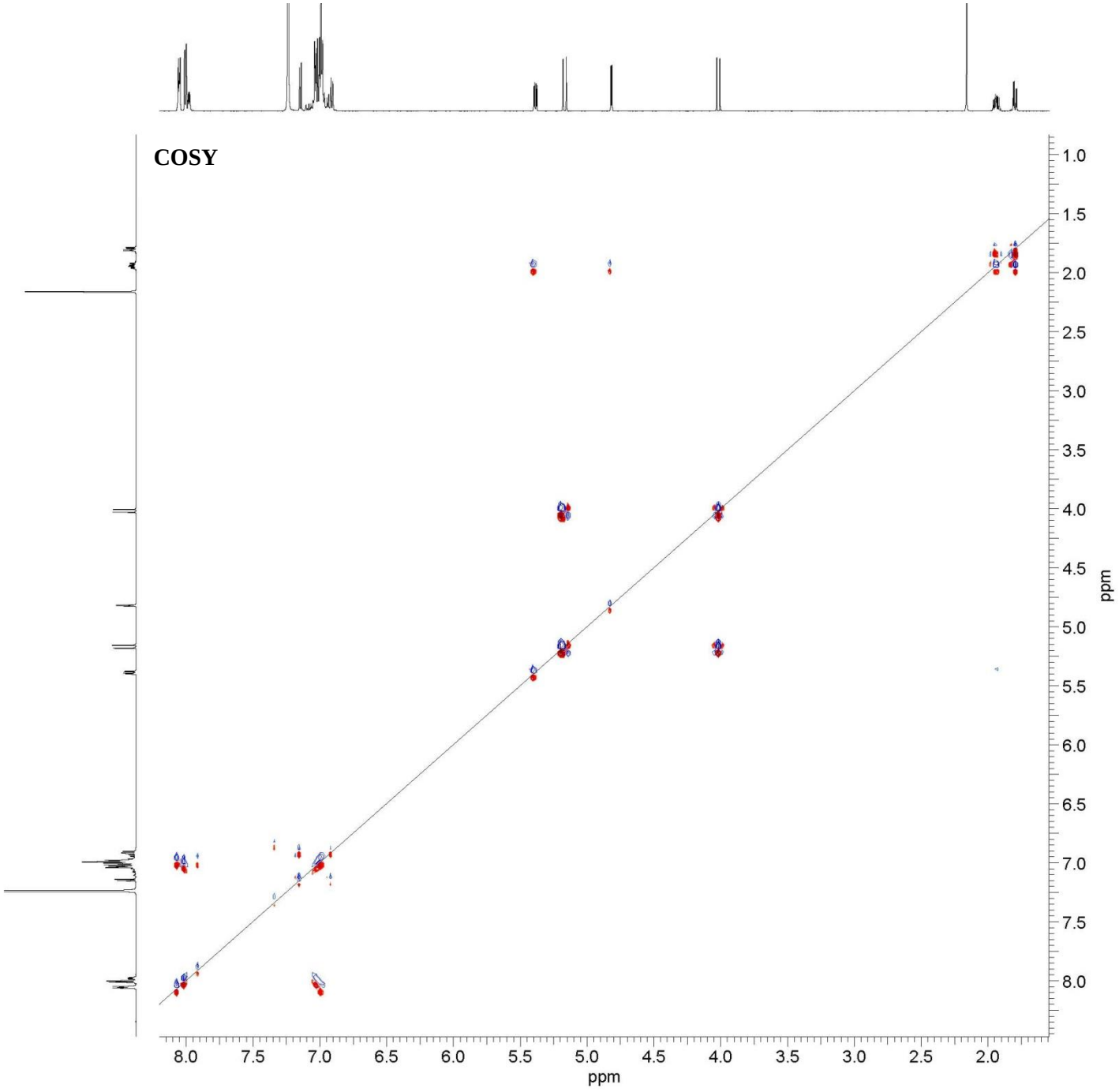


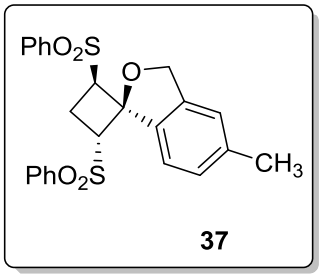


37

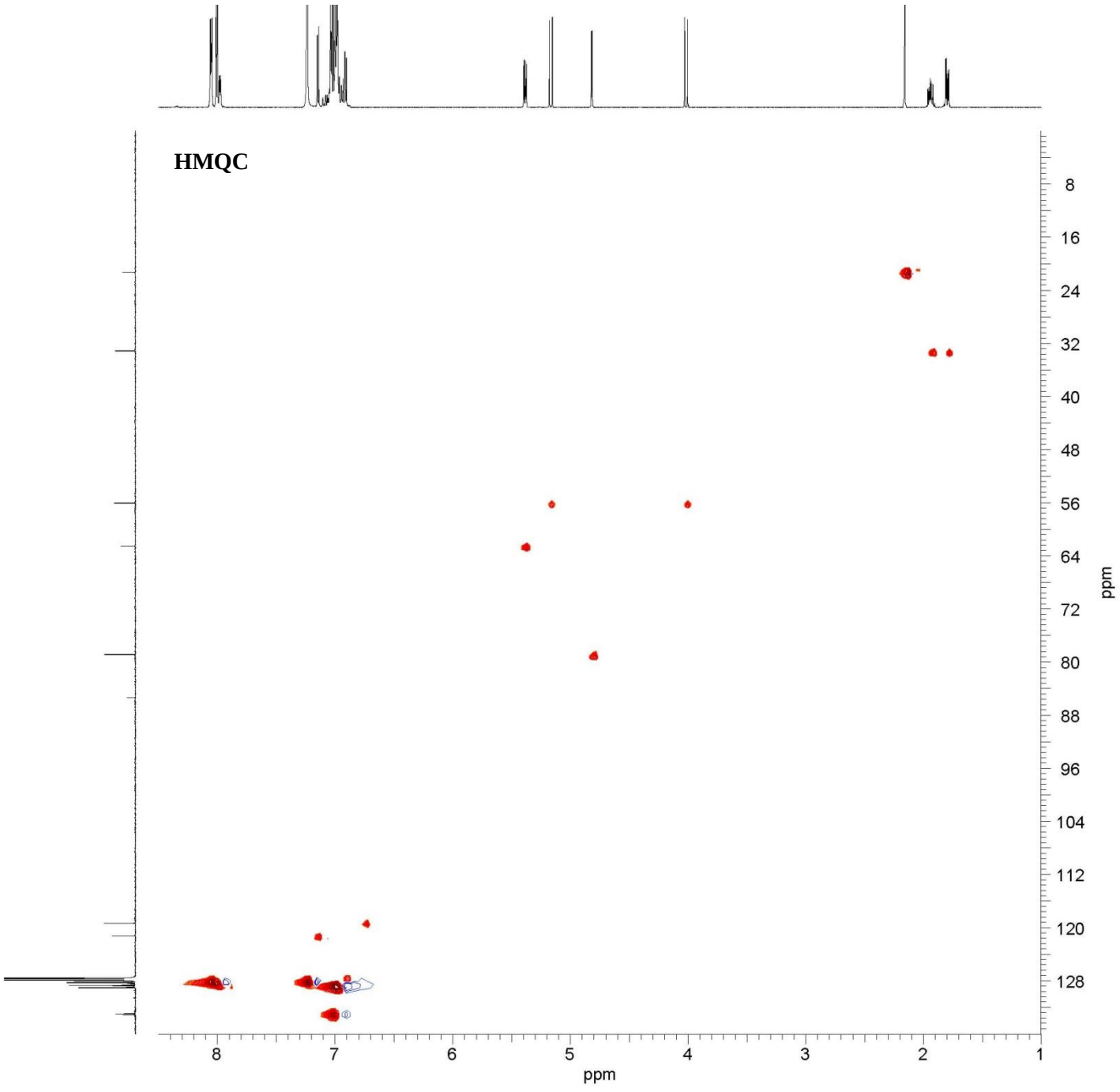


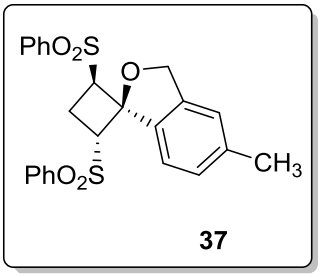
Formula	CalculatedMass	mDaError	ppmError	RDB
C10 H18 O9 Na	305.084304	0.2964	0.971532	1.5
C16 H17 O4 S	305.084207	0.39254	1.286657	8.5
C17 H13 N4 S	305.085545	-0.944772	-3.096749	13.5


COSY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
ppm

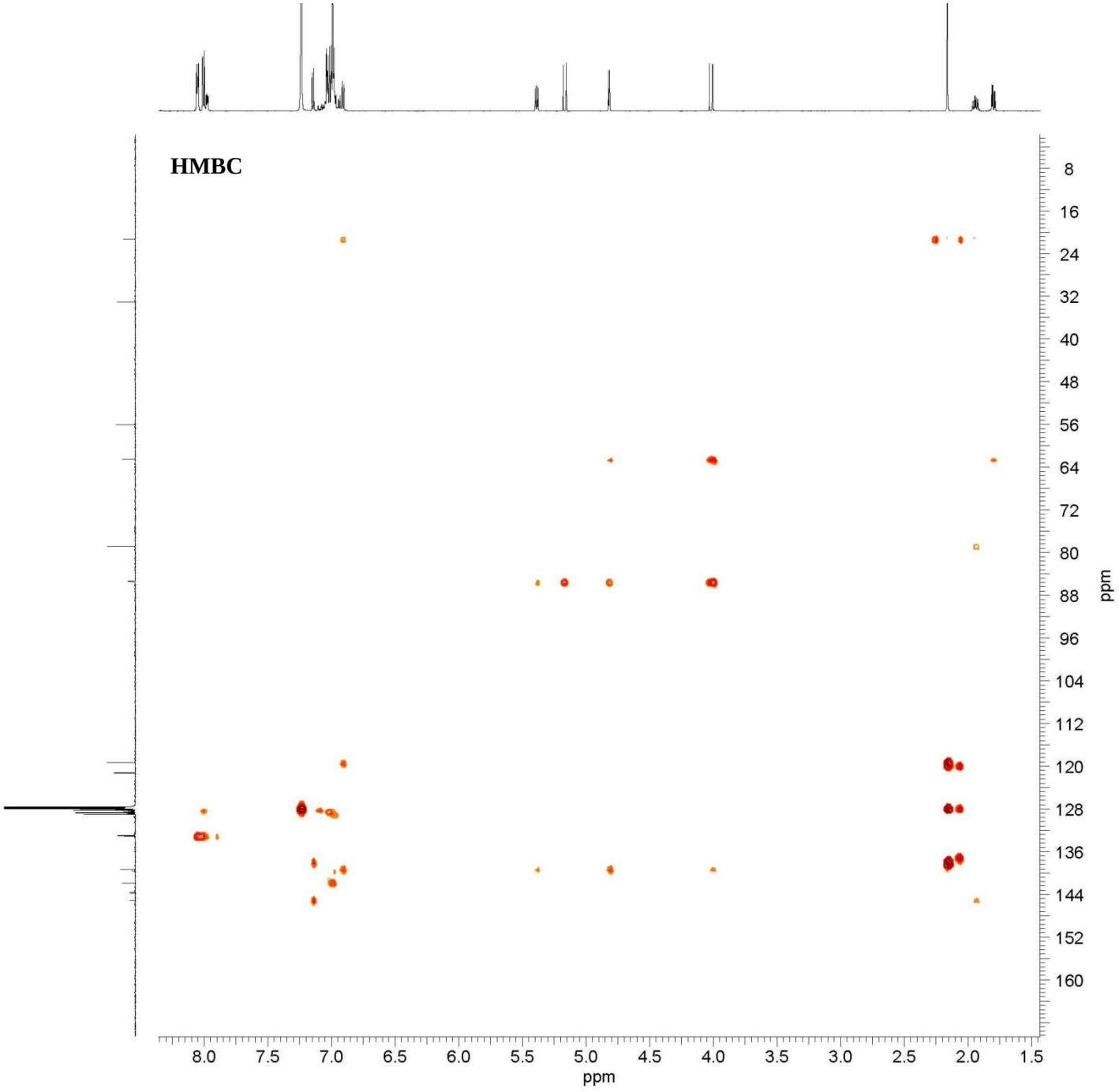

PhO2S
O
PhO2S
CH3

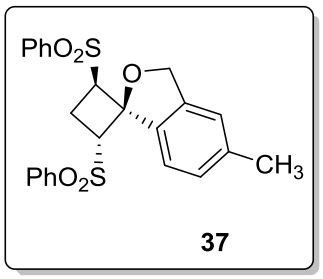
37


HMQC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
ppm
8
7
6
5
4
3
2
1
ppm

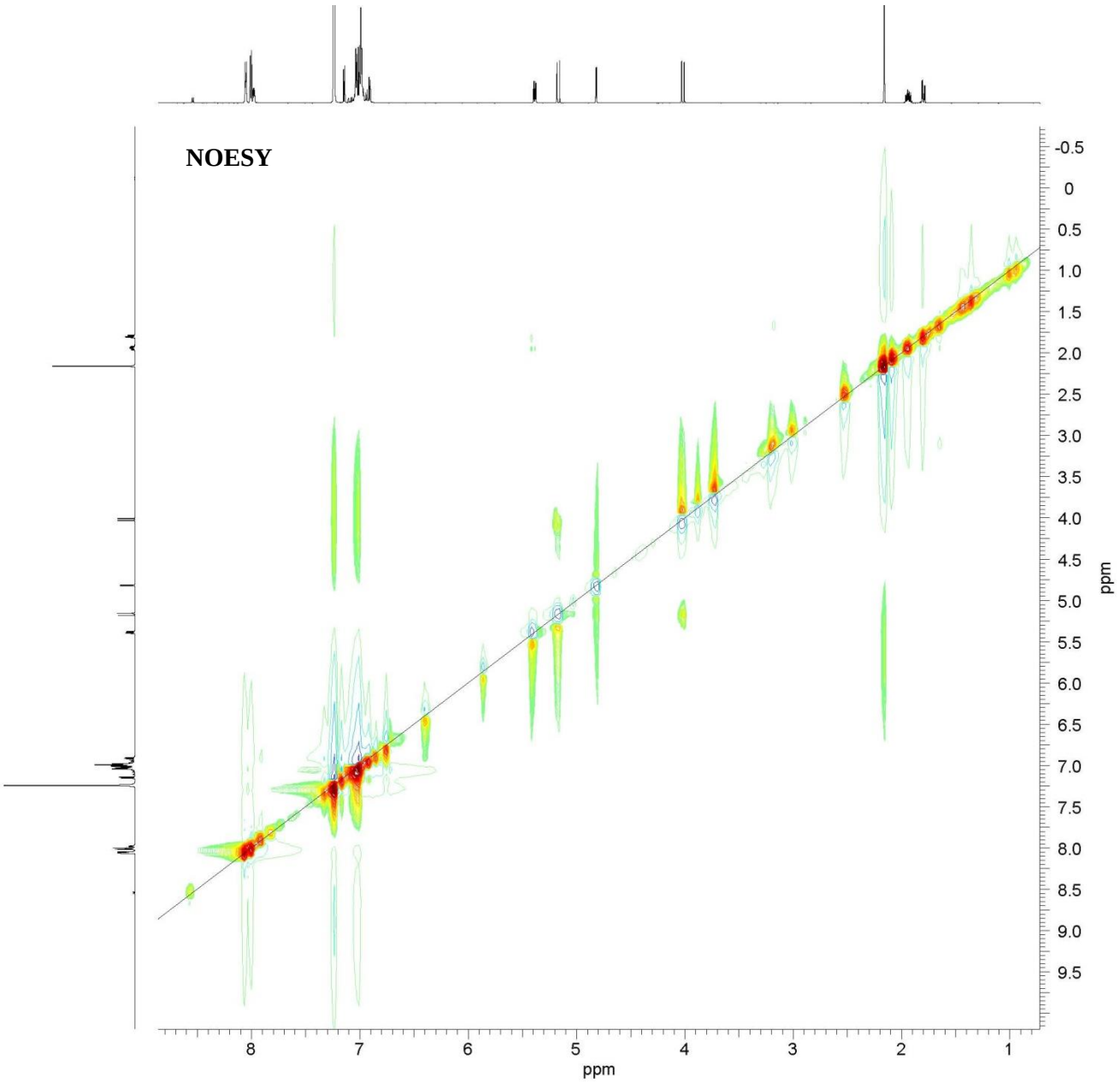

PhO2S
O
PhO2S
CH3

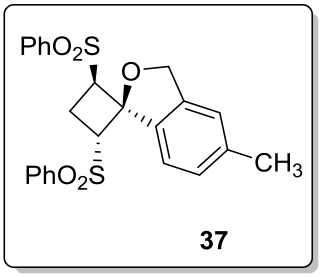
37


HMBC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
160
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

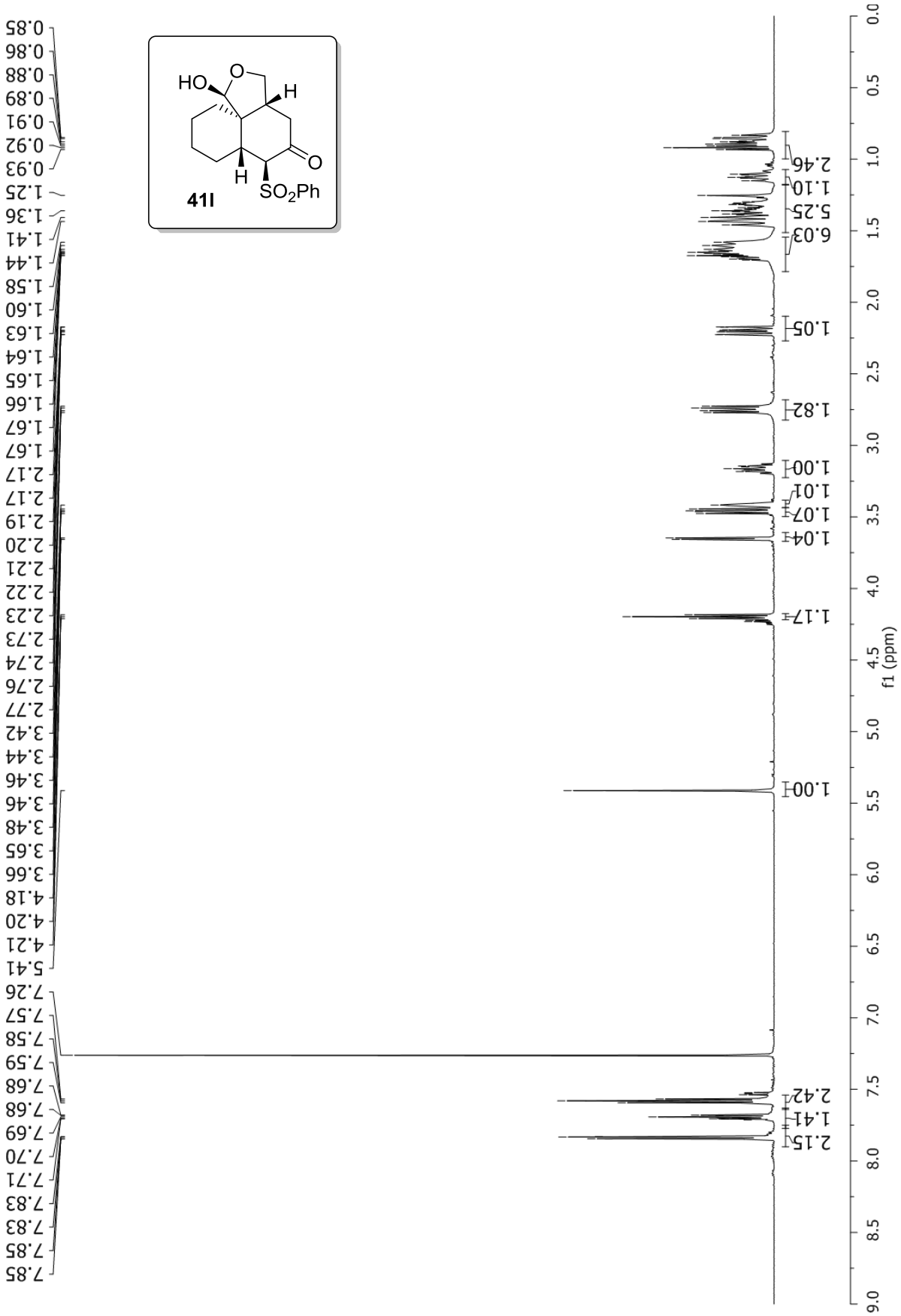

PhO2S
O
PhO2S
CH3

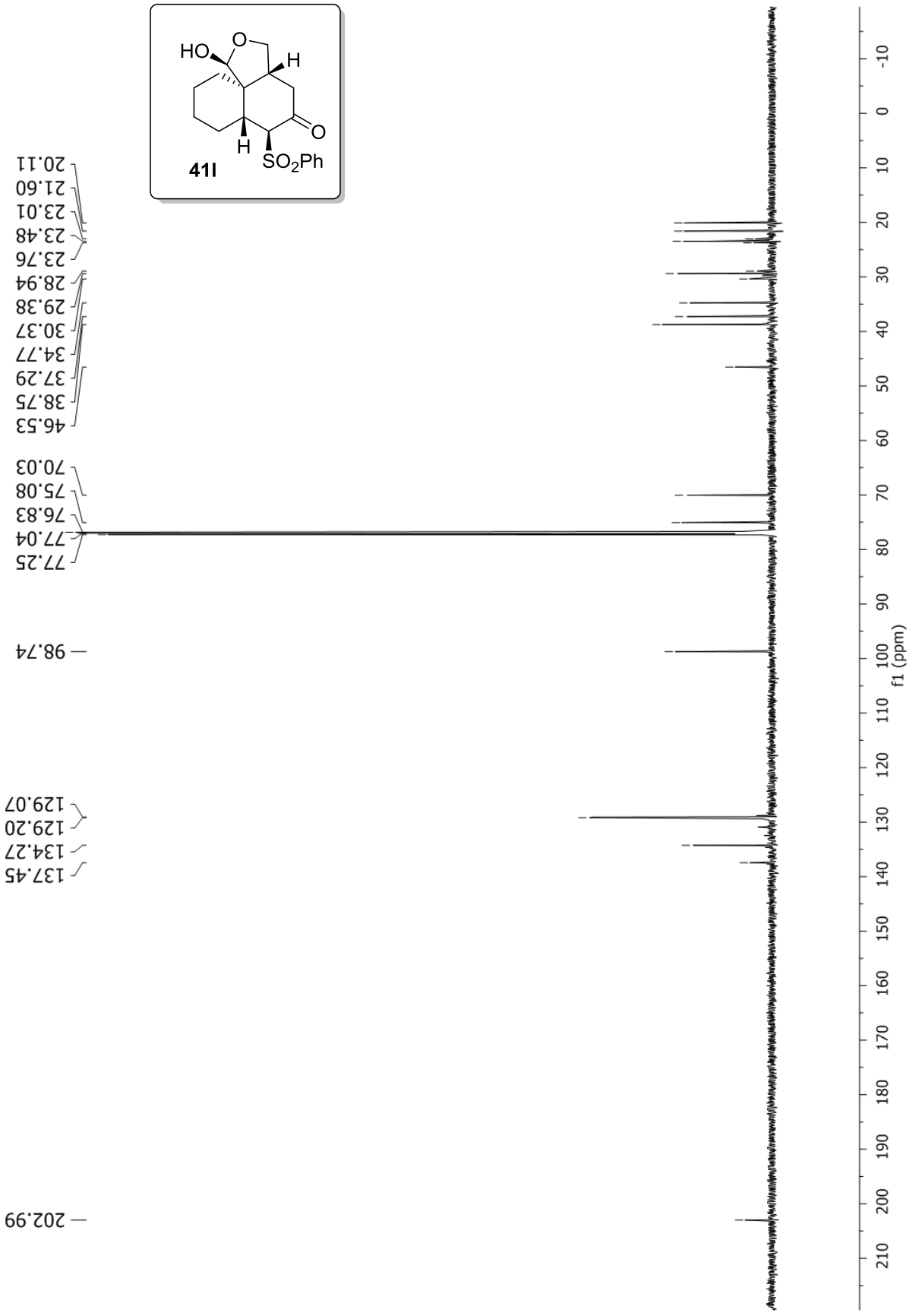
37

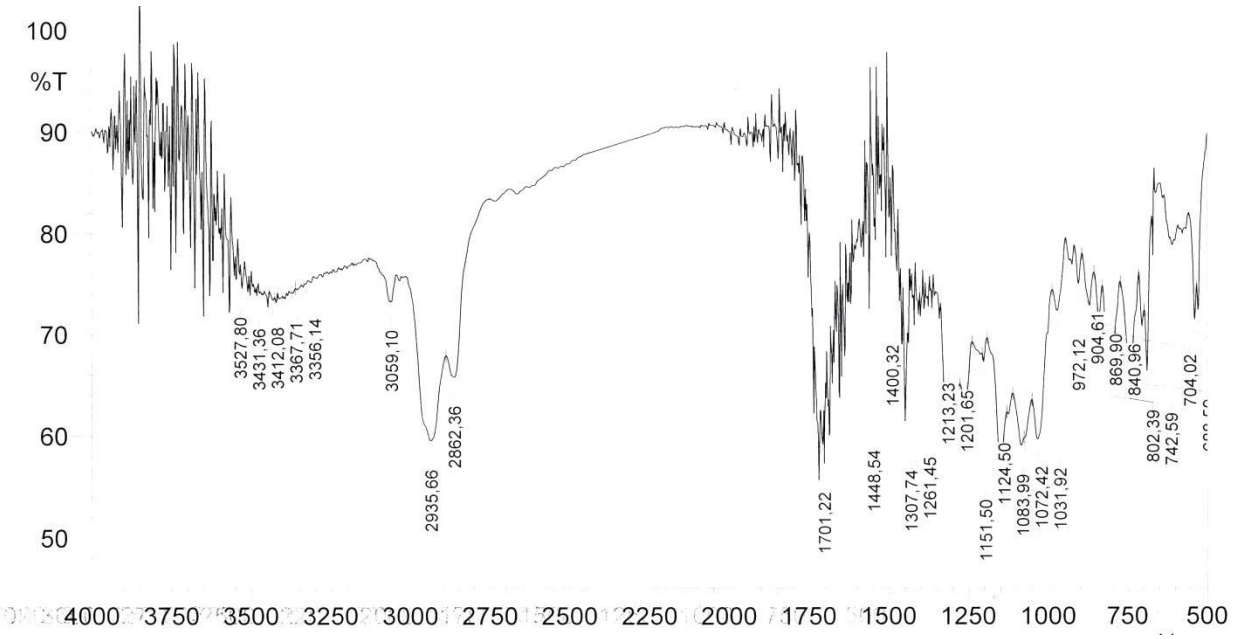

NOESY
-0.5
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
ppm
8
7
6
5
4
3
2
1
ppm

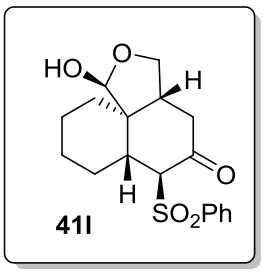

PhO2S
O
PhO2S
CH3

37

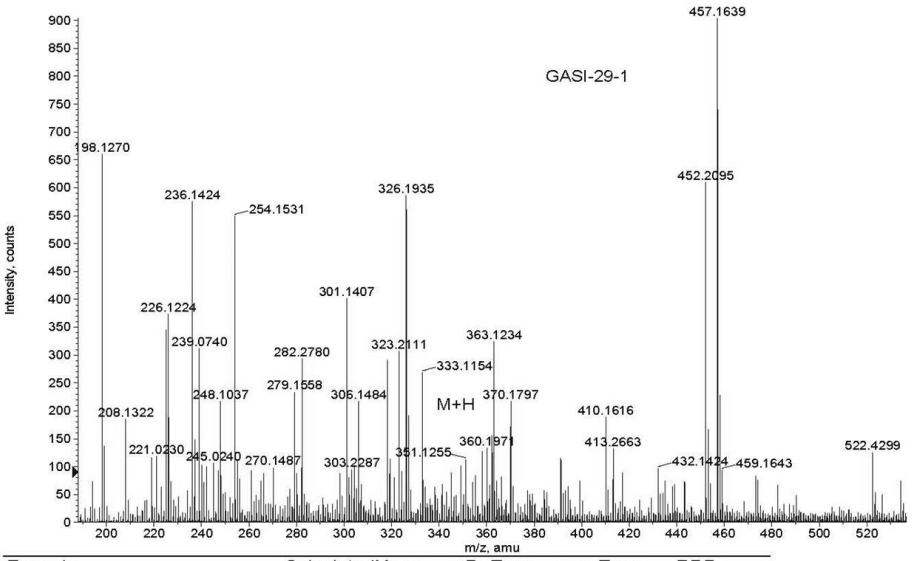

HO
O
H
O
H
SO2Ph
41l
f1 (ppm)


HO
O
H
H
O
SO2Ph
41l
20.11
21.60
23.01
23.48
23.76
28.94
29.38
30.37
34.77
37.29
38.75
46.53
70.03
75.08
76.83
77.04
77.25
98.74
129.07
129.20
134.27
137.45
202.99
f1 (ppm)

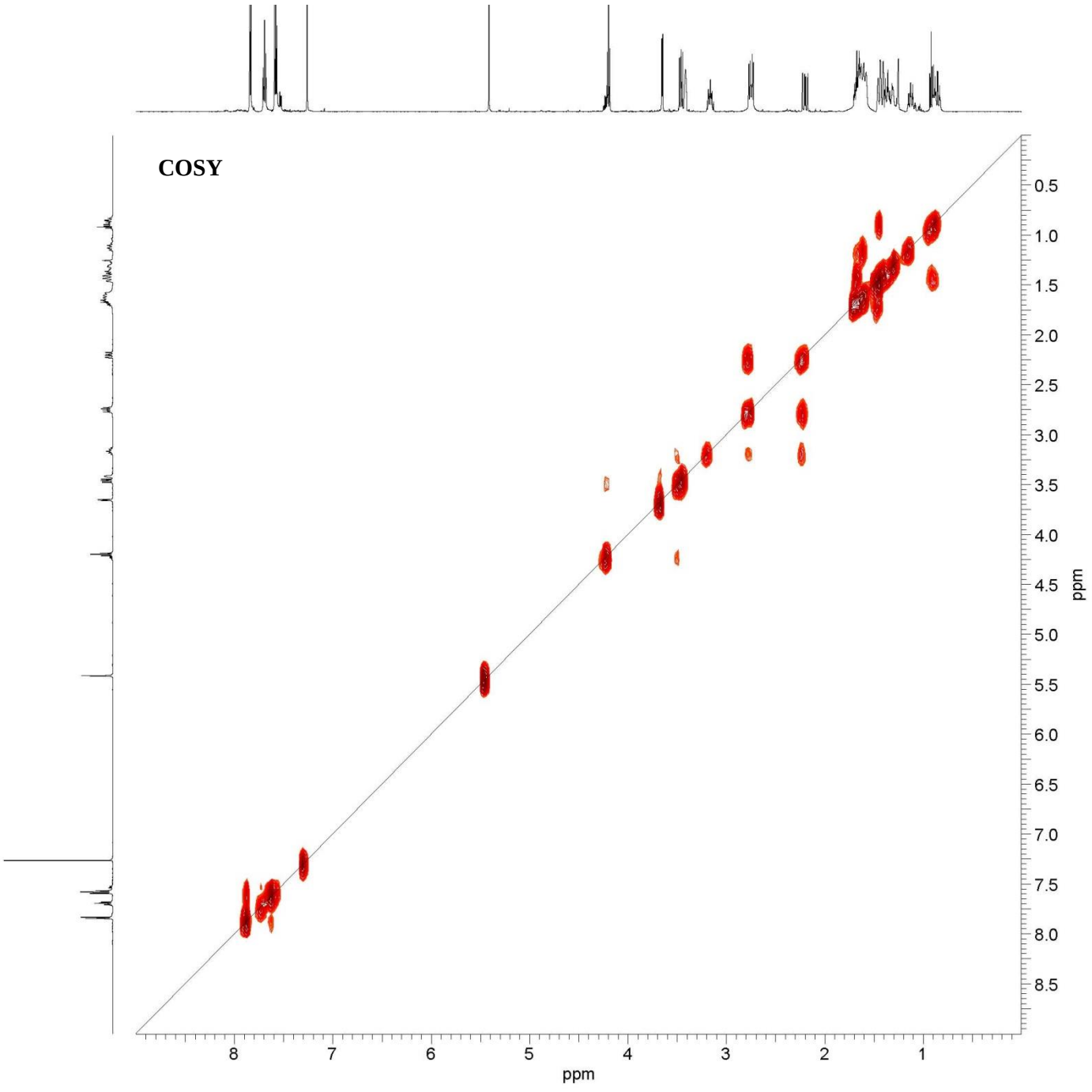


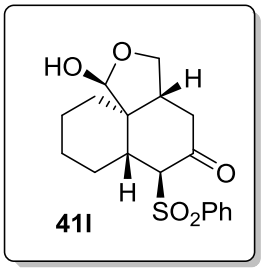


41l

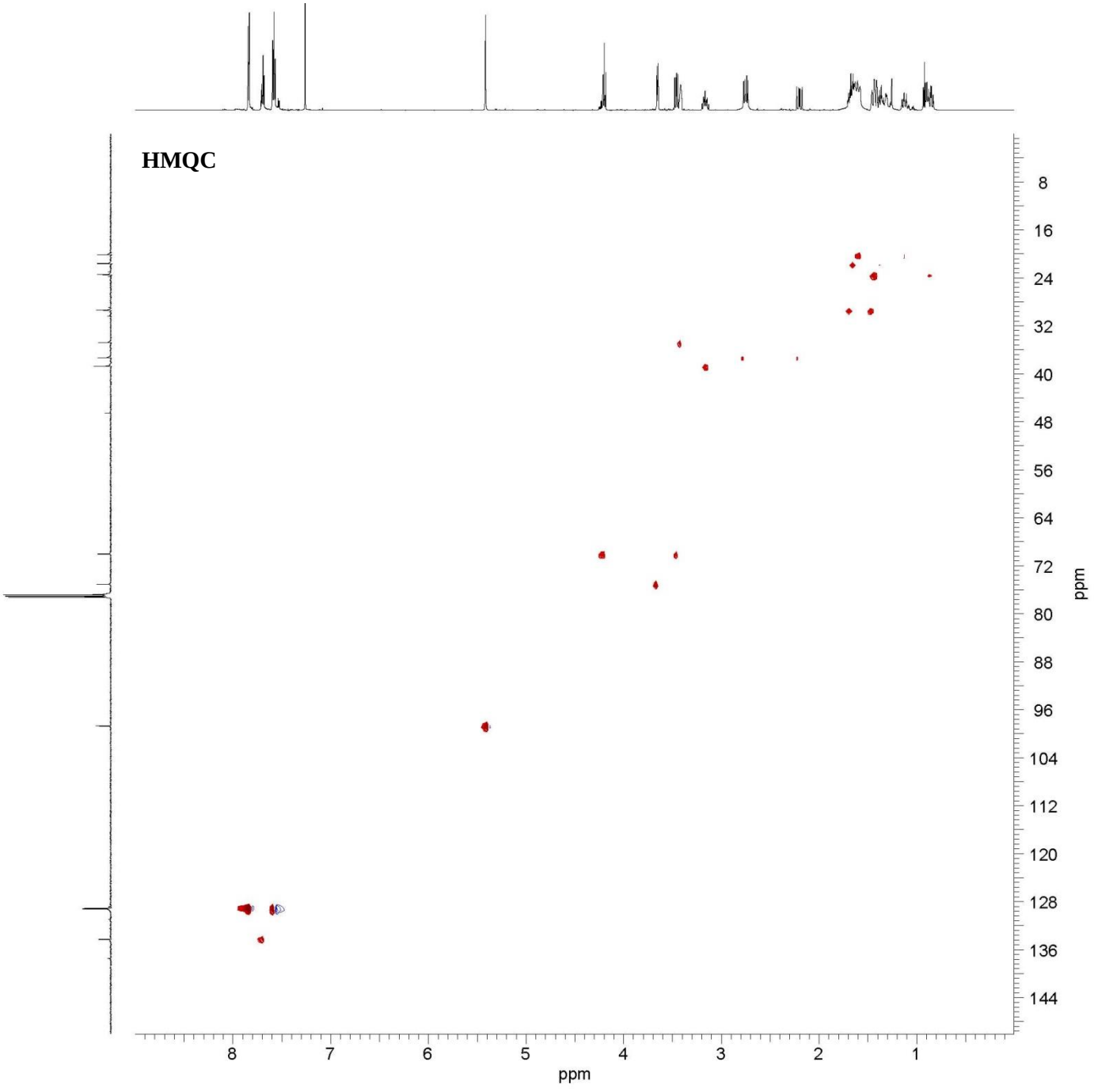


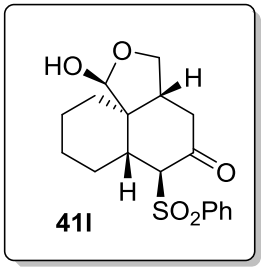
Formula	CalculatedMass	mDaError	ppmError	RDB
C17 H20 N4 O Na S	351.125004	0.495608	1.411482	9.5
C18 H23 O5 S	351.126072	-0.57234	-1.630013	7.5
C16 H24 O5 Na S	351.123667	1.83292	5.22012	4.5
C19 H19 N4 O S	351.12741	-1.909652	-5.438651	12.5
C13 H23 N2 O7 S	351.12205	3.450364	9.826568	3.5


COSY
8
7
6
5
4
3
2
1
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm

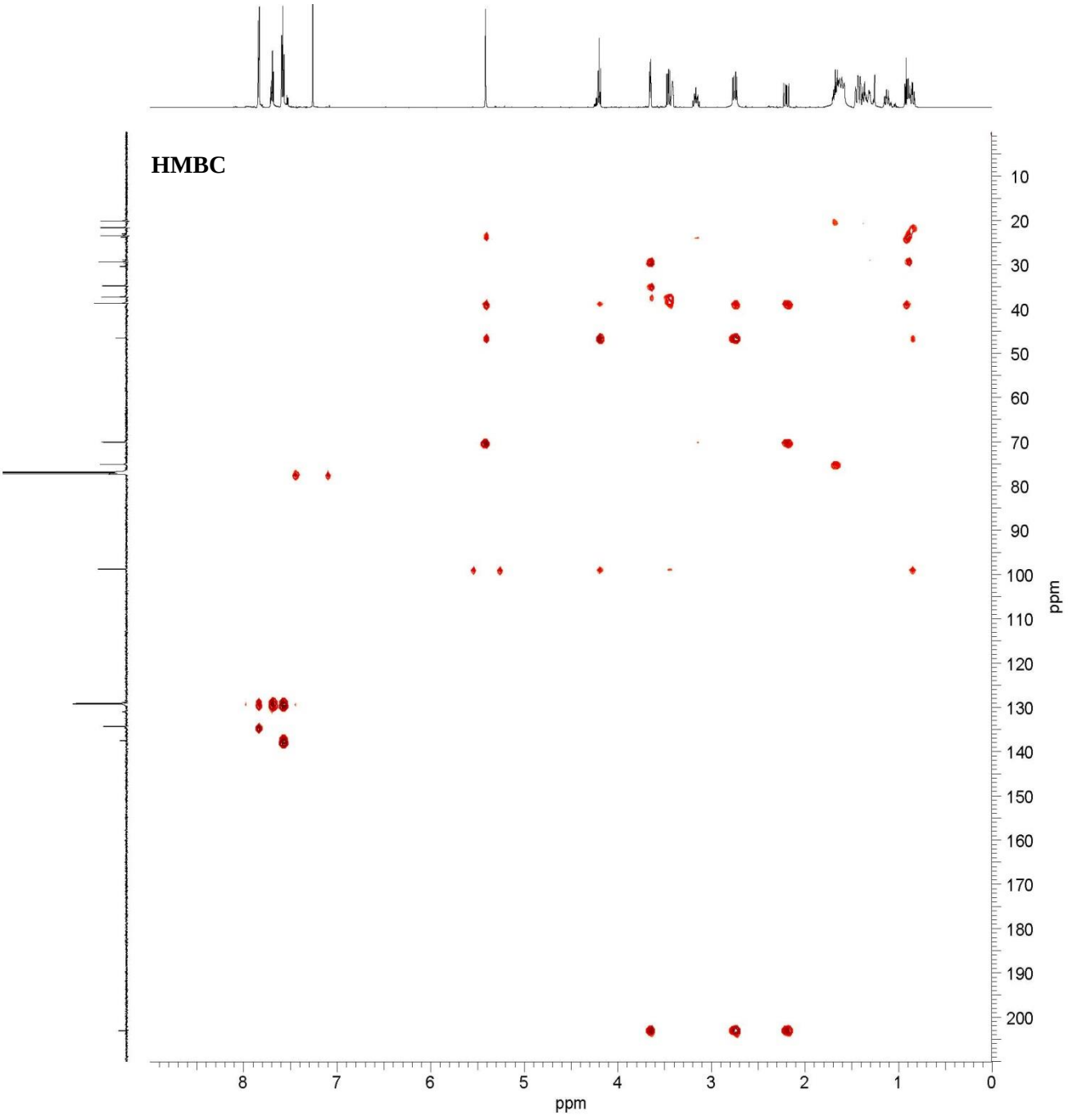

HO
O
H
O
H
SO2Ph

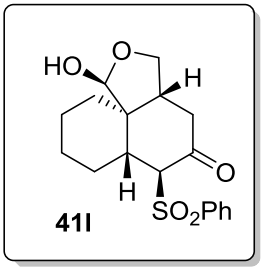
41l


HMQC
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
ppm
8
7
6
5
4
3
2
1
ppm

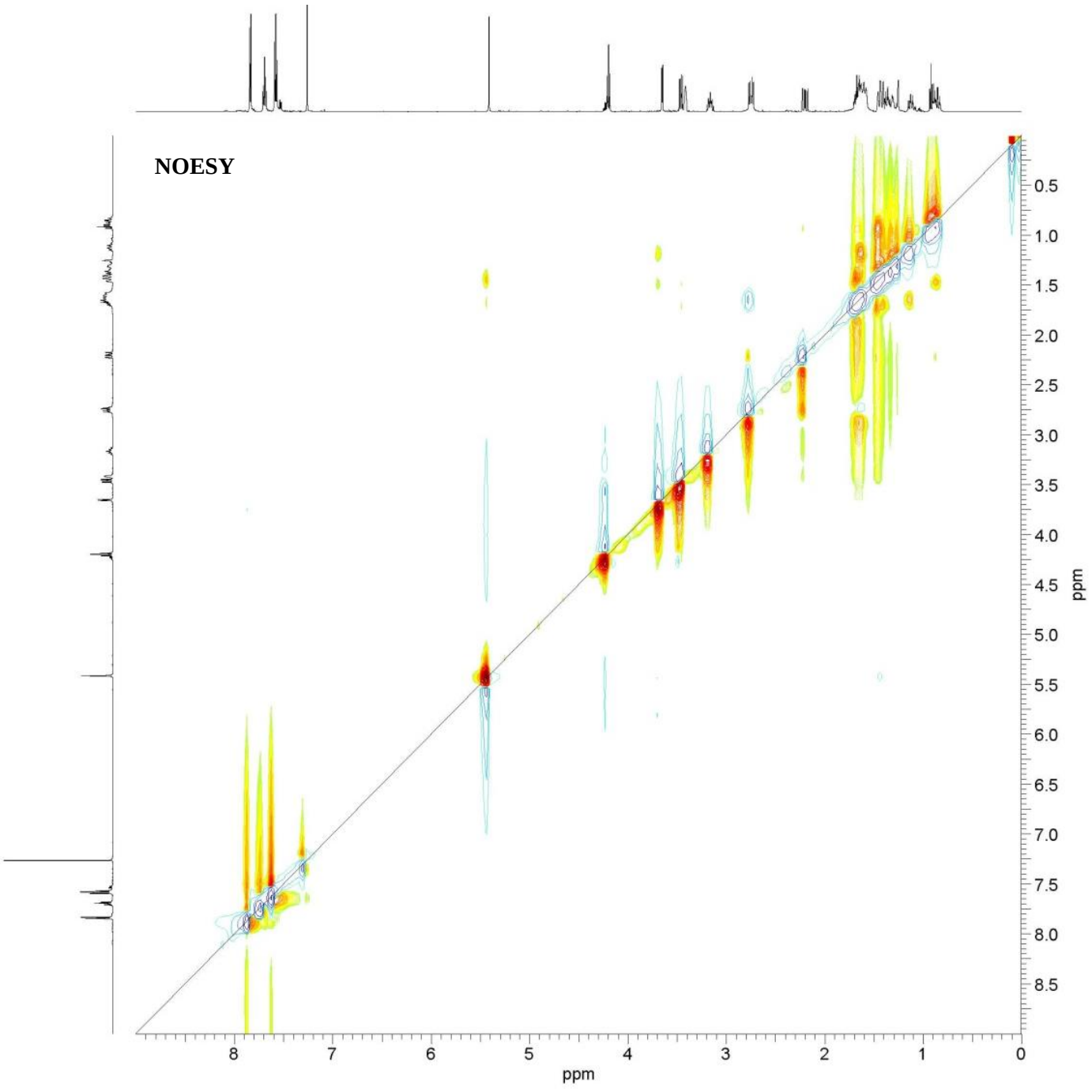

HO
O
H
O
H
SO2Ph

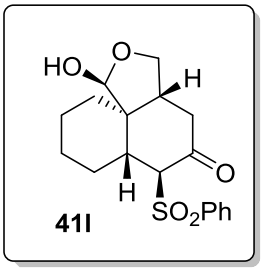
41l


HMBC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
ppm
8
7
6
5
4
3
2
1
0
ppm

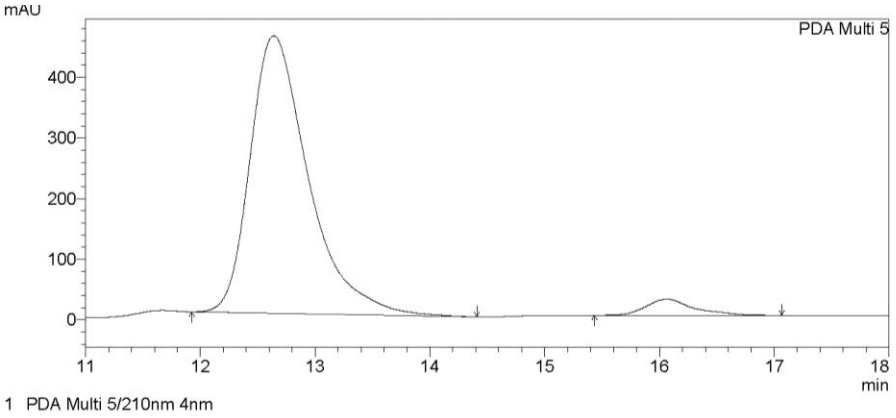

HO
O
H
H
O
SO2Ph

41l


NOESY
8
7
6
5
4
3
2
1
0
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm


HO
O
H
H
O
SO2Ph

41l

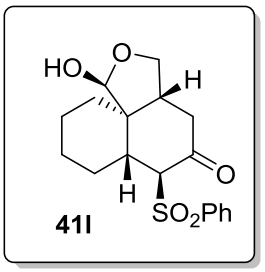


1 PDA Multi 5/210nm 4nm

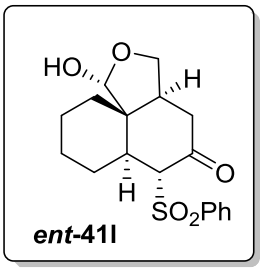
PeakTable

PDA Ch5 210nm 4nm

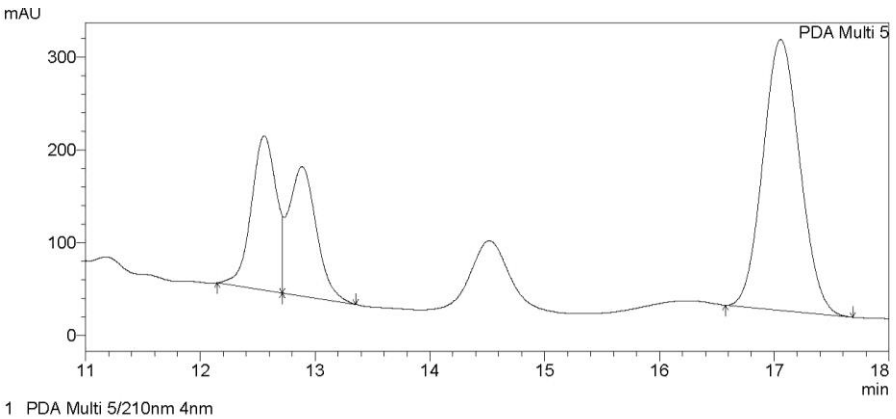
Peak#	Ret. Time	Area %
1	12.634	95.502
2	16.055	4.498
Total		100.000



41l



***ent*-41l**



1 PDA Multi 5/210nm 4nm

PeakTable

PDA Ch5 210nm 4nm

Peak#	Ret. Time	Area %
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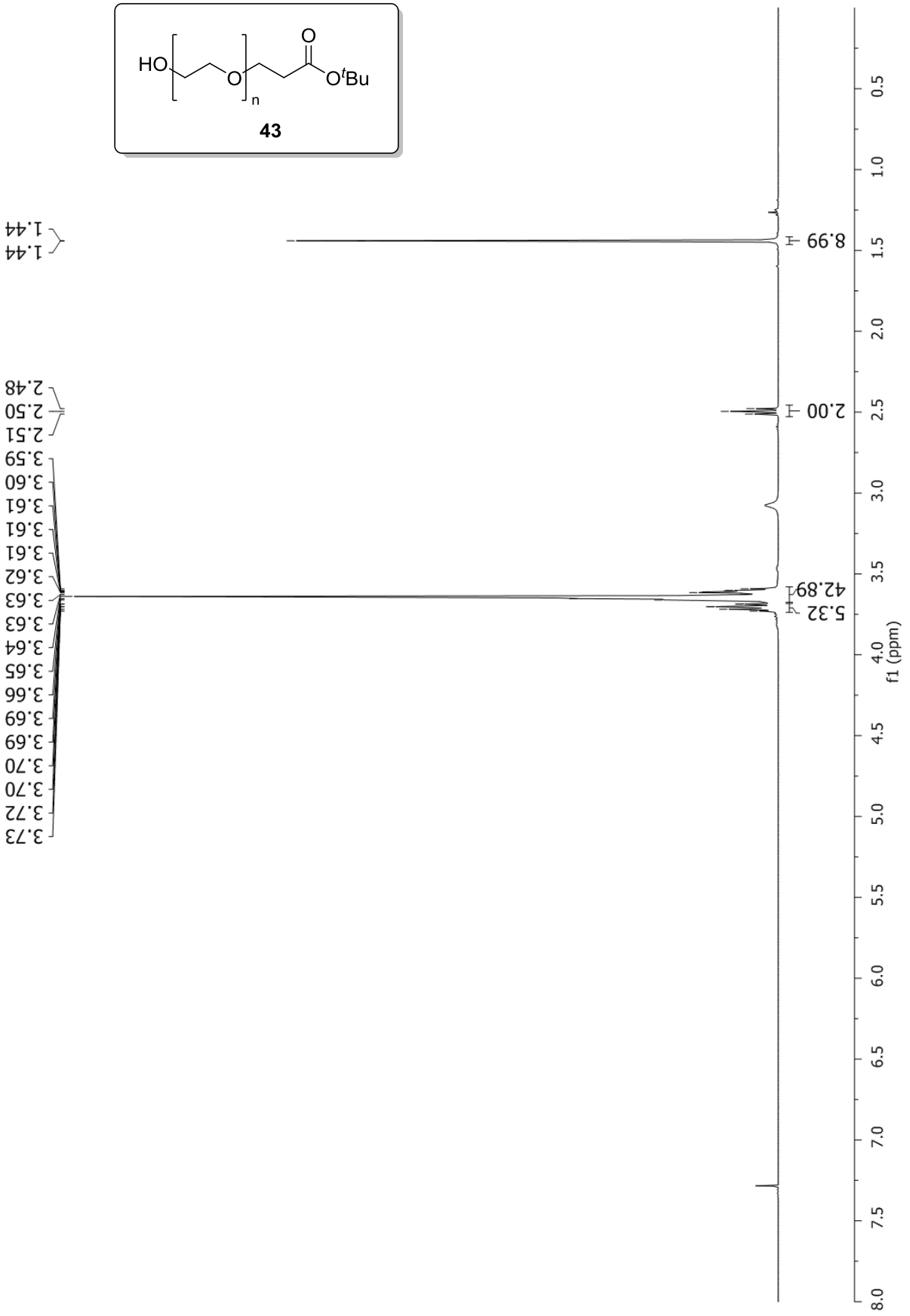
2	12.880	20.520
3	17.050	57.263
Total		100.000


HO
O
n
O
O^{t}Bu
43
1.44
1.44
2.48
2.50
2.51
3.59
3.60
3.61
3.61
3.61
3.62
3.63
3.63
3.64
3.65
3.66
3.69
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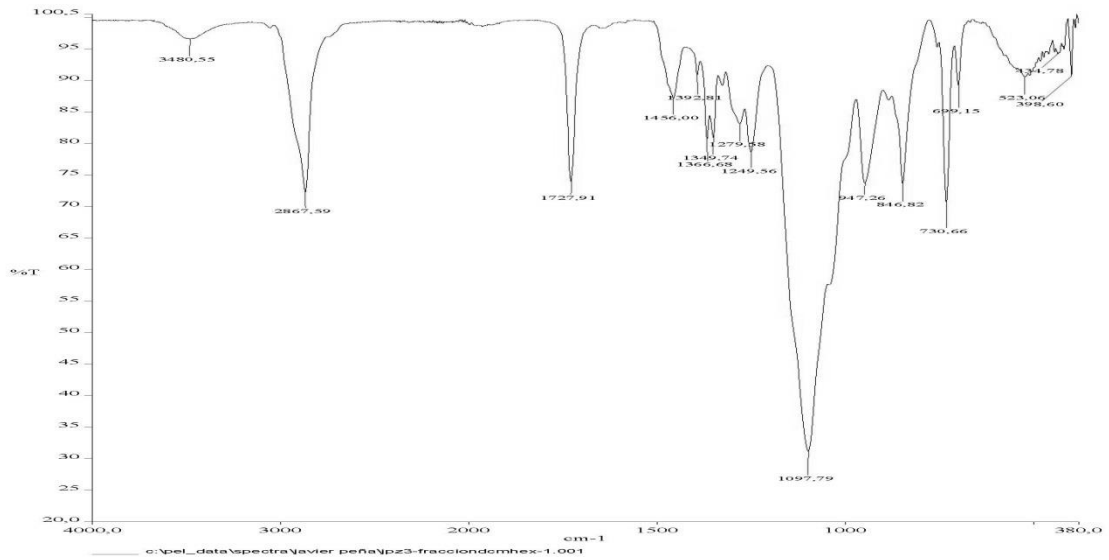
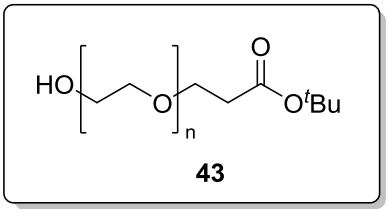
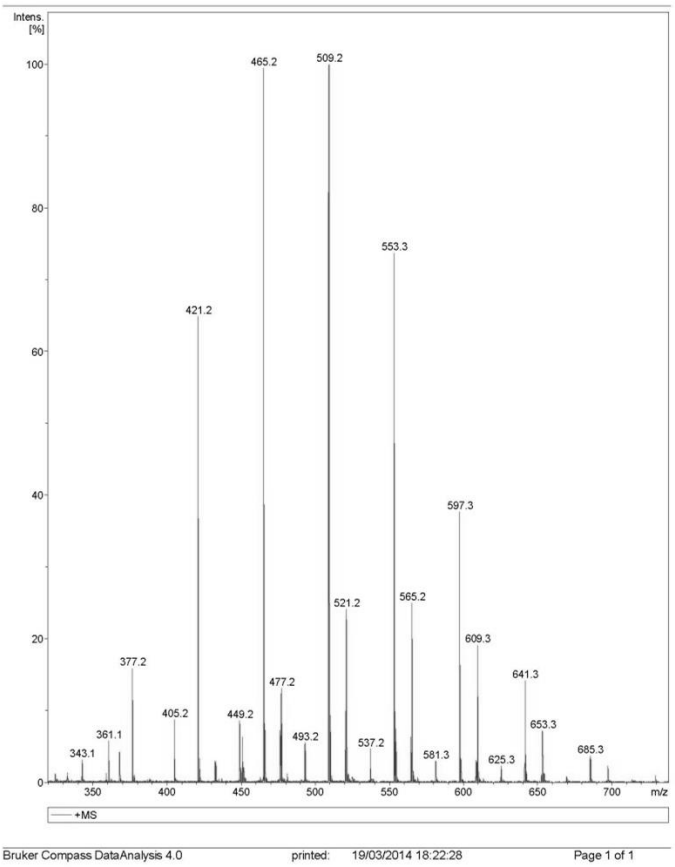
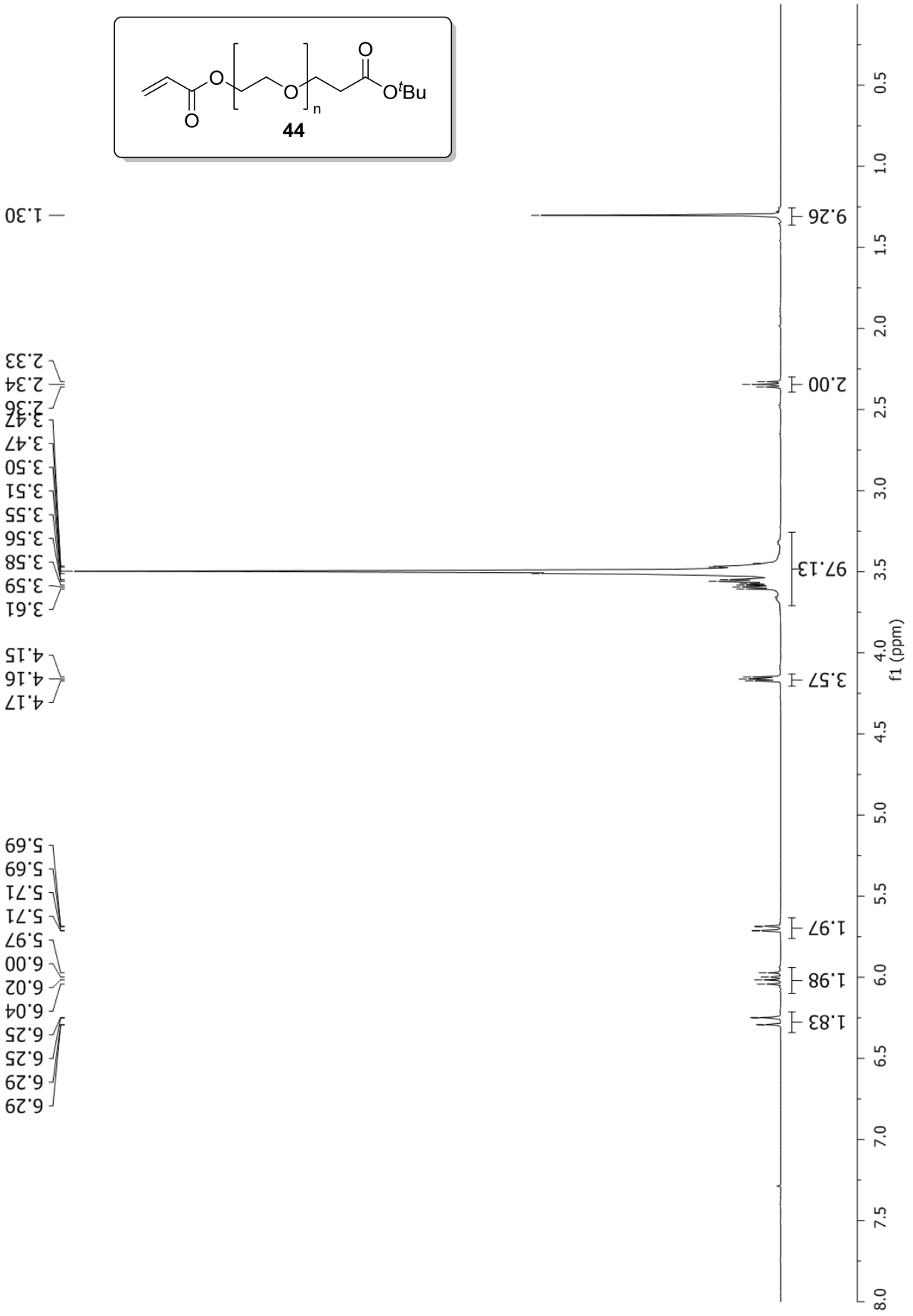
3.73
8.99
2.00
42.89
5.32
f1 (ppm)

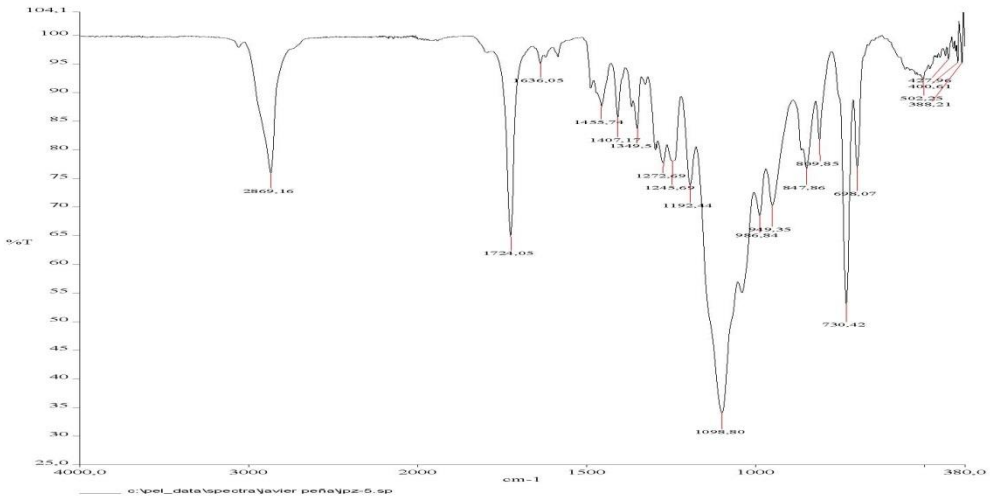

100,5
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20,0
%T
4000,0
3000
2000
1500
1000
380,0
cm-1
3480,55
2867,39
1727,91
1456,00
1392,81
1366,68
1349,74
1279,98
1249,56
1097,79
947,26
846,82
730,66
699,15
523,09
398,60
c:\pel_data\spectra\javier peña\jpz3-fraccionclcmhex-1.001

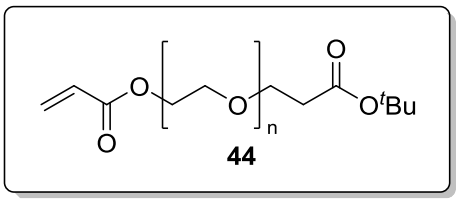

HO
O
n
O
O
tBu

43

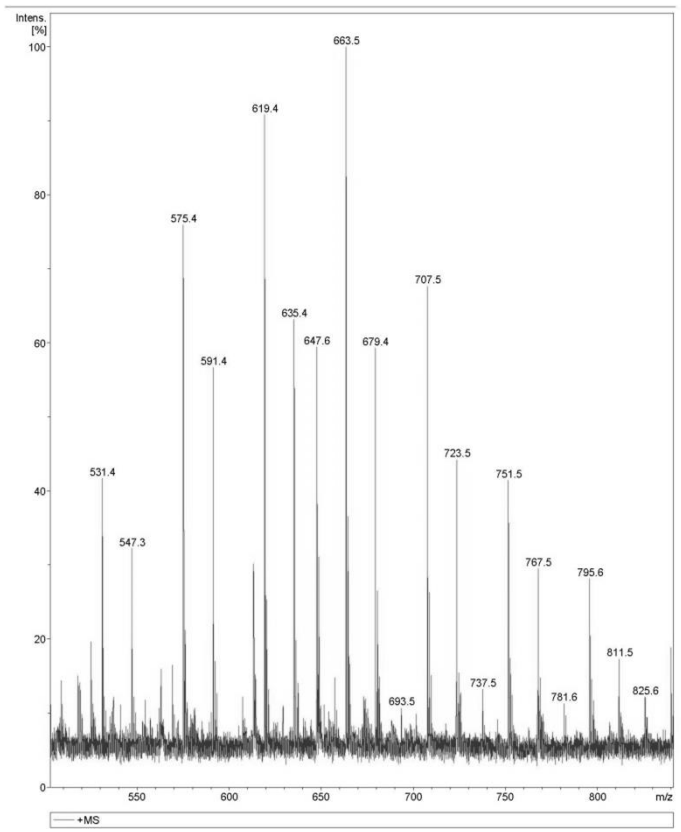

Intens.
[%]
100
80
60
40
20
0
350
400
450
500
550
600
650
700
m/z
465.2
509.2
553.3
421.2
597.3
521.2
565.2
609.3
377.2
641.3
477.2
405.2
449.2
653.3
493.2
361.1
537.2
685.3
343.1
581.3
625.3
+MS
Bruker Compass DataAnalysis 4.0
printed: 19/03/2014 18:22:28
Page 1 of 1

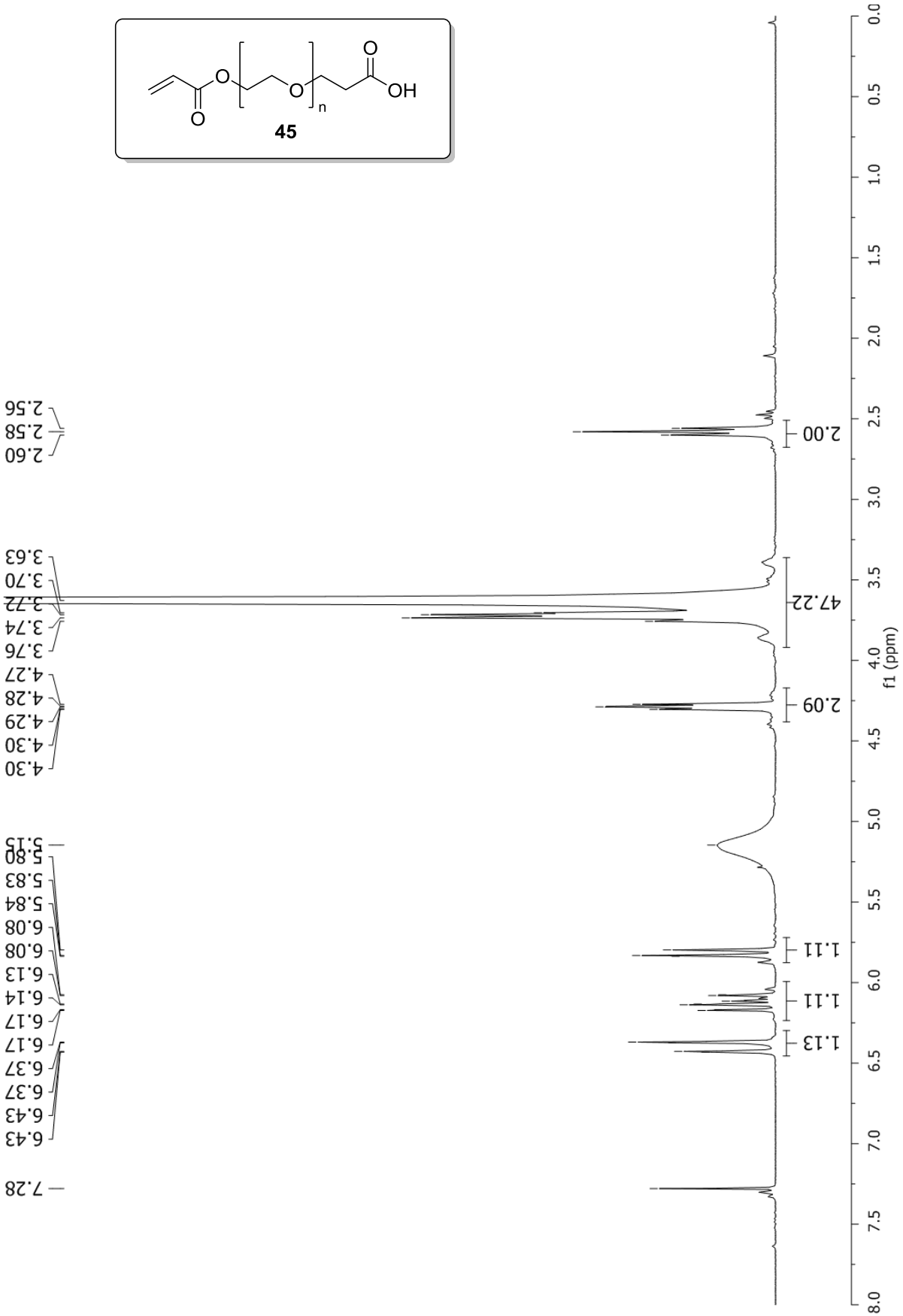

O
O
O
O
n
O
tBu
44
1.30
2.33
2.34
2.36
3.47
3.47
3.50
3.51
3.55
3.56
3.58
3.59
3.61
4.15
4.16
4.17
5.69
5.69
5.71
5.71
5.97
6.00
6.02
6.04
6.25
6.25
6.29
6.29
9.26
2.00
97.13
3.57
1.97
1.98
1.83
f1 (ppm)


%T
cm-1
2869,16
1724,03
1636,03
1455,74
1407,17
1349,5
1372,69
1345,69
1192,44
1098,80
986,84
919,35
847,86
809,85
730,42
698,07
427,98
400,61
502,25
388,21
c:\pel_data\spectra\javier peña\jpz-5.sp


O
O
O
O
n
O
tBu

44


Intens.
[%]
663.5
619.4
575.4
707.5
635.4
647.6
679.4
591.4
723.5
531.4
751.5
547.3
767.5
795.6
811.5
737.5
781.6
825.6
693.5
m/z
+MS


45
2.56
2.58
2.60
3.63
3.70
3.72
3.74
3.76
4.27
4.28
4.29
4.30
4.30
5.15
5.80
5.83
5.84
6.08
6.08
6.13
6.14
6.17
6.17
6.37
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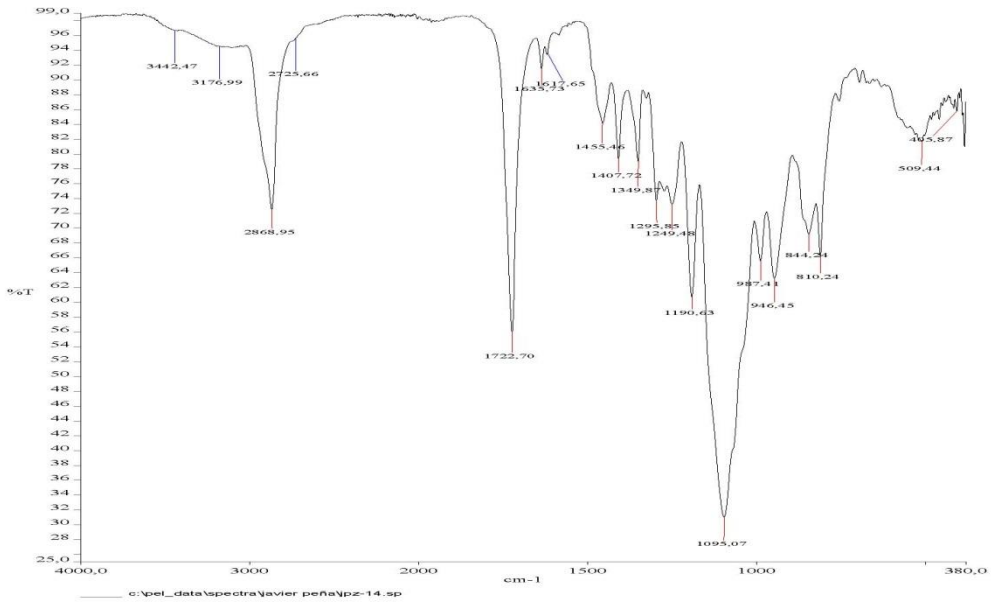
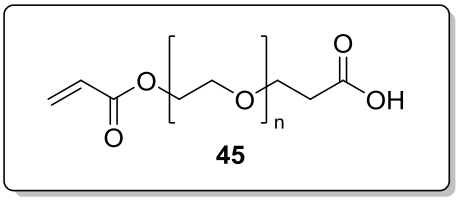
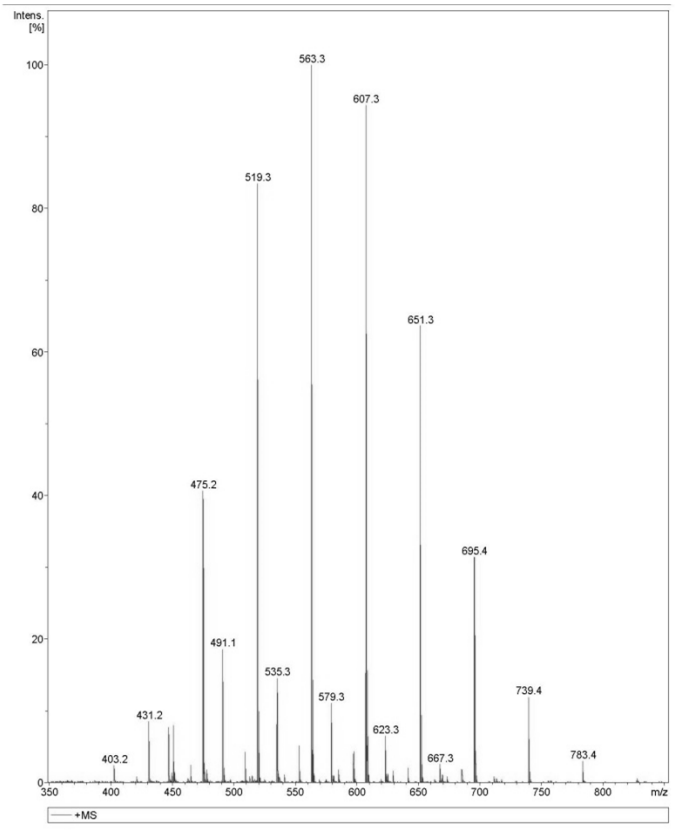
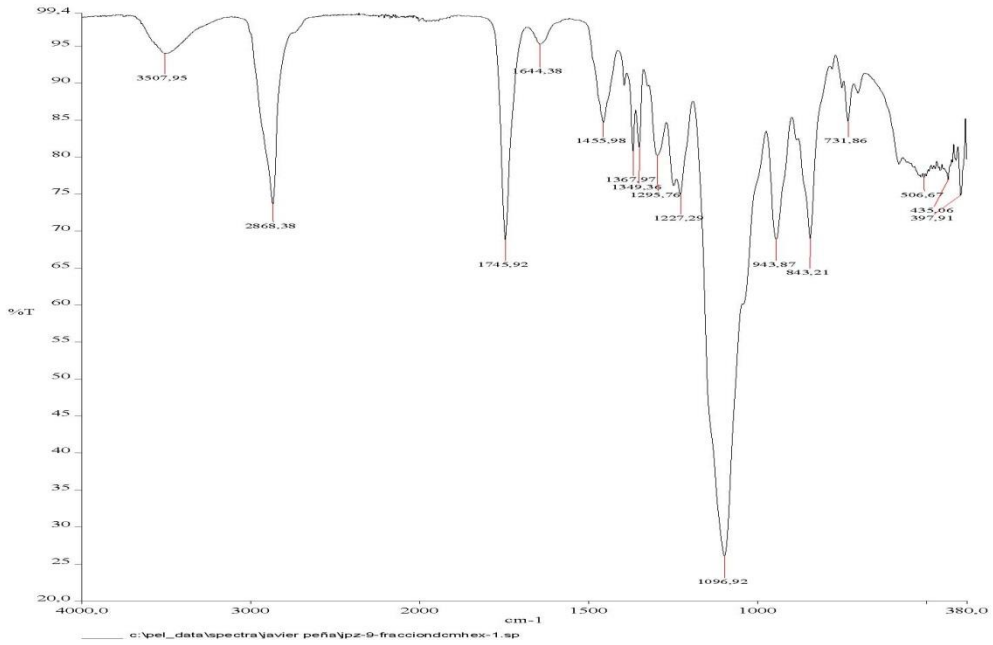
2.09
1.11
1.11
1.13
f1 (ppm)


%T
cm-1
3442,47
3176,99
2725,66
2868,95
1722,70
1633,93
1617,65
1455,46
1407,72
1349,8
1295,85
1249,48
1190,63
1095,07
987,41
946,45
844,24
810,24
485,87
509,44
c:\pel_data\spectra\javier peña\pz-14.sp


O
O
O
n
O
OH

45


Intens.
[%]
563.3
607.3
519.3
651.3
475.2
695.4
491.1
535.3
579.3
739.4
431.2
623.3
667.3
783.4
403.2
m/z
+MS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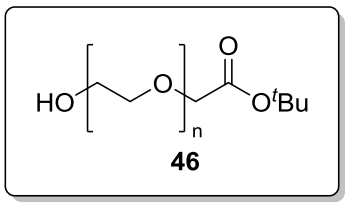
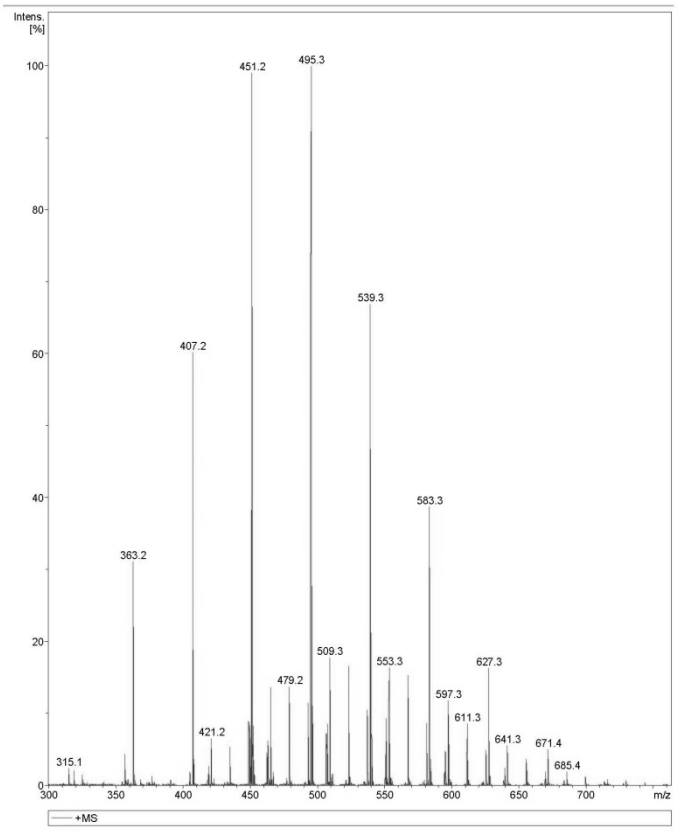
2868,38
1745,92
1644,38
1455,98
1367,97
1349,36
1295,76
1227,29
1096,92
943,87
843,21
731,86
506,67
435,06
397,91
%T
cm-1
c:\pel_data\spectra\javier peña\jpz-9-fracciondcmhex-1.sp


HO
O
O
O
tBu
n

46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[%]
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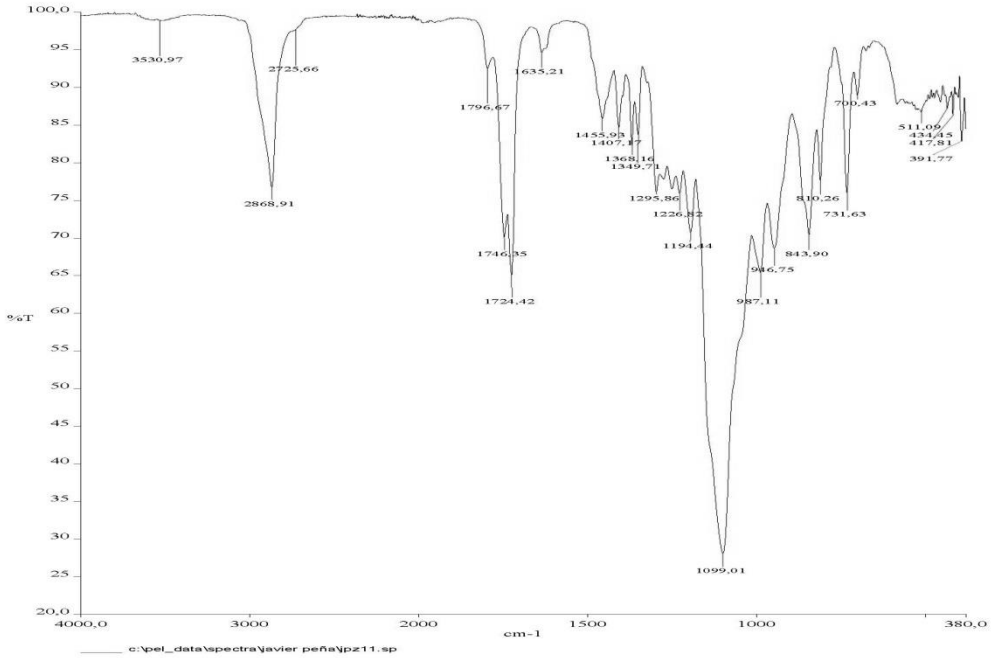
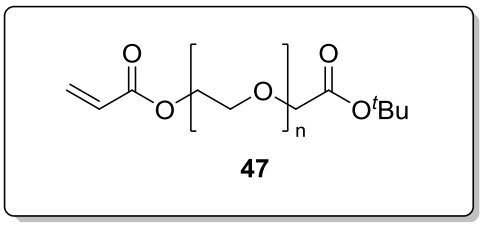
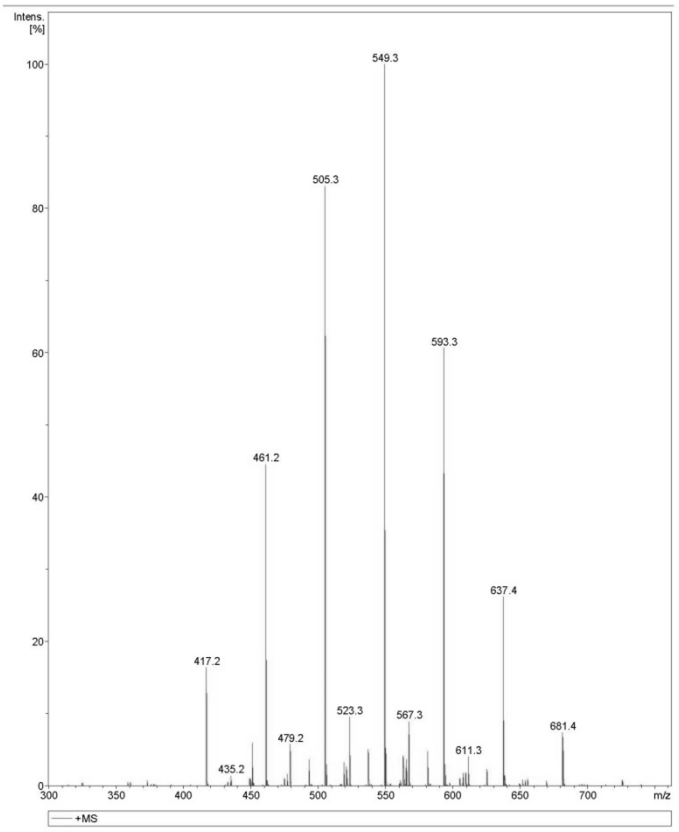
495.3
539.3
407.2
583.3
363.2
509.3
553.3
627.3
479.2
597.3
611.3
421.2
641.3
671.4
315.1
685.4
m/z
+MS


100,0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20,0
%T
4000,0
3000
2000
1500
1000
380,0
cm-1
3530,97
2725,66
2868,91
1796,67
1635,21
1746,35
1724,42
1455,93
1407,47
1368,16
1349,71
1295,86
1226,82
1194,44
1099,01
987,11
946,75
843,90
810,26
731,63
700,43
511,09
434,45
417,81
391,77
c:\pel_data\spectra\javier peña\jpz11.sp


O
O
O
O
n
O^{t}Bu

47


Intens.
[%]
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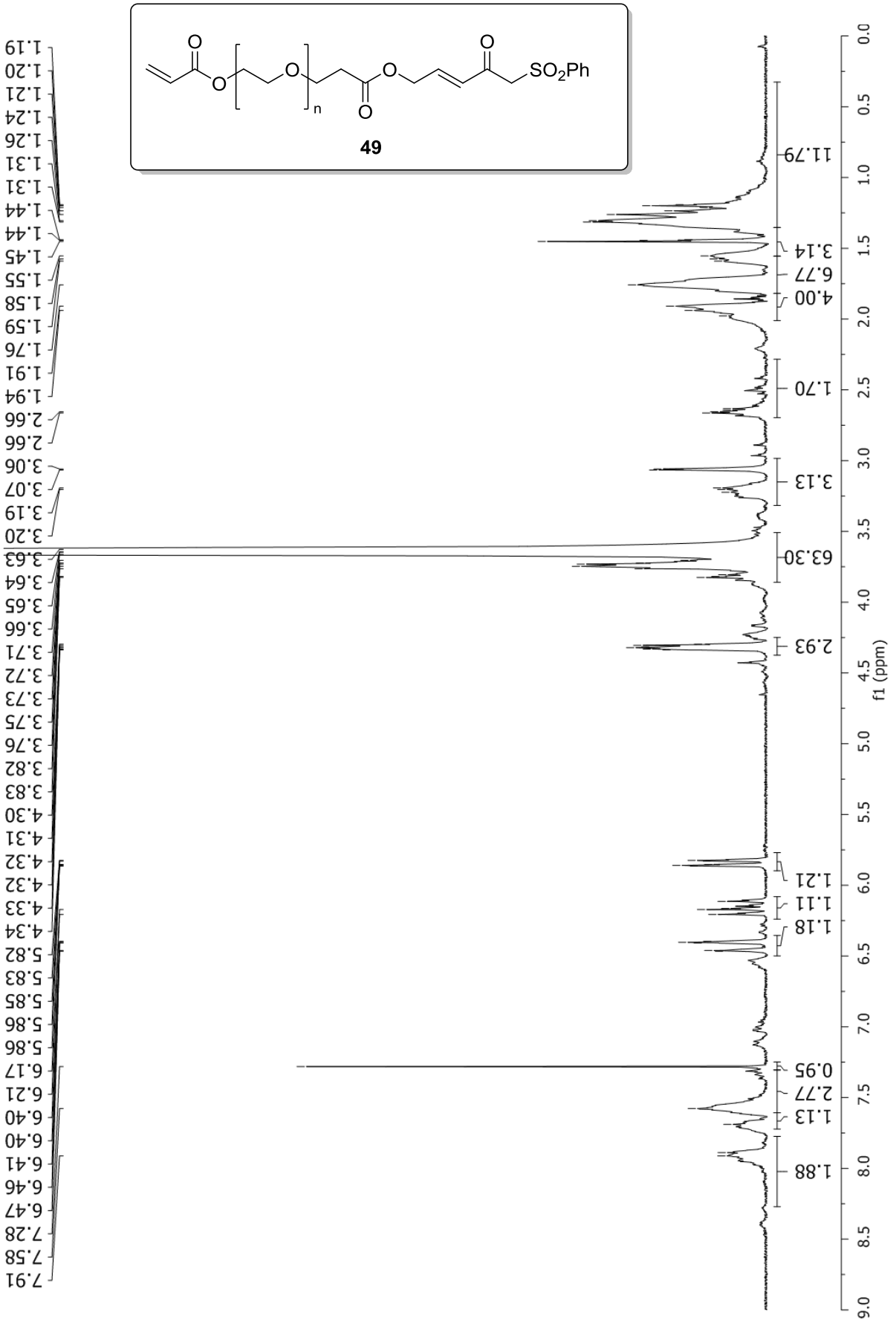
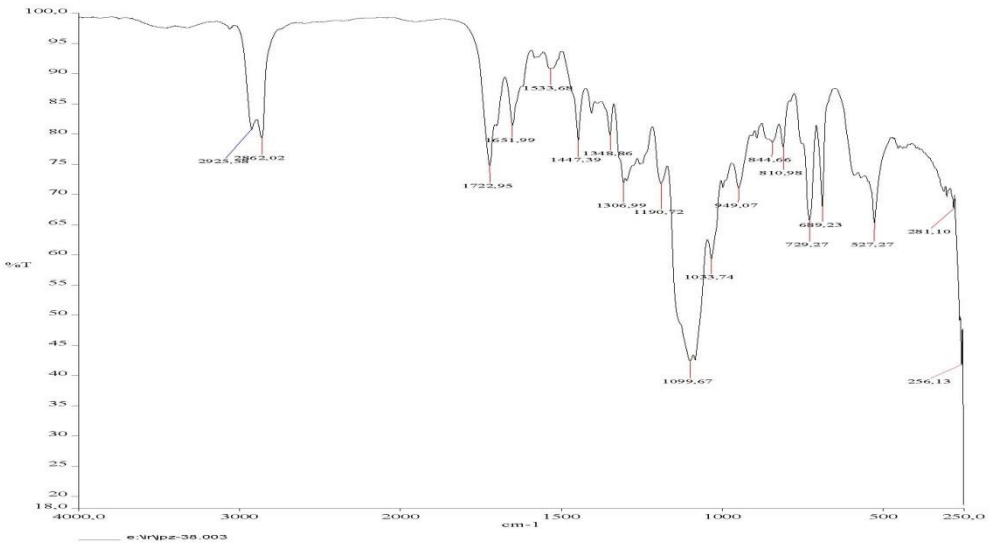
80
60
40
20
0
549.3
505.3
593.3
461.2
637.4
417.2
523.3
567.3
681.4
479.2
611.3
435.2
300
350
400
450
500
550
600
650
700
m/z
+MS


O
O
O
O
O
n
O
SO2Ph
49
f1 (ppm)


100,0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
18,0
%T
4000,0
3000
2000
1500
1000
500
250,0
cm-1
2925,38
2862,02
1722,95
1651,99
1533,68
1447,39
1348,86
1306,99
1190,72
1033,74
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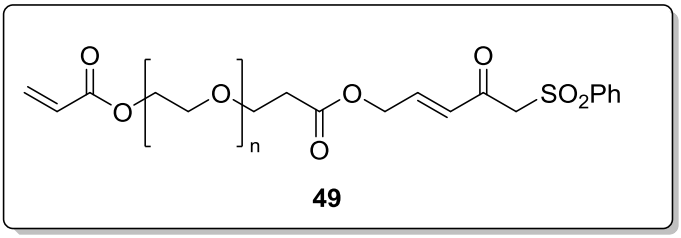
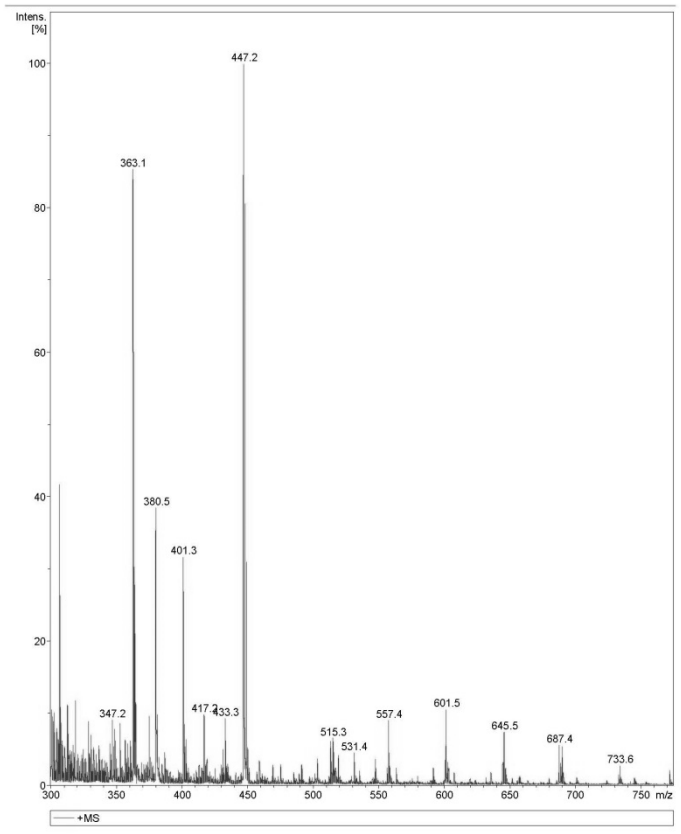
810,98
689,23
729,27
527,27
281,10
256,13


O
O
O
O
n
O
O
O
SO2Ph

49


Intens.
[%]
100
80
60
40
20
0
447.2
363.1
380.5
401.3
347.2
417.2
433.3
515.3
531.4
557.4
601.5
645.5
687.4
733.6
300
350
400
450
500
550
600
650
700
750 m/z
+MS

CRYSTALLOGRAPHIC DATA

1. X-Ray data for compound 16.

A suitable single crystal of **16** compound was mounted on glass fibre for data collection on a Bruker Kappa APEX II CCD diffractometer. Data were collected at 298(2) K using Cu K_α radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL^{TM} program package. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. H atoms attached to C10, C13 and C14 were located in a difference Fourier map and the rest of the hydrogen atoms were positioned geometrically.

a) Crystal data for **16**: $C_{16}H_{18}O_4S$, M = 306.36, monoclinic, space group $P2_1$ (nº 4), a = 11.1121(3) Å, b = 5.54790(10) Å, c = 12.8138(3) Å, $\alpha = \gamma = 90°$, β = 97.629(2) °, V = 782.96(3) Å^3, Z = 2, D_C = 1.299 Mg/m^3, m = (Cu-K_α) = 1.951 mm^{-1}, F(000) = 324. 5649 reflections were collected at 3.48 ≤ 2θ ≤ 67.17 and merged to give 2468 unique reflections (R_{int} = 0.0265), of which 2336 with I > 2 σ (I) were considered to be observed. Final values are R = 0.0363, *w*R = 0.1024, GOF = 1.047, max/min residual electron density 0.349 and -0.209 e. Å^{-3}.

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material nº. CCDC 975368.

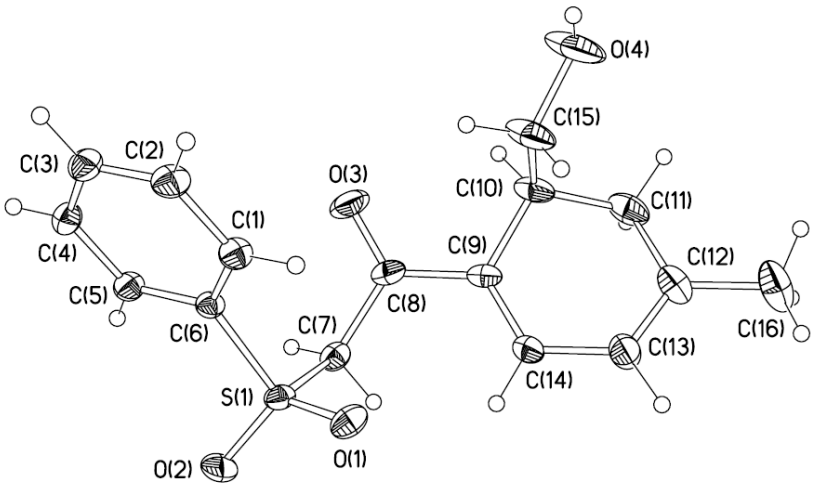


Figure 1. ORTEP diagram for compound **16**.

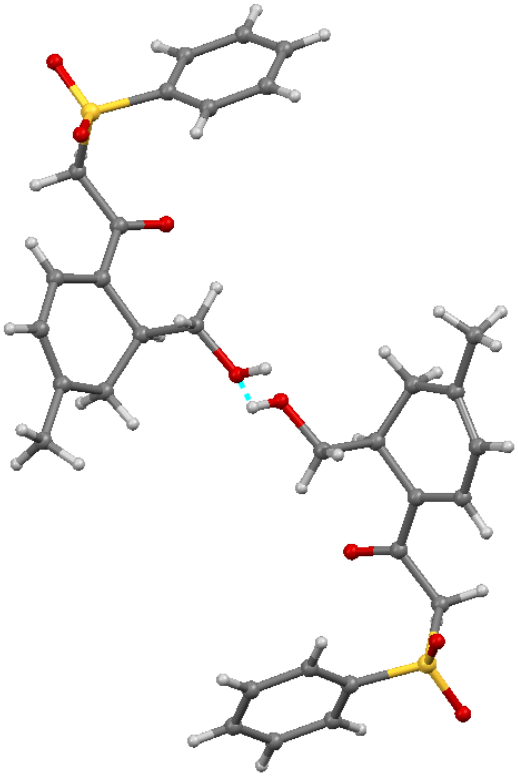


Figure 2. Interactions O-H-O.

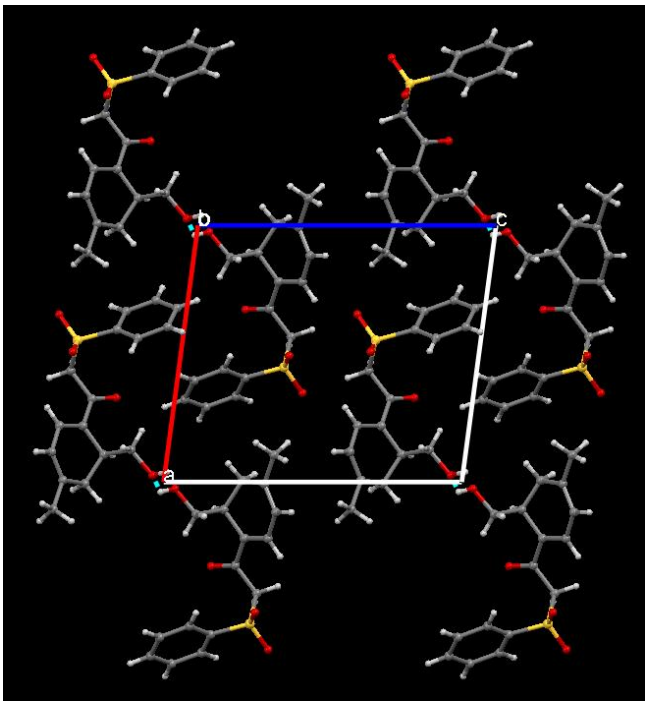


Figure 3. Packing along b-Axis.

2. X-Ray data for compound 24.

Suitable single crystal of the **24** compound was mounted on glass fibre for data collection on a Bruker Kappa APEX II CCD diffractometer. Data were collected at 298(2) K using Cu K_α radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL™ program package. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. H atoms of SP^3 hybridised carbons were located directly in a difference Fourier map and freely refined. The rest of the hydrogen atoms were positioned geometrically.

Crystal data for **24**: $C_{23}H_{30}O_7S$, M = 450.53, monoclinic, space group C2 (nº 5), a = 21.294(3) Å, b = 6.6141(10) Å, c = 16.324(2) Å, $\alpha = \beta = 90.00°$, γ = 105.491(10) °, V = 2215.5(5) $Å^3$, Z = 4, D_C = 1.351 Mg/m^3, m = (Cu-K_α) = 1.658 mm^{-1}, F(000) = 960. 4599 reflections were collected at $2.81 \leq 2\theta \leq 66.38$ and merged to give 2754 unique reflections (R_{int} = 0.0787), of which 2144 with $I > 2\sigma(I)$ were considered to be observed. Final values are R = 0.1035, *w*R = 0.3323, GOF = 1.311, max/min residual electron density 0.474 and -0.429 e. $Å^{-3}$.

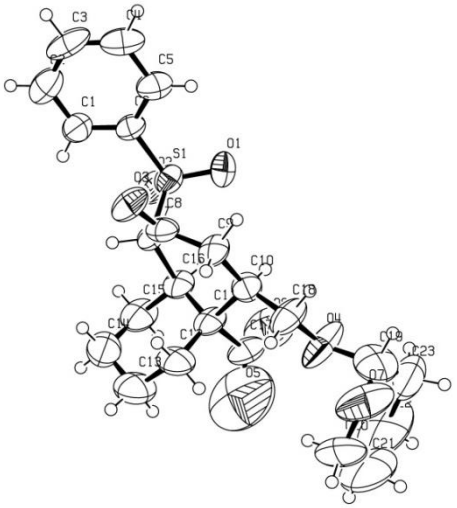


Figure 4. Ortep diagram for compound **24**.

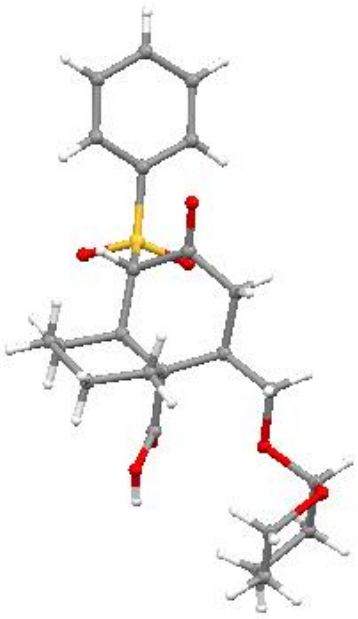


Figure 5. X-ray structure for compound **24** ($C_{23}H_{30}O_7S$).

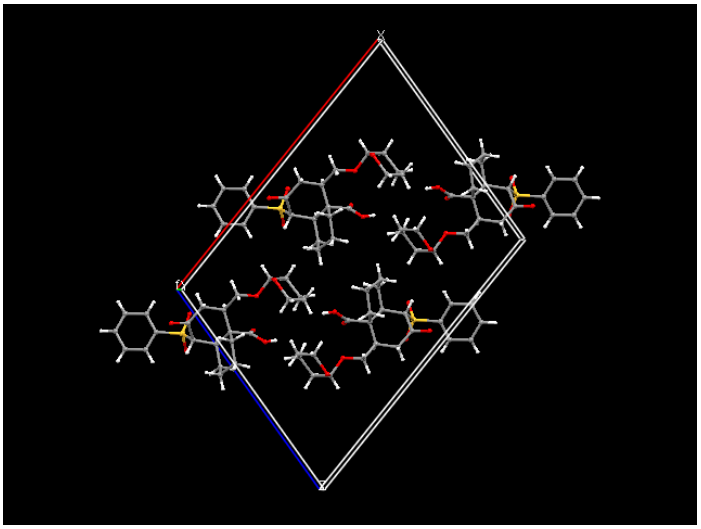


Figure 6. Packing along c-Axis for compound **24**.

3. X-Ray data for compounds 41l and *ent*-41l.

Suitable single crystals of **41l**, and ***ent*-41l** were mounted on glass fibre for data collection on a Bruker Kappa APEX II CCD diffractometer. Data were collected at 298(2) K using Cu K_α radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL™ program package. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. H atoms of SP^3 hybridized carbons were located directly in a difference Fourier map and freely refined. The rest of the hydrogen atoms were positioned geometrically.

a) Crystal data for **41l**: $4(C_{18}H_{22}O_5S)$ x O, M = 1417.66 , orthorhombic, space group $P2_12_12$ (nº 18), a = 13.6843(4) Å, b = 37.7715(10) Å, c = 6.6336(2) Å, $\alpha = \beta = \gamma = 90.00°$, V = 3428.75(17) $Å^3$, Z = 2, D_C = 1.373 Mg/m^3, m = (Cu-K_α) = 1.913 mm^{-1}, F(000) = 1504. 26312 reflections were collected at $5.69 \leq 2\theta \leq 66.90$ and merged to give 5766 unique reflections (R_{int} = 0.0517), of which 5196 with $I > 2\sigma(I)$ were considered to be observed. Final values are R = 0.0345, *w*R = 0.0778, GOF = 1.045, max/min residual electron density 0.208 and -0.209 e. $Å^{-3}$.

b) Crystal data for ***ent*-41l**: $4(C_{18}H_{22}O_5S)$ x O, M = 1417.66, orthorhombic, space group $P2_12_12$ (nº 18), a = 13.6802(3) Å, b = 37.7616(8) Å, c = 6.62530(10) Å, $\alpha = \beta = \gamma = 90.00°$, V = 3422.54(12) $Å^3$, Z = 2, D_C = 1.376 Mg/m^3, m = (Cu-K_α) = 1.916 mm^{-1}, F(000) = 1504. 28071 reflections were collected at $3.44 \leq 2\theta \leq 67.29$ and merged to give 5746 unique reflections (R_{int} = 0.0490), of which 5059 with $I > 2\sigma(I)$ were considered to be observed. Final values are R = 0.0352, *w*R = 0.0781, GOF = 1.051, max/min residual electron density 0.228 and -0.228 e. $Å^{-3}$.

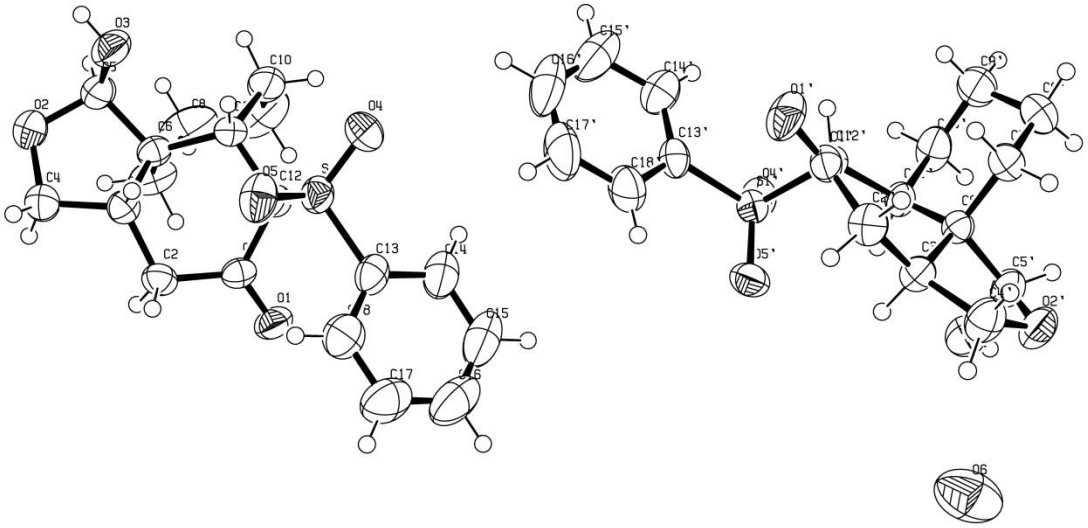


Figure 7. ORTEP diagram for compound **41l**.

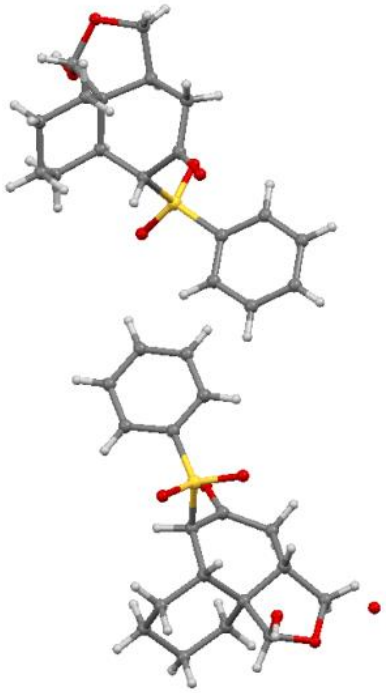


Figure 8. X-ray structure for compound **41l** ($C_{18}H_{22}O_5S$), O.

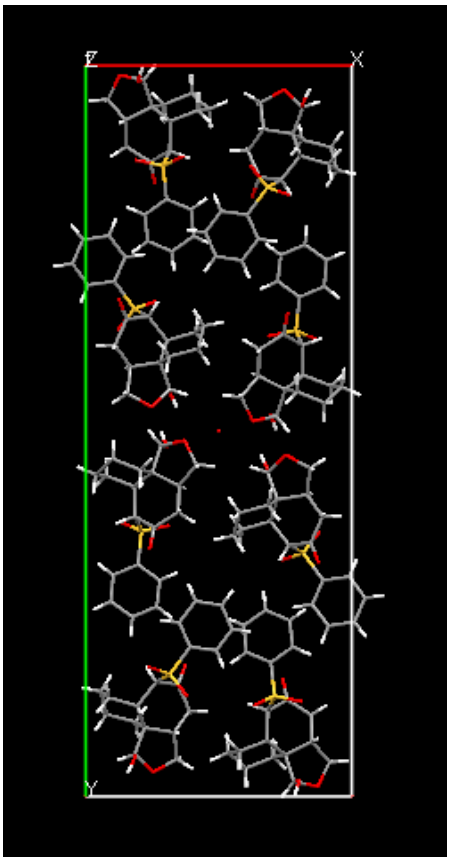


Figure 9. Packing along c-Axis for compound **41l** ($C_{18}H_{22}O_5S$), O.

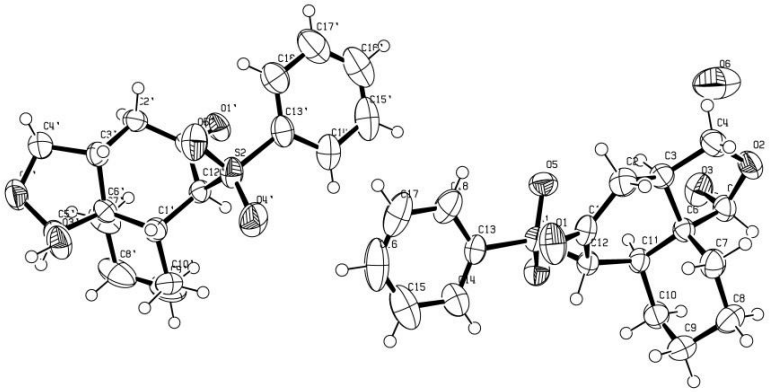


Figure 10. ORTEP diagram for ***ent*-41l**

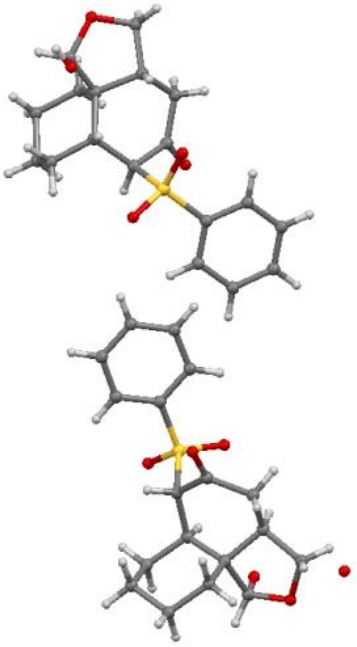


Figure 11. X-ray structure for compound ***ent*-41l** (C18H22O5S), O.

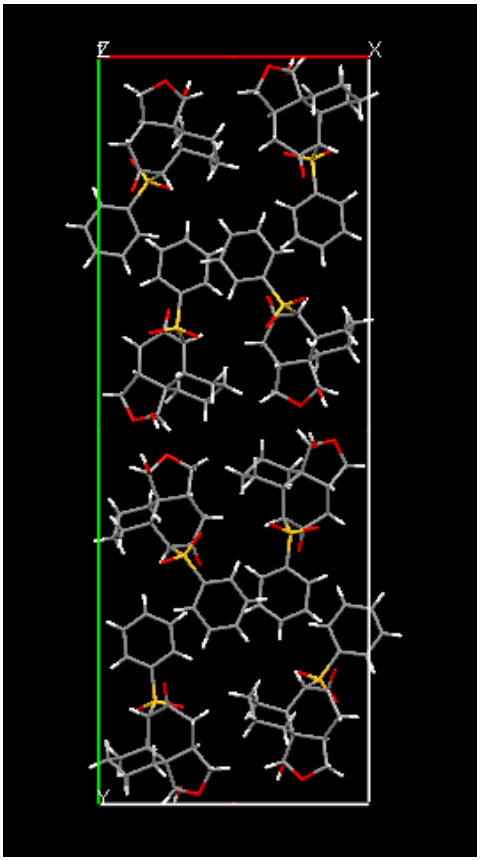
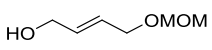


Figure 12. Packing along c-Axis for compounds ***ent*-41l** (C18H22O5S), O.

ANNEX

These are the molecules synthesised and the main commercial catalysts and additives used in this work. The number in *italics* written under each compound corresponds to the page number where the experimental procedure for its synthesis is described. The number in *(parentheses)* corresponds to the page number where spectroscopic data can be found. When only one number is shown, both experimental procedure and spectroscopic data are in that same page.



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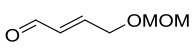

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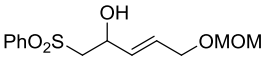

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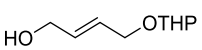

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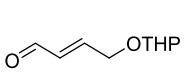

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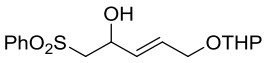

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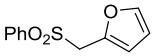

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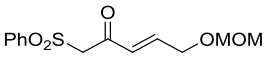

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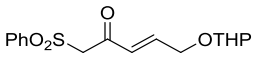

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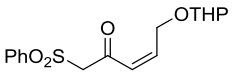

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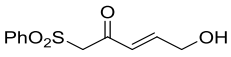

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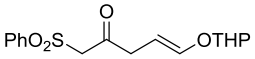

I-E

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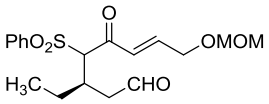

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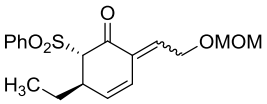

11a*E*/*Z*

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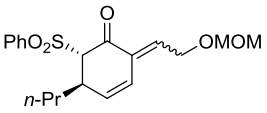
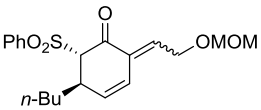


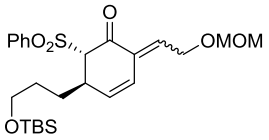
11b*E*/*Z*

277



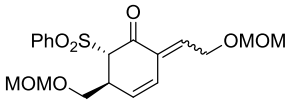
11c*E*/*Z*

278



11d*E*/*Z*

278 & 283 (279)



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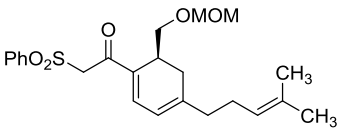
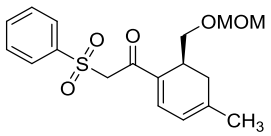


13a

280 & 283 (280)

280 & 283 (281)



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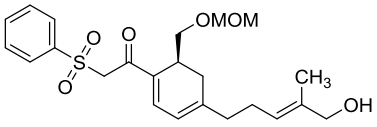

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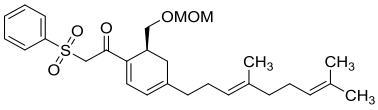

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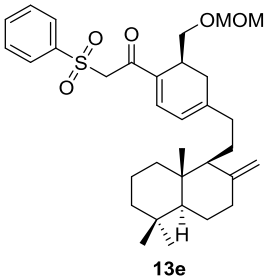

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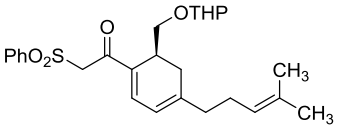

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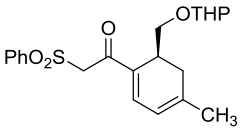

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285 (287)

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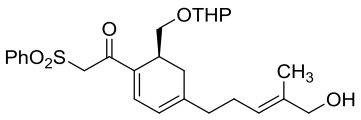

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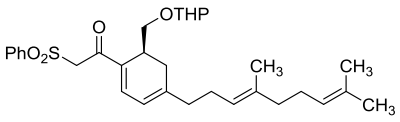

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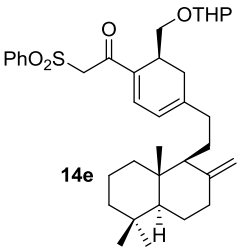

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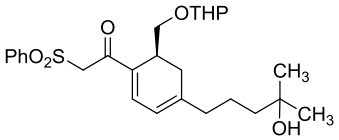

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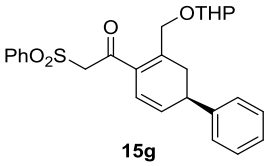

15g

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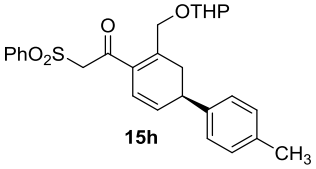

15h

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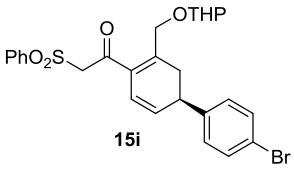

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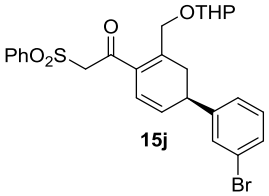

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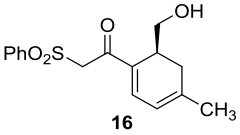
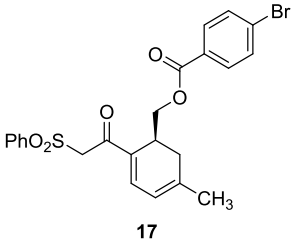


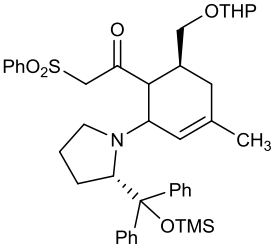
16

295



17

296



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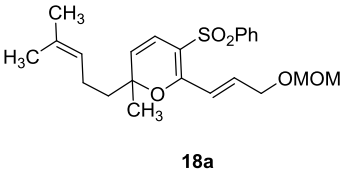

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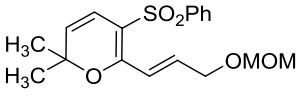

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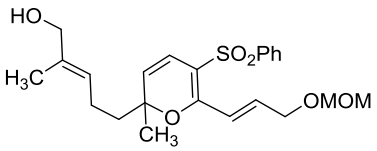

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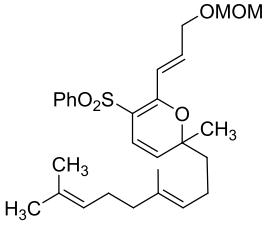

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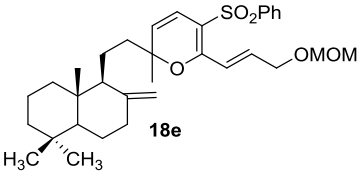

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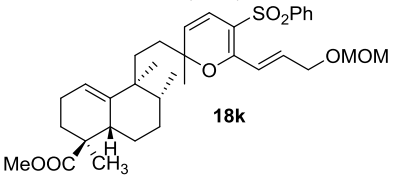

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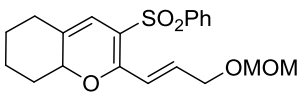

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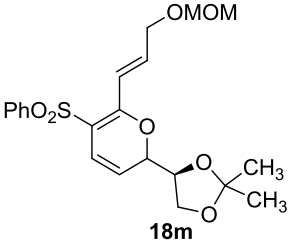

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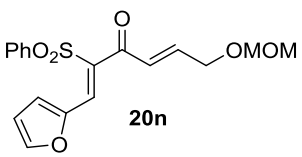

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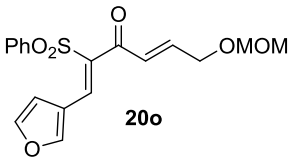

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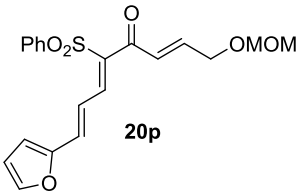

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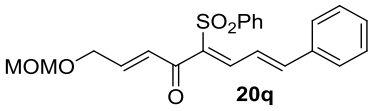

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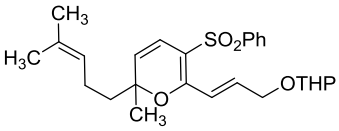

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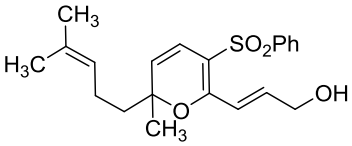

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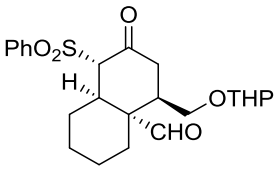

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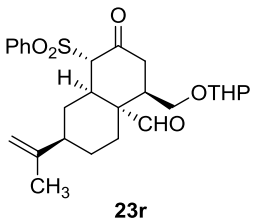

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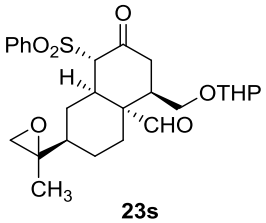

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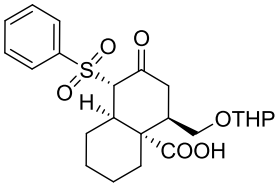

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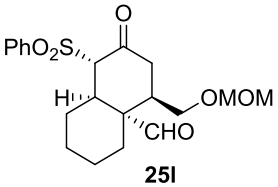

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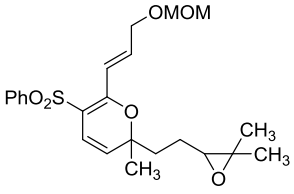

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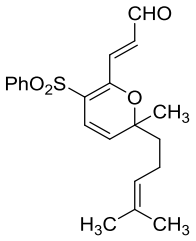

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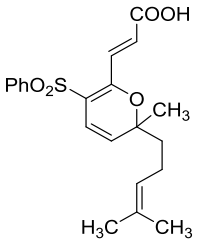

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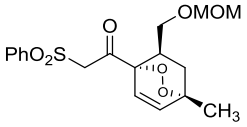

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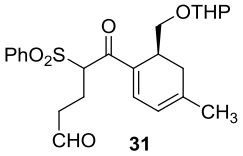

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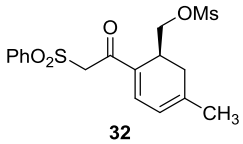

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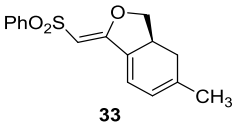

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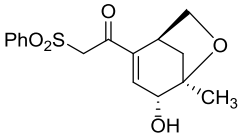

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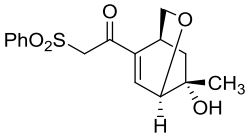

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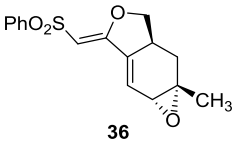

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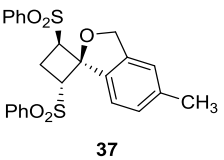

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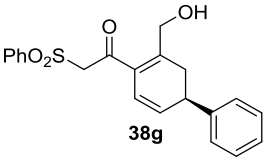

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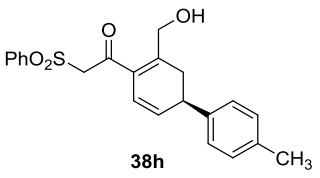

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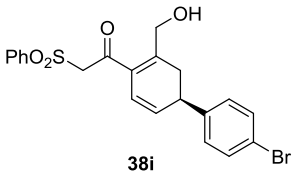

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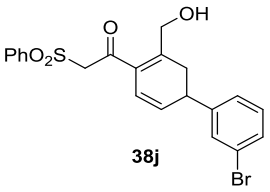

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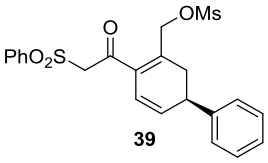

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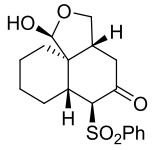

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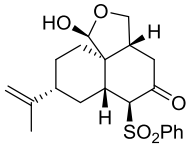

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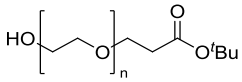

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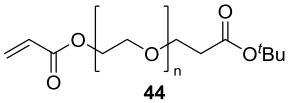

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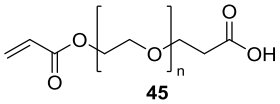

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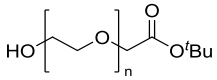

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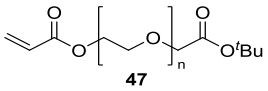

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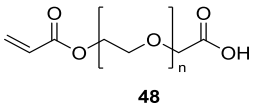

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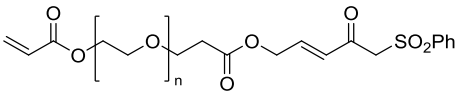

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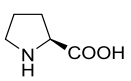
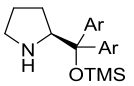
328

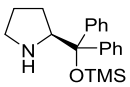
Main commercial catalysts and additives used in this work:



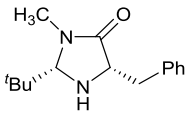
L-proline



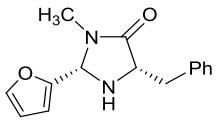
III, Jørgensen
Ar = 3,5-$(CF_3)_2$-C_6H_3



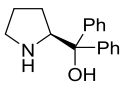
XXV, Hayashi-Jørgensen



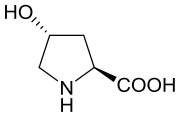
XXVII



XXVIII



XXIX



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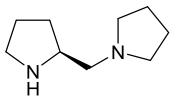
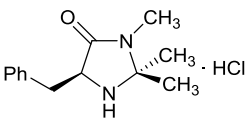
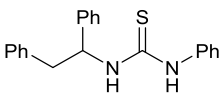


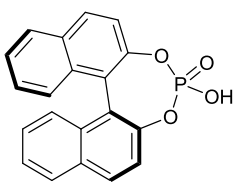
XXXI



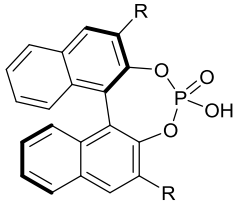
XXXII



XXXIII



XXXIV BinapPOH (*S*)



XXXV CF_3-BinapPOH (*R*)
R = 3,5-bis(trifluoromethyl)phenyl