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STUDY OF THE REACTIVITY OF CYCLOOCTADIENE CARBOXYLATES AND APPLICATIONS IN ASYMMETRIC SYNTHESIS

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English summary

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This manuscript is the section "*English Summary*" included in the work entitled: "Estudio de la reactividad de Ciclooctadiencarboxilato y aplicaciónes en síntesis asimétrica" (Study of the reactivity of cyclooctadiene carboxylates and application in asymmetric synthesis).

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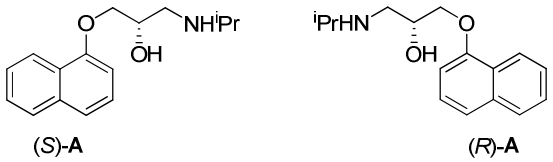
1. INTRODUCTION:

Nowadays, one of the biggest challenges that modern organic chemistry has to face is the efficient synthesis of enantiomerically pure chiral molecules.[1] This interest has been stimulated by the growing awareness about the importance of molecular chirality in biological systems and the need in their reproducibility through synthetic routes of compounds that have a high added value.

Many biological processes in nature are chiral. Enzymes and particular active positions of the receptors which control these processes are formed by *L*-amino acids or *D*-carbohydrates. The interaction between a racemate and an enzyme or receptor will lead to the formation of two diastereoisomeric complexes wherein the two enantiomers from one compound will have the ability to bind selectively to another enzyme or receptor and therefore to exhibit different biological effects. A common example is Propranolol **A** (Figure 1), which enantiomer (*S*) is antihypertensive and antiarrhythmic and it is used in the treatment of coronary heart disease whereas the enantiomer (*R*) is used as contraceptive.[2]



(*S*)-**A** (*R*)-**A**

Figure 1. Propranolol enantiomers

As a result to the contribution on this topic and the great importance in the synthesis of enantiomerically pure drugs to be produced at industrial scale, it can be found in literature three routes normally used for the production of chiral molecules: resolution, handling of natural products[3] and asymmetric synthesis which covers this research.

1. 1 ASYMMETRIC SYNTHESIS:

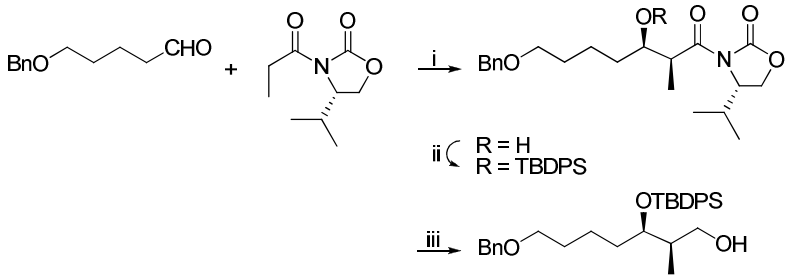
The term "*asymmetric synthesis*" was introduced by Marckwald in 1904,[4] defining as asymmetric synthesis the reaction between an achiral substrate and a chiral agent to form an optically active compound. This definition was subsequently reviewed by Morrison in 1971, defining it as a reaction in which an achiral unit by interaction with a substrate is converted by action of a reagent

[1] (a) Koskinen, A. "*Asymmetric synthesis of natural products*", **1993**, John Wiley and Sons. New York (b) Nógrádi, M. "*Stereoselective synthesis*", **1995**, 2nd Edition VCH, Weinheim Publisher.
[2] Parker, D. *Chem. Rev*. **1991**, *91*, 1441-1457.
[3] Hanessian, S. "*Total synthesis of natural products: the Chiron approach*", **1983**, Pergamon Pres.
[4] (a) Marckwald, W. *Ber. Dtsch. Chem. Ges*. **1904**, *37*, 1368. (b) Bringmann, G.; Helmchen, G.; *et.al. Stereoselective synthesis,* **1996**, Workbench ed. E21 - V1. Publication: Methods of organic chemistry Stuttgart; New York: Thieme.

into a chiral unit which is a mixture of enantiomers produced in different proportions.[5] This postulation involves different fields of research such as: the use of chiral auxiliaries, chiral reagents, asymmetric catalysis and organocatalysis.

1.1.1 Use of chiral auxiliaries:

This field utilizes chiral molecules that are capable of transferring their chirality to achiral substrates, recovering the compound or chiral auxiliary inductor at the end of the reaction. The use of chiral auxiliaries is binding to a prochiral substrate, transforming the groups or enantiotopic faces into diastereotopic, which means that diastereoisomers are afforded selectively and also can be separated by standard techniques of purification. Subsequent removal of the chiral auxiliary leaves to enantiomerically enriched product. Its main advantages are: first, the chiral auxiliary can often be recycled which leads to produce as much chiral material from a relatively small amount of chiral reagent; second, the auxiliary can be used to control the stereochemistry of the stereogenic centers formed in the reaction; finally, in highly stereoselective reactions, although are favorable, they are not necessary in this approach as soon as the diastereomeric products before the rupture of the auxiliary can be separated resulting in high enantiomeric excess. Scheme 1 shows an example of how the chiral oxazolidinones developed by Evans[6] can act as effective chiral auxiliaries.



Scheme 1. *Reagents and conditions*: (i) Bu_2BOTf, Et_3N, DCM, -78°C. (ii) TBDPSCl, imidazole, DMF. (iii) $LiBH_4$, MeOH, THF, 0°C.

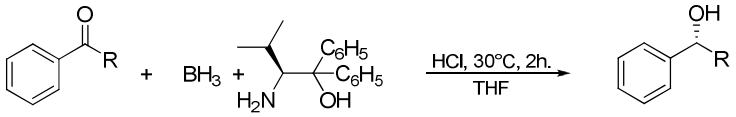
1.1.2 Chiral Reagents:

In this field a chiral reagent reacts with a prochiral substrate to yield the desired chiral product. Unlike the use of chiral auxiliaries, in this case is not necessary to remove the reagent because it is stoichiometrically consumed during the reaction. As an example, the reduction of prochiral aromatic ketones with the Itsuno`s reagent (Scheme 2). This reagent is prepared from a chiral β-

[5] Morrison, J. D.; Mosher, M. S.: *Asymmetric organic reactions* **1971**, Prentice Hall, Englewood Cliffs, New Jersey.

[6] (a) Evans, D. A. *Aldrichimica Acta*, **1982**, *15*, 23-32. (b) Armstrong, A.; Barsanti, P. A.; Blench, T. J.; Ogilvie, R. *Tetrahedron*, **2002**, *59*, 367-375.

amino alcohol, sterically congested and borane. The reduction of ketones to secondary alcohols can reach enantiomeric excess between 94 and 100%.[7]

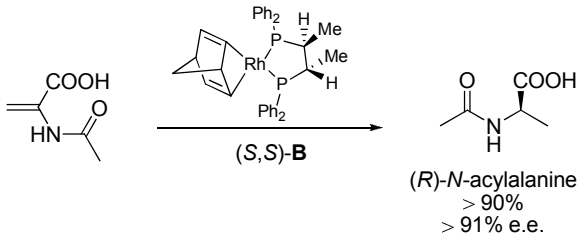


Scheme 2. Aromatic ketone reduction with Itsuno`s reagent

1.1.3 Asymmetric catalysis:

This method, which includes the use of catalysts often consist of a transition metal bounded to a organic chiral auxiliary or enzyme, using the chirality of a catalytic reagent to conduct the formation of one or more stereogenic centers in a prochiral substrate. In contrast to the use of chiral auxiliaries, which allows purification of the diastereoisomeric products to reach favorable enantiomeric excess, this approach depends entirely on highly diastereomeric reactions and as with the chiral auxiliary recyclable catalytic approach is particularly attractive since allows the production of a large chiral amount of material from very small amount of chiral reagent.

One area which has received the most attention is the catalytic hydrogenation of Carbon-Carbon double bonds, using homogeneous catalysts of Rhodium or Ruthenium attached to chiral phosphines as ligands. The example of Scheme 3 shows the use of a Rhodium complex (*S*,*S*)-B which possesses the ligand (*S*,*S*)-Chiraphos for yielding optically active amino acids such as (*R*)-*N*-acyl alanine with a large enantiomeric excess and it is one of the many examples in this broad field in expansion.[8]



Scheme 3. Catalytic hydrogenation of double bonds

[7] (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun*. **1983**, 469-470. (b) Itsuno, S.; Nakano, M.; Miyazaky, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans 1*. **1985**, 2039-2044.

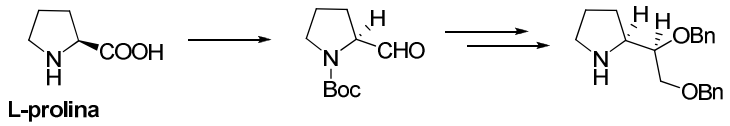
[8] (a) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc*. **1977**, *99*, 6262-6267. (b) Noyori, K. *Asymmetric catalysis in organic synthesis*, **1994**, John Wiley and Sons, New York. (c) Knowles, W. S.; Noyori, R. and Sharpless K. B. The Nobel Prize in Chemistry **2001**, *Angew. Chem. Int. Ed*. **2002**, *41*, 2008-2022.

1.1.4 Organocatalysis:

In the recent years, there has been an impressive development in organocatalysis, consisting of the acceleration of chemical reactions with substoichiometric quantities of an organic compound containing no metal atom, [9] which involves two great advantages, the development of a first metal-free chemistry which reduce the potential toxicity and the second the low cost that this entails.

The amino acids have been widely used as chirality inducers whereas peptides have been less used in asymmetric chemistry being the most outstanding those having fewer than 50 amino acids in its structure.[10]

The *L*-proline[11] is the most used amino acid as an organic catalyst. Although it was used by Hajos-Parrish-Eder-Sauer-Wiechert in 1971,[12] it was not described any application with this amino acid until 2000, except for some isolated examples of intramolecular Michael additions catalyzed by stoichiometric amounts of this one.[13] In our research group, Díez *et al*.[14] have synthesized numerous proline analogs (Scheme 4) which are used as catalysts in organic reactions which proceed *via* intermediate enamine type such as Michael additions of ketones to nitro styrenes, obtaining very good yields and excellent diastereo and enantioselectivity.



Scheme 4. *L*-proline and analogs

One of the largest and most recent achievements of organic synthesis has been the development of reactions observed in biosynthetic natural processes *via* metal-free asymmetric catalysis, starting

[9] (a) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304-308. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.

[10] (a) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl*. **2001**, *40*, 1456-1460. (b) Gilberston, S. T.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc*. **2000**, *122*, 6522-6523 (c) Gilberston, S. T.; Wang, X.; Hoge, G. S.; Klung, C.; Schaefer, A. *J. Organometallics* **1996**, *15*, 4678-4680. (d) Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun*. **1990**, 135-136. (e) Akabori, S.; Sakkurai, S.; Izumi, Y.; Fujii, Y.; Nature **1956**, *178*, 323.

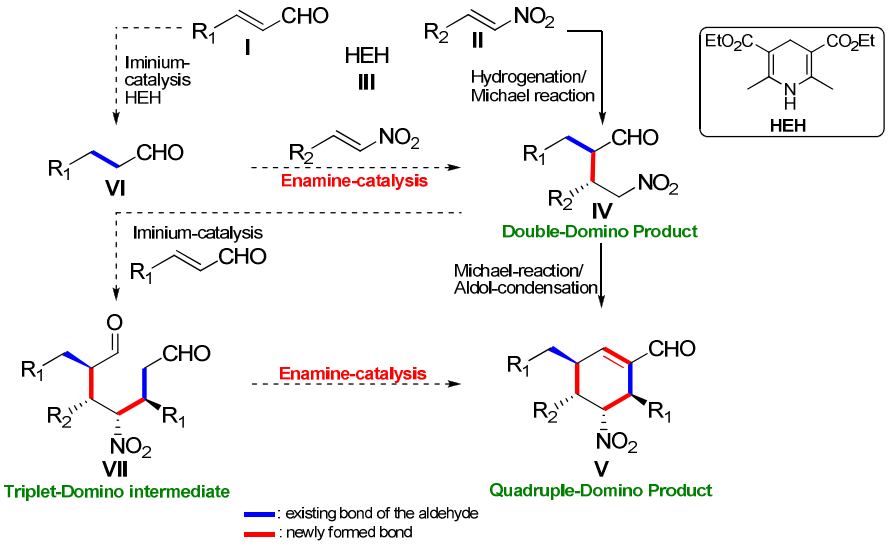
[11] (a) Movassaghi, M.; Jacobsen, E. N.; *Science* **2002**, *298*, 1904-1905.(b) List, B. *Tetrahedron* **2002**, *58*, 5573-5590. (c) List, B. *Synlett* **2001**, 1675-1686. (d) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726-3748.

[12] (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed*. **1971**, *10*, 496-497. (b) Parrish, D. R.; Hajos, Z. G. *J. Org. Chem*. **1974**, *39*, 1615-1621.

[13] (a) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem Soc. Perkin Trans 1*, **1992**, 517-524. (b) Kozikowski, B.; Mugrage, B. *J. Org. Chem*. **1989**, *54*, 2274-2275.

[14] Díez, D.; Antón, A. B.; García, P.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2008**, *19*, 2088-2091.

from simple reagents to produce compounds with complex structures and multiple stereocenters in a few steps giving access to a wide variety of skeletons essentially for biological assays. Inspired by the efficiency of enzymatic processes which often are held on domino reactions,[15] and the multiple components,[16] makes that several research groups are working on it, Rueping *et al*.[17] have shown that by controlling the concentration of the substrates **I**, **II** and **III** (HEH, Hantzsch dihydropyridine) can reach double domino reactions (compound-**IV**) and quadruple (compound-**V**), as seen in the following scheme.



Scheme 5. Reaction sequence of the double- and quadruple- domino reaction cascade

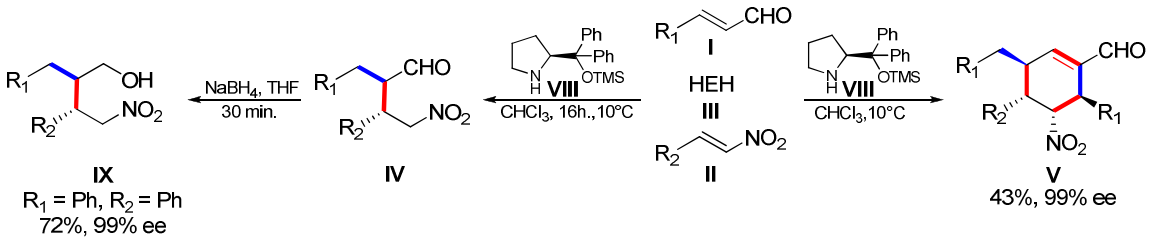
The key step in the two sequences is the conversion of the α,β-unsaturated aldehyde *via* hydrogen transfer in the presence of HEH. The functional groups present in the reaction product **IV** are available to continue reacting and if the concentration of **I** increases, the nitroaldehyde-**IV** can react through a Michael addition to form the catalyzed imino intermediate **VII**, which has two aldehyde groups facilitating intramolecular aldol condensation to give the carbon cycle **V**. To validate this design, several experiments were performed to find the optimal conditions for the addition-reduction sequence (Scheme 6) using *L*-proline derivative, diphenyl ether-TMS-prolinol and second different concentrations of substrates, observing that the reaction of the aldehyde α,β-

[15] (a) Tietze, L. F. *Chem. Rev*., **1996**, *96*, 115-136. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 131-163. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**. (d) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354-366.

[16] (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602-1634. (b) Zhu, J.; Benaymé, H. "*Multicomponent Reactions*", Wiley-VCH, Weinheim, **2005**. (c) D`Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095-1108.

[17] Rueping, M.; Haack, K.; Ieawsuwan, W.; Sundén, H.; Blanco, M.; Schoepke, F. R. *Chem. Commun*. **2011**, *47*, 3828-3830.

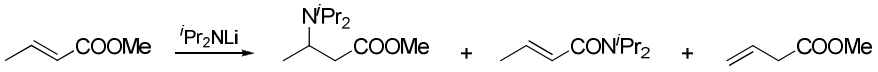
unsaturated **I**, the nitrostyrene **II** and the dihydropyridine **III** in a ratio relation of 4.0:1.0:2.2 led to the formation of the product **V** and **IV**, being the first example of a quadruple domino reaction cascade controlled only by the substrates` concentration.



Scheme 6. Reduction and addition sequence

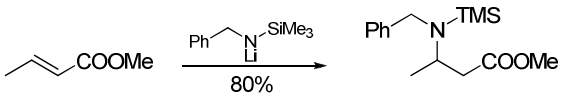
1.2 ADDITION OF LITHIUM AMIDES:

In the chapter of chiral auxiliaries, lithium amides recently have become very useful reagents in organic chemistry. Their application has been practically limited to their use as non-nucleophilic strong bases, as is the case of LDA, which can produced stoichiometric deprotonation of enolizables carbonyls without problems of addition type 1,2 (Scheme 7). In addition, lithium amides have also been used successfully in asymmetric synthesis as bases.[18]



Scheme 7. Reactivity of LDA

The first case of conjugated addition of lithium amides dates back to 1973 observed by Schlessinger`s research group while performing a deprotonation in γ of ethyl crotonate with LDA.[19] However, the issue was not investigated further until 1987, when Yamamoto[20] began to publish works on the addition type 1,4 of lithium amides derived from *N*-benzyl trimethylsilylamine (LSA) as shown in the following scheme.



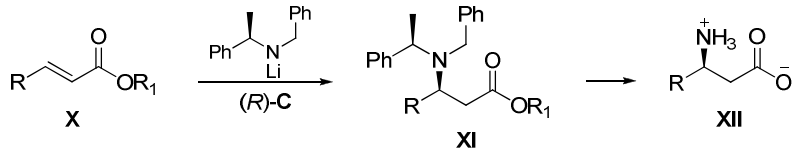
Scheme 8. Conjugate addition of Lithium amides

[18] Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry*. **1991**, *2*, 1-26.
[19] Hermann, J. C.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett*. **1973**, 2433-2436.
[20] (a) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem Commun*. **1987**, *18*, 1410-1411. (b) Uyehara, T.; Asao, N.; Yamamoto, Y. *Tetrahedron*, **1988**, *44*, 4173-4180. (c) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem Commun*. **1989**, 113. (d) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron*, **1990**, *46*, 4563-4572. (e) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem*. **1992**, *57*, 3139-3145.

1.2.1 Lithium amides as chiral reagents:

Hawkins *et al.* [21] reported the first conjugate asymmetric addition reaction by reagent control using lithium amides as nucleophile. They achieved diastereomeric excess of up to 97% by addition of a chiral binaphthyl amide to (*E*)-crotonic esters. This amide besides being costly particularly in chiral form is also difficult to remove once the addition is carried out.[22]

The research group of Professor Davies has been studied extensively the conjugate addition of different chiral lithium amides as nucleophiles, containing the *N*-α-methylbenzyl to esters (*E)*-α,β-unsaturated and to amides, producing the desired reaction product with a high level of π-facial selectivity.[23] This methodology has been extended to the enantioselective synthesis of various β-amino acids and β-amino esters using lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, (*R*)-**C**, (Scheme 9).



Scheme 9. Enantioselective synthesis of β-amino esters and β-amino acids by addition of the chiral lithium amide (*R*)-**C**

The benzyl groups of amine **XI** can be easily removed by hydrogenolysis reaction and high enantiomeric excess is obtained in this addition, the added appeal for this methodology is that both enantiomeric forms (*R*) and (*S*) of the α-methylbenzylamine are available.

1.2.2 Origin of the selectivity of the Michael addition of (*R*)-C:

To understand the origin of the high stereoselectivity in the conjugate addition of lithium amides a study was conducted using as a model reaction the addition of lithium (*R*)-*N*-benzyl-*N*-α-

[21] (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem*. **1986**, *51*, 2820-2822. (b) Rudolf, K.; Hawkins, J. M.; Loncharich, R. J.; Houk, K. N. *J.Org. Chem.* **1988**, *53*, 3879-3882.

[22] Hawkins, J. M.; Lewis, T. A. *J. Org. Chem*. **1992**, *57*, 2114-2121.

[23] (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry*, **1991**, *2*, 183-186. (b) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun*. **1993**, 1154. (c) Davies, S. G.; Bull, S. D.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett*, **2000**, *9*, 1257-1260. (d) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Organic & Biomolecular Chemistry.* **2008**, *6*, *9*, 1655-1664. (e) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernandez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Organic & Biomolecular Chemistry*. **2008**, *6* (9), 1665-1673.(f) Davies, S. G.; Smith, A. D.; Price,P. D. *Tetrahedrom: Asymmetry,* **2005,** *16*, 2833-2891.

methylbenzylamide, (*R*)-**C**, to *tert*-butyl cinnamate,[24] the molecular modeling package Chem-X was used to calculate the energies of its transition states. Figure 2 shows a transition state consistent with the selectivity observed in these chiral reagents.

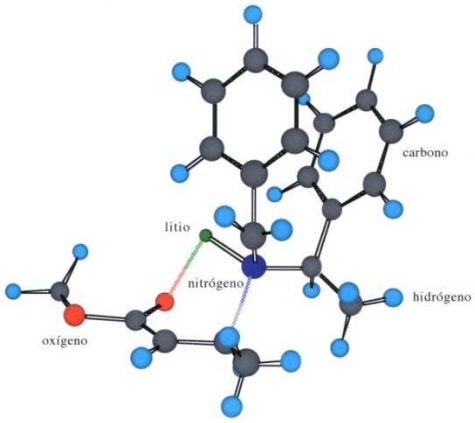


Figure 2. Modelization of a transition state for the Michael addition reaction

The determinant factors of this transition state are:

- Chelation of the lithium with the oxygen from the carbonyl group thus promoting the reaction only through the s-*cis* conformation of the enolate.[24(b)]
- Adoption of the "butterfly conformation" by the benzyl groups, with the planes of the aromatic rings approximately parallel, due to steric reasons and π interactions of the aromatic electron clouds.
- The methyl group in α position is located in an available position which presents less steric congestion.

The postulate on the chelating directing the addition is in agreement with the observation that the lactone **XIII** which cannot adopt the s-*cis* conformation does not lead to the conjugate adduct and the dienoate **XIV** only produces addition type 1,4 and 1,6 (Figure 3). This factor has allowed to exploit their synthetic utility. Then, it seems that the geometry (*E*) to the ester α,β-unsaturated is necessary for this type of conjugate additions[25] and consistent with the experimental observation where acceptors which adopt the s-*trans* conformation takes place only addition type 1,2 or γ-deprotonation.[26]

[24] (a) Davies, S. G.; Costello, J. F.; Ichihara, O. *Tetrahedron: Asymmetry*, **1994**, *5*, 1999-2008. (b) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833-2891.
[25] O'Brien, P. *J. Chem. Soc., Perkin Trans 1*, **2001**, 95-113
[26] Ichihara, O. D. Ph. D. *Thesis*, Oxford, **1995**.

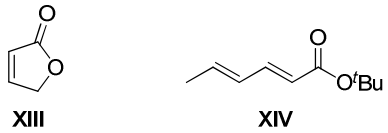
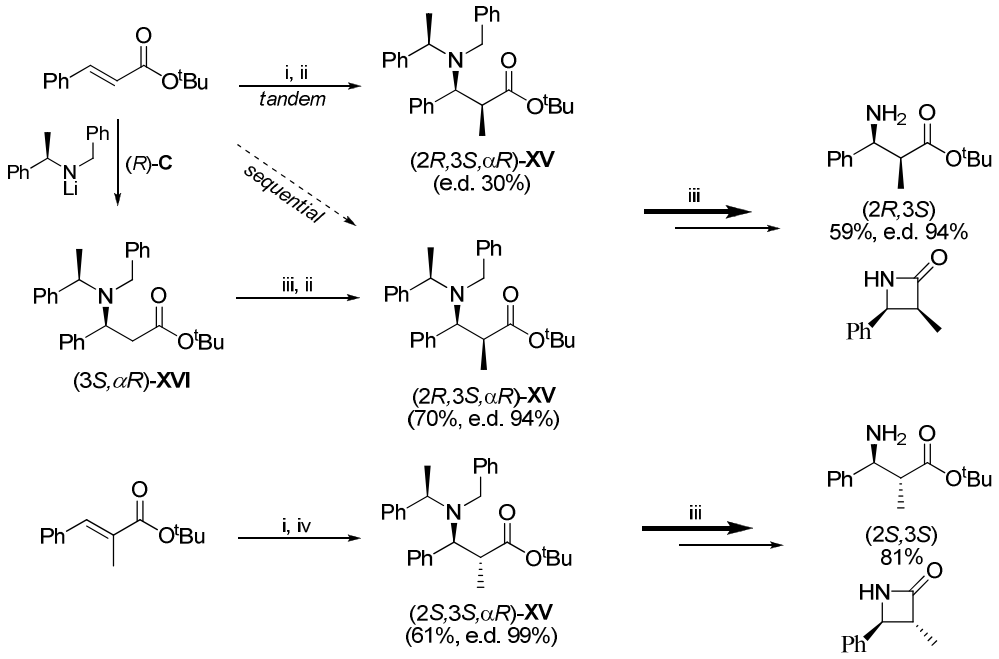


Figure 3.

1.3 SELECTIVITY IN THE MICHAEL ADDITION OF (*R*)-C AND SUBSEQUENT PROTONATION OR ALKYLATION:

1.3.1 *Tandem* and *sequential* reactions:

Once the stereochemistry of the β-centre is controlled, it is very desirable to establish the α-centre by an alkylation reaction or protonation (if already exist the alkyl group), this methodology has been carried out efficiently by Davies, as shown in Scheme 10 and allows fully enantioselective synthesis of the four possible diastereoisomers of the α-methyl-β-phenylalanine and related β-lactams.[27]

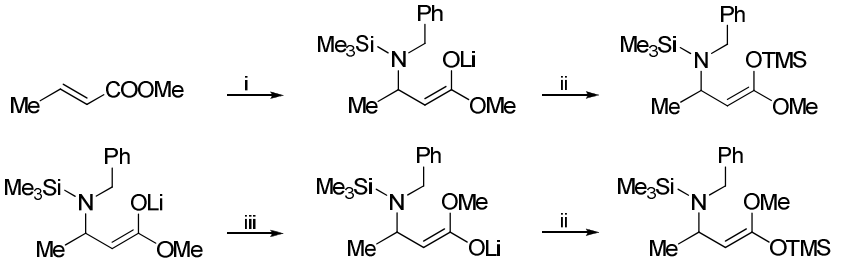


Scheme 10. *Reagents and conditions*: (i) (*R*)-**C**, Toluene. (ii) MeI. (iii) LDA. (iv) 2,6-di-*tert*-butylphenol, THF.

To obtain the same diastereoisomer (2*R*,3*S*,α*R*)-**XV** the diastereoselectivity is very different if the reaction is done in one step (*tandem*) from *tert*-butyl cinnamate or previously isolating the Michael addition adduct (3*S*,α*R*)- **XVI** and perform subsequent alkylation of the enolate derivative, where the d.e. obtained is 94%.

[27] Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun*. **1993**, 1153-1155.

Yamamoto *et al.*[28] in their publication entitled "Stereodivergent synthesis of the enolates of a β-amino ester by using lithium *N*-benzyltrimethylsilyl amide" show how the selectivity of the reaction depends upon the mode of the enolate`s preparation, either performing a *tandem* process or *sequential*. In the *tandem* procedure, the addition to the intermediate formed by adding the amide to the acceptor takes place in situ without isolation of the intermediate adduct, while the *sequential* or *stepwise* procedure prior to the addition, the adduct intermediate is isolated and the enolate is regenerated with LDA. It has been shown the different geometry adopted by enolates (*Z* in *tandem* and *E* in *sequential*) which were trapped by addition of trimethylsilyl chloride and studied by NOE experiments (Scheme 11).



Scheme 11. *Reagents and conditions*: (i) LSA, -78°C. (ii) Me_3SiCl. (iii) LDA, -78°C

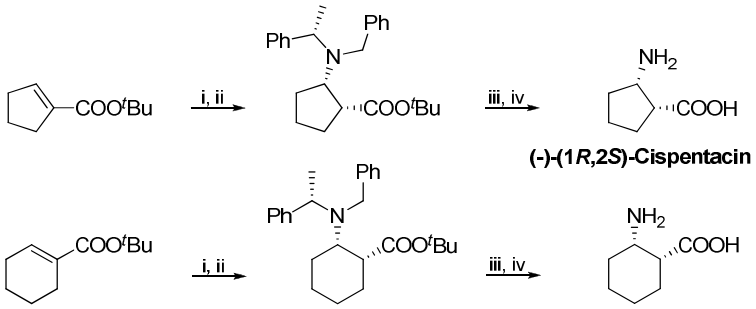
The *E* selectivity generated in this step process is explained by the deprotonation model of Ireland, which assumes that the reaction proceeds through a cyclic transition state in a chair conformation.[29] In this case the face from the enolate where the amine with two bulky groups is less accessible for electrophile attacking and exerts greater facial discrimination than in the cyclic intermediate state which is generated in the *tandem* reaction.

1.4 APPLICATIONS OF THE CHIRAL LITHIUM AMIDE ADDITION:

1.4.1 Addition to cyclic systems:

The addition of lithium amides have also been conducted on ring systems as *tert*-butyl cyclopent-1-ene carboxylate and *tert*-butyl-cyclohex-1-ene carboxylate which lead to the enantioselective synthesis of *cis*-disubstituted cyclic systems and culminate in the total asymmetric synthesis of (-)-(1*R*,2*S*)-Cispentacin and its cyclohexanic counterpart (Scheme 12).[30]

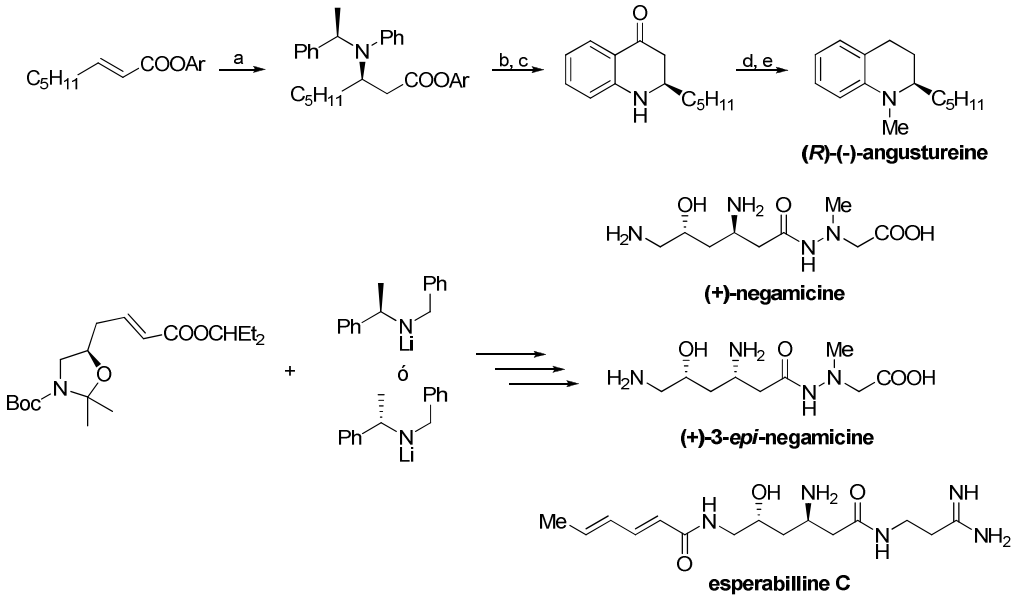
[28] Asao, N.; Uyehara, T. and Yamamoto Y. *Tetrahedron*, **1990**, *46*, 4563-4572.
[29] Ireland, R. E.; Mueller, R. H. and Willard A. K. *J Am. Chem. Soc.* **1976**, *98*, 2868-2877.
[30] (a) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett*, **1993**, 461-462. (b) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem Soc. Perkin Trans 1*, **1994**, 1411-1415.



Scheme 12. *Reagents and conditions*: (i) (*S*)-**C**, toluene. (ii) 2,6-di-*tert*-butilphenol, THF. (iii) H_2 (4 atm.), Pd/C. (iv) TFA/ Dowex 50X8-200.

1.4.2 Addition of chiral lithium amides in the synthesis of natural products:

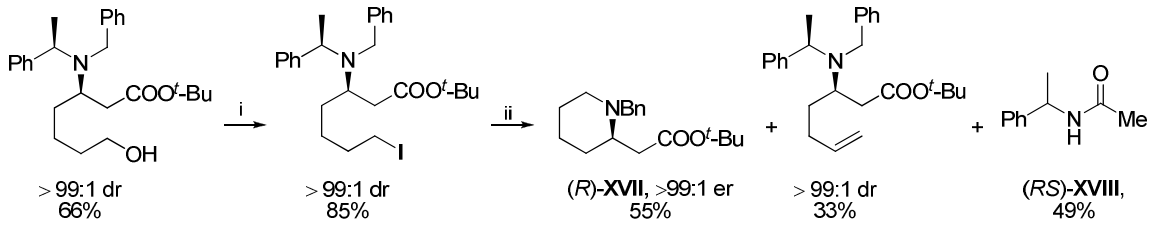
Recently, Davies *et al*. have used this methodology for the asymmetric synthesis of natural products such as the tetrahydroquinoline alkaloid (*R*)-(-)-angustureine[31] and the compounds (+)-negamicine, (+)-3-*epi*-negamicine and esperabilline C[32] as shown in scheme 13.



Scheme 13. *Reagents and conditions*: (a) (*R*)-**C**, THF, -78°C. (b) LiOH, THF/H_2O, 40°C. (c) PPA, 100°C. (d) $LiAlH_4$, THF, reflux. (e) MeI, K_2CO_3, THF, reflux.

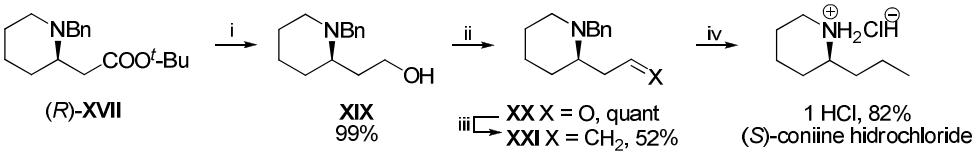
Recently, Davies *et al.*[33] have contributed to the asymmetric synthesis of (*S*)-coniine and (*R*)-δ-coniceine through a conjugate addition of an enantiomeric pure amide to an ζ-hydroxy-α,β-unsaturated ester, followed by a one-pot ring- closing reaction and *N*-debenzylation.

[31] Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett*. **2011**, *13*, 2544-2547.
[32] Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216-227.



Scheme 14. *Reagents and conditions*: (i) PPh_3, imidazole, I_2, PhMe/MeCN (v/v 4:1), 65°C, 2 h. (ii) $AgBF_4$, MeCN, 80°C, 16 h.

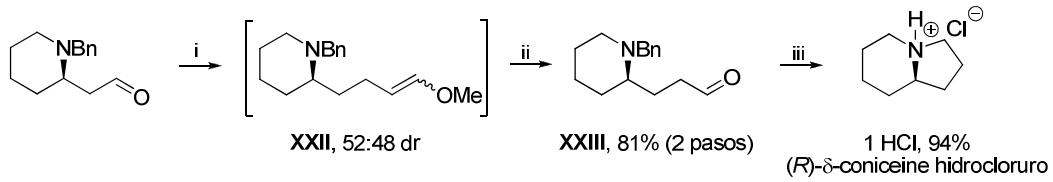
With the optimized methodology all the attention was focused on the synthesis of the Hemlock`s alkaloids (*S*)-coniine[34] y (*R*)-δ-coniceine.[35] As shown in the following scheme, the *tert*-butyl functionality was reduced to give the alcohol **XIX** which was subjected to a Wittig reaction to yield the homoallylic amine **XXI**. After performing a *tandem* reaction where hydrogenation and hydrogenolysis reactions took place and followed by treatment with HCl led to the hydrochloride of (*S*)-coniine with 82% yield.



Scheme 15. *Reagents and conditions*: (i) DIBAL-H, THF, 0°C-r.t. 6 h. (ii) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C-r.t. (iii) $[Ph_3PMe]^+[Br]^-$, KO^{t}Bu, THF, 0°C-r.t. 16 h. (iv) $Pd(OH)_2/C$ (20% wt), H_2 (1 atm), MeOH, r.t, 48 h., HCl.

For the synthesis of (*R*)-δ-coniceine (Scheme 16), it was necessary a chain extension in aldehyde **XXVII** through a Wittig reaction in the presence of triphenylphosphonium bromide to give the enol-ether as a ratio mixture 52:48 of geometric isomers **XXII**. The hydrolysis of this mixture gave the γ-amino aldehyde **XXIII** which by treatment under Pearlman`s Catalyst at 1 atm. of H_2 leads to the alkaloid which was isolated as its corresponding hydrochloride in 94% yield.

[33] Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975-9992.
[34] Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett*, **2000**, *2*, 155-158 and references cited therein.
[35] Panchgalle, S. P.; Bidwai, H. B.; Chavan, S. P.; Kalkote, U. R. *Tetrahedron: Asymmetry* **2010**, *21*, 2399-2401 and references cited therein.



Scheme 16. *Reagents and conditions*: (i) $[Ph_3PCH_2OMe]^+[Br]^-$, KO^tBu, THF, 0°C-r.t. 16 h. (ii) DCM/HCO_2H (v/v 4:1), r.t 16 h. (iii)) $Pd(OH)_2/C$ (20% wt), H_2 (1 atm.), MeOH, r.t, 48 h., HCl.

1.4.3 Recent applications:

One of the latest applications of the Michael addition of chiral lithium amides has been published by Davies` research group,[36] developing the first and most efficient asymmetric synthesis of (-)-(*S*,*S*)-homaline in 8 steps and 18% of overall yield. The family of alkaloids from the homalium gender (Figure 4) has been isolated from the leaves of an African species *Homalium* and *Homalium pronyense Guillaum* found them in the forest of New Caledonia. (-)-(*S*,*S*)-homaline is the only one from its family that presents symmetry and has been the target of several research groups, although there was no asymmetric synthesis been reported so far.

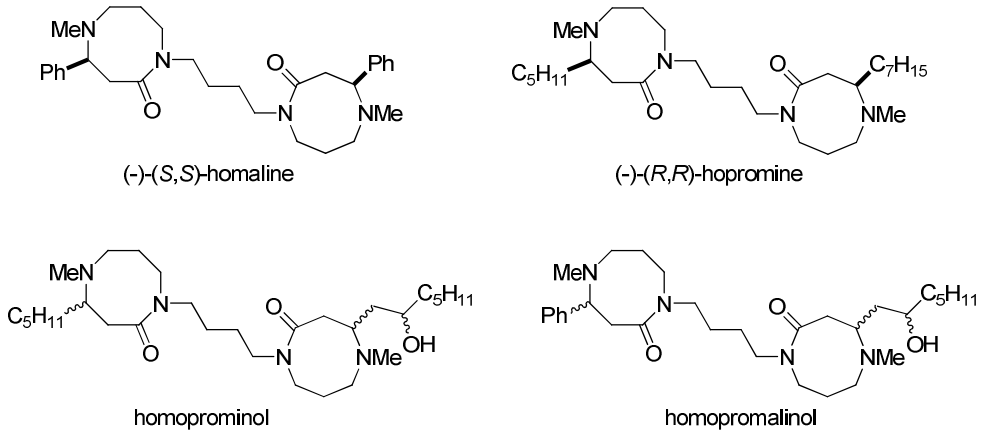


Figure 4. Alkaloids` family from the gender *homalium*

1.5 β-AMINO ACIDS:

The efficient synthesis of β-amino acids is of great importance since many kind of natural products contain fragments derived from this family as terpenes, alkaloids, peptides, β-lactams, antibiotics, etc. Some enantiomeric pure β-amino acids have been made available *via* manipulation of the

[36] Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *Tetrahedron Letters*, **2012**, *53*, 1119-1121.

"Chiral pool".[37] While approaches to their asymmetric synthesis has been focused on the use of chiral auxiliaries providing homochiral enolates and homochiral α,β-unsaturated acids to perform addition of imines[38] and Michael additions,[39] respectively. For example, derivatives of β-phenylalanine which was synthesized by Davies *et al*. in 1993 by addition of chiral lithium amides to *tert*-butyl cinnamate[40] are constituents of several natural origin taxane alkaloids and pseudopeptides as andrimide (Figure 5),[41] which exhibit antibiotic activity and has been investigated for several groups.[42]

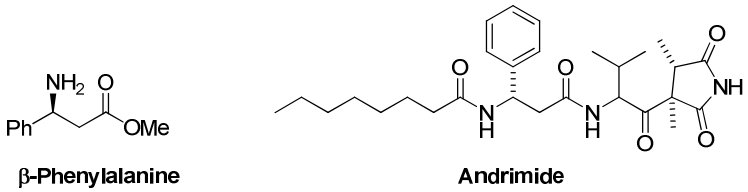


Figure 5. β-amino acids as alkaloids constituents

Among this β-amino acids group, are also α-hydroxy-β-amino acids which constitute an important group of amino acids which are present in several enzyme peptides inhibitors such as bestatin, amastatin and pepstatin.

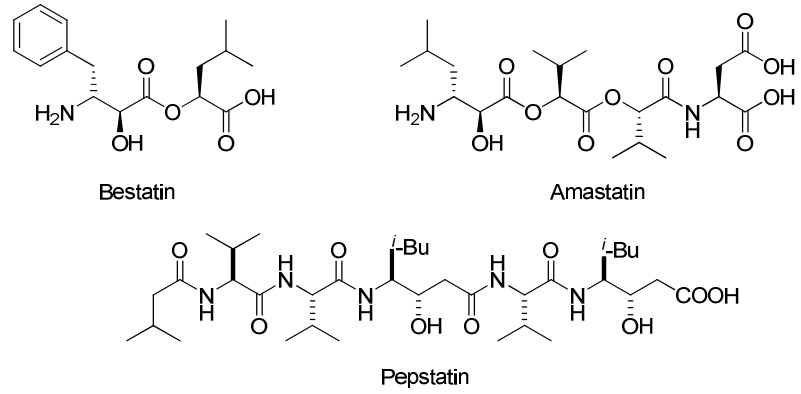


Figure 6. Examples of de α-hydroxy- β-amino acids with biological activity

[37] (a) Baldwin, J. E.; Adlington, R. M.; O`Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *Chem. Comm*., **1989**, 1852-1854.
[38] (a) Broadley, K.; Davies, S. G. *Tetrahedron Letters*, **1984**, *25*, 1743-1744. (b) Liebeskind, L. S.; Welker, M-E.; Fengl, R. W. *J. Am. Chem. Soc*. **1986**, *108*, 6328-6343.
[39] D`Angelo, J.; Maddaluno J., *J. Am. Chem. Soc*., **1986**, *108*, 8112-8114.
[40] (a) Graf, E. and Boeddeker, H. *Ann. Chem*. **1958**, *613*, 111-120. (b) Graf, E.; Weinandy, S.; Koch, B.; Breitmaier, E. *Liebigs Ann. Chem*. **1986**, *7*, 1147-1151.
[41] Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc*. **1987**, *109*, 4409-4411.
[42] (a) McWhorter, W.; Fredenhagen, A.; Nakanishi, K.; Komura, H. *J. Chem. Soc., Chem. Commun.* **1989**, 299-301. (b) Needham, J.; Kelly, M. T.; Ishige, M.; Andersen, R. J. *J. Org. Chem*. **1994**, *59*, 2058-2063.

1.5.1 Cyclic β-amino acids:

In 1989 two independent groups isolated and effective antifungal antibiotic, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid known as Cispentacin (Figure 7).[43] From that moment the interest for these kind of cyclic β-amino acids has increased, appearing new compounds such as 2-aminocyclohexenecarboxylic acid or (1*R*,2*S*)-2-amino-4-methylencyclopentanecarboxylic acid (BAY 10-8888), both with antifungal activity.[44]

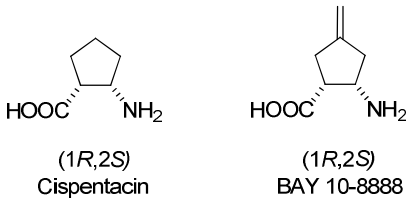


Figure 7. Examples of cyclic β-amino acids (β-CAA)

More recently, studies with β-CAA have focused primarily on the value that they present in the synthesis of β-peptides, which is particularly attractive to help to expand our understanding of the protein structure, its stability when folded and their use as non-biological polymers. As well as their α-peptides counterparts which contain amide bonds capable of forming bonds as stabilizing intramolecular hydrogen bonds. Moreover, due to its structural rigidity, appears as useful tools for building conformationally controlled peptides. The first incorporation of β-peptides CAA was described in 1991 by Goodman *et al*.[45]

Several years later, Gellman *et al*. had described very stable β-peptides foldamers[46] with a great tendency to adopt specific compact conformations[47] where the term "compact" refers to the tertiary structure of the proteins, among these we can find those ones which incorporate the *trans*-pentacin unit and cyclohexanic homologous which fold in water and can facilitate the design of β-peptides with appropriate substituents in the cycle for biological applications due to their stabilization in the

[43] (a) Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J Antibiot.* **1989**, *42*, 1749. (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J Antibiot.* **1989**, *42*, 1756-1762. (c) Iwamoto, T.; Tsujii, E.; Ezaki, M. *J Antibiot.* **1990**, *43*, 1-7. (d) Kawabata, K.; Inamoto, Y.; Sakane, K. *J Antibiot.* **1990**, *43*, 513-518.
[44] (a) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859-1876. (b) Kunisch, F.; Babczinski, P.; Arlt, D.; Plempel, M. Ger. Offen. DE 4028046 A1. *Chem. Abstr.* **1992**, *117*, 20486.
[45] (a) Yamazaki, T.; Zhu, Y-F.; Probstl, A.; Chadha, R. K.; Goodman, M. *J. Org. Chem.* **1991**, *56*, 6644-6655. (b) Yamazaki, T.; Probstl, A.; Schiller, P. W.; Goodman, M. *Int. J. Pept*ide *Protein Res.* **1991**, *37*, 364.
[46] (a) Gellman, S. H.; Compton, T. *J. Biol. Chem*. **2006**, *281*, 2661-2667.(b) Gellman, S. H. *Acc. Chem. Res.* **1998**, 31, 173-180. (c) Appella, D. H.; Christianson, L. A.; Gellman, S. H. *Nature* **1997**, 387, 381.
[47] Price, J. L.; Horne, W. S.; Gellman, S. H. *J. Am. Chem. Soc*. **2010**, *132*, 12378-12387.

enzymatic hydrolysis, for this reason make them important candidates for development of new drugs (Figure 8).[48]

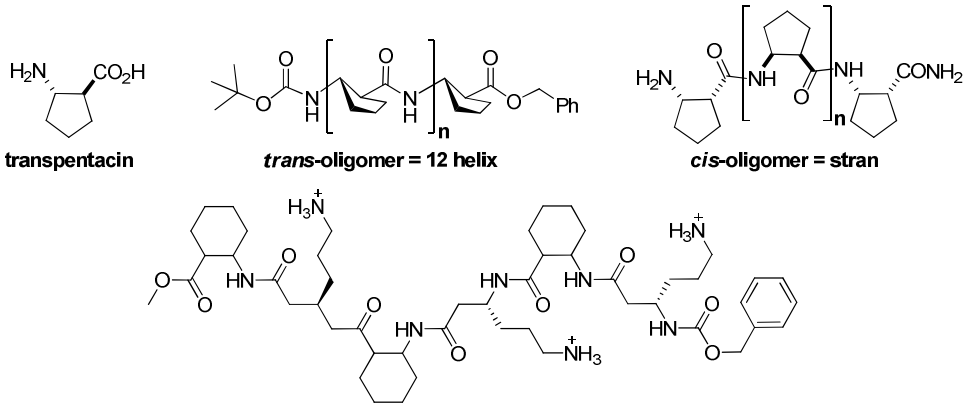


Figure 8. Examples of β-peptides foldamers

In addition, the insertion of polar groups that increase the solubility in water (Figure.9).[49]

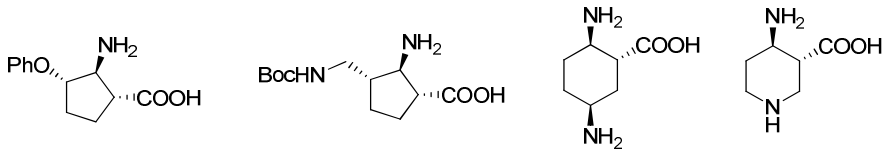
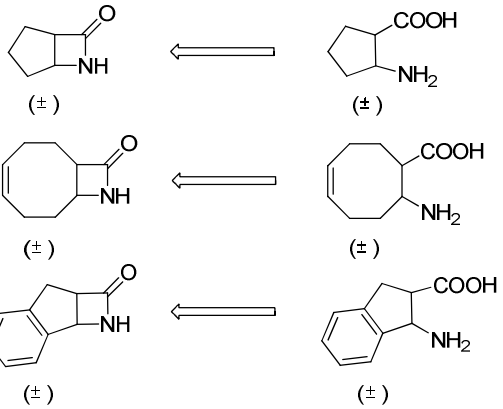


Figure 9. Polyfunctional β-CAA

1.5.2 Cyclooctanic β-amino acids:

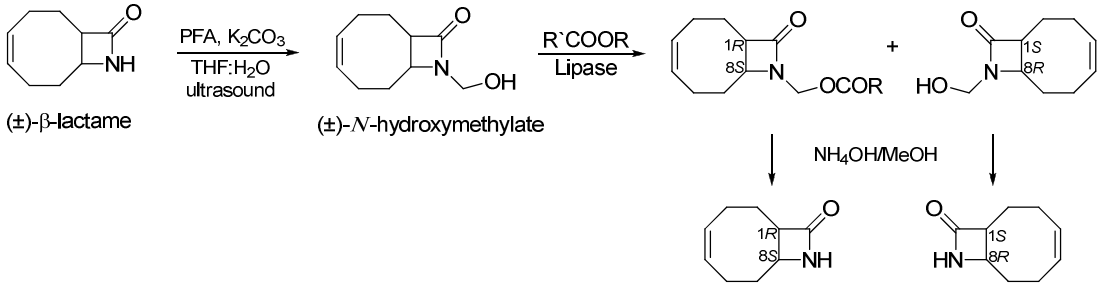
Recently, Fülöp *et al.*[50] had published the asymmetric synthesis of β-cyclic amino acids incorporating 5 to 8 carbons through the catalytic lipase B from *Candida Antarctica*, which act enantioselectivity in the ring-opening of inactive alicyclic β-lactams in organic media (Scheme 17). The obtained β-amino acids have been incorporated into various oligomers, as a route to offer a wide range of β-peptides and contribute to the growth of conformational peptides libraries.[51]

[48] (a) Woll, M. G.; Fisk, J. D.; LePlae, P. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12447-12452. (b) Wang, X.; Espinosa, J.; Gellman, S.; *J. Am. Chem. Soc.* **2000**, *122*, 4821.
[49] Arvidsson, P. I.; Rueping, M.; Seebach, D. *Chem. Commun*. **2001**, 649-650.
[50] (a) Forró, E.; Fülöp, F. *Org. Lett*. **2003**, *5*, 1209-1212; (b) Forró, E.; Árva, J.; Fülöp, F. *Tetrahedron: Asymmetry* **2001**, *12*, 643-649.
[51] Fülöp, F.; Forró, E.; Tóth, G. K., *Org. Lett*. **2004**, *6*, 4239-4241.



Scheme 17. Synthesis of β-CAA from 5 to 8 carbons

From the previous cyclooctane-(±)-β-lactam, Fülöp *et al*. has prepared its derivative *N*-hydroxymethyl which through a lipase-catalyzed asymmetric acylation of the primary alcohol present in the stereogenic center (*S*) led to the production of the ester and alcohol enantiomerically enriched (ee ≥92%). Treatment of these two compounds previously isolated with NH_4OH/MeOH led to the formation of the corresponding β-lactams (1*R*,8*S*) and (1*S*,8*R*) (ee ≥93%) which are important intermediates in the synthesis of Anatoxin-a (Scheme 18).[52]



Scheme 18. Synthesis of potential derivatives in the synthesis of Anatoxin-a

Kaushik *et al*.[53] have reported the synthesis of cyclooctanic β-amino acids (Figure 10) incorporated in peptide chains where compounds **XXIV** and **XXV** exhibit antimalarial activity (IC50 = 3.87 and 3.64 μg/mL, respectively).

[52] Forró, E.; Árva, J.; Fülöp, F. *Tetrahedron: Asymmetry*, **2001**, *12*, 643-649.
[53] Sathe, M.; Thavaselvam, D.; Srivastava, A. K.; Kaushik, M. P. *Molecules* **2008**, *13*, 432-443.

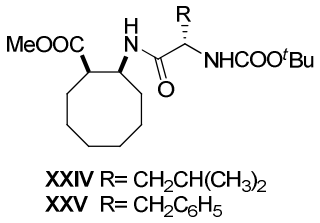


Figure 10. Examples of Cyclooctanic β-amino acids

1.5.3 Synthesis of functionalized cyclooctanic β-amino acids:

Among these ones, the synthesis of cyclic hydroxy β-amino acids (Figure 10) play an important role in the medicinal chemistry field as they are present in many essential products such as Paclitaxel (Taxol ®) and its synthetic derivative Docetaxel (Taxotere ®) which have significant effects on chemotherapy.[54] In this field, Fülöp *et al*. have recently reported the asymmetric synthesis of 2-aminocyclooctanecarboxylic acids mono- and di-hydroxy-substituted **XXVI** and **XXVII** (Figure 11).[55]

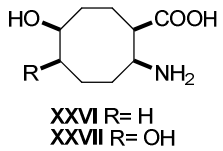


Figure 11. Polyfunctionalized β-amino acids

[54] (a) Wust, P. G. M.; Gu, R. L.; Northuis, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2117-3123. (b) Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115-5121. (c) Nicolaou, K. C. *Tetrahedron* **2003**, *59*, 6683-6738.

[55] Palkó, M.; Benedek, G.; Forró, E.; Wéber, E.; Hänninen, M.; Sillanpää, R.; Fülöp, F. *Tetrahedron: Asymmetry* **2010**, *21*, 957-961.

1.6 APPLICATION OF β-AMINO ACIDS TO THE SYNTHESIS OF ALKALOIDS:

1.6.1 Tashiromine:

Tashiromine is part of the indolizidine alkaloids group (Figure 12).[56] This class of alkaloids has been extracted from various sources such as ants, poisonous frogs, fungi and plants. They exhibit different activities including phytotoxic, insecticidal, antibacterial, antifungal[57] and also neurological properties.[58]

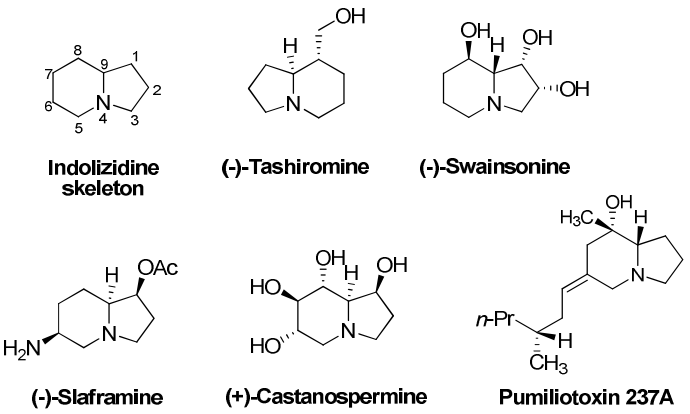


Figure 12. Indolizidine alkaloids

1.6.2 Anatoxin-*a*:

As it name says is a potent neurotoxin produced by certain types of blue-green alga, *Anabaena flos aquae* (figure 13),[59] which is responsible for several poisonings of wildlife in North America. This toxin is a potent agonist of the nicotinic acetylcholine receptor, **nAChR**, and is able to join it in the same way that acetylcholine does it by blocking the nervous system and causing death by respiratory arrest with an LD_{50} (intraperitoneal in mouse) of 0.2 mg/Kg.

[56] (a) Giomi, D.; Alfini, R.; Micoli, A.; Calamai, E.; Faggi, C.; Brandi, A. *J. Org. Chem*. **2011**, *76*, 9536-9541. (b) Michael, J. P. in "*The Alkaloids: Chemistry and Pharmacology*"; Cordell, G. A., Ed.; Academic Press: San Diego, **2001**; Vol. 55, p. 92. (c) Takahata, H.; Momose, T. in "*The Alkaloids: Chemistry and Pharmacology*"; Cordell, G. A., Ed.; Academic Press: San Diego, **1993**; Vol. 44, Chapter 3, p. 189. (d) Howard, A. S.; Michael, J. P. in "*The Alkaloids: Chemistry and Pharmacology*"; Brossi, A., Ed.; Academic Press: New York, **1986**; Vol. 28, Chapter 3. (e) Grundon, M. F. *Nat. Prod. Rep*. **1985**, *2*, 235-243.

[57] (a) Michael, J. P. *Nat. Prod. Rep*. **1997**, 21-41. (b) Michael, J. P. *Nat. Prod. Rep*. **1993**, 51-70. (c) Ohmiya, S.; Kubo, H.; Saito, K.; Murakoshi, I.; Otomasu, H. *Chem. Pharm. Bull*. **1991**, *39*, 1123-1125.

[58] Daly, J. W.; Spande, T. F. In "*Alkaloids: Chemical and Biological Perspectives*"; Pelletier, S. W., Ed.; Wiley: New York, **1986**; Vol. 4, Chapter 1, p.1.

[59] (a) Carmichael, W. W.; Biggs, D.F. and Gorham, P.R. *Science*, Washington, D.C. **1975**, *187*, 542-544. (b) Carmichael, W. W.; Biggs, D. F. *Can. J. Zool*. **1987**, *56*, 520

Acetylcholine deficiencies are implicated in neuronal pathologies such as Alzheimer, so the asymmetric synthesis of analogues of Anatoxin-*a* with less toxic level are of great interest for their possible application in the treatment of these neuronal disorders.

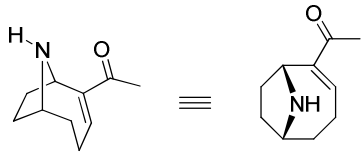
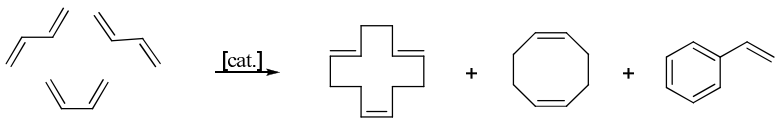


Figure 13. Anatoxin-*a*

The synthesis of Tashiromine and Anatoxin-*a* have been the target by several research groups as in this work, where we made a study and approach to their synthesis using cycloocta-1,5-diene as starting material.

1.7 CYCLOOCTA-1,5-DIENE:

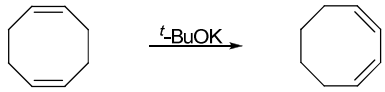
Cycloocta-1,5-diene is an inexpensive commercial product which is used in this study as a precursor of unsaturated cyclic esters to use them as a Michael acceptors. Its low cost is because it is a by-product in the process of obtaining *trans,trans,cis*-cyclododeca-1,5,9-triene by trimerization of butadiene catalyzed by Ni^0, Cr or $TiCl_4$-$Al(C_2H_5)Cl_2$-$Al(C_2H_5)$ complexes (Scheme 19). Shell business group has facilities depending on the catalyst to produce cycloocta-1,5-diene or *trans,trans,cis*-1,5,9-triene.[60]



Scheme 19. Obtaining cycloocta-1,5-diene.

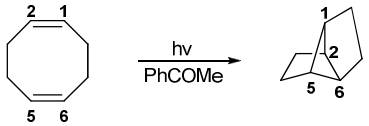
Its reactivity is very peculiar, highlighting the trend in basic medium to the conjugation of its double bonds due to the higher thermodynamic stability of the latter one, as shown in the following scheme.[61]

[60] Weissermel, K.; Arpe, H. J. "*Industrial Organic Chemistry*", 2nd ed., VCH, Weinheim, **1993**.
[61] (a) Huber, A. J.; Reimlinger, H. *Synthesis* **1969**, 97-112. (b) Huber, A. J.; Reimlinger, H. *Synthesis* **1970**, 405-430.



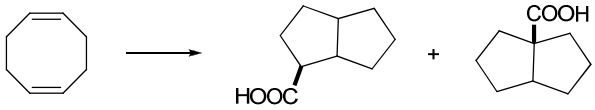
Scheme 20. Reactivity of cycloocta-1,5-diene in basic media

Also, it can exhibit photochemical reactions showing as a result an intramolecular cyclization 2+2.[62]



Scheme 21. Intramolecular cyclization 2+2 of the cycloocta-1,5-diene.

Besides, transannular cyclization which can be carried out by a variety of electrophiles, such $HF/H_2O/CO$ or HCO_2/H_2SO_4, leads to a high range of bicycles [3.3.0] octane, which has found a valuable application in organic synthesis.[63]



Scheme 22. Transannular cyclization of cycloocta-1,5-diene.

[62] Coyle, J. D. *Chem. Soc. Rev*., **1974**, *3*, 329-353.
[63] (a) Hanack, M. and Kaiser, W. *Angew. Chem*., **1964**, *76*, 572. (b) Paquete, L. A. *Top. Curr. Chem*., **1984**, *119*, 1.

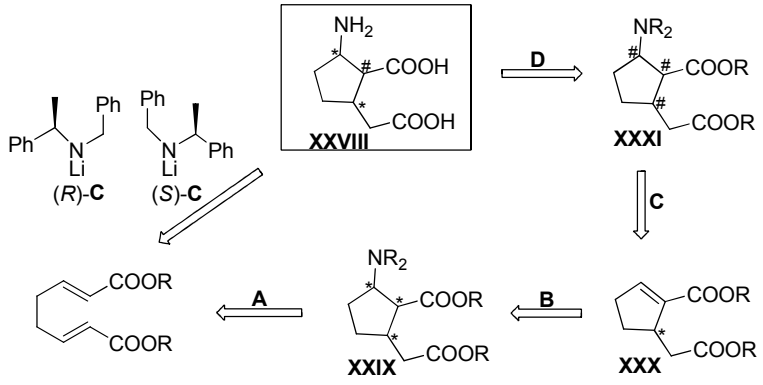
BACKGROUND

2. BACKGROUND:

In previous works we have began to study the methodology and application of the reactivity of di-unsaturated di-esters with chiral lithium amides.[64] By addition of lithium amides such as (*R*)-**C** and (*S*)-**C** to di-unsaturated esters has succeeded in obtaining mono-addition, di-addition or cyclic products, depending on the used conditions or the employed esters.[65]

By an inter- or intramolecular domino addition of chiral lithium amides (*R*)-**C** and (*S*)-**C** to dimethyl octa- and nona-diendioate are obtained the corresponding cyclopentane[66] and cyclohexane derivatives, respectively, **XXIX** *trans*,*trans*-trisubstituted, with very good yield and excellent stereo and enantioselectivity. Furthermore, the cyclic products with a different stereochemistry sequence (*trans*,*cis*-trisubstituted) can be obtained from the mono-addition intermediate with the no-conjugated double bond by treatment with a base.

In the cyclic products, the elimination reactions of the nucleophile and new addition allows to achieve all the possible diastereoisomers in this system as indicated below. In this line, it has been reported the asymmetric synthesis of eight diastereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylic acid (**XXVIII**),[67] by using the strategy shown in the following retrosynthetic scheme.



Scheme 23. A: Stereoselective domino addition reaction inter- and intramolecular. **B**: Stereospecific elimination *syn*. **C**: Stereoselective conjugated addition. **D**: Deprotection

[64] (a) Sara Hernández Domínguez. *"Metodología de Aplicación de la Reactividad de Di-ésteres Di-insaturados con Amiduros de Litio Quirales"*. Tesis Doctoral. Salamanca, **2001**. (b) Garrido, N. M.; Díez, M.; Domínguez, S. H.; Sánchez, M. R.; García, M.; Urones, J. G. *Molecules.* **2006**, *11*, 435-443.

[65] Urones, J. G., Garrido, N. M., Díez, D., Domínguez, S. H., Davies, S. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1637-1641.

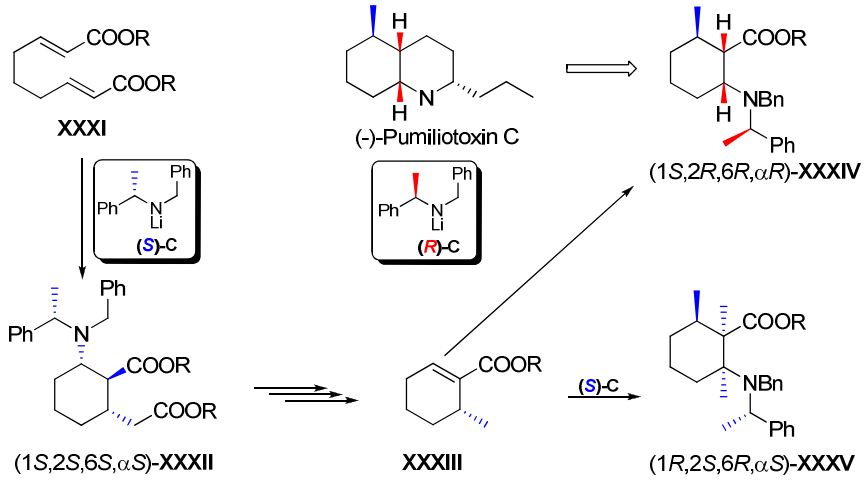
[66] Urones, J. G., Garrido, N. M., Díez, D., Domínguez, S. H., Davies, S. G. *Tetrahedron: Asymmetry* **1997**, *8*, 2683-2685.

[67] Urones, J. G., Garrido, N. M., Díez, D., El Hammoumi, M. H., Domínguez, S. H., Casaseca, J. A., Davies, S. G., Smith, A. D., *Org. Biomol. Chem*., **2004**, *2*, 364-372 and references cited therein.

It is noteworthy that it was only used (*E*,*E*)-dimethyl-octa-2,6-diendioate as a prochiral precursor and the addition strategies to produce the cyclic intermediates (**XXIX)**, Cope`s elimination (**XXX**) and re-addition (**XXXI**) together with the complementarity of the lithium amides (*R*)-**C** and (*S*)-**C** allows the synthesis of the eight optically pure diastereoisomers.

In the same way, it has also initiated the study of the reactions that allow the stereochemical control in the cyclohexane rings. [68]

As it has been indicated, by addition of lithium *N*-benzyl-*N*-α-methylbenzylamide (*S*)-**C** to (*E*,*E*)-nona-2,6-diendioate **XXXI** is obtained stereoselectivity **XXXII** with full control of the three new formed stereogenic centers.

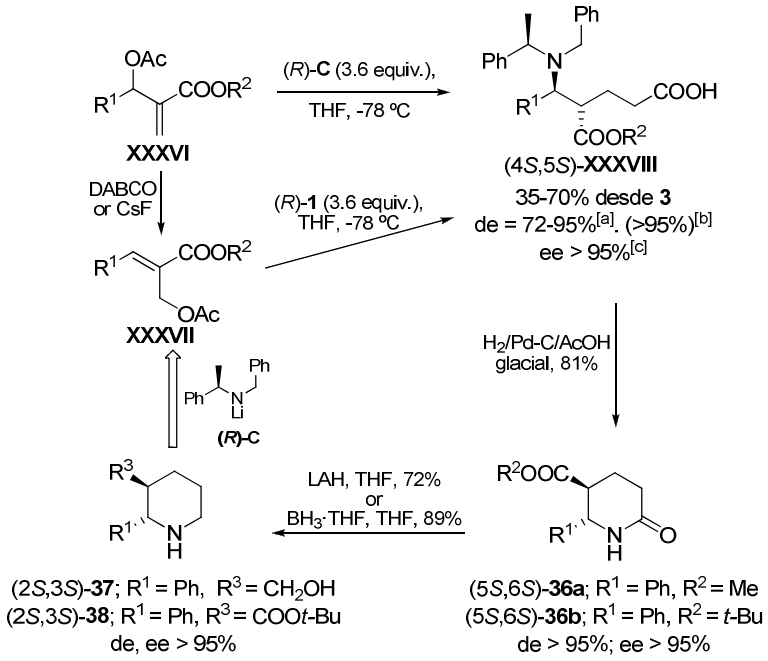


Scheme 24. Asymmetric synthesis of (1*S*,2*R*,6*R*,α*R*)-**XXXIV** as a intermediate in the synthesis of (-)-Pumiliotoxin-C.

The above scheme describes the methodology used in the asymmetric synthesis of the cyclohexane system *cis*,*cis*- and *cis*,*trans*-trisubstituted by a combined strategy initiated by the asymmetric domino Michael addition reaction of (*S*)- and/or (*R*)-**C** and subsequent 6-exo-trigonal cyclization, Cope`s elimination, selective hydrolysis and removal of the generated acid by the Barton`s elimination.[69] Once the methyl with the desired stereochemistry in **XXXIII**, the new addition of (*R*)- and (*S*)-**C** is the key for the stereochemical control to give **XXXIV** or **XXXV**. Compounds **XXXIV** involves the formal synthesis of (-)-Pumiliotoxin C, having been already used in its total synthesis.[70]

[68] (a) Garrido, N. M.; Díez, D.; Domínguez, S. H.; García, M.; Sánchez, M. R.; Davies, S. G. *Tetrahedron: Asymmetry* **2006**, *17*, 2183-2186. (b) Davies, S. G.; Díez, D.; Domínguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, D. *Org. Biomol. Chem*. **2005**, *3*, 1284-1301.
[69] Barton, D. H. R.; Samadi, M. *Tetrahedron*, **1992**, *48*, 7083-7090.
[70] Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493-6502.

Recently, it was reported the synthesis of piperidines and nipecotic acid derivatives.[71] Thus, when 3-acetoxy-2-benzylidene-propanoate **XXXVII** is treated with the chiral lithium amide (*R*)-**C** is afforded stereoselectively (4*S*,5*S*,α*R*)-5-(*N*-benzyl-*N*-α-methylbenzylamino)-5-phenyl-4-metoxycarbonyl-pentanoic acid, being the result of a novel domino stereospecific reaction initiated by a rearrangement of Ireland-Claisen followed by an asymmetric Michael addition of the used amide as a single reagent in the reaction. This reaction can be generalized to different groups and can be scaled. It has been applied the described methodology to the total asymmetric synthesis of (+)-L-733.060[72] which is a potent antagonist of the receptor hNK1.



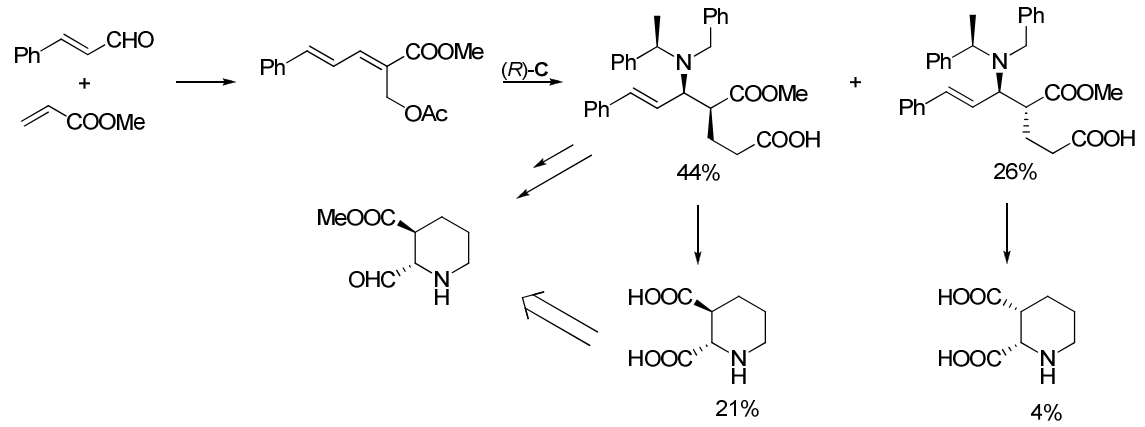
Scheme 25. Synthesis of piperidines and nipecotic acid derivatives

This methodology allows us to obtain cyclic β-amino acids with the nitrogen incorporated in the ring. Recently, it has been applied to the asymmetric synthesis of *cis*-(2*S*,3*R*)- and *trans*-(2*S*,3*S*)-piperidinedicarboxylic acids using domino allylic acetate and stereoselective Ireland-Claisen rearrangements and asymmetric Michael addition as key steps to obtain δ-aminoacids as shown in the following scheme and from which biological amino di-acids were synthesized in eight steps in 21% and 4% overall yields, respectively.[73]

[71] (a) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G., *Org. Lett.,* **2008**, *10* (9), 1687-1690. (b) Mercedes García García, *"Metodología y aplicación de la reactividad de aductos de Baylis-Hillman con amiduros de litio quirales"*. Tesis Doctoral, Salamanca, **2006**.

[72] Garrido, N.M.; García, M.; Sánchez, M. R.; Díez, D.; Urones, J. G. *Synlett*, **2010**, *3*, 387-390.

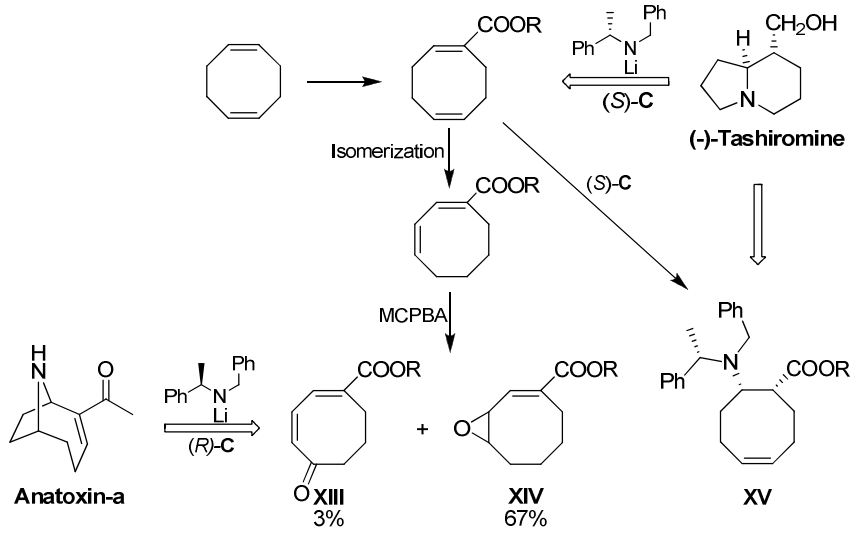
[73] Garrido, N. M.; Sánchez, M. R.; Díez, D.; Sanz, F.; Urones, J. G., *Tetrahedron: Asymmetry*, **2011**, *22*, 872-880.



Scheme 26. Synthesis of piperidinedicarboxylic acids

Taking into account the multifunctionality present in the obtention of formyl derivatives during the development of this synthetic route, further work is currently underway in our laboratory to develop different piperidine derivatives.

In our research group, at one time was thought to use a commercial available product as the cycloocta-1,5-diene to increase the diversity of the cyclic β-amino acids that have been reported. When we started to work with cycloocta-1,5-diene it could be observed that primary derivatives which were afforded were appropriated as a starting material in the synthetic approximation to natural products such as (-)-Tashiromine[74] and Anatoxin-*a*.[75]



Scheme 27. Retrosynthetic plan of the synthesis of (-)-Tashiromine and Anatoxin-a from cycloocta-1,5-diene.

[74] María Jesús Simón López, "*Reactividad de ciclooctadiencarboxilatos, aproximación a la síntesis de alcaloides (Tashiromina)*". Grado de Salamanca, **2001**.

[75] Imanol Fernández Cascón "*Estudio de la reactividad de ciclooctadiencarboxilatos. Aproximación a la síntesis asimétrica de Anatoxina-a*". Grado de Salamanca, **2006.**

As is shows the above scheme, the key step is the stereochemical control in the addition of the chiral lithium amides to the unsaturated cyclooctadiencarboxylates.

In this research work the main objective is the study of the reactivity of cyclooctadiencarboxylates and their applications in the asymmetric synthesis as is the synthesis of cyclooctanic β-amino acids to increase the diversity of the already obtained results and to carry on and contribute with to the approximation of Tashiromine and Anatoxin-a synthesis.

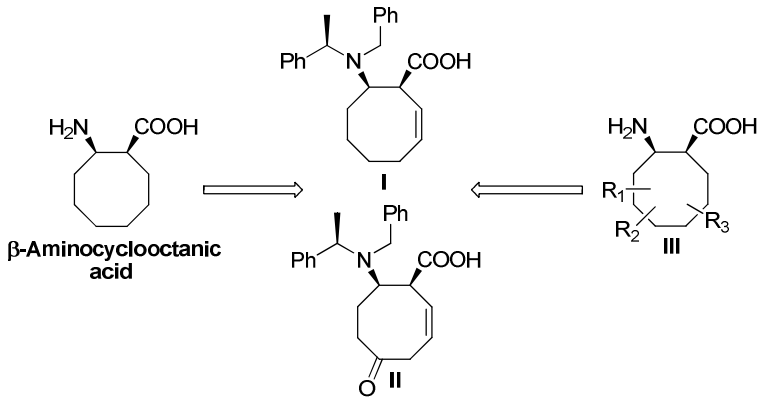
OBJECTIVES

OBJECTIVES:

Taking into account the progress that has been made in the study of the reactivity of cyclooctadienecarboxylates and its different applications in asymmetric synthesis through application of the Michael addition of chiral lithium amides methodology, in this work we want to carry on with the contribution to these different fields that have been studied and have been of interest in the research group:

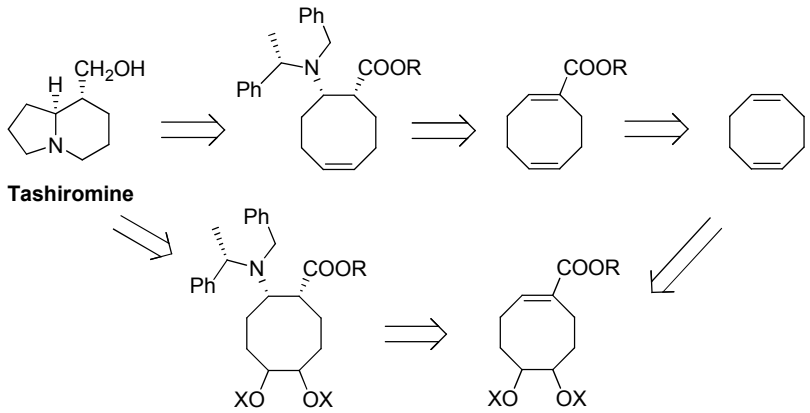
- Asymmetric synthesis of β-aminocyclooctane carboxylic acids.
- Approximation to the synthesis of Tashiromine.
- Study of the reactivity of (1*E*,3*Z*)-*tert*-butyl 5-oxocycloocta-1,3-dienecarboxylate, as a key adduct in the synthesis of Anatoxin-a.
- Approximation to the synthesis of Anatoxin-a.

Given the importance that the synthesis of β-amino acids with conformational rigidity for the formation of controlled shape oligomers has had in the recent years, we find interesting to study β-aminocyclooctane carboxylic acids as shown in the following scheme and derivatives such as **III**, wherein different substituents can be introduced into the cyclooctanic system and can modify both the tertiary structure and the solubility in water of the final β-peptide.



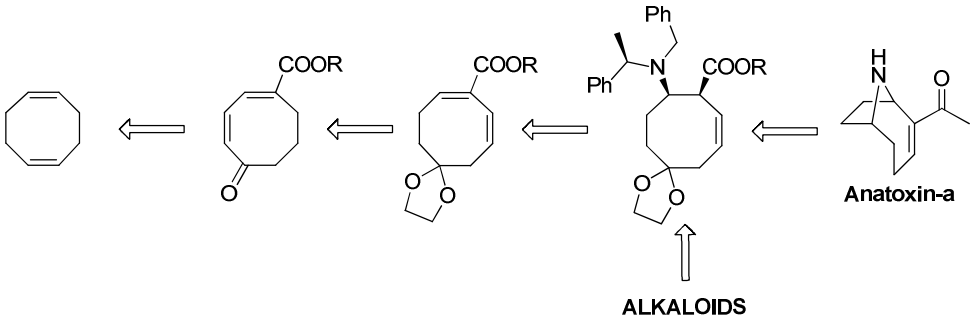
Scheme 28.

Due to the high potential of some found adducts during the course of the β-aminocyclooctane carboxylic acid synthesis to be used in the synthesis of alkaloids, there is concern regarding to the development of a synthesis aimed to obtain Tashiromine as part of the indolizidine alkaloids group, which can be afforded as stated in the following retrosynthetic scheme.



Scheme 29.

In search of a key adduct to the development of the synthetic route of Anatoxin-a, we get to the optimization of 5-oxo functionalized adduct, which required a detailed study and whose reactivity occupies a considerable part of this research work and the derivatives synthesized from this one can be possible precursors for the production of different types of alkaloids.



Scheme 30.

Specific Objectives:

1. Synthesis of starting materials:
   - Cyclooctadiene α,β-unsaturated esters additional functionalized as a Michael acceptors.
2. Study of the Michael addition reactions of chiral lithium amides to cyclooctane carboxylates mono- and di-unsaturated systems.
3. Asymmetric synthesis of β-aminocyclooctane carboxylic acid.
4. Study of the reactivity of (1*E*,3*Z*) *tert*-butyl 5-oxo-cycloocta-1,3-dienecarboxylate:
   a) Reactivity with chiral lithium amides.
   b) Reactivity with primary, secondary and tertiary amines.
   c) Reactivity with aniline.

5. Reactivity of *tert*-butyl and methyl 5,5-ethylenedioxycycloocta-1,7-diene-1-carboxylate in the approximation to the synthesis of Anatoxin-a.

6. Study of the reactivity and stereochemistry of the obtained adducts by:

a) Chemical transformation.

b) Spectroscopic analysis.

7. Mechanistic interpretation of the achieved products.

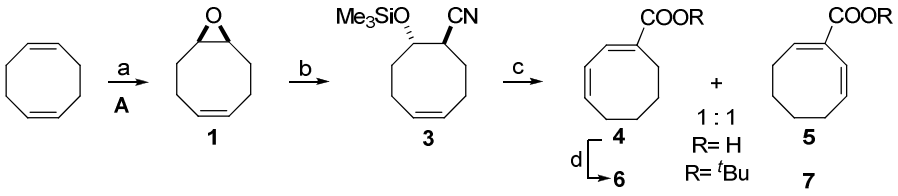
RESULTS AND DISCUSSION

PREPARATION OF STARTING MATERIALS:

Reactions of Cycloocta-1,5-diene and cyclooctene:

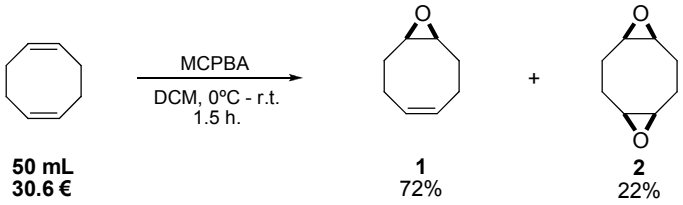
Preparation of di-unsaturated esters:

The synthesis of intermediates **6** and **7** were achieved using cycloocta-1,5-diene as starting material, which is commercially available, following route **A** (Scheme 31).



Scheme 31. *Reagents and conditions:* (a) MCPBA, DCM, 0°C-r.t, 72%. (b) Me_3SiCN/Et_2AlCl, 100%. (c) i: KOH/ ethylenglycol. ii: HCl aq, quant., 98% 1:1. (d) TFAA/^{t}BuOH, 80% (15% of the acid are recovered).

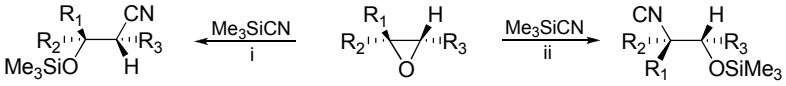
Treatment of cycloocta-1,5-diene with MCPBA for 90 min provided by vacuum fractional microdistillation: monoepoxide **1** with 72%, di-epoxide **2** with 22% and recovery of starting material 6%.



Scheme 32. Oxidation reaction of cycloocta-1,5-diene with MCPBA.

Under treatment with cyanotrimethylsilane using Et_2AlCl as catalyst, compound **1** was set to react and yielded regio and stereoselectively 2-trimethylsiloxy-cyclooct-5-enocarbonitrile **3** in 100% yield. The studies of Utimoto,[76] showed the effect of the catalyst in the regio and stereoselective opening of oxiranes using cyanotrimethylsilane and depending on the reaction conditions, it could be obtained isonitriles or nitriles due to the ambident character of the reagent, as it can be observed in Scheme 33.

[76] Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013-1016.



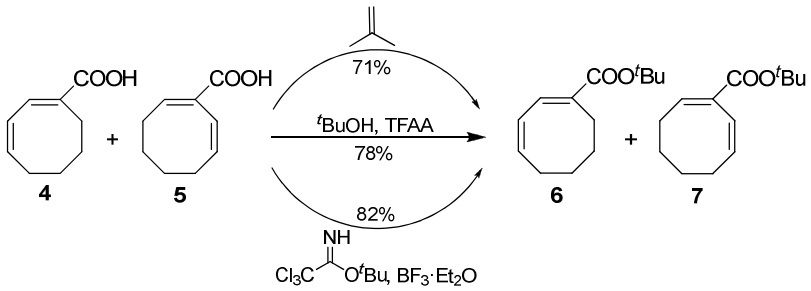
Scheme 33. *Reagents and conditions:* (i) $Al(O\textit{i}\text{-}Pr)_3$, $iBu_2AlO\textit{i}\text{-}Pr$, Et_2AlCl. (ii) $Pd(CN)_2$, $SnCl_2$, Me_3Ga

In previous studies conducted in our research group, different catalysts have been tested in the opening of monoepoxide **1** and in the presence of cyanotrimethylsilane, as $\textit{i}Bu_2AlO\textit{i}Pr$, $Al(OiPr)_3$ and Et_2AlCl. It was observed that in the reaction where Et_2AlCl was used as catalyst, this one was quantitative and regioselective affording compound **3** which presents the two substituents in *trans*-disposition as it showed the geminal proton-proton coupling (7.9 Hz) and the signal at 2241 cm^{-1} in its IR spectrum confirms the presence of the nitrile group.

By treatment of the nitrile **3** with KOH followed by HCl addition[77] it was obtained a 1:1 mixture of the acids **4** and **5** that could be resolved by column chromatography, but are best isolated by the CC at the ester stage.

It has been studied different methods to esterify the mixture of the acids **4** and **5** to optimize this step (Scheme 34). In all of them, it was obtained the unsaturated *tert*-butyl esters **6** and **7**, respectively, as a 1:1 mixture. The reaction in the presence of isobutylene was carried out in acid media at 78°C,[78] to afford the esters in 71% yield. The reaction with *tert*-butanol was set up at room temperature but the addition of TFAA and the alcohol was carried out at 0°C,[79] to afford the esters in 78% yield. On the other hand, the addition of *tert*-butyl trichloroacetimidate[80] in the presence of $BF_3.Et_2O$ leads to the same results with 82% yield. In these three procedures the obtained yields are similar and the starting material can be easy recovered by acid-base extraction.

[77] Prout, F. S.; Hartman, R. J.; Huang, E. P-Y.; Korpics, C. J.; Tichelaar, G. R. *Org. Synth. Coll*. **1963**, *4*, 93-98.
[78] (a) "Síntesis Asimétrica de β-aminoácidos ciclopentánicos vía Adición de Amiduros de Litio Quirales y Resolución Cinética Paralela". Mohamed Merouane El Hammoumi, *Tesis Doctoral* **2002**.(b) Garrido, N.M.; El Hammoumi, M.M.; Díez, D.; García, M. and Urones, J. G. *Molecules* **2004**, *9*, 373-382.
[79] (a) Greene, T. W.; Wuts, P. G. "*Protective Groups in Organic Synthesis*". Wiley-Interscience publication. **1998**, p. 373, 404-407, 506-507. (b) Kocienski, P. J. "*Protecting Groups*". Foundations of organic chemistry series. **1994**.
[80] (a) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Letters*, **1988**, *29*, 2483-2486. (b) Baldwin, J.E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron*, **1990**, *46*, 4733-4748.

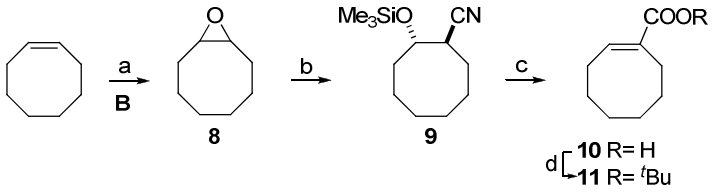


Scheme 34. Methods to esterify the mixture of the acids **4** and **5**.

In spite that the higher yield is obtained with *tert*-butyl trichloroacetimidate, the conditions that we chose as the best procedure were with TFAA and ^{t}BuOH because this reaction presents operational advantages and the recovery of starting material is easier and faster.

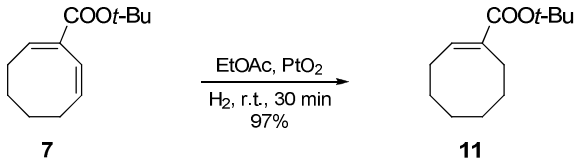
Preparation of monounsaturated esters:

Alternatively, starting with cyclooctene, route B (Scheme 35) and following the same path of reactions: epoxydation, opening of epoxide and hydrolysis we obtained compound **10** that by esterification led to the parent ester **11**. This route gave poor yield, especially in the opening of the epoxide even when we tried with different Lewis acid catalysts.



Scheme 35. *Reagents and conditions:* (a) MCPBA, DCM, 0°C-r.t, 100%. (b) Me_3SiCN/Et_2AlCl, 20%. (c) i: KOH/ ethylenglycol. ii: HCl aq, quant., 85% 1:1. (d) TFAA/^{t}BuOH, 80% (15% of the acid are recovered)

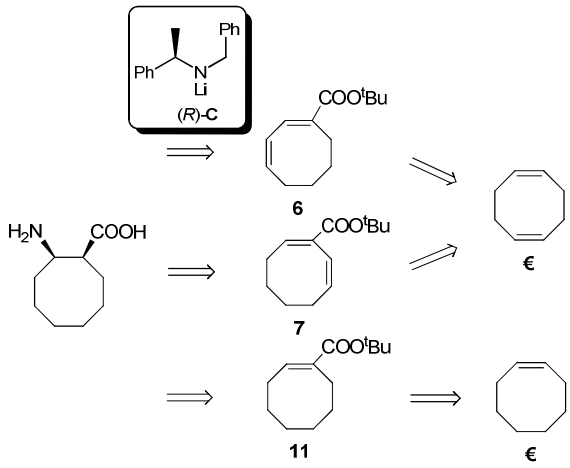
Nevertheless, hydrogenation of **6** and **7** separately, or as a mixture, gave compound **11** with excellent yield.



Scheme 36. Hydrogenation reaction conditions

ASYMMETRIC SYNTHESIS OF (1*S*,2*R*)-2-AMINOCYCLOOCTANECARBOXYLIC ACID:

With the *tert*-butyl cyclooct-1-ene carboxylates **6**, **7** and **11** in hand, we tried the protocol of asymmetric Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**C**, to obtain precursors adducts of the β-amino acid target molecule *via* different starting materials, in order to simplify and get the most efficient synthetic route (Scheme 37).



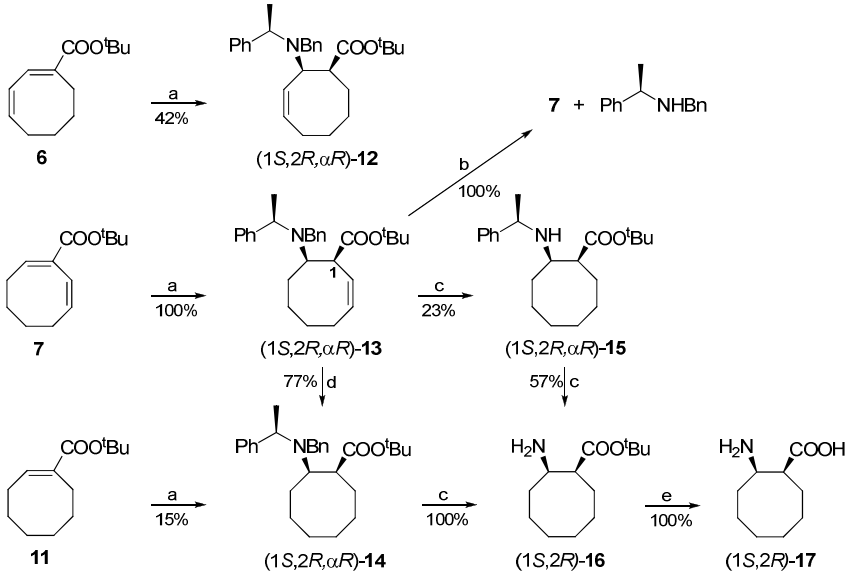
Scheme 37. Retrosynthetic analysis for the asymmetric synthesis of β-cyclooctanic amino acid

Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-C:

The methodology and procedure followed for the Michael addition of (*R*)-**C**, as previously mentioned, is that one introduced by Davies *et al.*[23(f)] who have recently published a comprehensive review in this area of chemistry covering the scope, limitations and synthetic applications of the use of enantiomerically pure lithium amides as homochiral ammonia equivalents in conjugate addition reactions.

As it can be observed in Scheme 38, the corresponding β-amino ester derivatives: (1*S*,2*R*,α*R*)-**12**, (1*S*,2*R*,α*R*)-**13** and (1*S*,2*R*,α*R*)-**14** were achieved stereoselectively, in 42%, 100% and 15% yields, respectively. Contrary to (1*S*,2*R*,α*R*)-**12** and (1*S*,2*R*,α*R*)-**14**, that were stable upon purification. However, chromatography on silica gel of the crude containing (1*S*,2*R*,α*R*)-**13** led to the required compound in 22% yield, which allowed its characterization, together with cycloocta-1,7-dienecarboxylate-**7** and (*R*)-*N*-benzyl-*N*-α-methylbenzylamine. Due to the instability of compound **13**, retro-Michael reaction of the latter leads back to **7** which is more stable on silica gel. To assess this reaction, a solution of (1*S*,2*R*,α*R*)-**13** with SiO_2 in DCM was stirred for 1 hour, and the retro-

Michael compounds **7** and (*R*)-*N*-benzyl-*N*-α-methylbenzylamine were obtained quantitatively. The higher acidity of H-C-1 within (1*S*,2*R*,α*R*)-**13** related to the other Michael adducts accounts for this behavior and could be used in synthetic targets.[81] Nevertheless, crude (1*S*,2*R*,α*R*)-**13** could be used for further reaction or purified by crystallization in a mixture of hexane and ether (Annexe **A**).



Scheme 38. Reagents and conditions: (a) lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**C**, THF, -78 ^{o}C, 2h. (b) SiO_2, DCM, quant. (c) Pd/C, H_2, AcOH, 4 atm, 24 h. (d) PtO_2, H_2, EtOAc, 3 h. (e) TFA, quant, 1.5 h, r.t.

The results obtained suggest a way to differentiate by reactivity the Michael acceptors **6** and **7** (Table 1). Interestingly, when a 1:1 mixture of **6** and **7** was subjected to reaction with (*R*)-**C** (1.6 equiv, Entry 4) over 30 min (1*S*,2*R*,α*R*)-**13** was obtained together with **6** and a minimum amount of (1*S*,2*R*,α*R*)-**12** that can be easily separated.

Table 1.

Entry	6 : 7	t (min)	(*R*)-C (eq.)	6 (%)	(1*S*,2*R*,α*R*)-12 (%)	(1*S*,2*R*,α*R*)-13 (%)
1	1 : 0	120	2.4		42	
2	0 : 1	120	2.4			100
3	1 : 3	120	2.4		10	60
4	1 : 1	30	1.6	26	2	49

The ^{1}H NMR spectrum of (1*S*,2*R*,α*R*)-**12** shows a NOE effect between H-C-1 and H-C-2 confirming a *cis* relationship (Fig. 14), which was anticipated by the established way of addition of lithium amide (*R*)-**C** and when the acceptor has and α-alkyl substituent, as applied by Davies *et al.* to the synthesis of cispentacin.[30]

[81] Garrido, N. M.; Díez, D.; Domínguez, S. H.; García, M.; Sánchez, M. R.; Davies, S. G. *Tetrahedron: Asymmetry,* **2006**, *17*, 2183-2186.

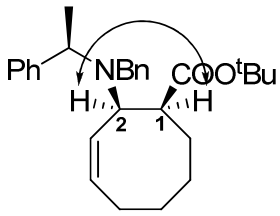


Figure 14. Nuclear Overhauser Effect correlations of compound **12**

The configuration of the newly formed stereogenic centre was confirmed to be (1*S*,2*R*) through single-crystal X-Ray structure analysis (Fig. 15), in the case of (1*S*,2*R*,α*R*)-**13** product,[82] and corroborated the stereochemistry of related compounds.

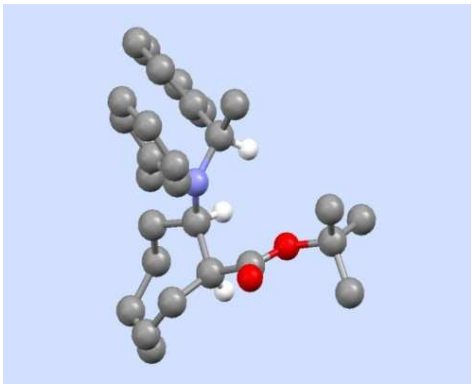
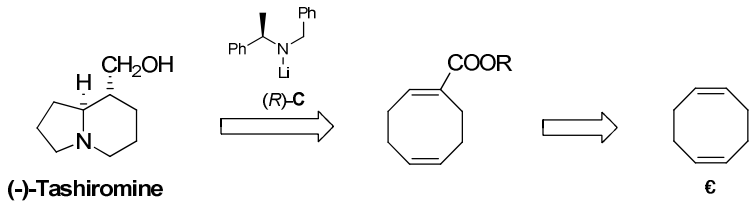


Figure 15. Representation of the molecular structure of (1*S*,2*R*,α*R*)-**13** obtained by X-Ray

As a background of this research, it was proposed initially that the structure of the di-unsaturated ester-**6** corresponded to the cycloocta-1,5-dienecarboxylate which led to formulate that this ester after the Michael addition will be a potential precursor in the asymmetric synthesis of tashiromine (Scheme39) and also to formulate a hypothesis to explain the different reactivity and yields obtained after the addition of the chiral lithium amide between **6** and **7**.[83]



Scheme 39. Retrosynthetic analysis of (-)-Tashiromine from cycloocta-1,5-dienecarboxylate

[82] Crystallographic data (excluding structure factors) for this structure has been deposited at the Cambridge Crystallographic Data Centre as supplementary material nº. CCDC 705369.
[83] Garrido, N. M.; Blanco, M.; Cascón, I. F.; Díez, D.; Vicente, V. M.; Sanz, F. and Urones, J. G. *Tetrahedron: Asymmetry* **2008**, *19*, 2895-2900.

Initial analysis of ^{1}H NMR spectrum of compound **6** suggested an almost symmetric structure for this compound. There are only two signals at downfield: 5.69 and 6.92 ppm and three signals at high field: 2.06, 2.33 and 1.43 ppm to be observed (Fig. 16), which agrees with a symmetric structure. On the other hand the ^{1}H NMR spectrum from compound **7** (Fig. 17) shows according to the Pascal`s triangle, which is normally introduced in the discussion of proton magnetic resonance, a triplet (*J* 8.0) for H-C-2 at 6.85 ppm, a doublet (*J* 11.2) for H-C-8 at 6.09 ppm and a doublet of triplets (*J* 11.2 and 7.2) for H-C-7 at 5.80 ppm.

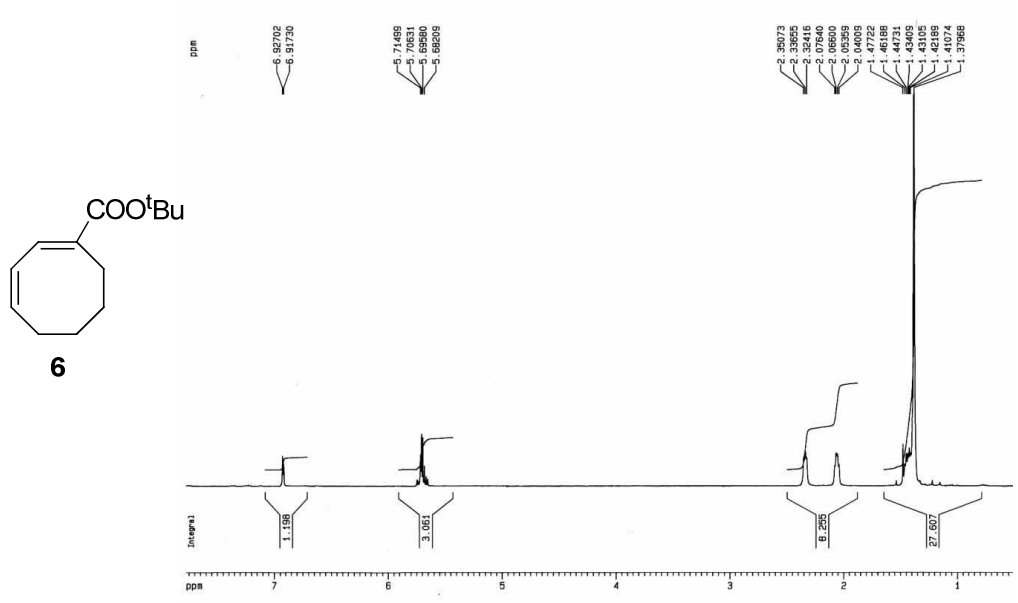


Figure 16. ^{1}H NMR spectrum of compound **6**

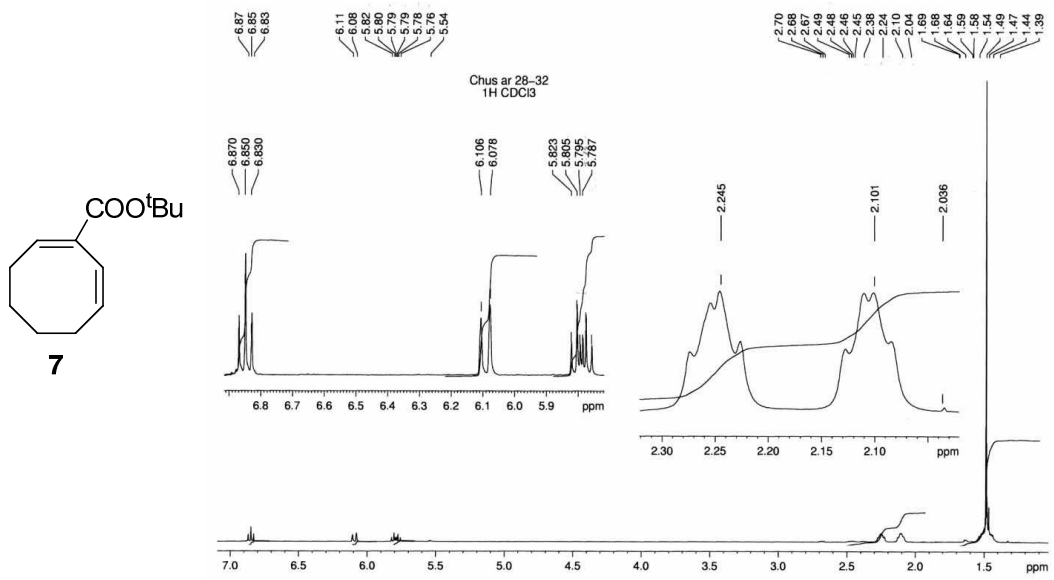


Figure 17. ^{1}H NMR spectrum of compound **7**

Full characterization of **6** was carried out using 2-D NMR techniques (Table 24, see 2D NMR part), to establish its structure unambiguously. Correlation between H-2 and H-3 was observed by COSY (Fig. 18).

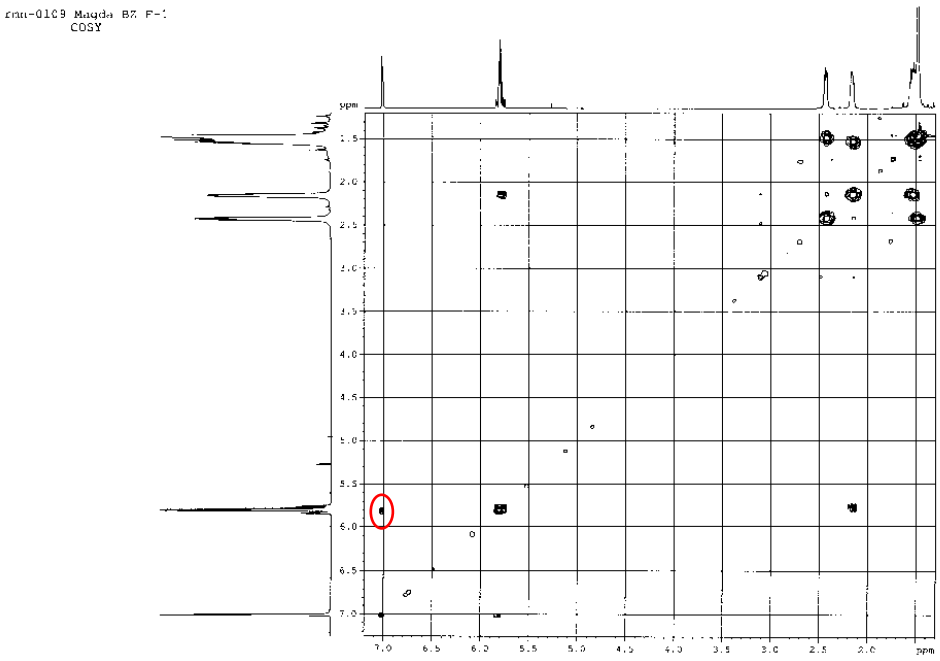


Figure 18. COSY spectrum from compound **6**

Table 2. One bond and long-range 2D ^{1}H-^{13}C correlations for compound **6**

C	**δ_C**	**One bond δ_H**	**Long-range connected protons**
1	133.6		3
2	135.7	6.92	4, 8
3	135.4	5, 69	1, 5
4	124.5	5, 69	6
5	29.8	2.06	3
6	21.9	1.43-1.52	4
7	24.1	1.43-1.52	5
8	26.3	2.33	2, 6
***C*OOC(CH$_3$)$_3$**	166.0		2, 8
COO*C*(CH$_3$)$_3$	79.9		(CH$_3$)$_3$
COOC(*C*H$_3$)$_3$	28.2	1.43	*C*(CH$_3$)$_3$

After exhaustive determination of the structure of compound **6** and due to the great difference in reactivity by addition of the chiral lithium amide (*R*)-**C** between compounds **6**, **7** and **11**, it was decided to carry out a conformational analysis of these substrates. The presence of an additional double bond, in the conjugate esters **6** and **7**, might change the conformational profile of the substrates, which are determinant in the posterior asymmetric Michael addition. For this reason was carried out with Jaguar v. 7.6.,[84] applying Density Functional Theory (DFT) with the Becke`s[85] three-parameter hybrid exchange (B3) together with the Lee-Yang-Parr`s[86] (LYP) correlation functional (B3LYP). 6-31G(d)[87] basis set has been chosen to perform the calculations because it provides good accuracy/time ratio.

First, the structures of the substrates were minimized, using OPLS-AA as force field. Then, conformational search was achieved to each structure with the same parameters: those results within a 10 kJ/mol range from the minimum were recorded to subsequent DFT optimization. The choice of this energy range permits to take the 99.8% of the conformational structures due to its population according with Boltzmann distribution at 195.15 K (-78ºC, reaction temperature). The selected structures were then optimized through DFT B3LYP/6-31G(d). Final vibrational mode analysis was accomplished to check the nature of the minima. The results are showed in Table 3, together with those internal coordinates which best defines each conformer.

Table 3. Relative energies and populations of the obtained conformers

Conformer	Relative-energy kJ/mol [a]	Population percent [b]	Relative Michael conformation	Dihedral angle (º) [c]
11a	0.31	26%	*s-trans*	-98.8
11b	0.00	32%	*s-trans*	98.7
11c	0.27	27%	*s-cis*	98.8
11d	1.29	14%	*s-cis*	-98.8
6a	0.00	58%	*s-trans*	-83.3
6b	0.53	42%	*s-cis*	-83.3
7a	0.00	84%	*s-cis*	82.6
7b	2.71	16%	*s-trans*	82.7

[a] Relative energy to the most stable conformer in each series.
[b] Population at 195.15 K.
[c] The dihedral angle listed is the C(4)-C(5)-C(6)-C(7) dihedral angle.

[84] *Jaguar*, version 7.6, Schrodinger, LLC, New York, NY, **2009**.
[85] Becke, A. D.; *J. Chem. Phys*. **1988**, *38*, 3098.
[86] Lee, C.; Yang, W.; Parr, R. G.; *Phys. Rev. B,* **1988**, *37*, 785.
[87] Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A.; *Ab Initio Molecular Orbital Theory*, Wiley, New York, NY, **1986**.

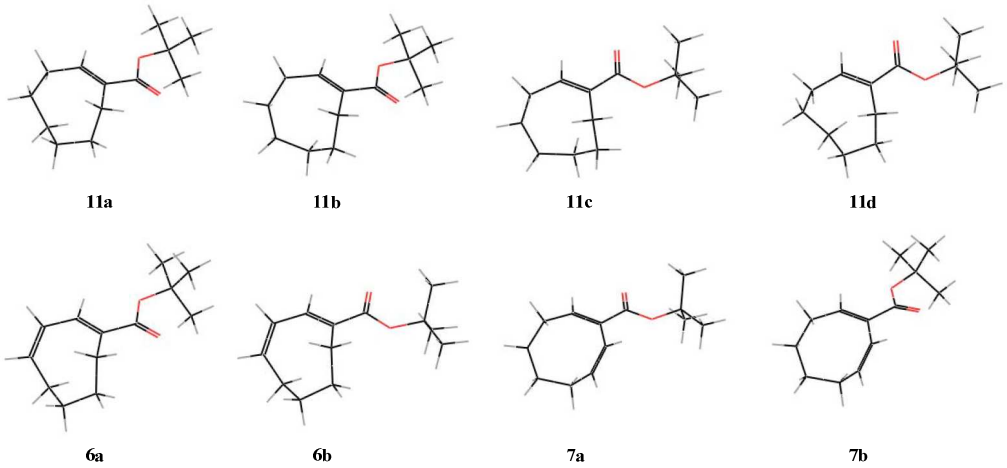


Figure 19. Structure of the minimized conformers of the three Michael acceptors.

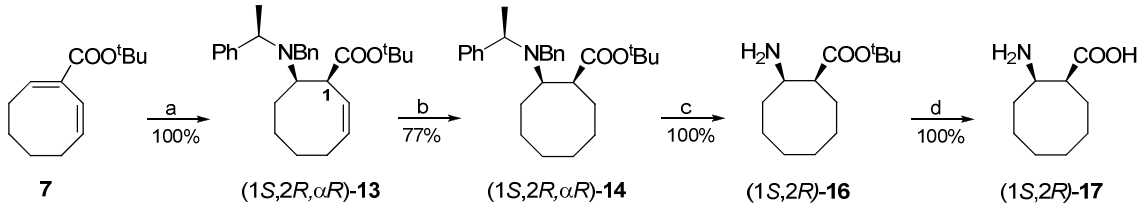
In compound **11**, four conformations were founded (Fig. 19), whose main differences are from two dihedral angle changes: endocyclic C(4)-C(5)-C(6)-C(7) dihedral and the exocyclic O(ester)-C(ester)-C(1)-C(2) torsion. Observing the Table, there is no special selectivity to a defined conformer, so the ratio between them is almost equimolecular at 195.15 K.

Compound **6** only shows two major conformers, differing in the relative disposition of the carbonyl double bond. The ratio of almost 1:1 is remarkable, which is equal to the ratio *s-trans/s-cis* of **11**. In **6** and **7**, the disposition of both endocyclic *Z* double bonds is non planar, otherwise the steric tension of the ring would be too much higher.

On the other hand, compound **7** shows a different behavior, being **7a** the most stable conformer without any doubt. This is reasonable, having a look to the structures in Figure 19: the *s-trans* conformer has a strong interaction between the π orbitals of the carbonyl system and the 7,8-double bond, which has an energy penalty for this conformer. Then, the *s-cis* conformer is more stable than the other analogs and according to the importance reported by Davies *et al.*[24(b)] of the *s-cis* conformation in the conjugated addition, due to a six member transition state characterized.
So, it is reasonable to think that the conformational predisposition of the substrates is a limiting factor in the posterior asymmetric conjugate addition. Nevertheless, a more detailed mechanism reaction pathway study is required to check these results and further studies involving this issue are being developed.

Finally, returning to the explanation of Scheme 38 as it is summarized below, hydrogenolysis of (1*S*,2*R*,α*R*)-**13** gave the monodebenzylated compound (1*S*,2*R*,α*R*)-**15** in poor yield due to retro-Michael reaction, but the strategy of hydrogenation to give (1*S*,2*R*,α*R*)-**14** (77%), followed by

hydrogenolysis (100%), provided (1*S*,2*R*)-**16** with an excellent overall 77% yield in four steps. Treatment of (1*S*,2*R*)-**16** with trifluoroacetic acid gave rise to the β-amino acid (1*S*,2*R*)-**17** quantitatively, $[\alpha]_D^{26}$= -16.5 (*c* 0.7, H_2O), [lit.[88] For (1*R*,2*S*)-**17** $[\alpha]_D^{26}$= +17.8 (*c* 0.4, H_2O)].

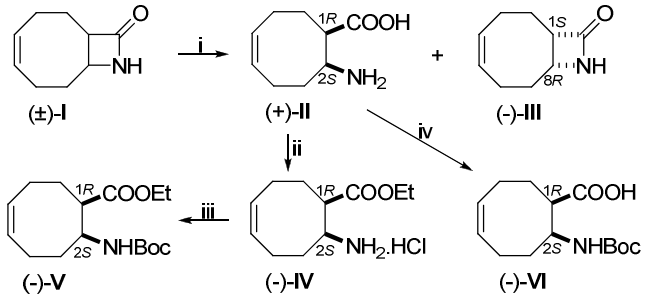


Scheme 40. Reagents and conditions: (a) lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**C**, THF, -78 °C, 2h. (b) PtO_2, H_2, EtOAc, 3 h. (c) Pd/C, H_2, AcOH, 4 atm, 24 h. (d) TFA, quant, 1.5 h, r.t.

[88] Forró, E. and Fülöp, F. *Org. Lett*. **2003**, *5*, 1209-1212.

FUNCTIONALIZED CYCLOOCTANE-β-AMINO ACIDS:

The contribution made by Fülöp *et al*. in 2010,[55] introduced to literature as the first time examples of mono and di-hydroxylated cyclooctanic-β-amino acids, which can be used as staring materials in the synthesis of peptides and different heterocycles with high biological potential. This research work is focused in the functionalization of the double bond from the *cis*-2-aminocyclooct-5-enecarboxylic acid with the amine group protected (Scheme 41).

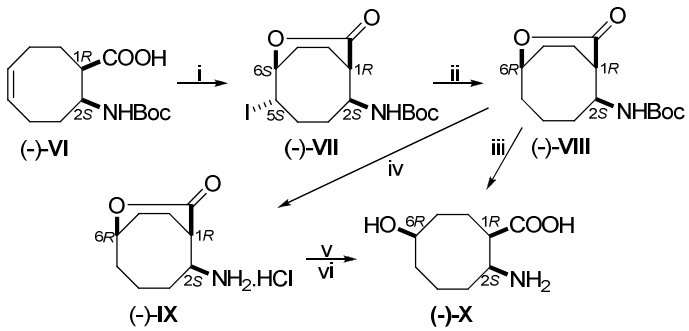


Scheme 41. *Reagents and conditions*: (i) Lipase, *i*Pr_2O, 70°C. (ii) $SOCl_2$, EtOH, 30 min, 0°C, 3 h r.t, 1 h, Δ, 88%. (iii) Et_3N, Boc_2O, THF, 2 h, r.t, 91%. (iv) Dioxane/H_2O, Boc_2O, 4 h, r.t, 76%.

The racemic β-lactam (±)-**I** was prepared by 1,2 cycloaddition of chlorosulfonyl isocyanate (CSI) in dry DCM at room temperature. The β-amino acid (+)-**II** was synthesized from (±)-**I** by highly enantioselective lipolase-catalysed ring opening with 1 equiv of H_2O in *i*Pr_2O at 70°C.[89] The enantiopure amino acid (+)-**II** (ee > 99%) was esterified in the presence of EtOH and $SOCl_2$ to furnish amino ester hydrochloride (-)-**IV**, which was then reacted with *tert*-butoxy pyrocarbonate, affording the *N*-Boc amino ester (-)-**V**. An alternative synthesis of (±)-**V**, which was used in the case of racemic compounds, comprised hydrolysis of (±)-**I** with 22% ethanolic HCl at room temperature to give (±)-**IV**, which was then acylated (Scheme 41).

The starting material in the iodolactonization reaction was cis-2-*tert*-butoxycarbonylaminocyclooct-5-enecarboxylic acid (-)-**VI**, which was prepared from (+)-**II** with Boc_2O, while (±)-**VI** was synthesized by the ring opening of (±)-**I** with 18% aqueous HCl and after acylation with di-*tert*-butyl dicarbonate.

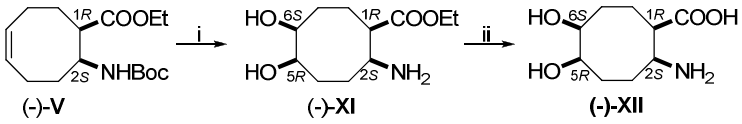
[89] Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2875-2880.



Scheme 42. *Reagents and conditions*: (i) I_2/KI, $NaHCO_3$, DCM. 20 h, r.t, 71%. (ii) Bu_3SnH, DCM, 20 h, 40°C, 76%. (iii) Microwave irradiation, H_2O, 1h, 150°C, 65%. (iv) 10% HCl/H_2O, 24 h, 82%. (v) Microwave irradiation, H_2O, 1 h, 150 °C, 65%. (vi) propylene oxide, 1 h, Δ, 62%.

The *N*-protected acid (-)-**VI** reacted with I_2/KI/aqueous $NaHCO_3$ in DCM to give iodolactone a (-)-**VII** regio- and diastereoselectively as a white crystalline product, in good yield. Reduction of the iodo group with Bu_3SnH in DCM yielded lactone (-)-**VIII** which, after hydrolysis with microwave irradiation gave (1*R*,2*S*,6*R*)-2-amino-6-hydroxycyclooctanecarboxylic acid (-)-**X** in good yield. When ring opening of the Boc-lactone (-)-**VIII** was attempted with HCl, deprotected lactone (-)-**IX** was observed, which was transformed to hydroxy-amino acid (-)-**X** upon microwave irradiation followed by heating in propylene oxide (Scheme 42).

The 5,6-dihydroxy β-amino acid (-)-**XII** (Scheme 43) was yielded by *cis*-hydroxylation catalyzed reaction with OsO_4 and *N*-methyl-morpholine *N*-oxide (NMO) as the stoichiometric co-oxidant afforded the desired product (-)-**XI** as a single diastereoisomer in good yield.



Scheme 43. *Reagents and conditions*: (i) 2.0% w/w OsO_4/*t*-BuOH, NMO, acetone, 4 h, r.t, 91%. (ii) Microwave irradiation, H_2O, 1 h, 150°C, 69%.

APPROXIMATION TO THE SYNTHESIS OF TASHIROMINE:

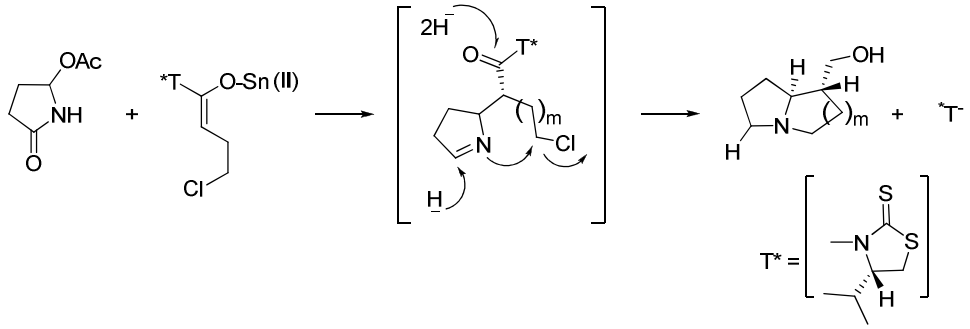
Tashiromine is an indolizidine alkaloid, was first isolated in 1990 from *Maackia Tashiroi*, a bush from subtropical Asia and due to the low isolated quantity, its rotation power an absolute configuration was unknown[90] until 1997, which total asymmetric synthesis was reported by

[90] Ohmiya, S.; Kubo, H.; Otomasu, H.; Saito, K.; Murakoshi, I. *Heterocycles*, **1990**, *30*, 537-542.

Branchaud research group,[91] through an alkylation of pyrroles, this methodology was used a years later by Smith *et al*.[92]

Tashiromine has been a popular objective among the synthetic chemist and until today there have been reported around 15 total synthesis, obtaining (±)-tashiromine,[93]as well as each of its enantiomer using a large number of synthetic steps aimed specially to the establishment of the asymmetric centers. Due to the large number of articles published about this topic, we will focus on the most recent and relevant for the development of this work.

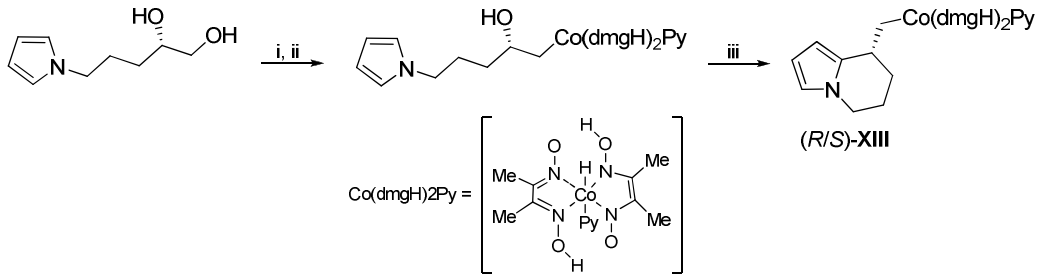
The first synthesis of tashiromine was carried out in 1990 by Nagao (Scheme 44),[94] this synthesis was developed using as a key step the alkylation of 5-Acetoxy-2-pyrrolidinone employing chiral tin(II) enolates obtained from treatment of the corresponding 3-acyl-4(*S*)- or 4(*R*)-isopropyl-1,3-thiazolidine-2-thiones to control the diastereoselectivity of the reaction.



Scheme 44. First reported synthesis of tashiromine

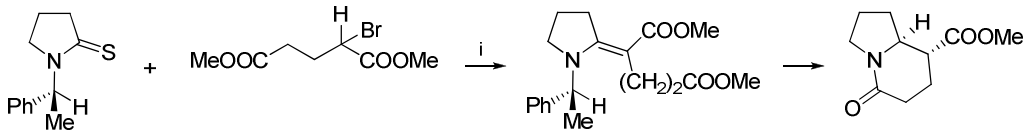
In 1997 the synthesis of both tashiromine enantiomers was performed in 13 steps by Bruce Branchaud.[95] Cyclization of (5-*N*-pyrrolyl-2-hydroxypentyl)-cobaloxime proceeded by intramolecular electrophilic aromatic substitution of a cobaloxime π cation onto the pyrrole ring to provided 6-exo cyclization product **XIII** in 95% yield and this cyclization is highly enantioselective (Scheme 45).

[91] Gage, J. L.; Branchaud, B. P. *Tetrahedron Letters* **1997**, *38*, 7007-7010.
[92] Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem*. **2004**, *2*, 157-159.
[93] For selected syntheses of racemic tashiromine, see: (a) Beckwith, A. L. J.; Westwoods, S. W. *Tetrahedron* **1989**, *45*, 5269-5282. (b) Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett*. **1993**, *34*, 4861-4864. (c) Kim, S. –H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem*. **1999**, *64*, 6771-6775. (d) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654-656. (d) McElhinney, A. D.; Marsden, S. P. *Synlett* **2005**, 2528-2530. (e) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron*, **2009**, *65*, 3222-3231.
[94] Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem*. **1990**, *55*, 1148-1156.
[95] Gage, J. L.; Branchaud, B. P.; *Tetrahedron Letters*, **1997**, *38*, 7007-7010.



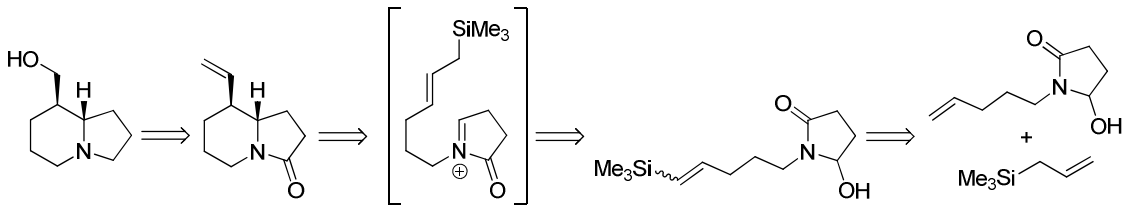
Scheme 45. *Reagents and conditions*: (i) TsCl, Et_3N, DMAP, DCM. (ii) $Na[Co(dmgH)_2Py]$, MeOH. (iii) PPTS, $CHCl_3$, r.t.

In 1999, Gerard Lhommet *et al*.[96] carried out the synthesis through an asymmetric reduction of a β-enamine di-ester controlled by the auxiliary (*S*)-α-methylbenzyl joined to the pyrrolidinic nitrogen as shown in scheme 46.



Scheme 46. *Reagents and conditions*: (i) Ph_3, NEt_2, CH_3CN.

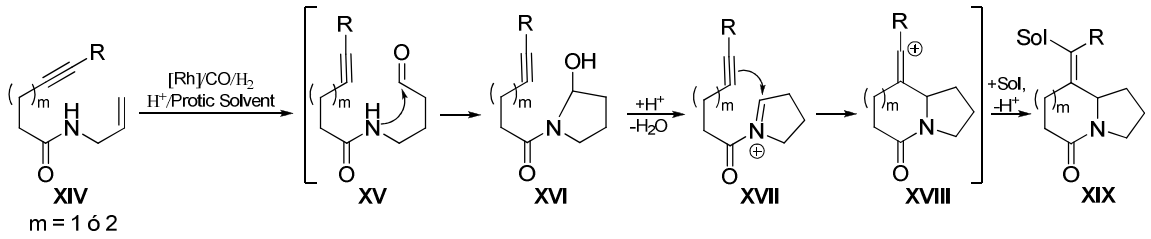
Other approximation was reported by McElhinney and Marsden,[97] through an intramolecular addition of allylsilane to *N*-acyliminium ion to obtain the indolizidine skeleton [4.3.0]-azabicyclo (Scheme 47), wherein the vinyl group acts like a handle to install the lateral chain which incorporates the hydroxy-methyl proper of the tashiromine. A years later, this research group reported the racemic synthesis of tashiromine using the same methodology and new advances aimed to its asymmetric synthesis.[98] The synthesis of azabicyclos assembled by intramolecular cyclizations of allylsilane/N-acyliminium where first studied by Hiemstra and Speckamp in 1985.[99]



Scheme 47. Formation reaction of the indolizidine [4.3.0]-azabiciclo skeleton

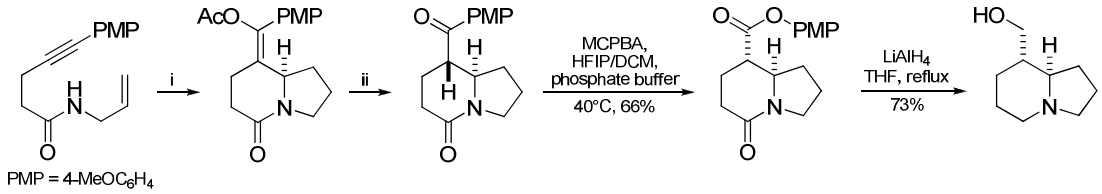
[96] David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M-C.; Haviari, G.; Célérier, J-P.; Lhommet, G.; Gramain, J-C.; Gardette, D. *J. Org. Chem*., **1999**, *64*, 3122-3131.
[97] McElhinney, A. D.; Marsden, S. P. *Synlett*, **2005**, 2528-2530.
[98] Marsden, S. P.; McElhinney, A. D. *Beilstein Journal of Organic Chemistry*, **2008**, *4*, No. 8.
[99] Hiemstra, H.; Sno, M. H. A.M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem*. **1985**, *50*, 4014-4020.

Among the most recent published synthesis is that made by Chiou *et al.*,[100] wherein a novel domino reaction, alkyne-mediated domino hydroformylation/double cyclization was carried out for rapid preparation of indolizidine type alkaloids (Scheme 48).



Scheme 48. Domino reaction in the obtention of indolizidine type alkaloids

The bicyclization process is initiated by Rh-catalyzed hydroformylation of amide **XIV**, affording exclusively linear aldehyde **XV** as the major product. This aldehyde through a spontaneous intramolecular cyclization leads to the formation of the hemiamidal **XVI**. In the presence of an acid, dehydration of hemiamidal **XVI** yields *N*-acyliminium **XVII**. Subsequent intramolecular cyclization of *N*-acyliminium **XVII** with the alkyne moiety as a π carbon nucleophile leads to formation of a cation intermediate **XVIII**, followed by solvent addition to yield bicyclo product **XIX**, which completes the whole bicyclization process. To demonstrate the viability of this novel methodology, it was easy to achieved the synthesis of (±)-Tashiromine (Scheme 49).

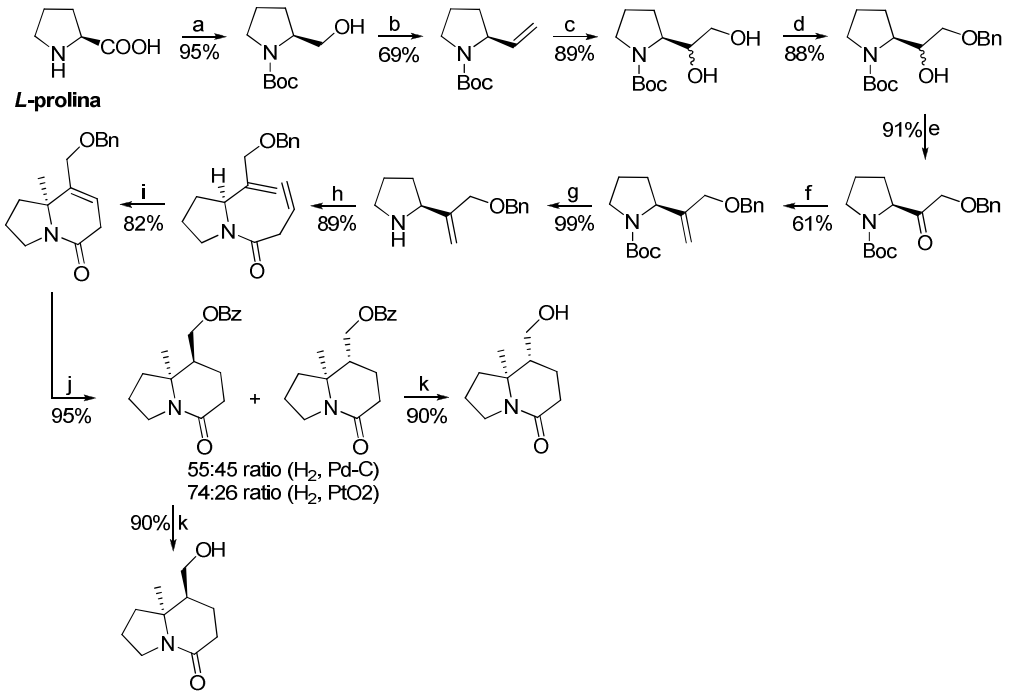


Scheme 49. *Reagents and conditions*: (i) $Rh(acac)(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), CO (2 atm), H_2 (2 atm), *p*-TSA (10 mol%), AcOH, 60°C. (ii) K_2CO_3 (25 mol%), MeOH, r.t

By treatment of the ketone using the Uneyama protocol,[101] it can be obtained the indolizidine ester showed in the previous scheme with 66% yield and by a reduction reaction with $LiAlH_4$ it can be achieved Tashiromine in 73%. The overall yield of this synthetic route is 33% and the alkaloid can be reached in 4 steps.

[100] Chiou, W-H.; Lin, Y-H.; Chen, G-T.; Gao, Y-K.; Tseng, Y-C.; Kao, C-L.; Tsai, J-C. *Chem. Commun*., **2011**, *47*, 3562-3564.
[101] Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron*, **2003**, *59*, 1547-1552.

Other recent approach to the synthesis of indolizidine alkaloids like Tashiromine has been developed by Rao *et al.*,[102] utilizing ring closing metathesis followed by a stereoselective hydrogenation and using *L*-proline as starting material.



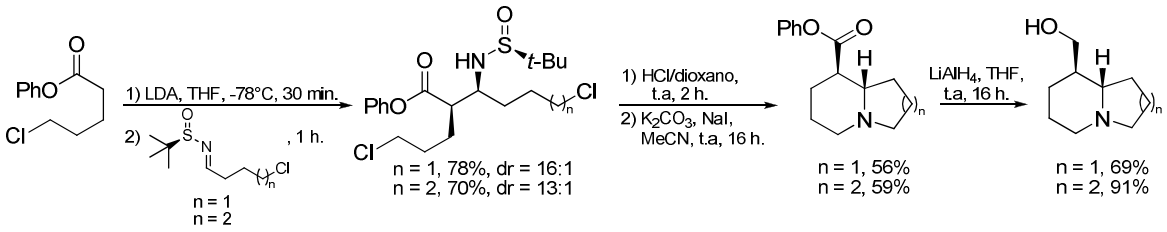
Scheme 50. *Reagents and conditions*: (a) $LiAlH_4$, THF, 0°C-t.a, 1 h. (b) (i) DMSO, $(COCl)_2$, Et_3N, DCM, -78°C, 1 h. (ii) $Ph_3P{=}CH_2$, THF, -10°C, 3 h. (c) OsO_4, NMO, acetone/H_2O (3:1), 0°C-rt, 6 h. (d): (i) Bu_2SnO, toluene, Δ, 8 h. (ii) BnBr, TBAI, Δ, 16 h. (e) TEMPO, NaBr, NaOCl, $NaHCO_3$, toluene/EtAc/H_2O (3:3:1) 0°C, 1 h. (f) $Ph_3P{=}CH_2$, THF, -10°C, 4 h. (g) TFA/DCM (1:1), Et_3N, 0°C, 1 h. (h) 3-butenoic acid, ethylchloroformate, NMM, THF, 0°C-rt, 3 h. (i) 10 mol% Grubbs cat.1ª generation, DCM, 50°C, 6 h. (j): (i) H_2, Pd-C, MeOH, rt, 2 h. (ii) benzoyl chloride, Et_3N, cat DMAP, DCM, 0°C, 2 h. (k) K_2CO_3, MeOH, rt, 2 h.

As shown in scheme 50, by the reduction of *L*-proline with LAH is obtained the alcohol, which was converted to the olefin through Swern oxidation, followed by the Wittig homologation. The di-hydroxylation of the olefin led to the diastereoisomeric mixture of diols, followed by a regioselective benzylation with Bu_2SnO in toluene and addition of benzyl bromide in the presence of catalytic TBAI gave the protected hydroxy-derivative in 88% yield. The secondary alcohol was oxidized to ketone by treatment with TEMPO and subsequent converted in olefin by a Wittig homologation. Deprotection of the amine followed by neutralization of the resultant TFA salt with Et_3N gave the secondary amine in 99% yield. Latter derivative was subjected to an acylation reaction by addition of 3-butenoic acid, ethylchloroformate and NMM in THF achieving the compound with the required lateral chain to obtain the Tashiromine bicyclo, which underwent ring-closing metathesis with 1st generation Grubbs` catalyst to yield the unsaturated cycle derivative in 82% yield. Hydrogenation in the presence of PtO_2 followed by protection of the

[102] Reddy, K. K. S.; Rao, B. V.; Raju, S. S. *Tetrahedron: Asymmetry*, **2011**, *22*, 662-668.

hydroxy group such as benzoate gave *cis*- and *trans*-diastereomers in 74:26 ratio, respectively, unlike the obtained in the presence of Pd-C (55:45), this last one could be isolated by preparative HPLC. Deprotection of the benzoate group in each of the isomers by treatment with K_2CO_3 in MeOH led to obtention of closest indolizidine derivatives to the Tashiromine structure.

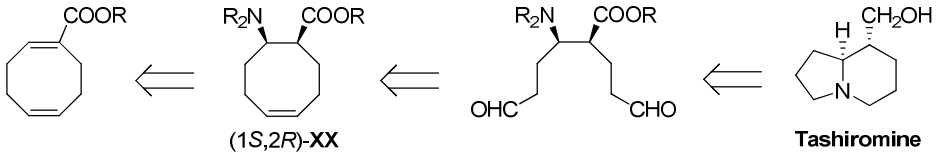
The last one and most recent is the total synthesis of (-)-Tashiromina. It has been developed by the research group of Brown,[103] using imino-aldol reactions of enolates derived from phenyl 5-chlorovalerate. High levels of *syn* selectivity (dr~13-16:1) were obtained using lithium enolates of phenyl esters in combination with *tert*-butylsulfinyl imines. The imino-aldol adducts were deprotected and cyclized to afford (-)-epilupinine y (-)-tashiromine, as shown in the following scheme.



Scheme 51. Synthesis of (-)-Epilupinine (n=2) y (-)-Tashiromine (n=1)

[103] Cutter, A. C.; Miller, I. R.; Keily, J. F.; Richard, K. B.; Light, M. E.; Brown, R. C. D. *Organic Letters*, **2011**, *13*, 3988-3991.

FUNCTIONALIZED CYCLOOCTANE-β-AMINO ACIDS:



Scheme 52. Retrosynthetic pathway for the synthesis of Tashiromine

Our initial plan in the synthesis of Tashiromine intended as a key step, after the Michael addition of the chiral lithium amide, to perform the double bond rupture by an ozonolysis reaction to afford the corresponding di-aldehyde, which by a hydrogenolysis reaction will lead in just one step to the indolizidine skeleton, which by a reduction reaction of the ester will bring us to the desired alkaloid (Scheme 52). As we have obtained the 1,3-diene isomer, we tried to model within it the proposed reactivity and at the same time to afford high functionalized derivatives.

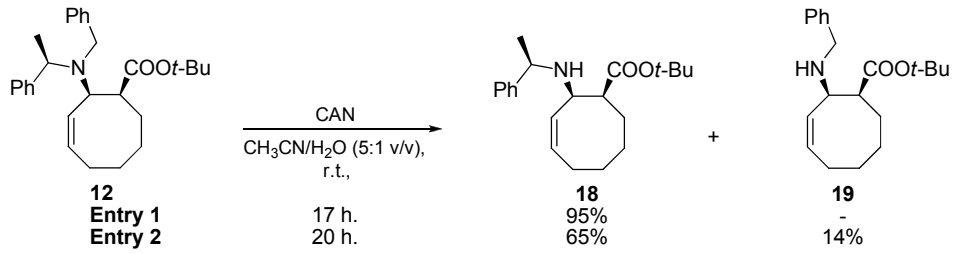
Reactivity of *tert*-butyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cyclooct-3-ene-carboxylate 12:

Firstly, the reactivity of isomer (1*S*,2*R*,α*R*)-**12** was studied. Cleavage of the double bond in **12** would lead to a di-aldehyde, which in turn could be then transformed into its amino-tri-acid (Scheme 55).

Cleavage of the double bond in compound **12** by direct treatment with ozone did not provide the expected results and even strong reaction conditions, treatment with $HCl_{(g)}$[104] previous to oxidation also failed. It was suggested to attenuate the reactivity of the amine by getting an amide. As it can be observed in Scheme 53, treatment of the homochiral tertiary amine **12** with ceric ammonium nitrate in aqueous acetonitrile resulted in clean *N*-mono-debenzylation[105] to yield exclusively, by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, the corresponding homochiral secondary amine **18** which was isolated in 95% yield after column chromatography (Entry 1). Unexpectedly, only in one reaction compound **19** could be obtained in low yield. Davies *et al.*[106] have demonstrated that CAN mediated *N*-debenzylation protocol proceeds in uniformly good yields for acyclic *tri*-, *di*- and mono-*N*-benzyl tertiary amines that do not contain *N*-Me or *N*-Et

[104] Garrido, N. M.; Rubia, A. G.; Nieto, C.; Díez, D. *Synlett*, **2010**, *4*, 587-590.
[105] Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, S.; Smith, A. D. *Chem. Commun*., **2000**, 337-338.
[106] Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, S.; Smith, A. D. *J. Chem. Soc., Perkin Trans 1*, **2000**, 3765-3774.

substituents, with preferential cleavage of umbranched *N*-benzylic substituents over α-branched *N*-benzylic substituents (Scheme 53).

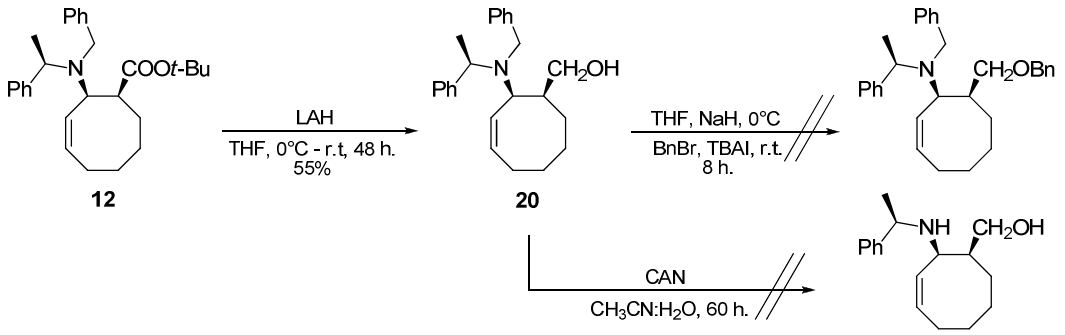


Scheme 53. *N*-Benzyl elimination reaction of compound**12** with CAN

Thus, cleavage of *N*-α-methylbenzyl fragment by CAN treatment goes against the published results, but in spite of the fact that the only difference between the two entries was the reaction time; the only evidence to prove that this kind of elimination took place was the isolation and full characterization of compound **19** yielded in 14%, whose ^{1}H and ^{13}C NMR spectra show the absence signals for the methyl group. In spite of this, the major reaction product in Entry 2 is compound **18** obtained in 65% yield and previously characterized in Entry 1.

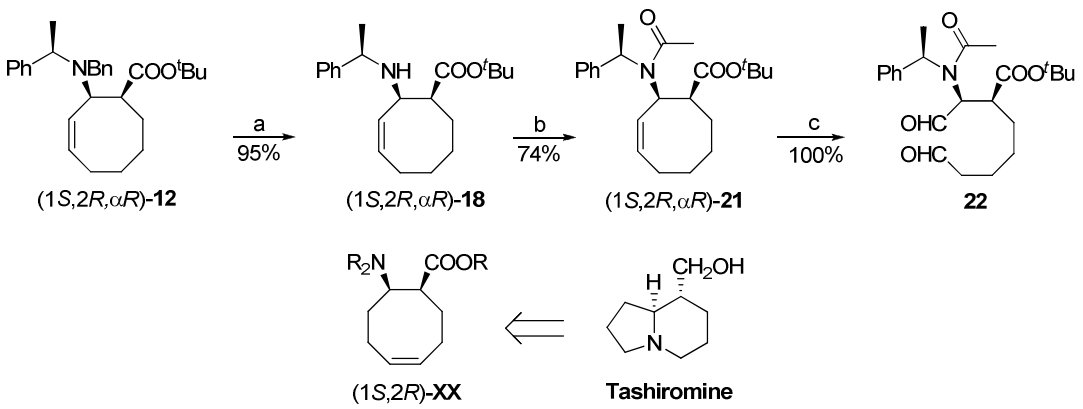
According to the literature and related to the mechanism of this *N*-benzyl elimination from tertiary amines,[106] competitive experiments with tertiary *N*-benzyl-*N*-4-methoxybenzyl-substituted amines indicate that the outcome of the reaction is unaffected by arene substitution, implying initial single electron oxidation by CAN at the tertiary nitrogen centre of the amino nitrogen rather than at the arene ring of the *N*-benzyl substituent but further mechanistic studies within this area are currently ongoing to delineate the reaction mechanism.

Different derivatives were prepared from (1*S*,2*R*,α*R*)-**12** like (1*S*,2*R*,α*R*)-2-*N*-(benzyl-*N*-α-methylbenzylamino)-cyclooct-3-enyl-methanol **20** (Scheme 54) by a reduction reaction with lithium aluminium hydride achieved **20** in 55% yield, which was submitted to protection of the alcohol by introducing a benzyl group, the ^{1}H NMR spectrum of the crude showed the recovery of starting material.



Scheme 54. Preparation of other derivatives from compound **12**

Compound **20** was also used as starting material in the preparation of a secondary amine by addition of CAN. In spite of the long reaction time, the ^{1}H NMR spectrum of the crude showed the recovery of starting material. Formation of an intramolecular hydrogen bond is the most reasonable explanation why the elimination of the benzyl group did not take place.

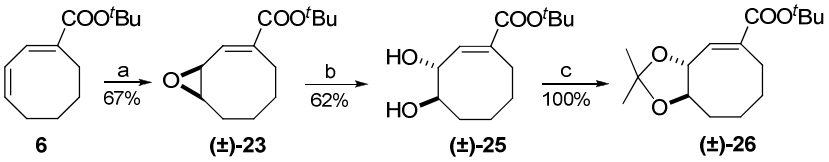


Scheme 55. *Reagents and conditions*: (a) CAN, CH_3CN/H_2O (5:1 v/v). (b) Et_3N, AcCl, THF. (c) O_3, DCM, Me_2S, -78°C

Upon reaction with Boc_2O at different temperatures and conditions (Table 14, see experimental part) and acetic anhydride the protection of the secondary amine in compound **18** did not happen either. However, under addition of acetyl chloride provided the required amide (1*S*,2*R*,α*R*)-**21** in 74% yield that quantitatively afforded the di-aldehyde **22** by cleavage of the double bond with ozone (Scheme 55). The ^{1}H NMR spectrum of compound **22** clearly shows the existence of a formyl group in position β to the ester group and α to the amine, establishing the structure that is indicated in the Scheme 55 (3.78 ppm (1H, dd, *J* 6.0 and 1.8, H-2) and 9.64 ppm (1H, d, *J* 1.8, C*H*O). Despite that this route did not bring us to the desired alkaloid product, this polifunctionalized β-aminoester could be a potential key intermediate in asymmetric synthesis, and also the way to the synthesis of Tashiromine when we will try the described reactions with (1*S*,2*R*)-**XX** (Scheme 55), the aforementioned alkene isomer of (1*S*,2*R*,α*R*)-**12**.

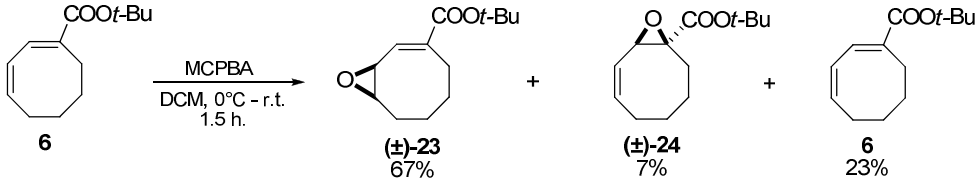
Reactivity of *tert*-butyl cyclooct-1,3-dienecarboxylate 6: Asymmetric synthesis of 3,4-dioxygenated β- aminocyclooctane carboxylate derivatives.

According to literature, very few cyclooctanic β-amino acids functionalized are known.[55]



Scheme 56. *Reagents and conditions*: (a) MCPBA, 0°C, 1.5 h. (b) $HClO_4$, Dioxane/H_2O (1:9 v/v), 0°C-r.t, 9.5 h. (c) Acetone, 2,2-DMP, CSA, 80°C.

In order to get further oxygenated β-aminocyclooctane carboxylic acid derivatives, it was proceeded as shown in Scheme 56. Oxidation of **6** with MCPBA give rise to the monoepoxide (1*E*,3*R**,4*S**)-*tert*-butyl cycloocta-1,2-diene carboxylate 3,4 oxide (±)-**23** (67%) together with S.M. (23%) and (1*R**,2*S**,3*E*)-*tert*-butyl cycloocta-3,4-diene carboxylate 1,2 oxide (±)-**24** (7%) (Scheme 57).



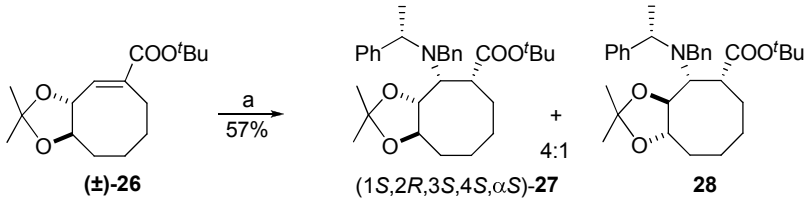
Scheme 57. Epoxidation reaction of compound **6** with MCPBA

Compound (±)-**23** was subjected to addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, recovering starting material after the work up. This reaction did not take place probably due to the extra-reactivity of the epoxide. For this reason, different conditions were used in the epoxide ring opening reaction of (±)-**23**. The diol (±)-**25** was only afforded upon treatment with perchloric acid during 9.5 hours in 62% yield and recovery of staring material (20%). Then it was subjected to treatment with dimethoxypropane to obtain the corresponding isopropilidendioxi (±)-**26** as a racemic mixture.

The protocol of asymmetric Michael addition of the chiral lithium amide base (*S*)-**C** was performed for compound (±)-**26**, obtaining stereoselectively the corresponding 3,4-dioxygenated β-amino ester (1*S*,2*R*,α*S*)-**27** and (1*S*,2*R*,α*S*)-**28** in 57% yield and 4:1 ratio, (Scheme 58).

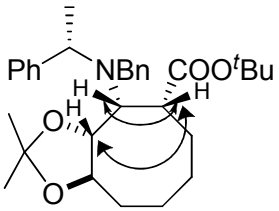
The spectroscopy data analysis of compound **27** showed the incorporation of *N*-benzyl-*N*-α-methylbenzylamide in its ^{1}H NMR spectrum at 1.15 ppm (3H, d, *J* 8.0, C(α)*Me*), 4.02 ppm (2H,

CH_AH_B, CH_2-N), 4.47 (1H, q, *J* 8.0, CH(α)) and 7.40 ppm (10H, m, H-Ar). Furthermore, it is found that the signal from the double bond in the cyclooctadiene ring has disappeared.



Scheme 58. *Reagents and conditions*: (a) Lithium *N*-benzyl-*N*-α-methylbenzylamide (*S*)-**C**, -78°C, 2h.

In Figure 20 are shown the observed correlations in the NOE experiments. The NOE between H-1 and H-3 led us to establish the stereochemistry of this structure.

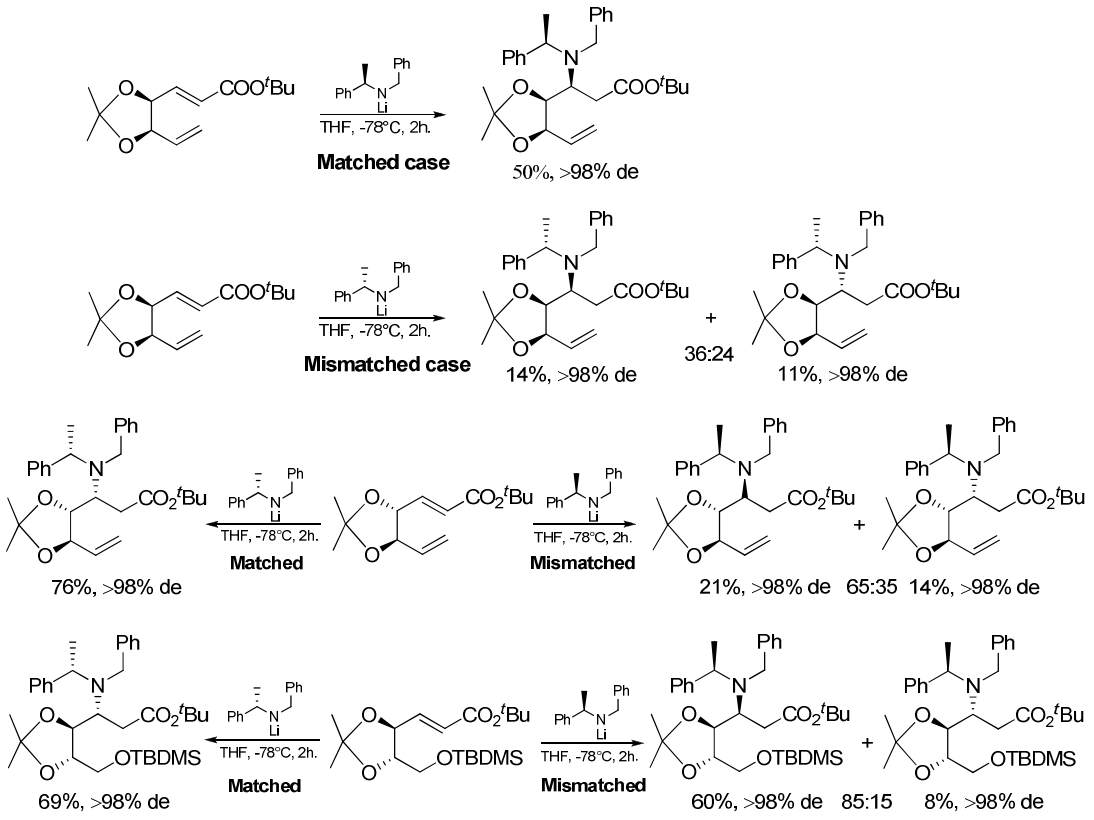


(1*S*,2*R*,3*S*,4*S*,α*S*)-**27**

Figure 20. Nuclear Overhauser Effect correlations of compound **27**

The conjugate addition to a homochiral α,β-unsaturated ester containing a *cis* and *trans*-dioxolane units has been studied recently by Davies *et al*.[107] concluding that doubly diastereoselective conjugate addition reaction of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of homochiral α,β-unsaturated ester containing a *cis* and *trans*-dioxolane units result in "matching" and "mismatching" effects. In the "matched" cases a single diastereoisomer of the corresponding β-amino ester is produced. Upon conjugated addition to an α,β-unsaturated ester containing a *cis*-dioxolane unit in the "mismatched" case it is the stereocontrol of the substrate which is dominant over that of the lithium amide, whilst upon addition to α,β-unsaturated ester containing a *trans*-dioxolane unit the stereocontrol of the homochiral lithium amide is dominant (Scheme 59). Consistent with these observations, upon conjugated addition of lithium *N*-benzyl-*N*-isopropylamide to homochiral α,β-unsaturated esters, modest to high levels of substrate control leading to the corresponding 3,4-*anti*-diastereoisomeric β-amino ester product are observed in each case, which can be rationalized by invoking a modified Felkin-Anh transition state.

[107] Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M., Kurosawa, W.; Lee, J. A.; Nicholson, R. L. Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem*., **2009**, *7*, 761-776.

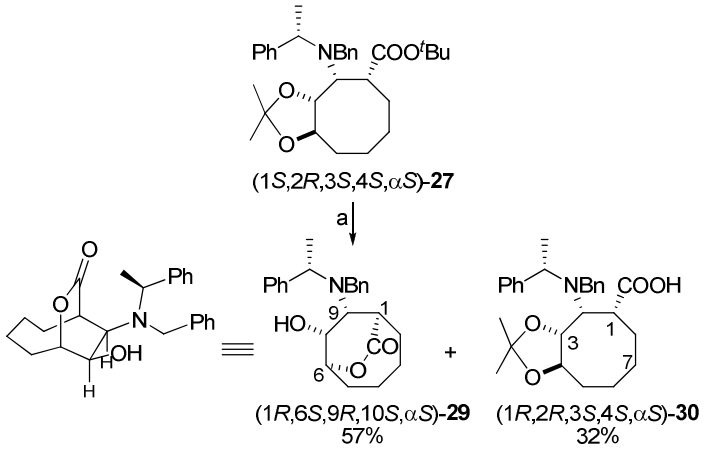


Scheme 59. Doubly diastereoselective conjugated addition of homochiral lithium amides to homochiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units

The conclusion from this study is in agreement and support the results we have obtained, being in this case the matching conditions where the homochiral lithium amide is dominant over the substrate. Its approximation takes place on the same face from the oxygen in C-3 position, for this reason the major product from the addition of the amide is the single diastereoisomer of the corresponding β-amino ester observed by ^{1}H NMR spectroscopy in the reaction crude and according to Masamune`s theory[108] resulting in compound **27**. The reaction of (*S*)-**C** with the other enantiomer corresponds to the mismatched pair, where the stereocontrol from the lithium amide is as well dominant given rise to **28** and probably it could be obtained the other diastereoisomer where the stereocontrol is carried out by the substrate in the mismatched pair, but in this case it was not isolated.

Different experiments were performed for the acetal opening reaction, just when **27** was treated with PTSA it was achieved a mixture of **29** and **30** in 57% and 32% yield, respectively (Scheme 60).

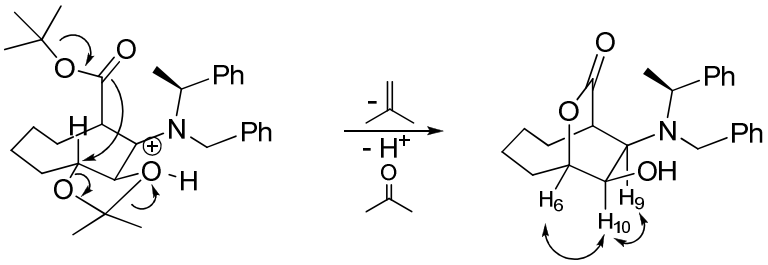
[108] Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1-76.



Scheme 60. *Reagents and conditions*: (a) HCl $_{(gas)}$, PTSA, H_2O, 4 h

It is deduced from the spectroscopy data analysis of compound **30** the deprotection of the ester wherein both its ^{1}H and ^{13}C NMR spectra show the absence of the *tert*-butyl signal and the downfield shift of the carbon from the acid group present at 176.6 ppm (C, *C*OOH).

The spectroscopy data analysis of compound **29** (Table 27, see 2D NMR part) showed the formation of the 7-oxabicyclo[4.2.2]decan-8-one wherein its nOe shows correlations of H-9 at 3.09 ppm (1H, dd, *J* 9.2 and 2.1) with H-10 at 3.94 ppm (1H, dd, *J* 9.2 and 5.6) and this one with H-6 at 4.63 ppm (1H, td, *J* 5.6, 3.0) as shown in Scheme 61.



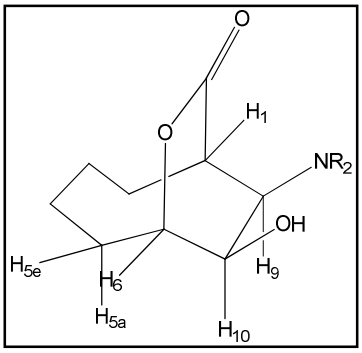
Scheme 61. Formation mechanism and Nuclear Overhauser Effect correlations of compound **29**

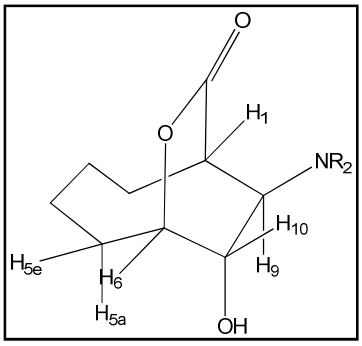
The previous reactivity should be studied more deeply because of its nature and because it brings to the synthesis of compound **29** and **30** which are of great importance in the contribution to the functionalized cyclooctanic-β-amino acids through deprotection protocol of the amides by hydrogenolysis reaction.

However, in order to check the stereochemical nature of the proposed structure, conformational analysis was achieved in each epimer and forward H-H coupling constants were calculated.

First, conformational search was carried out over each epimer employing OPLS-AA[109] as force field under the TINKER[110] software. For epimer **1**, seven conformers were founded within a 5 Kcal/mol barrier form the minimum energy structure. On the other hand, forty eight conformers were founded for epimer **2**. This great difference is due to the relative *cis* conformation between the amine and the free hydroxyl group, establishing a hydrogen bond (1.847 Å approx.), which appears in all the conformers: this leads to a significant decrease of the energy of this conformational cluster related to the total conformational space. In epimer **2**, the *trans* conformation leads to a 2.465 Å distance between the nitrogen and the hydrogen of the hydroxy group, leading to a hydrogen bond much longer: such intramolecular interaction is no intense and no lower energy cluster was found. Later, a DFT (Density Functional Theory) optimization was carried out with the B3LYP/6-31G* theory[111] through Jaguar v 7.6.[112] In epimer **1**, all the conformers were minimized, while in epimer **2** only the set of six minimum conformers were taken to the forward optimization. No solvent interactions were taken into account: the geometrical optimizations in gas phase are enough to obtain valuable data. Finally, H-H coupling constants were measure by means the Haasnoot-de Leeuw-Altona[113] empirical equation, which is a significant improvement of Karplus equation due to the inclusion of the substituents group electronegativities. MestreJ was employed in this measure.[114]

[109] Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J.; *J. Am. Chem. Soc.*, **1996**, *118* , 11225-11236.
[110] Ponder, J. W. *TINKER Molecular Modeling Package*, v. 5.1; Washington University Medical School: St. Louis, MO, **2010**.
[111] (a) Becke, A. D.; *J. Chem. Phys*. **1988**, *38*, 3098-3100. (b) Lee, C.; Yang, W.; Parr, R. G.; *Phys. Rev. B,* **1988**, *37*, 785-789.
[112] *Jaguar*, version 7.6, Schrodinger, LLC, New York, NY, **2009.**
[113] Altona, C. In *Encyclopedia of Nuclear Magnetic Resonance*; Grant, D. M., Harris, R. K., Eds.; Wiley: Chichester, U.K., **1996**, p 4909.
[114] Navarro-Vázquez, A.; Cobas, J. C.; Sardina, F. J.; Casanueva, J.; Diez, E.; *J. Chem. Inf. Comput. Sci*., **2004**, *44(5)*, 1680-1685.





Epimer 1			Epimer 2		
Conformer	**E/kcalmol$^-$**	**%**	**Conformer**	**E/kcalmol$^-$**	%
1	0.00	63.5	**1**	0.00	0.24
2	2.41	8.6	**2**	0.52	0.15
3	1.38	20.2	**3**	0.03	0.23
4	3.65	3.1	**4**	1.00	0.10
5	4.78	1.2	**5**	0.38	0.17
6	4.11	2.1	**6**	0.95	0.11
7	4.71	1.3			

Figure 21. Found conformers for Epimer **1** and Epimer **2**.

Table 4. Calculation of dihedral angle and coupling constant for each previous conformer of epimer 1

Dihedral angle (°)					***J* (HLA)**				
H_1-C-C-H_9	**H_9-C-C-H_{10}**	**H_{10}-C-C-H_6**	**H_6-C-C-H_{5a}**	**H_6-C-C-H_{5b}**	**H_1,H_9**	**H_9,H_{10}**	**H_{10},H_6**	**H_6,H_{5a}**	**H_6,H_{5b}**
-81.4	-17.6	103.7	-69.3	44.6	1.40	7.43	1.32	1.22	5.46
-82.2	-17.8	104.2	-69.4	44.5	1.35	7.41	1.35	1.21	5.47
-81.3	-14.5	103.0	-43.9	69.5	1.40	7.61	1.28	4.42	1.96
-80.6	-16.9	105.4	-44.2	69.3	1.44	7.47	1.44	4.37	1.98
-91.0	-4.3	97.4	-71.8	42.1	1.07	7.93	1.00	1.05	5.86
-79.4	-19.8	106.9	-69.4	44.6	1.52	7.27	1.55	1.21	5.46
-80.9	-18.7	106.6	-69.6	44.4	1.43	7.34	1.53	1.19	5.46
			Weighted average		1.40	7.47	1.32	1.96	4.65
			Experimental		2.10	9.20	5.60	3.00	5.60

Table 5. Calculation of dihedral angle and coupling constant for each previous conformer of epimer 2

Dihedral angle (°)					***J* (HLA)**				
H_1-C-C-H_9	**H_9-C-C-H_{10}**	**H_{10}-C-C-H_6**	**H_6-C-C-H_{5a}**	**H_6-C-C-H_{5b}**	**H_1,H_9**	**H_9,H_{10}**	**H_{10},H_6**	**H_6,H_{5a}**	**H_6,H_{5b}**
-112.8	161.5	-54.3	-54.3	58.4	2.05	7.85	4.27	2.84	3.33
-121.6	165.4	-58.0	-90.0	23.3	3.20	8.31	3.79	0.93	8.52
-118.2	164.4	-58.0	-90.3	23.1	2.72	8.20	3.79	0.95	8.54
-112.6	160.4	-52.3	-53.8	58.9	2.03	7.71	4.53	2.91	3.26
-121.4	165.0	-57.9	-89.9	23.4	3.17	8.27	3.80	0.93	8.50
-118.1	163.7	-56.2	-89.9	23.4	2.70	8.12	4.02	0.93	2.66
			Weighted average		2.71	8.10	4.02	1.56	6.19
			Experimental		2.10	9.20	5.60	3.00	5.60

These results are in both cases in reasonable agreement with those obtained experimentally, although only the epimer **1** has got a *syn* arrangement with the lactone and the hydroxy group consistent with the proposed mechanism. Furthermore, the coupling constant $J_{9,10}$ = 9.2 Hz, observed experimentally for **29**, it is identically to the observed for the $J_{2b,3}$ in the bicyclo[2.2.2]octane (Fig. 22), which structure has been corroborated by X-Ray spectroscopy and is discussed in chapter IV.

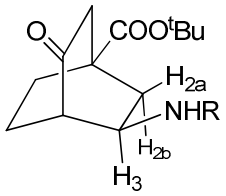
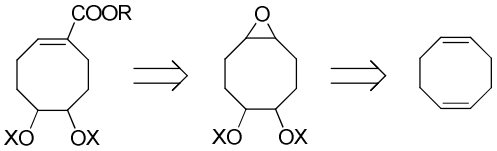


Figure 22. bicyclo[2.2.2]octane

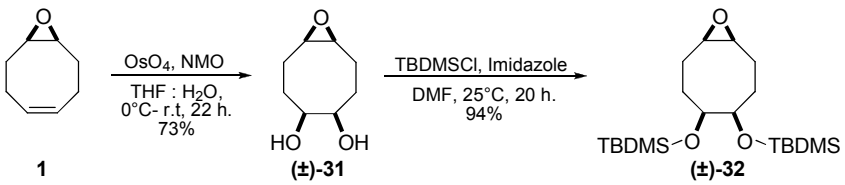
Approximation to the synthesis of Tashiromine:

In order to control the functionality in C-5 and C-6 which is susceptible to migration when it is a double bond, previously observed when a hydrolysis reaction of the nitrile group was carried out for compound **3**, it was decided to establish oxygen functions in this position to allow the bond cleavage.



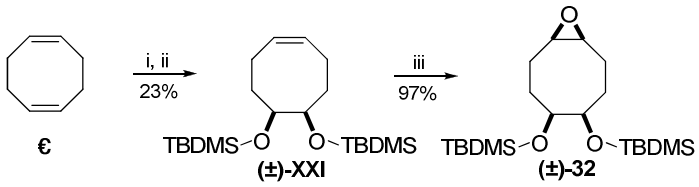
Scheme 62. Potential synthesis pathway to establish oxygen functions in C-5 and C-6

Thus in Scheme 63, dihydroxylation with OsO_4-NMO of 1,2-epoxicyclooct-5-ene **1** previously obtained, led to epoxydiol (±)-**31** in 73% yield after isolation by continuous extraction. Due to its polarity it was protected and full characterized in deuterated toluene at 85°C as 4,5-*tert*-butyldimethylsilyloxy (±)-**32** obtained in nearly quantitative yield.



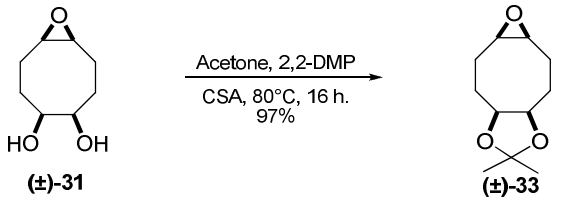
Scheme 63. Dihydroxylation reaction of compound **1** with OsO_4-NMO

This route is more efficient than the approach previously studied by Hodgson *et al. via* the alkene (5*R**,6*S**)-5,6-Bis(*tert*-butyldimethylsilyloxy)cyclooctene **XXI** and it uses less OsO_4, (Scheme 64).[115] Epoxidation of compound **XXI**, available from cycloocta-1,5-diene by dihydroxylation and subsequent protection, resulted in exclusive formation of epoxide (±)-**32** (97%), assigned as the all *cis* compound (*vide infra*), this *cis* assignment has been also corroborated in (±)-**33**, a compound that is described below by NOE experiments.



Scheme 64. *Reagent and conditions*: (i) cat. OsO_4, NMO, THF/Acetone/H_2O (1:1:1), 0°C to 25°C, 16 h. (ii) TBDMSCl, imidazole, DMF, 2 °C, 18 h. (iii) MCPBA, Na_2CO_3, DCM, 0°C to 25°C, 30 min.

Different protected diols were synthesized in order to explore the reactivity of different derivatives. Treatment with dimethoxypropane, catalyzed by Camphor sulfonic acid and refluxed at 80°C achieved the corresponding isopropilidendioxi (±)-**33** in 97% yield.



Scheme 65. Protection reaction of the diol (±)-**31**

Experiments 2D NMR were submitted for this reaction product and the NOE spectrum corroborates the *cis* assignment for compound (±)-**33** and the rest of derivatives which starting material has been compound (±)-**31** (Fig. 23).

[115] Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2161-2174.

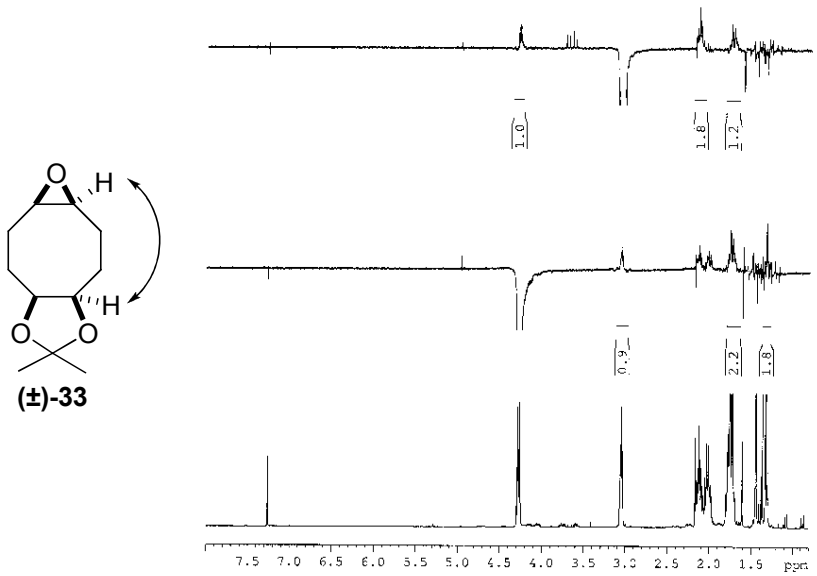
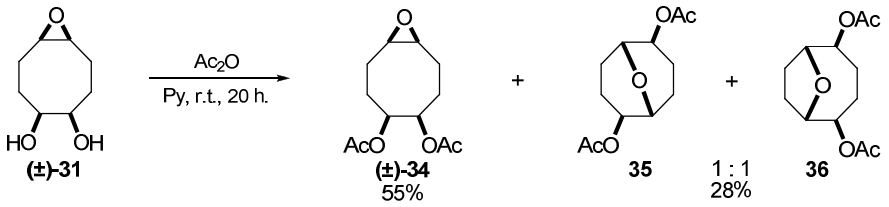


Figure 23. NOE spectrum of compound (±)-**33**

Acetylation reaction of compound (±)-**31** by addition of acetic anhydride in pyridine was performed at room temperature achieving compound (±)-**34** in 55% yield and a 1:1 ratio mixture of compound **35** and **36** in 28% yield.

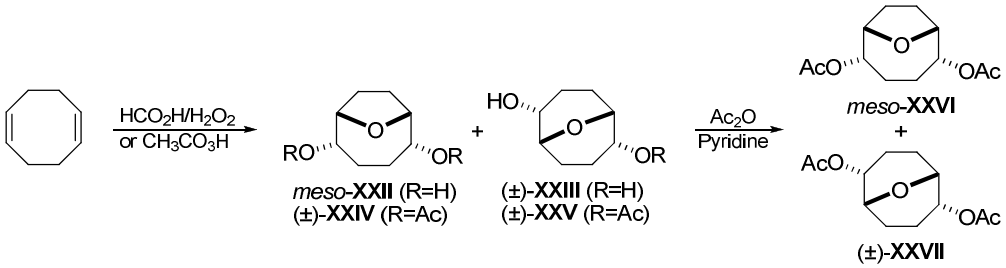


Scheme 66. Acetylation reaction of compound **31**

The ^{1}H NMR spectrum of compound (±)-**34** reflects the symmetry present in this molecule, characteristic of the existence of a plane of symmetry. The low yield, quantity, formation of secondary products and purification problems comparing with the other two protections makes it a not suitable adduct to carry on with the synthesis of the α,β-unsaturated ester. The formation of compounds **35** and **36** under protection reaction conditions is interesting and can be perfectly observed in the ^{13}C NMR spectrum due that the signals are more or less duplicated. Some related diastereoisomers have been obtained by Duthaler *et al.*,[116] in 1972 and their enantiomers by Haufe *et al*.,[117] in 2004 through three different routes, all from cycloocta-1,5-diene (Scheme 67). With performic acid formed in situ from formic acid and 30% hydrogen peroxide to obtain 38:62

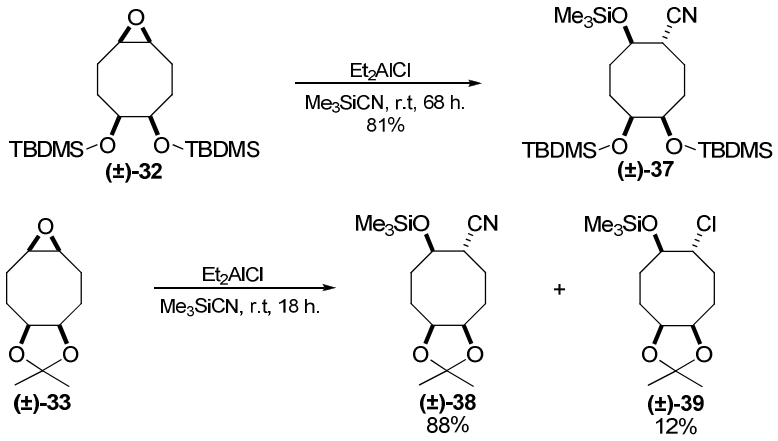
[116] Duthaler, R. O.; Wicker, K.; Ackermann, P. and Ganter, C. *Helvetica Chimica Acta* **1972**, *55*, Fasc. 5, 1809-1827.
[117] Hegemann, K.; Fröhlich, R. and Haufe G. *Eur. J. Org. Chem*. **2004**, 2181-2192.

mixture of *meso*-**XXII** and (±)-**XXIII** in 70% combined yield, whereas a 1:1 mixture of these products was obtained by treatment with peracetic acid and subsequent saponification reported by Duthaler, with rather low yield of 28%. A third alternative pathway by acid-catalyzed ring opening of the bis-epoxide of cycloocta-1,5-diene and transannular O-heterocyclization gave mixture of *meso*-**XXII** and (±)-**XXIII** in 55% overall yield base on starting material. The separation of the isomeric diols *meso*-**XXII** and (±)-**XXIII** or the corresponding diacetates *meso*-**XXVI** and (±)-**XXVII** by either crystallization or column chromatography was as well very difficult.



Scheme 67. Reported formation of these kind of bicycles

Having the protected alcohols in hand, with good yields and under control of the C-5 and C-6 positions, the idea is to follow the pathway made for the synthesis of unsaturated esters to obtain the α,β-adduct for the Michael addition. Compound (±)-**32** and (±)-**33** were set to react with cyanotrimethylsilane using Et_2AlCl as catalyst, and (1*R**,2*R**,5*S**,6*R**)-5,6-bis-(*tert*-butyldimethylsilyloxy)-2-(trimethylsilyloxy)-cyclooctane-carbonitrile (±)-**37** in 81% yield and (1*R**,2*R**,5*S**,6*R**)-5,6-isopropilidendioxicyclooct-2-trimethylsilyloxy-1-carbonitrile (±)-**38** in 88% yield were obtained regio and stereoselectively (Scheme 68). The signal at 2240 cm^{-1} in the I.R. spectrum of compound (±)-**37** confirms the presence of the nitrile group and for compound (±)-**38** at 2241 (C≡N) cm^{-1}.



Scheme 68. Opening reaction of the epoxides

The formation of (1*R**,2*R**,5*S**,6*R**)-5,6-isopropilidendioxicyclooct-2-trimethylsilyloxy-1-chloride (±)-**39** is not usually observed but the competition between Cl^- or CN^- could account for it. The absence of signals in the I.R. spectrum for the region of C≡N or $N^+{\equiv}C^-$ corroborates the presence of other group and its mass spectroscopy (**$C_{14}H_{27}O_3SiCl$:** 329.1310; **found** 329.1300; **Δ** = -3.0 ppm) confirms the group as a Chloride.

Treatment of the nitrile (±)-**37** with KOH at 200°C for 20 hours followed by HCl addition (Table 6) led to acid **40** (Entry 1), which was purified by column chromatography with 59% yield, but due to its polarity it was best isolated at the ester stage **43** (80%).

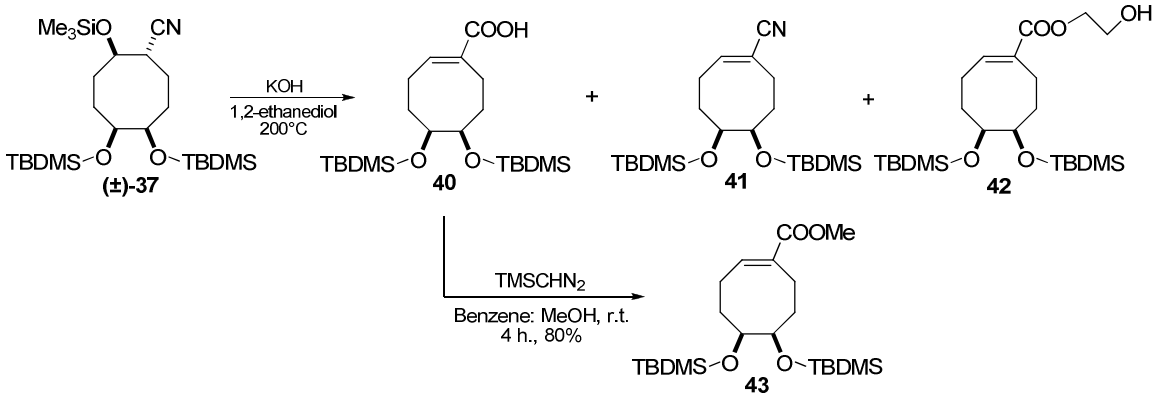


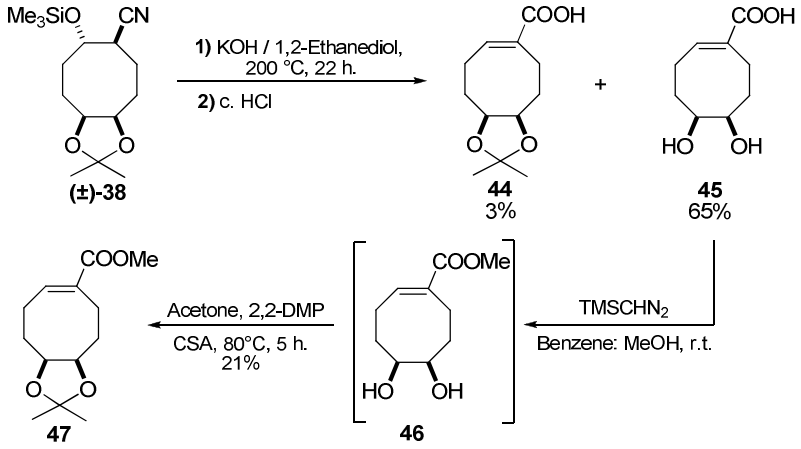
Table 6. Hydrolysis reaction of the nitrile group in compound (±)-**37**

Entry	(±)-37 (mmol)	KOH (mmol)	1,2-Ethanediol (mL)	t (h.)	40 (%)	41 (%)	42 (%)
1	0.30	1.8	2.0	20	59	-	-
2	0.90	4.3	4.0	21	37	26	-
3	0.30	1.6	2.0	54	47	-	14

The formation of the α,β-unsaturated ester can be corroborated by the spectroscopy of compound **43** (Table 28, see 2D NMR part), which shows in its I.R. 1727 cm^{-1} (C=O), has a triplet signal at downfield in 6.91 ppm (*J* 8.0, H-2) and at 141.3 ppm (CH, C-2) in their ^1H and ^{13}C NMR spectra, respectively. In Entry 2, almost at the same conditions of Entry 1 the acid **40** was yielded in 37% and it was also observed that the hydrolysis of the nitrile did not take place but it yield an α,β-unsaturated nitrile **41** confirmed by its signal in the I.R. spectrum at 2218 cm^{-1} (C≡N), a triplet at 6.17 ppm (1H, *J* 8.0, H-2) and 146.2 ppm (CH, C-2) in their ^1H and ^{13}C NMR spectra, respectively. A longer reaction time led to acid **40** in 47% yield (Entry 3) and a secondary α,β-unsaturated hydroxy-ester. This latter product could be obtained in situ by esterification of the acid with excess of 1,2-ethanediol present in the media. Its spectroscopy data show in I.R. the characteristic signals like 3449 (O-H), 1720 (C=O) cm^{-1}, in ^1H NMR a triplet at 6.68-7.11 ppm

(1H, *J* 7.8, H-2) and in ^{13}C NMR at 61.6 (CH_2, CH_2CH_2OH), 66.1(CH_2, CH_2CH_2OH), 142.7 (CH, C-2) and 167.7 (C, *C*OO) ppm.

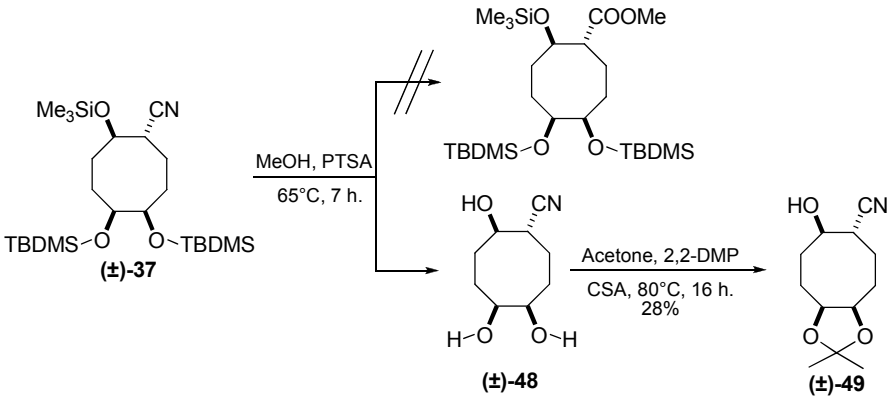
By treatment of (±)-**38** with KOH followed by HCl addition, the hydrolysis reaction of the nitrile group took place as it can be observed in Scheme 69, but deprotection of the diols took place due to the strong conditions and just a low yield of compound **44** (3%) was recovered from the Et_2O extraction, the deprotected product was extracted using *n*-butanol. Expected from the nature of this polar compound it was necessary esterification and protection for its isolation and characterization.



Scheme 69. Hydrolysis reaction of the mixture 1:1 (±)-**38**

The spectroscopy of compound **47** show distinctive signals like 1711 (C=O), 1214 (C-O) and 1039 (C-O-C) cm^{-1} in its I.R spectrum; 6.96-7.02 (1H, dt, *J* 5.4 and 2.0, H-2) and 141.7 (CH, C-2) and 168.5 (C, *C*OOMe) ppm in its ^{1}H and ^{13}C NMR spectra, respectively.

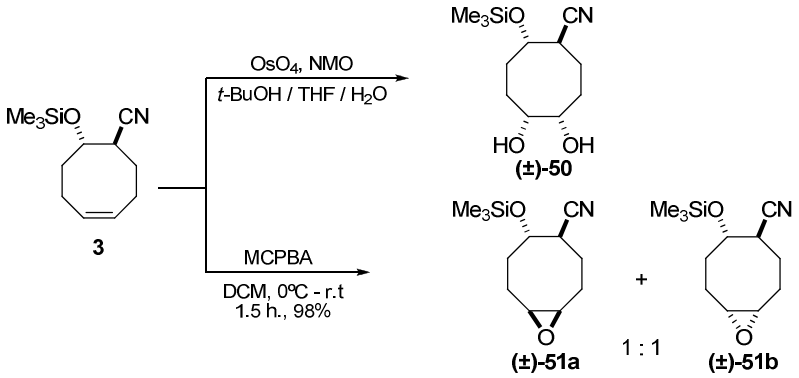
In spite that the best results obtained in the synthesis of α,β-unsaturated ester with C-5 and C-6 functionalized have been those ones using compound (±)-**32**. An alternative would be desirable in order to find another way to increase the yield avoiding the strong conditions of the hydrolysis reaction of the nitrile. In this way, direct ester formation reaction of the nitrile would be an appropriate route (Scheme 70).



Scheme 70. Direct ester formation reaction of compound

Under esterification conditions, the only product observed in the crude of the reaction was (±)-**48**, due to the presence of 1 eq. of PTSA compound (±)-**37** suffers complete deprotection and due to its polarity is best isolated by CC at the 5,6-isopropilidendioxi-stage. The hydroxy and nitrile group can be observed in its I.R. spectrum at 3444 and 2243 cm^{-1}, respectively.

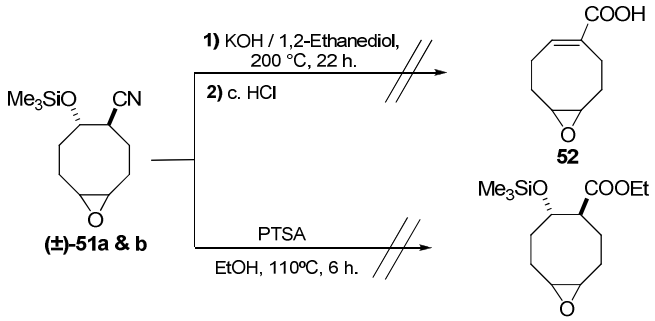
Other pathway was studied using 2-trimethylsiloxi-cyclooct-5-ene-1-carbonitrile **3** as starting material, which incorporates a double bond in C-5 and C-6, used previously in the first synthetic route (Scheme 71).



Scheme 71. Addition of oxygen functions in compound **3**

Dihydroxylation with OsO_4-NMO possibly gave compound (±)-**50** but it could not be recovered after extraction. Epoxidation by addition of MCPBA gave 1:1 ratio mixture of (±)-**51a** and **b** in nearly quantitative yield. As its spectroscopy results reveal, characteristic signals are present in its I.R. spectrum at 2218 and 1252 cm^{-1} corresponding to C≡N and C-O functional groups and in its ^{1}H and ^{13}C NMR spectra show the vanished of the double bond signal and obvious presence of the diastereoisomeric mixture because all the signals are duplicated.

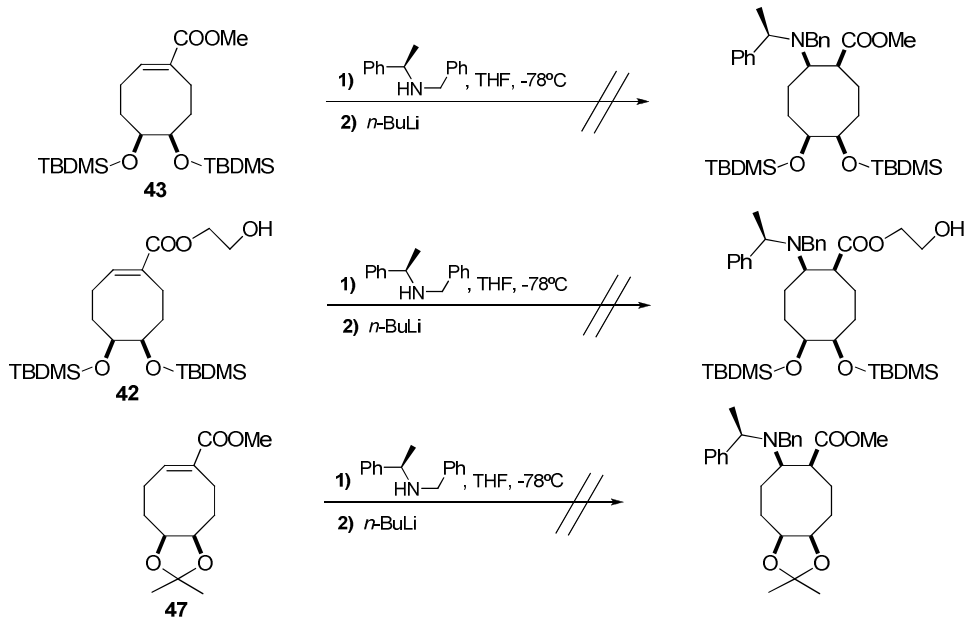
Treatment of mixture (±)-**51a** and **b** with KOH at 200°C for 22 hours followed by HCl addition (Scheme 72) led to the acid **52** present in the ^{1}H NMR spectrum of the crude but due to the low quantity and presence of impurities it was not efficient to carry on its isolation. Furthermore, direct ester formation was performed for reducing the strong conditions of the hydrolysis but unfortunately with not results.



Scheme 72. Reactivity of (±)-**51a** and **b** under hydrolysis and esterification of the nitrile group

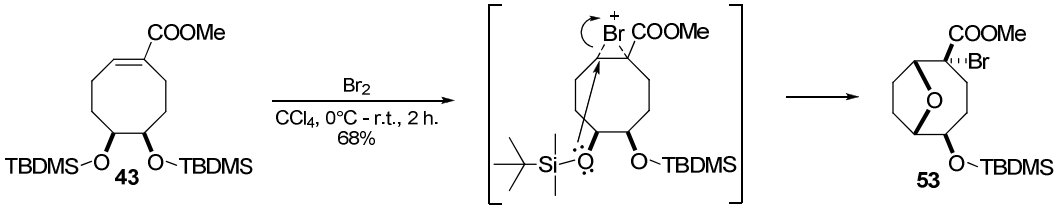
The optimization and recovery of products were not performed at the moment since we already have the necessary products to check their reactivity.

With the cyclooct-1-encarboxylates **42**, **43** and **47** in hand, the protocol of asymmetric Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**C** was performed for these compounds, to obtain precursors adducts in the synthesis of Tashiromine (Scheme 52) but the addition did not work out in none of the explored alternatives (Scheme 73).



Scheme 73. Asymmetric Michael addition of chiral lithium (*R*)-**C**

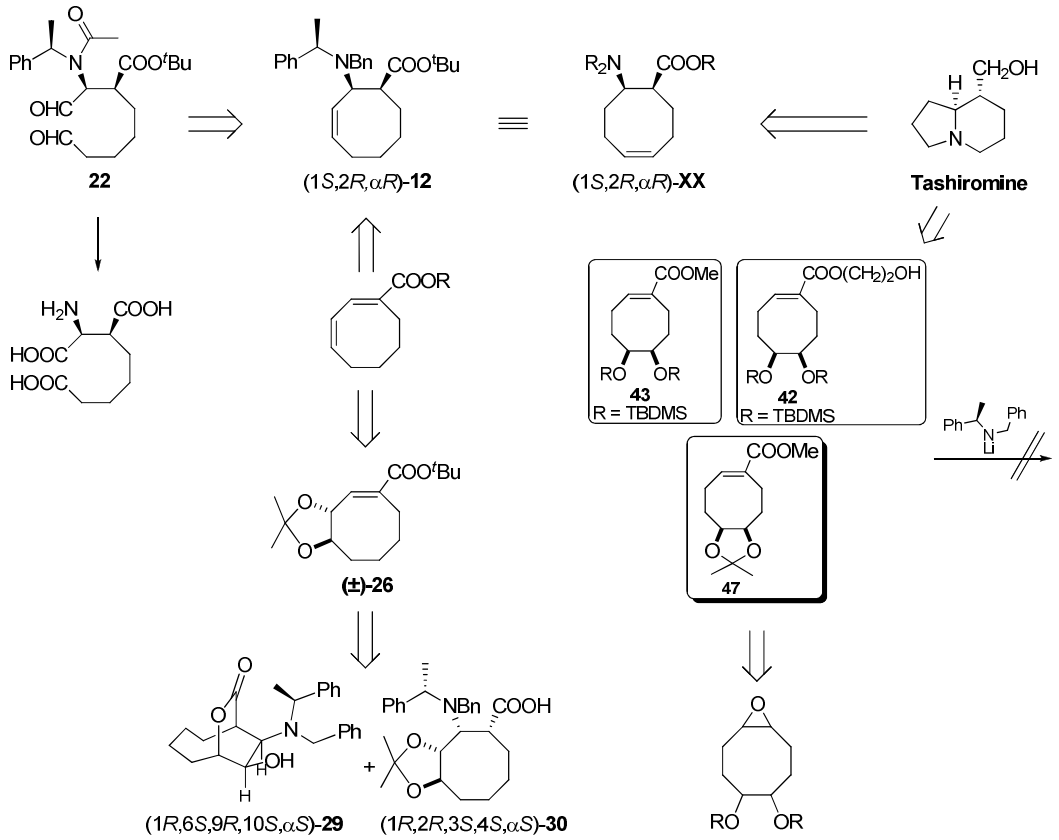
In order to get a diene from the double bond in C-1, a bromination reaction of compound **43** was performed (Scheme 74).



Scheme 74. Reactivity of the double bond in compound **43**

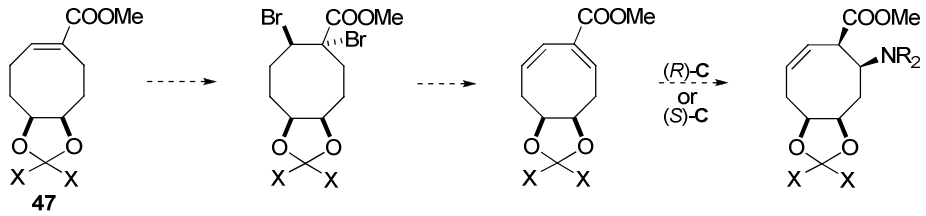
The obtention of compound **53** shows the facility of these types of compounds to carry out intramolecular cyclizations as it was previous observed when compound (±)-**31** was submitted to a normal acetylation reaction. The HMRS of **53** shows a molecular ion at 415.0915 *u*, whose results reveals that the molecular formula corresponds to $C_{16}H_{29}O_4SiBrNa$, the proposed structure in the previous Scheme.

Despite the great effort to find adducts that could bring us to the synthesis of the alkaloid Tashiromine (Scheme 75), this study helped us to design its synthesis from (1*S*,2*R*,α*R*)-**XX**. Compound (1*S*,2*R*,α*R*)-**12** needs appropriate amine protection to perform an ozonolysis reaction to afford the di-aldehyde **22** which can be converted into its β-amino tri-acid. Furthermore, we have been demonstrated the synthesis of interesting functionalized cyclooctanic β-amino acids **29** and **30** *via* a fascinating and complex Michael addition of chiral lithium amide to the racemic mixture of isopropilidendioxi (±)-**26**.



Scheme 75.

From all the previous reactions carried out for the oxygen functionalization of C-5 and C-6, it was observed that the bromination reaction of compound **47** could be a pathway to obtain a Tashiromine precursor. The following alternatives are: use of substituents with less conformational freedom which could prevent the participation of oxygen in the opening of bromonium ion, and with the double-unsaturated ester compound in hand to perform experiments reactions of addition of chiral lithium amides to this favorable systems as shown in Scheme 76.



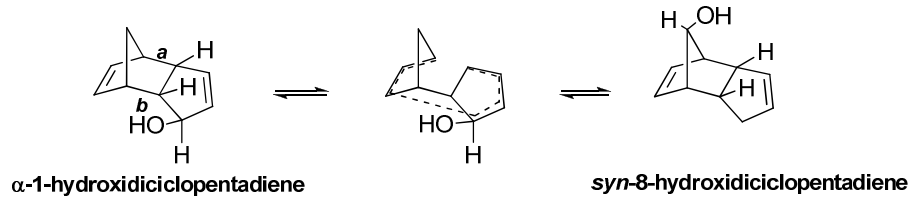
Scheme 76. Future synthetic proposal

PERICYCLIC REACTIONS AND REARRANGEMENTS:

A pericyclic reaction is a reaction in which bonds are formed or broken at the termini of one or more conjugated π systems. The electrons move around in a circle, all bonds are made and broken simultaneously and no intermediates intervene. The requirement of concertedness distinguishes pericyclic reactions from most polar or free-radical reactions, although for many pericyclic reactions reasonable alternative stepwise mechanism can also be drawn.[118] Between the concerted pericyclic reactions, almost always, such reactions turn out to be "symmetry allowed". That is, certain symmetry characteristics of the molecular orbitals involved in a transformation are necessary in order for a concerted reaction to occur.[119]

Some interesting rearrangements can be drawn within this kind of reactions and the stereoselectivity achieved understood by the reaction paths discussed in the comprehensive paper of Woodward and Hoffmann.[120]

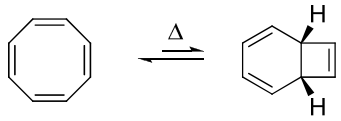
Woodward and Katz[121] observed an intramolecular rearrangement of the Diels-Alder adduct α-1-hydroxydicyclopentadiene at 140ºC, which could be explained by the rupture of the bond ***a***, followed by recombination of the resulting doubly allylic fragment, achieving *sin*-8-hydroxydicyclopentadiene, as shown in scheme 77.



Scheme 77. Intramolecular rearrangement at 140°C

[118] (a) Grossman, R. B. "The Art of Writing Reasonable Organic Reaction Mechanism" 2nd Edition, **2003**, Springer-Verlag, N.Y. (b) Miller, A. "Writing Mechanisms in Organic Chemistry". University of Connecticut, Academic press, Inc. San Diego, California, **1992**.
[119] Fukui, K. *Pure & Appl. Chem*., **1982**, *54*, 1825-1836.
[120] Woodward, R. B.; Hoffmann, R., *Angew. Chem. Int. Ed. Engl*., **1969**, *8*, 781-853; "The Conservation of Orbital Symmetry", Academic Press, New York, **1969**; and their preceding papers cited therein.
[121] Woodward, R. B.; Katz, T. J., *Tetrahedron*, **1959**, *5*, 70-89.

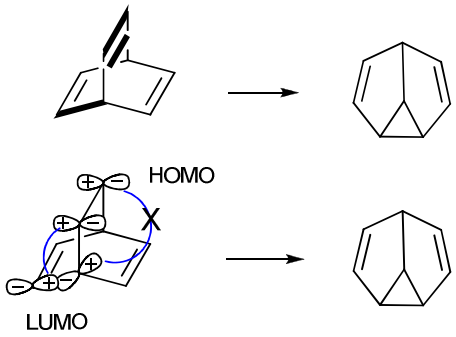
Other interesting example, is the thermal cyclization of cyclooctatetraene to bicyclo[4.2.0]octatriene (Scheme 78).



Scheme 78. Thermal cyclization example

Only 6 π electrons are necessary to affect this cyclization, and only these 6 electrons control the stereochemical course of the reaction. Thus, the thermal reaction follows a disrotatory mode, which gives *cis* orientation at the ring junction. If all eight electrons had been counted, a conrotatory process would have been predicted, leading to a *trans* ring junction which is unlikely for such a ring fusion. In practice, cyclooctatetraene is the more stable isomer and the presence of the bicyclic compound has been demonstrated only through trapping experiments.[118(b)]

An example of a reaction, in which a σ bond and a π bond are involved, is shown in the following intramolecular cycloaddition (Scheme 79).[122] The bonds reacting are highlighted.

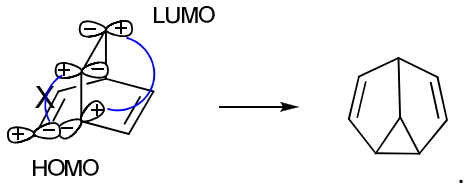


Scheme 79. Analysis of a [2+2] reaction

The lobes of the involved frontier orbitals, in the ground state configuration, are shown in the next equation. The π bond is the HOMO and the σ bond, the LUMO. There is no geometrically feasible way for both termini of each component to interact concerted in a bonding way. The appropriate lobes do not match in one of the necessary interactions. Thus, this reaction is not thermally allowed.

[122] Fukui, K. *Acc. Chem. Res*., **1971**, *4*, 57-64.

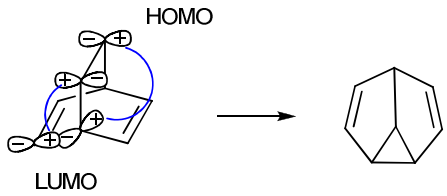
If the HOMO is the σ bond and the LUMO is the π bond, there is the same problem:



Scheme 80.

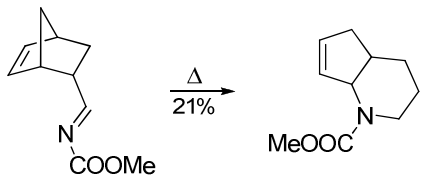
Now, it is the other end of the termini where the reaction is not feasible. The front lobe of the π bond does not extend far enough to the left and downward to overlap effectively with the necessary + lobe of the HOMO (Scheme 80).

The next thing to consider is a photochemical process. The HOMO is an antibonding π* orbital, because upon absorption of light, an electron is promoted from the bonding to the antibonding orbital of the double bond. (It is easy to photochemically excite a π bond than a σ bond). The symmetries now match for the transformation. Thus, this is a photochemically allowed reaction (Scheme 81).



Scheme 81. Photochemical process

It is also surprising the change of the structure that is shown in the following scheme. Starting from a bicycle[2.2.1]heptene system, it is achieved the piperidine via an aza-Cope rearrangement.[123]



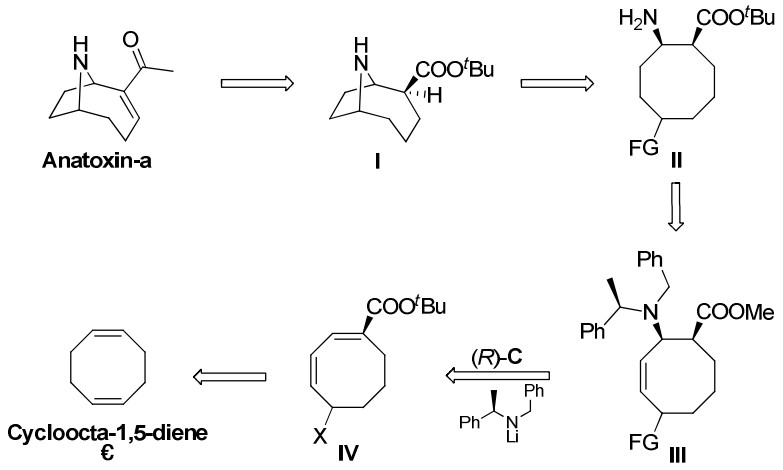
Scheme 82.

To sum up, this examples show the tendency of molecules with several double bonds to reorganize their structures and to give compounds with different skeletons from the starting materials.

[123] Wu, P.-L.; Chu, M.; Fowler, F. W., *J. Org. Chem*. **1988**, *53*, 963-972.

SYNTHESIS OF A FUNCTIONALIZED C-5 INTERMEDIATE IN THE APPROACH TO THE SYNTHESIS OF ANATOXIN-*A*

As it can be observed in Scheme 83, the objective compound Anatoxin-*a* could be obtained from the intermediate **I** through transformation of the ester group into methyl ketone and formation of the double bond. The 9-azabyciclo[4.2.1]nonane **I** can be generated from **II** throughout condensation of the amine group with the functional group in C-5 position. In turn, **II** comes from the hydrogenation reaction of the double bond present in **III** followed by a hydrogenolysis of the benzyl groups from the amine. The key step is the formation of the intermediate **III**, where the stereogenic centers have to be generated through the Michael addition of the chiral lithium amide (*R*)-**C** over **IV**, which can be easily afforded from cycloocta-1,5-diene. The intermediate **III** and its analogues can lead to important adducts in the synthesis of alkaloids by modification of the functionality in the conjugate unsaturated ester.

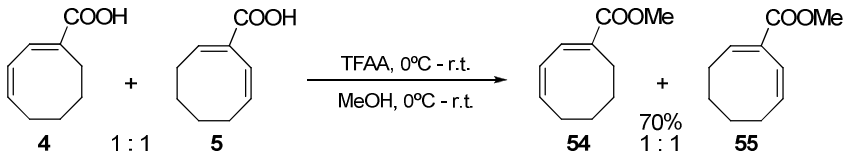


Scheme 83. Retrosynthetic analysis of Anatoxin-*a*

Synthesis and reactivity of (1*E*,3*Z*)-*tert*-butyl and methyl 5-oxo-cycloocta-1,3-diene carboxylate:

Preparation of starting materials:

The synthesis of *tert*-butyl cycloocta-1,3 and 1,7-dienecarboxylate, **6** and **7** respectively, were previously described. Due to the stability of the methyl esters, compounds **54** and **55** respectively prepared from the acids **4** and **5** (1:1 ratio) by addition of Trifluoroacetic anhydride and MeOH gave a 1:1 ratio mixture in 70% yield (Scheme 84). Through acidulation of the aqueous phase with HCl_c and extraction with DCM the unreacted mixture of the acids could be recovered (12%).



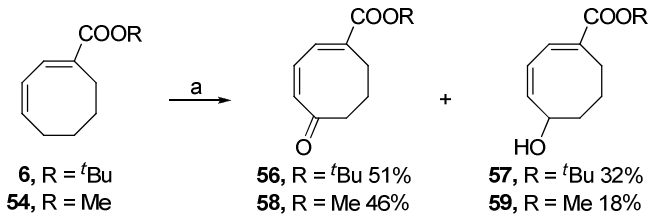
Scheme 84. Preparation of the methyl esters

This reaction can also be carried out by addition of $TMSCHN_2$ in benzene:MeOH (1:1 v/v), which generally provides very good yields.

Synthesis of (1*E*,3*Z*)-*tert*-butyl and methyl 5-oxocyclooct-1,3-diene carboxylate:

Taking into account that the key step in the synthesis of Anatoxin-*a* is the introduction of a functional group in C-5 position of the cycloocta-1,3-diene system. In our research group the reactivity of cyclooctadiene esters with different oxidants has been previously studied,[124] like MCPBA, Na_2CrO_4 and SeO_2, being well known the capacity of the last one to oxidate an allylic methylene position. The reaction of the unsaturated esters **6** and **54** by addition of SeO_2 led to the formation of functionalized compounds in the 5 position.

When compounds **6** and **54** were treated with SeO_2 to reflux in a mixture of glacial acetic acid and *tert*-butanol for 5.5 and 5 hours, respectively, the cyclooctadienones **56** and **58** were obtained with 51% and 46% yields after column chromatography. Cyclooctadienols **57** and **59** were also isolated with 32% and 18% yields (Scheme 85).

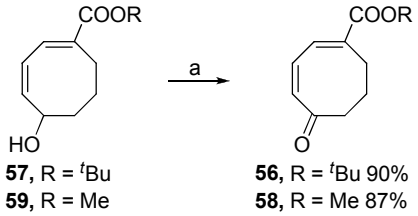


Scheme 85. *Reagents and conditions:* (a) SeO_2, CH_3COOH, *t*-BuOH, 105°C, R=^{t}Bu, 5.5 h., R=Me, 5 h.

The oxidation with TPAP of the allylic alcohols **57** and **59** (Scheme 86) led us to recover the important intermediates **56** and **58** in 90% and 87%. Similarly, oxidation of **57** with SeO_2 afforded

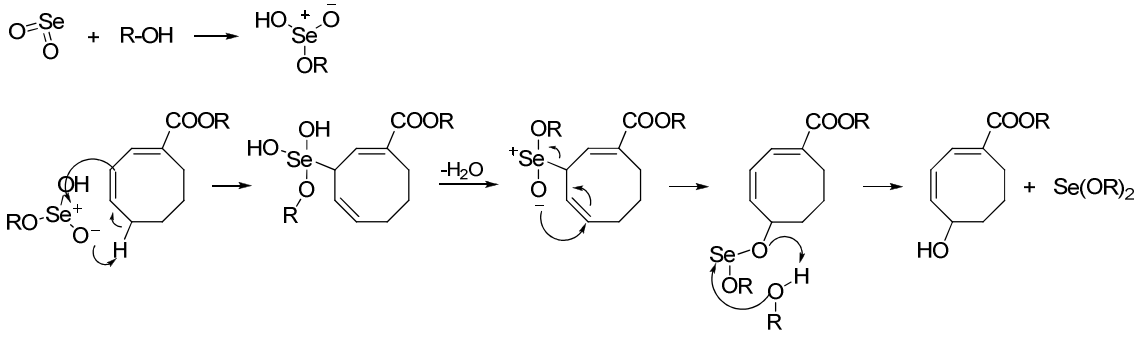
[124] Víctor M. Vicente Barbero "*Aproximación a la síntesis asimétrica de Anatoxina-a*" Grado de Salamanca, **2003**.

compound **56** with 62% yield, which suggests that the alcohol is an intermediate in the oxidation reaction of the ester to the ketone as it is shown below in Scheme 87.[125]



Scheme 86. *Reagents and conditions:* (a) TPAP/NMO, 3A Mol. Sieves, DCM.

Selenium dioxide will convert an allylic methylene group into the corresponding alcohol (Guillemonat-Sharpless allylic oxidation).[126] In terms of reaction mechanism, SeO_2 and the allylic substrate react *via* pericyclic process, beginning with an ene reaction that activates the C-H bond.[127] The second step is a [2,3] sigmatropic reaction.[128] In this kind of oxidations involving SeO_2, are often carried out with catalytic amounts of the selenium compound in presence of a catalyst or co-oxidant such as hydrogen peroxide or best *t*-BuOOH at room temperature.[129] Unlike this process, in our case, a large excess of SeO_2 was used, with glacial acetic acid as catalyst and *t*-BuOH as a solvent. Unreacted SeO_2 still present in the reaction medium will possibly continue the oxidation affording the unsaturated ketone. In addition, we have to take into account that epoxides or unsaturated ketones might also be formed in this kind of reactions.

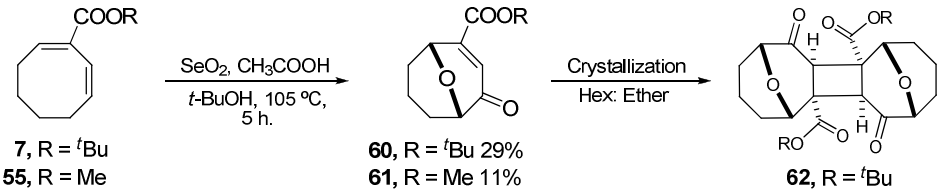


Scheme 87. Mechanism of Selenoxide oxidation

[125] C. Paulmier, "*Selenium Reagents and Intermediates in Organic Synthesis*", Pergamon Press, Oxford, **1986**.
[126] Guillemonat, A. *Ann. Chem*. (*Warsaw*), **1939**, *11*, 143.
[127] Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc*., **1973**, *95*(23), 7917-7919.
[128] Sharpless, K. B. and Lauer, R. F. *J. Am. Chem. Soc*., **1972**, *94*(20), 7154-7155.
[129] Jerussi, R. A. *Selected Org. Transf*. **1970**, *1*, 301.

Furthermore, it has been observed that when compound **6** is left at room temperature and atmospheric conditions for extended time (1 month) compound **56** is obtained by oxidation reaction with the atmospheric oxygen. The spectroscopy data analysis of compounds **56** allow us to deduce the incorporation of the carbonyl group in C-5 position as shown its ^{13}C NMR spectra at 205.2 ppm and the spectroscopy data analysis of compounds **57** and **59** show us the incorporation of the hydroxy group in C-5 position from their ^{1}H NMR spectra at 4.36 ppm (1H, dd, *J* 8.2 and 9.6) and 4.06-4.17 ppm (1H, dd, *J* 7.4 and 8.8), respectively.

On the other hand, treatment of compounds **7** and **55** under the same oxidation conditions with SeO_2 afforded *tert*-butyl and methyl 4-oxo-9-oxabicycle[3.3.1]non-2-ene-2-carboxylate **60** and **61** in 29% and 11% yield, respectively (Scheme 88) and 11% of by-products in each reaction, which could not be identified due to the low quantity obtained.



Scheme 88. Oxidation reaction of compounds **7** and **55** with SeO_2

The spectroscopy data analysis of compounds **60** and **61** allow us to deduce the incorporation of the carbonyl group in C-4 position in its ^{13}C NMR spectrum at 199.2 ppm and experiments 2D NMR (Table 29) corroborate the formation of the oxygenated bridge, specially by cross-peak between H-1 and C-5 (Fig. 24).

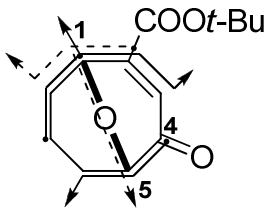
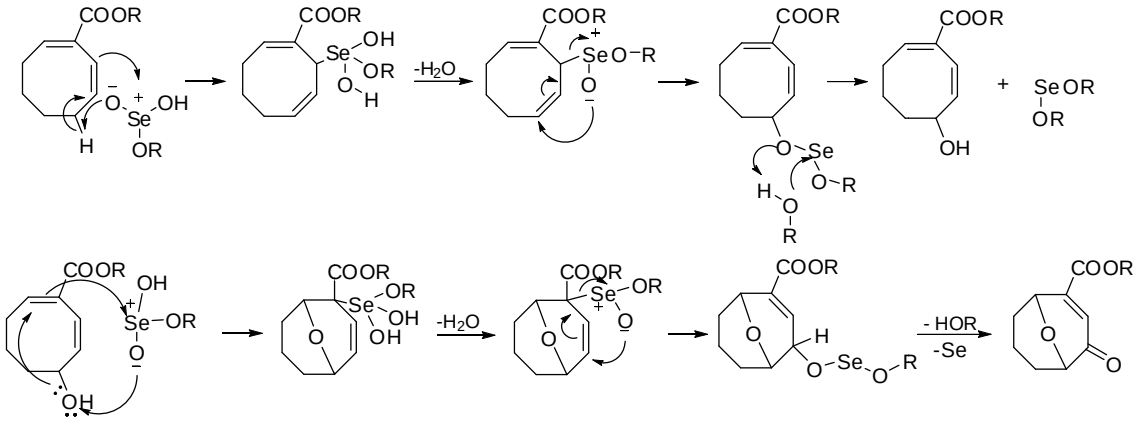


Figure 24. Heteronuclear multiple bond conectivity of compound **60**, ^{13}C-^{1}H long distance.

The mechanistic proposal for the formation of compounds **60** and **61** *via* Selenium dioxide will convert an allylic methylene group into the corresponding alcohol as it was above described for compounds **57** and **59**, followed by an intramolecular Michael addition where the enolate anion is facilitated by the selenium ion to give the intramolecular epoxide. The next step is [2,3]

sigmatropic reaction from the Selenoxide compound to give the oxygenated intermediate in C-4 position, which evolve to give the final ketone, as shown in Scheme 89.



Scheme 89. Mechanism proposal of Selenoxide oxidation of compounds **7** and **55**

To corroborated the structure of this compound, the two esters were left in a mixture of Hex:Ether (1:1 v/v) and after a month crystals from compound **62** coming from **60** were obtained. The structure shown in Scheme 88 was corroborated *via* X-Ray spectroscopy for compound **62** (Fig. 25, Annexe **C**). The NMR spectra are simple and similar to those ones from the monomer with the absence of the double bond due to the existence of a C2 symmetry axis (Table 30, see 2D NMR part).

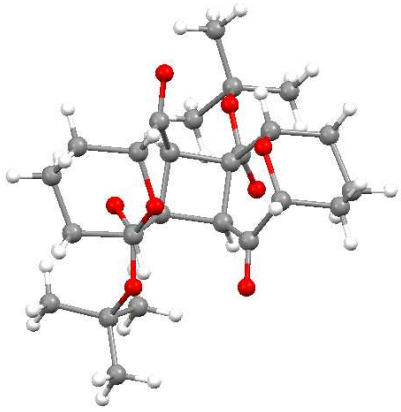
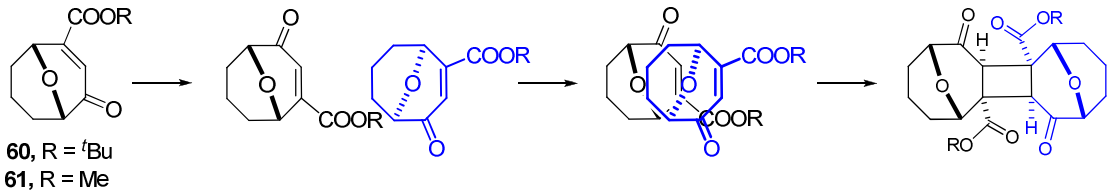


Figure 25. Molecular structure representation of Compound **62**

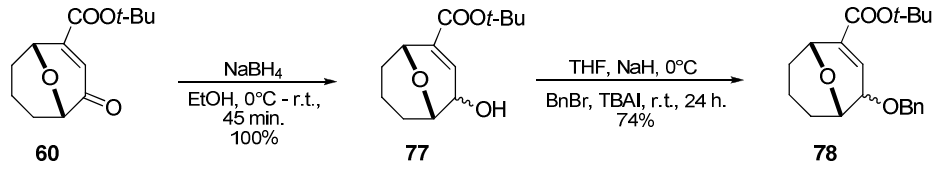
The reaction that takes place in the formation of dimer **61** is a photochemical cyclization $\pi_2 s + \pi_2 s$ which is allowed for the rules of Woodward and Hoffmann.[120]



Scheme 90. Mechanism proposal for the formation of the dimer

Attracted by the functionalization of these oxabicycles[3.3.1] **60** and **61** a short study of their reactivity was made.

With the functionalized oxabicycle[3.3.1] **60** in hand, we started with the normal Michael addition of (*R*)-**C** at -78°C which was left to react for 3 hours. Only starting material was recovered after work up. The possible formation of the conjugated enolate may prevent the α,β-unsaturated ester act like the Michael acceptor as observed for compound **56**. By reduction of the ketone group with sodium borohydride was quantitatively achieved compound **77**, which was protected by addition of benzyl bromide giving *tert*-butyl 4-benzyloxy-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate **78** with 74% yield (Scheme 91), which was full characterized.



Scheme 91. Deprotection and protection reactions

Spectroscopic data of compound **78** show new signals at 4.60 ppm (2H, s, C*H*$_2$Ph) and 7.35 ppm (5H, H-Ar) due to the addition of a benzyl molecule corroborated by its ^{13}C NMR at 71.7 ppm (CH$_2$, *C*H$_2$Ph), 127.9, 128.1 and 128.7 ppm (CH x 5, Ph) and 138.1(C, C$_{ipso}$).

With compound **78** in hand, we subjected it to addition of primary and secondary amines (Table 19, see experimental part) under different conditions with no results. In all cases, only starting material was quantitatively recovered after the works up, which show us the stability of its precursor bicycle ring and its ability to crystallize. Chiral lithium amides turn out to be unreactive as the lithium atom probably suffers chelation with the two oxygen atoms, which correspond to the ester and the epoxide, as shown in Figure 26.

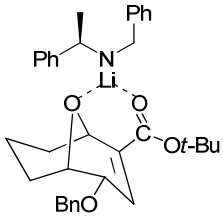
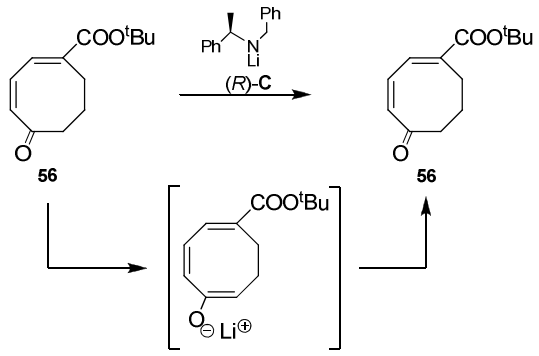


Figure 26.

Reactivity of (1*E*,3*Z*)-*tert*-butyl and methyl 5-oxocyclooct-1,3-diene carboxylate:

When compound **56** is submitted to react with (*R*)-**C** (2.2 eq.) in THF at -78°C, using the standard procedure, only starting material was recovered after 2 hours reaction. Deprotonation in α probably led to the formation of the conjugated enolate, which prevents the α,β-unsaturated ester act like the Michael acceptor (Scheme 92).



Scheme 92. Formation of the conjugated enolate

To avoid this we decided to protect the carbonyl group as an imine by treatment with primary amines.

Compound **56** was dissolved in ethanol and submitted to addition of benzylamine. The system was refluxed at 110°C for different periods changing the equivalents of benzylamine to optimize the reaction (Table 7).

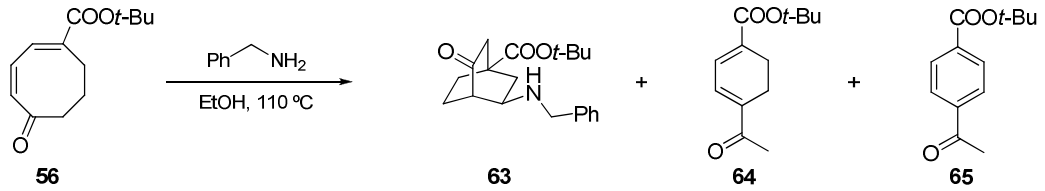
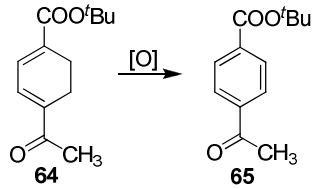


Table 7. Addition of benzylamine, variation of the concentration and reaction times

Entry	Benzylamine (Eq.)	t (h.)	63 (%)	64 (%)	65 (%)	Recovery of 56 (%)
1	1	20	30	25		23
2	1.2	24	40	40		
3	1.6	30	41	38	1	
4	1.6	114	42	23	5	

As it can be observed in the previous Table, the best yield of 63 (42%) was obtained by the addition of 1.6 eq. of benzylamine after 114 hours reaction. Compound **65** is formed by oxidation of **64** during purification by CC, being **64** the only by-product observed by ^{1}H NMR spectroscopy of the reaction crude. This fact was confirmed by the obtention of **65** when a solution of **64** was exposed at atmospheric oxygen for a period of time, being the aromatization the driving force of the process (Scheme 93).



Scheme 93. Oxidation under atmospheric conditions

The spectroscopy data analysis of compound **63** allow us to deduce the incorporation of benzylamine in its ^{1}H NMR spectrum at 7.21-7.32 ppm (5H, m, Ph) and 3.70 and 3.80 ppm (2H, S_{AB}, *J* 13.2, HN-C*H*$_2$-Ph). Furthermore, no signals of the double bond of the cyclooctadiene ring are observed. In the ^{13}C NMR spectrum the most remarkable signals are at 213.0 ppm (C, C-5) observed for a ketone group and the *tert*-butyl signals of the ester are present at 27.9 ppm (CH_3 x 3, COOC(*C*H$_3$)$_3$), 80.8 (C, COO*C*(CH$_3$)$_3$) and 173.8 (C, *C*OOC(CH$_3$)$_3$), respectively. Highlights the emergence of two methylenes at 45.6 ppm (CH_2, C-6) and 50.6 (HN-*C*H$_2$-Ph) as well as a quaternary carbon at 43.5 ppm (C, C-1) assigned to a bicycle system [2.2.2]octane incorporating a ketone and as a substituents *tert*-butoxicarbonyl and benzylamine groups. The 2D NMR experiments (Table 31) led us to establish its structure and the complete assignment of its spectroscopy data. Figure 27 shows the most relevant connectivities observed.

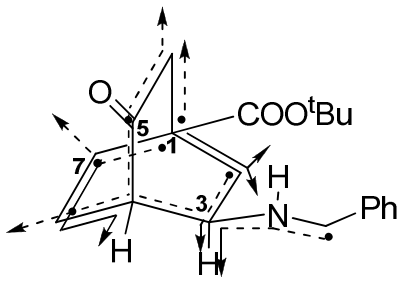


Figure 27. Heteronuclear multiple bond conectivity of compound **63**, ^{13}C-^{1}H long distance

Figure 28 shows the observed correlations in the NOE experiments spectrum. The NOE between H-3 and H-4 indicates the *cis*-configuration and other NOES led us to the assignation of the methylenes hydrogen like in α or β-position.

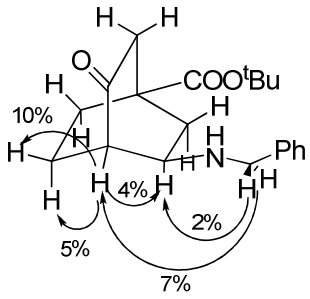


Figure 28. Nuclear Overhauser Effect correlations of compound **63**

However the proposed structure of the bicycle system [2.2.2]octane can be corroborated later by X-Ray spectroscopy data.

When compound **64** is isolated, it draws particular attention for the simplicity of its ^{1}H NMR spectrum: 1.49 (9H, s); 2.34 (3H, s); 2.46-2.48 (4H, m); 6.94 (1H, S.AB, *J* 6.0); 7.02 (1H, S.AB, *J* 6.0) and in its ^{13}C NMR spectrum also shows four olefinic carbons, two of them quaternaries at 136.0 and 140.3 ppm, and the other two methines at 130.8 and 138.3 ppm, the *tert*-butoxicarbonyl group, a carbonyl at 198.0 ppm, two methylenes at 20,4 and 21.8 ppm and a methyl at 25.4 ppm.

Given the unexpected ring contraction reaction from cyclooctane ring to a cyclohexanic system we decided to make the unequivocal assignment of the structure **64**. The 2D NMR experiments allow us to deduce the structure and to make the complete assignment of the signals. The most significant connectivities are shown in Figure 29 and Table 32 (see 2D NMR part).

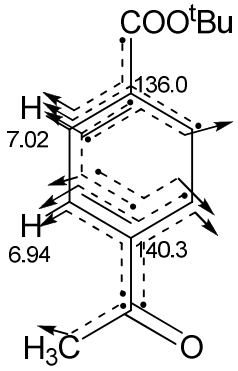
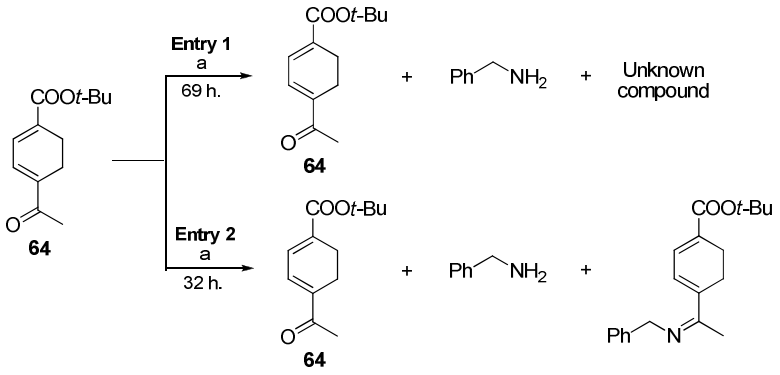


Figure 29. Heteronuclear multiple bond conectivity of compound **64**, ^{13}C-^{1}H long distance.

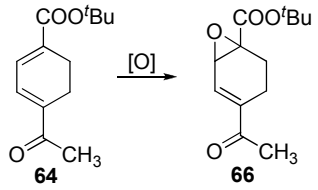
It is worth to mention that the correlation of the carbonyl at 198.0 ppm with the methyl and the hydrogen at 6.94 ppm fix the acetyl group conjugated to the double bond CH at 6.94 and 132.3 ppm. Correlation at three bonds of the carbons at 136.0 and 140.3 ppm with the hydrogens at 6.94 and 7.02 are relevant because they allow to establish the diene as a 1,4-disubstituted.

Taking into account that the isolation of the unexpected ring contraction **64** from this reaction is kind of surprising, this compound may take part as intermediate in the formation of the bicycle system [2.2.2]. For this reason it was submitted to react under the same conditions (Scheme 94). In Entry 1, the reaction was refluxed for 69 hours. In the ^{1}H NMR spectrum from the crude starting material, benzylamine and an unknown compound were detected. This last one could not be isolated after CC. A second reaction was refluxed for a shorter time (Entry 2) and the same ^{1}H NMR spectrum was obtained (annexed in spectroscopy part) which shows the three compounds, we proposed that the unknown compound might be the imine, which can be easily deprotected by the silica from the CC.



Scheme 94. *Reagents and conditions*: (a) Benzylamine (Entry 1=1.22 eq., Entry 2 = 1.6 eq.), EtOH, 110°C.

It is noteworthy that purification of fractions containing compound **64** after a time also afforded the aromatic compound **65** and a small quantity of the epoxidized compound **66** (Scheme 95), which structure has been corroborated by its spectroscopy data and 2D NMR experiments (Table 34).



Scheme 95. Oxidation under atmospheric conditions.

Figure 30 shows the most relevant observed correlations in the NOE experiments for compound **65** and **66**, like the 1,3 disposition for the epoxide diene precursor. This allows us to corroborate the 4 position of the acetyl group.

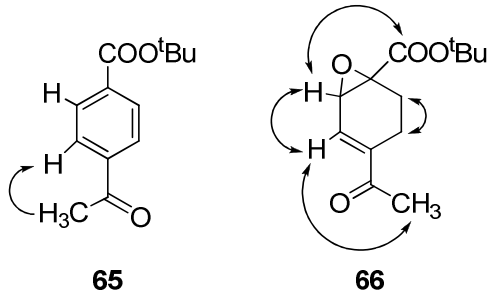


Figure 30. Nuclear Overhauser Effect correlations.

From the spectroscopy data of compound **66** the most important correlations are between the carbonyl carbon at 197.2 ppm and H-3 at 6.89 ppm, which fix the acetyl group conjugated to 131.9 ppm, also its long distance coupling with H-5_B at 2.72 ppm and at three bonds coupling of the methylenes at 18.9 ppm with H-2 at 3.62 ppm and at 21.1 ppm with H-3 at 6.89 ppm. The chemoselectivity exhibit by this reaction, being oxidized only the double bond at C-1 position is really interesting and can be used for synthetic purposes.

Given the ease to the partial oxidation of compound **64** to yield compound **65**, we decided to performed some oxidation reactions to afford aromatic compounds as it is described in bibliography[130] like indicates Table 8.

[130] (a) Fieser, L. F.; Ourisson, G. *J. Am. Chem. Soc*. **1953**, *75*, 4404-4414. (b) Zee-Cheng, K.-Y.; Cheng, C. C. *J. Heterocycl. Chem*. **1967**, *4,* 163. (c) Van Tamelen, E. E.; Hildahl, G. T. *J. Am. Chem. Soc*. **1956**, *78*, 4405-4410. (d) Jpn. Patent 56 055 345, *CA* **1981**, *95*, 186 653e.

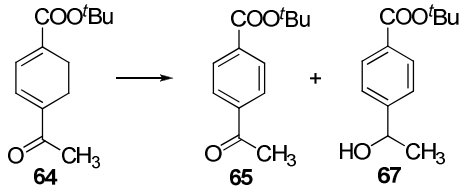
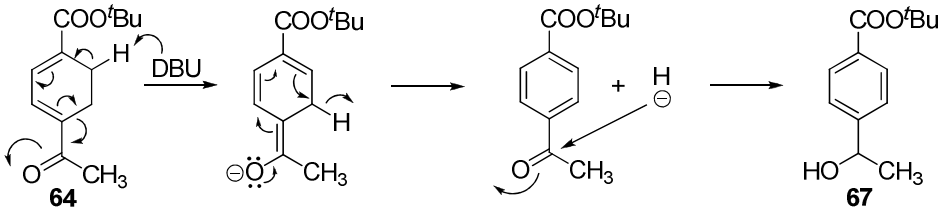


Table 8. Oxidation reactions to afford aromatic compound **65**

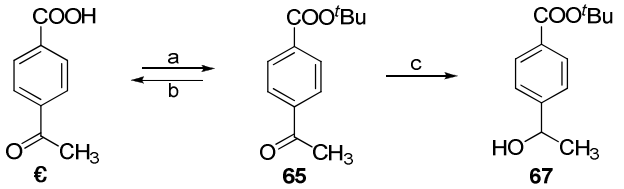
Entry	64 (mmol)	Reagent (mmol)	Solvent (mL)	t (h.)	Recovery of 64(%)	65 (%)	67 (%)
1	0.26	SeO_2 (0.54)	EtOH (10)	66	60	40	-
2	0.099	SeO_2 (0.39), CH_3COOH	*t*-BuOH	15	Decomposition of the starting material	-	-
3	0.049	DDQ (0.056)	PhH	20	41	52	-
4	0.13	DDQ (0.19)	PhH	62	31	50	-
5	0.06	DBU (0.11)	$PhCH_3$	20	7	64	12.5
6	0.015	Br_2 (0.03)	CCl_4	2	-	100	-

The aromatic compound **65** can be quantitative afforded by treatment under Br_2 (Entry 6) and probably with some of the reagents used but with longer reaction periods of time. The obtention of the alcohol **67** by addition of DBU is possibly due to the hydride extrusion in the aromatization of the original anion formed under basic treatment (Scheme 96).



Scheme 96. Mechanistic proposal of compound **67**

Finally, structures **64** and **65** have been corroborated by total synthesis using commercial 4-acetylbenzoic acid as starting material, as shown in Scheme 97.



Scheme 97. *Reagents and conditions:* (a) TFAA, *t*-BuOH. (b) TFA. (c) $NaBH_4$, MeOH.

The esterification reaction of the commercial available 4-acetylbenzoic acid with TFAA and *t*-BuOH afforded a compound with identical physic properties as compound **65** and this one by a reduction reaction with sodium borohydride quantitatively yielded compound **67**. Likewise, the hydrolysis of compound **65** with TFA produced the acid with 100% yield.

Going back to the reactivity of **56** with amines, the previous reaction afforded a racemic mixture because the substrate and reagent were not chiral. For this reason we decided to carry on the study of the reactivity by using chiral α-substituted amines, as shown in Table 9.

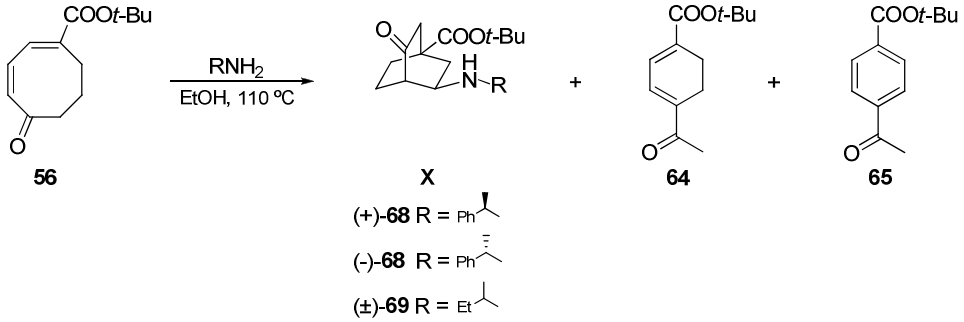


Table 9. Treatment of **56** under α-substituted amines

Entry	RNH_2 (eq.)	T (°C)	t (h.)	Recovery 56 (%)	X (%)	64 : 65 ratio (%)
1	(*R*)-*N*-α-methylbenzylamine (1.2 eq.)	110	40	-	(+)-**68** (26)	20 : 1 (50)
2	(*R*)-*N*-α-methylbenzylamine (1.6 eq.)	110	114	7	(+)-**68** (34)	13 : 1 (42)
3	(*S*)-*N*-α-methylbenzylamine (1.2 eq.)	110	48	19	(-)-**68** (33)	44 : 1 (45)
4[a]	(*S*)-*N*-α-methylbenzylamine (1.2 eq.)	110	45	7	(-)-**68** (23)	58 : 1 (59)
5[b]	(*S*)-*N*-α-methylbenzylamine (1.2 eq.)	130	96	-	(-)-**68** (30)	62 : 1 (63)
6	(*S*)-*N*-α-methylbenzylamine (1.6 eq.)	110	116	1	(-)-**68** (39)	18 : 1 (56)
7	(±)-*sec*-butyl amine (1.2 eq.)	110	96	14	(±)-**69** (18)	38 : 1 (39)

[a] Reaction under light, hv = 200 W.
[b] Reaction in the absence of light and Monoglyme (dimethoxyethane) was used as a solvent.

It is worth to emphasize the generality of the reaction, being applicable to different primary amines (substituted in α or not), although, there is a decrease in the yields when substituted amines are used or when the amines are not benzylic (Entry 7). Also, there is not a big difference when the reaction is performed in the presence or absence of light.

Once again, after performing purification by CC the rearrangement and contraction product **64** and the bicycle[2.2.2]octane were isolated. Analysis of the ^{1}H NMR spectra from the crudes did not

show the presence of other diastereoisomers, the e.e. is determined by the own homochiral amines employed. (e.e. >95%). For this reason, it can be set for compound (+)-**68** a d.e.>95% and e.e.>95%, data that agrees with the high optical rotation power measured as $[\alpha]_D^{20}$= +32.7 (*c* 0.90, $CHCl_3$), but it cannot be corroborated due that it is the first time that this compound has been obtained according to the literature review.

Compound (+)-**68** was crystallized in a mixture of Hex/EtOAc (1:1 v/v) and its structure and absolute configuration was corroborated by X-Ray spectroscopy (Fig. 31, Annexe **D**) and therefore the analogues obtained in this series of reactions. When the reaction is performed by addition of (*S*)-*N*-α-methylbenzylamine analogously (-)-**68** is obtained, with the same physic properties and spectroscopy data but with opposite rotation power $[\alpha]_D^{20}$ = -31.8 (*c* 0.99, $CHCl_3$) which allow us to propose it as the above enantiomer.

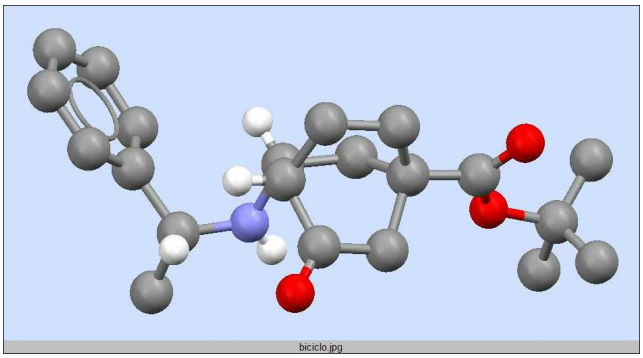
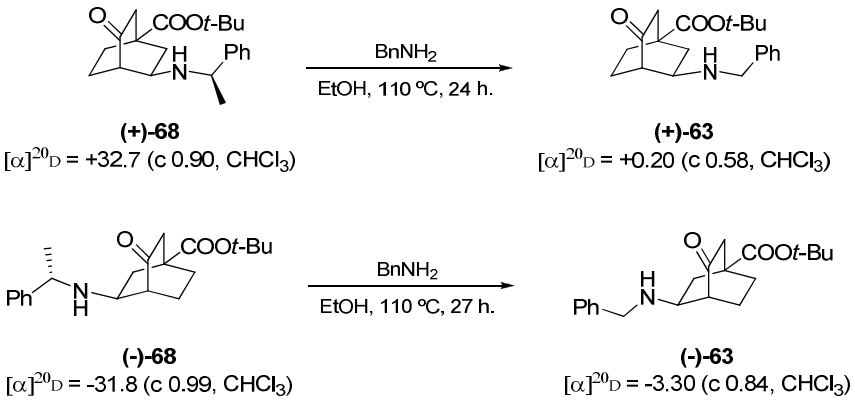


Figure 31. Molecular structure representation of Compound **(+)-68**

However, in an attempt to transform the carbonyl groups from compounds (+) and (-)-**68** into amine by treatment with benzylamine, compounds (+) and (-)-**63** were respectively achieved. These compounds have been previously described, although with rotatory powers measurement near to zero, which opens up new uncertainties about the absolute assigned stereochemistry and proposes the development of new pathways to determine it.



Scheme 98. Reactivity of compounds (+) and (-)-**68** with benzylamine

It remains to determine the mechanism of this transamination reaction where can be involucrate an anchimeric assistance of the carbonyl group or the formation of an oxetane by additional nucleophilic attack of the benzylamine to the carbonyl and elimination of the α-methylbenzylamine, and by a new opening of the oxetane by benzylamine regenerating the carbonyl group again. Currently, attempts to afforded the hydrogenolysis of compound (+) and (-)-**68** in order to determine the rotation powers of the amines products have been unsuccessful (Table 10) because the formation of a polymeric specie is detected and it might be avoided by previous protection of the carbonyl group.

The treatment of compound **56** by addition of secondary and tertiary amines could give us more information about the mechanism of the observed reactivity, for this reason were performed the following reactions as shown in Table 10.

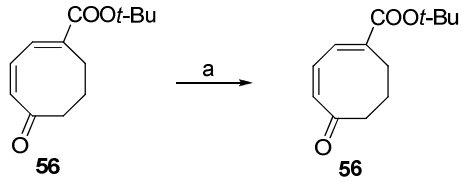
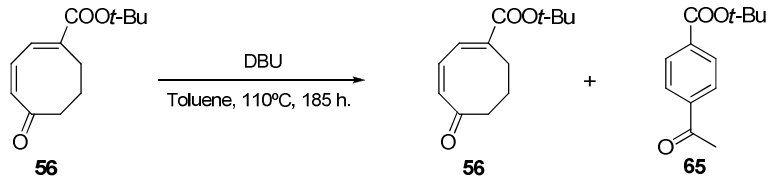


Table 10. Reactivity with secondary and tertiary amines and stability of compound **56**

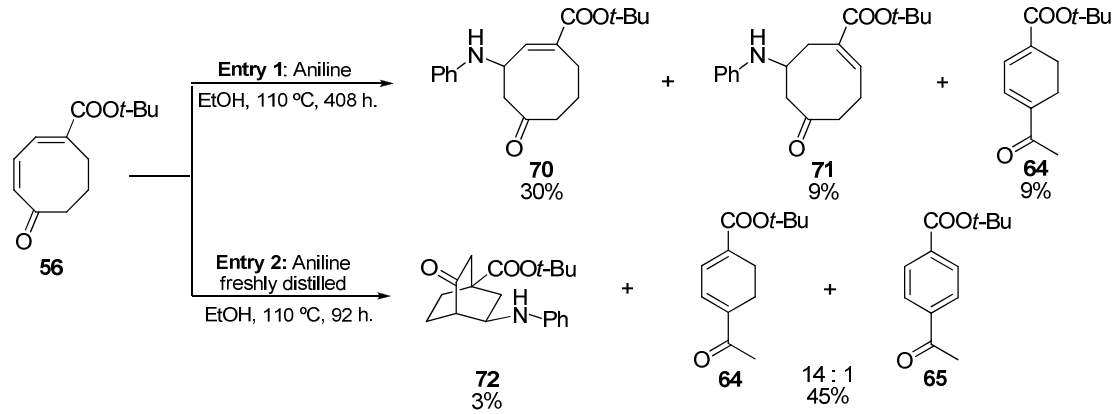
Entry	(a)	Solvent	T (°C)	t (h.)	Observations
1	-	EtOH	110	176	Recovery of **56** (S.M.)
2	Et_2NH	EtOH	110	54	Recovery of **56** (S.M.)
3	(*R*)-**C**	EtOH	110	40	Recovery of **56** (S.M.)
4	Et_3N	EtOH	110	84	Recovery of **56** (S.M.)
5	PTSA	THF	110	90	Recovery of **56** (S.M.)
6	DDQ	PhH	95	62	Recovery of **56** (S.M.)
7	DBU	$PhCH_3$	110	185	**56** (S.M.): **65** 2:1 ratio mixture

When compound **56** is refluxed in EtOH for a long period (Entry 1) the starting material is recovered unchanged which means that it is necessary to add a promoter even to obtain compound **64** and also made us to realize that it is not a simple thermodynamic reaction. The same happens when secondary amines like diethylamine or the chiral one (*R*)-*N*-benzyl-*N*-(α)-methylbenzylamine (Entry 3) or tertiary like triethylamine were added into the reaction systems. For going further into this study, it was also recovered compound **56** by addition of and oxidant like DDQ or strong acid like PTSA. Only when the reaction was performed by addition of DBU in toluene at 110°C for 185 hours reflux it afforded compound **56** and **65** in a 2:1 ratio mixture observed in the ^{1}H NMR spectrum from de crude (Scheme 99).



Scheme 99. Reactivity of compound **56** with DBU

Despite of the lower nucleophilicity shown by the nitrogen in the aniline, we decided to study the reactivity of compound **56** by addition of this one and in order to extent the range of amines (Scheme 100).



Scheme 100. Reactivity of compound **56** with aniline

In the first Entry, the reaction was set to react controlled by TLC, but after 408 hours it was stopped as no significant changes were observed by TLC; it was interesting to observed that when purification by CC of the crude from Entry 1 was performed, 5% of starting material was recovered in the last fractions in spite that it is the less polar compound, which means that a retro-Michael reaction took place in the chromatographic column as it was previously observed for other

Michael adducts such as compound (1*S*,2*R*,α*R*)-**13**. In the second entry we used freshly distilled aniline and compound **56** was submitted to react under the same conditions, after 92 hours different spots were observed by TLC, by analysis of the ^{1}H NMR spectrum from the reaction crude compound **72** could be identified and its yield was calculated from the spectrum.

The data analysis of compound **70** led us to deduce that in the initial structure the aniline molecule was incorporated due to the signals present at 7.21 ppm (2H, t, H-3`and H-5`), 6.78 ppm (1H, t, H-4`) and 6.60 ppm (2H, d, *J* 9.4, H-2` and H-6`). Furthermore, it was found that the signals from the previous double bond in C-3 have disappeared and it can be observed the displacement to low field of the proton bonded to the amine found at 4.72 ppm (1H, ddd, *J* 4.2, 8.5, 12.1, H-3). In its ^{13}C NMR it can be observed and ketone at 210.0 ppm, the characteristic signals of the *tert*-butyl ester at 28.0, 81.0 and 165.0 ppm, the appearance of two methines at 49.0 ppm (C-3) and the olefinic at 144.0 ppm (C-2) and also a quaternary carbon at 134.4 ppm (C-1). The four methines characteristic of the aromatic ring from the aniline can be observed at 113.3 ppm (2 x CH, C-2` and C-6`), 118.5 ppm (CH, C-4`) and 129.4 ppm (CH x 2, C-3`and C-5`) and finally its quaternary carbon at 146.0 ppm (C, C_{ipso}). The 2D NMR experiments led us to corroborate its structure and the complete assignment of the signals (Table 35, see 2D NMR part). The most relevant connectivities can be observed in Figure 32.

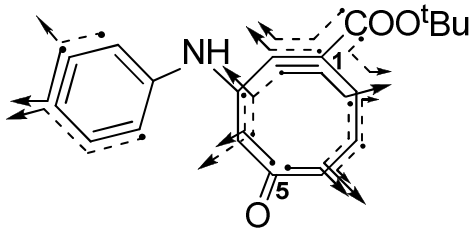
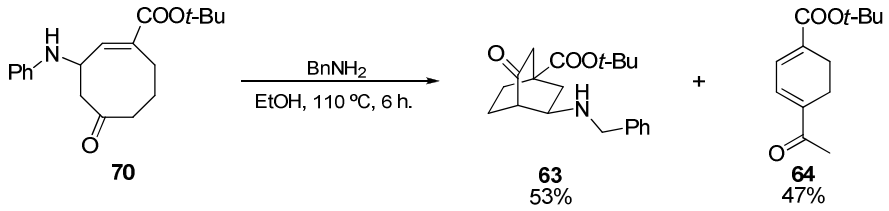


Figure 32. Heteronuclear multiple bond conectivity of compound **70**, ^{13}C-^{1}H long distance.

Compound **70** appears as an intermediate in the obtention of **72** and in spite that the aniline has lower nucleophilicity for reacting with the carbonyl, it does in a 1,4 Michael addition. The migration of the double bond to the C-7 position in compound **71** is something that we have been observing in these cyclooctanic systems.

As compound **70** is sensed as an intermediate in the formation of the bicycle system [2.2.2]octane and since the aniline does not react with the carbonyl group, it was subjected to react with benzylamine under the same conditions previously described. This reaction achieved with much better yield and in a shorter reaction time compounds **63** (53%) and **64** (47%) detected previously from the direct reaction of compound **56** and benzylamine (Scheme 101).

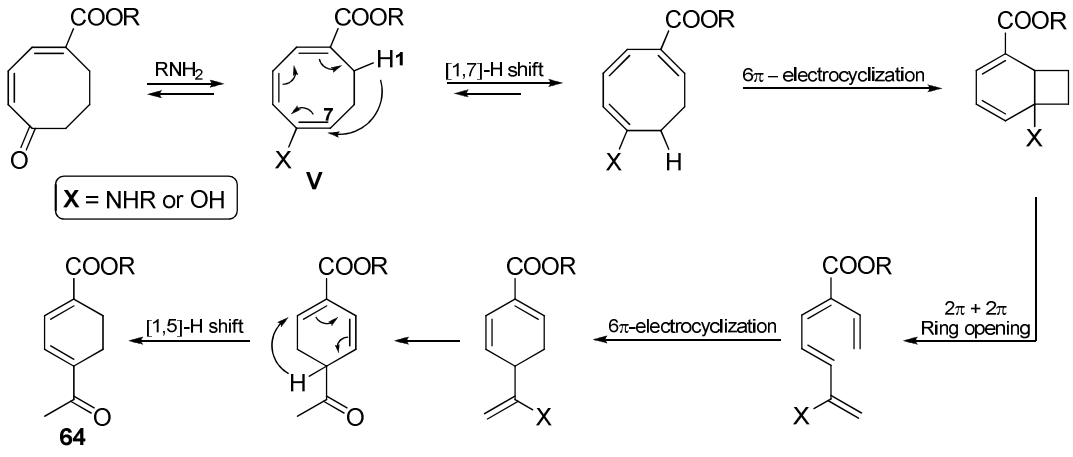


Scheme 101. Reactivity of compound **70** with benzylamine

According to our results based on the study of the achievements and limitations of *tert*-butyl 5-oxo-cycloocta-1,3-diene carboxylate, we proposed the following mechanisms for the formation of compound **64**, which has been yielded along this set of reactions and probably can give us a clue to propose a mechanism for the formation of the bicycle system [2.2.2]octane.

Proposed mechanism for the formation of compound 64:

The proposed mechanism for the formation of compound **64** as shown in Scheme 102, starts with enol or enamine formation to give intermediate **V**, followed by a [1,7] thermal hydride shift to produce the tri-unsaturated intermediate which by a 6π-electrocyclization turn into unstable bicycle, which suffers easily 2π+2π ring opening followed by an intramolecular 6π electrocyclization reaction affording the six member ring where, depending on the substituent, the enamine or the enol can turn into the ketone, this intermediate ends by a [1,5] thermal hydride shift to obtain compound **64**.

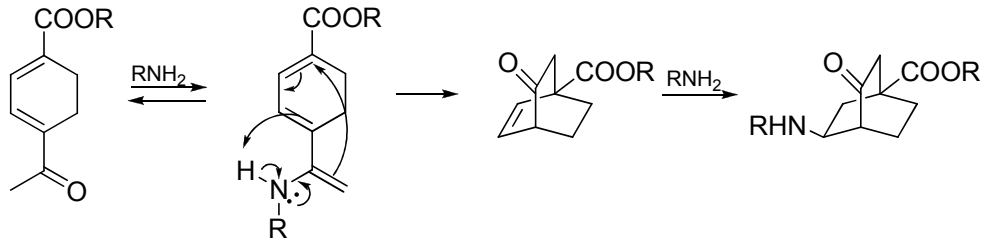


Scheme 102. Mechanism of formation compound **64**

Proposed mechanisms for the formation of the bicycle system [2.2.2]octane:

Mechanism A:

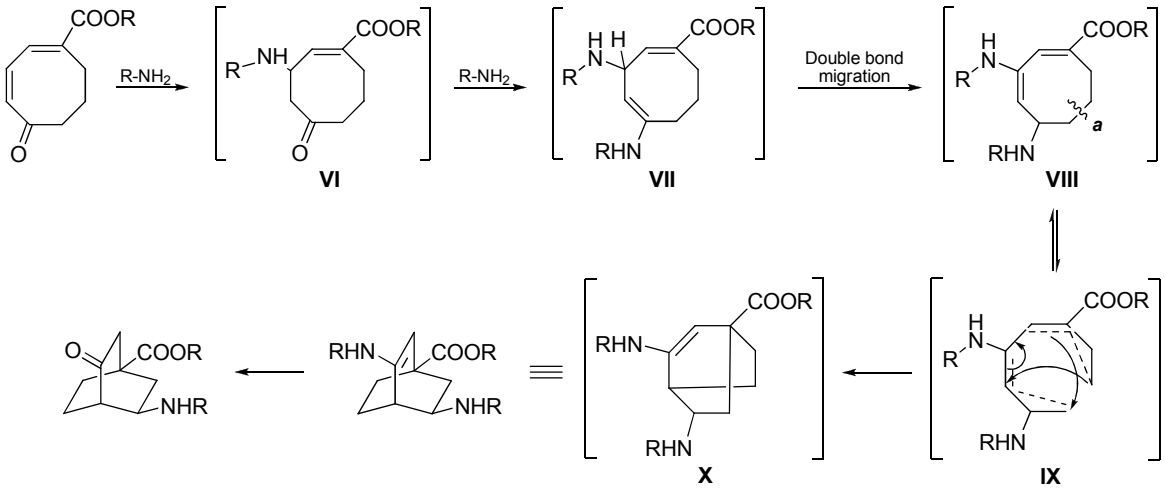
Using compound **64** as a potential intermediate in the formation of the bicyclic system [2.2.2]octane (Scheme 103). Reaction of the ketone with the amine provides the enamine which could rearrange to give the [2.2.2] bicyclo alkenone. Nevertheless, it is difficult to explain the formation of the final product from this and the ketone **64** does not provide the bicycle [2.2.2] octane experimentally.



Scheme 103. Proposed mechanism A

Mechanism B:

We proposed the following mechanism (Scheme 104) initiated by amine Michael addition (**VI**) followed by enamine formation (**VII**) and double bond conjugation (**VIII**). The breaking of bond ***a*** within intermediate **VIII** is the key step toward the obtention of the described bicycle [2.2.2] octane (**X**).



Scheme 104. Proposed mechanism B

The described mechanism (Scheme 104), due to its complexity needs further experimental contribution, but some facts that support it are:

- The initial formation of intermediate **VI** seems plausible since we have been able to isolate it when R= Ph. This fact also indicates that the conjugated carbonyl system is more reactive than the ester.
- The mobility of the double bonds in the cyclooctanic system observed throughout this investigation explains the rearrangement present from **VII** to **VIII**, favoured by the conjugation.
- In intermediate **VIII** by bond breaking of ***a*** a double homoallylic σ bond system leads to **IX** which evolves by electronic reorganization into another bicyclic isomer. To the best of our knowledge, this is the first time that a double homoallylic double σ bond breaks to produce this kind of bicycle [2.2.2] octane.
- The reaction can be described through a $\pi^4s + \sigma^2s$ intermediate type as shown in Figure 33, which it is thermodynamically allowed reaction and as it has been shown, it is the way that takes place experimentally.

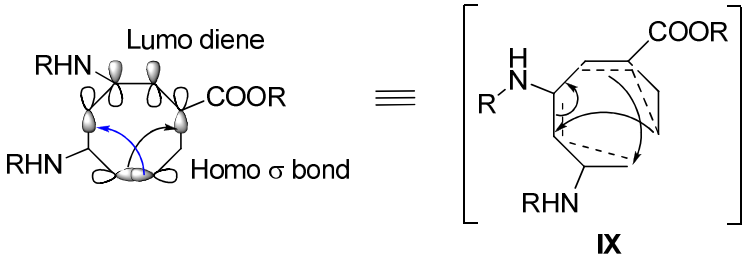
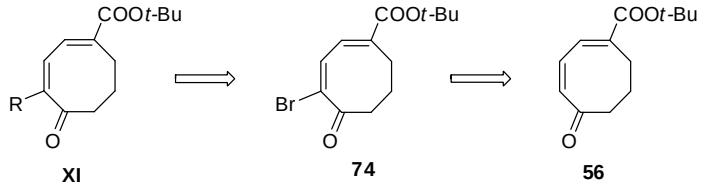


Figure 33.

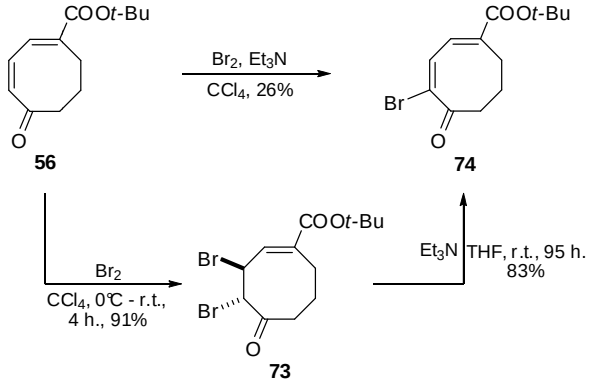
Due to the surprising reactivity found and since there are no bibliographic precedents for the formation of this type of bicycle[2.2.2]octane, it was decided to obtain new derivatives to see the results and to draw relevant conclusions.

The synthesis of functionalized intermediates at C-4 (**XI**) from the previous functionalized derivative (1*E*,3*Z*)-*tert*-butyl 5-oxocycloocta-1,3-dienecarboxylate **56** would be good candidates in order to contribute to the herein studied reactivity. As indicated in the following retrosynthetic Scheme 105, the strategy will be the synthesis of a bromo derivative such as **74**.



Scheme 105. Retrosynthetic analysis of C-4 functionalized derivatives

Although literature[131] describes the production of a vinyl bromide from a carbonyl α,β-unsaturated in just one step by treatment with Br_2 and Et_3N, in our case these conditions achieved the di-bromide derivative **73** with low yield (26%). The best conditions found involved a two steps reaction, as shown in Scheme 106.



Scheme 106. Obtention of Bromide **74**, C-4 functionalized.

Treatment of **56** with Br_2 in CCl_4 let us to get the di-bromide compound **73** with 91% yield, which by addition of Et_3N in THF at room temperature for 95 hours yield the mono bromide compound **74** with 83%. Compound **74** crystallizes in Hex/EtOAc (1:1 v/v) and its structure has been corroborated by X-Ray espectroscopy (Fig. 34, Annexe **E**).[132]

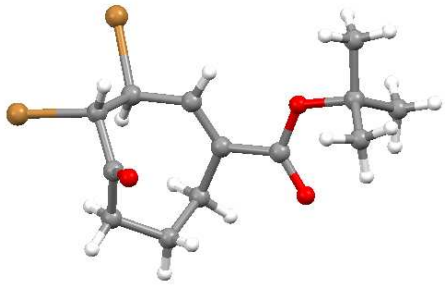
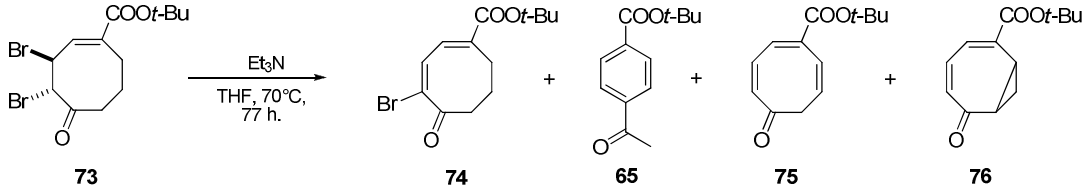


Figure 34. Molecular structure representation of Compound **73**

[131] Smith, A. B. III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M. ; Korn, A. *Org. Synth., Coll* **1990**, *7*, 271-275.
[132] Blanco, M.; Garrido, N. M.; Sanz, F.; Díez, D. *Acta Cryst.* **2012**, E 68, 0.

Significantly, the indicated conditions are the optimal, being crucial the temperature in the dehydrohalogenation process, because when we tested other conditions as indicated bellow (Scheme 107) we obtained different results. Thus, treatment of **73** with Et_3N in THF at 70°C for 77 hours yielded the expected mono-bromide derivative **74** in 18% yield together with the aromatic product **65** (3%), the trienone **75** (19%) and a bicycle sistem [5.1.0]octane **76** (10%).



Scheme 107. Dehydrohalogenation reaction of compound **75** at 70°C

The espectroscopy analysis of compound **76** led us to deduce that the estructure corresponds to a bicycle [5.1.0]octane wherein the protons H-1, H-7 and H-8 are coupled as follows from their coupling constants. The olefinic protons can be observed at 6.86 ppm (1H, d, *J* 7.8, H-3), 6.41 ppm (1H, dd, *J* 7.8 and 12.5, H-4) and 6.13 ppm (1H, d , *J* 12.5, H-5). In its ^{13}C NMR spectrum shows at 198.4 ppm the carbonyl group, the characteristic signal of the *tert*-butyl ester at 28.1, 82.0 and 165.6 ppm. The appearance of two methines sp^2 at 131.4 ppm (C-5) and 131.7 ppm (C-4) and the presence of the conjugated double bond with the ester at 127.2 and 141.1 ppm for C-3 and C-2, respectively. The 2D NMR experiments led us to corroborate its structure and to assign spectroscopy data (Table 36, see 2D NMR part). Figure 35, shows the most relevant connectivities.

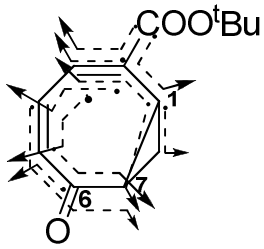
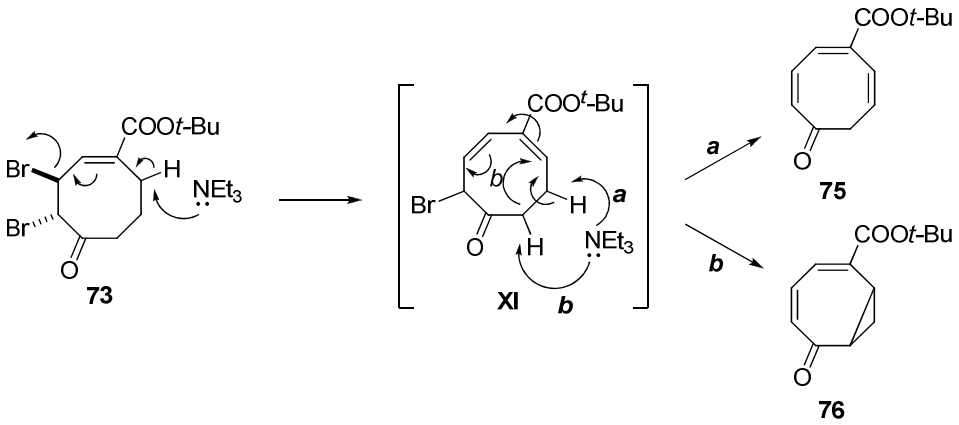


Figure 35. Heteronuclear multiple bond conectivity of compound **76**, ^{13}C-^{1}H long distance.

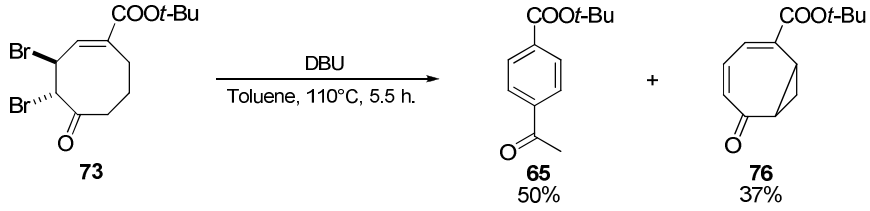
It is reasonable to think, that under the reaction conditions compound **75** and **76** have the same intermediate precursor (**XI**), yielded by dehydrohalogenation reaction of **73** as shown in Scheme 108.



Scheme 108. Mechanism proposal for the formation of compound **75** and **76**

The abstraction of different hydrogen atom in C-7 (route *a*) or C-6 (route *b*) by the amine produces a new dehydrohalogenation intermediates, which leads to the formation of the isomers **75** and **76**.

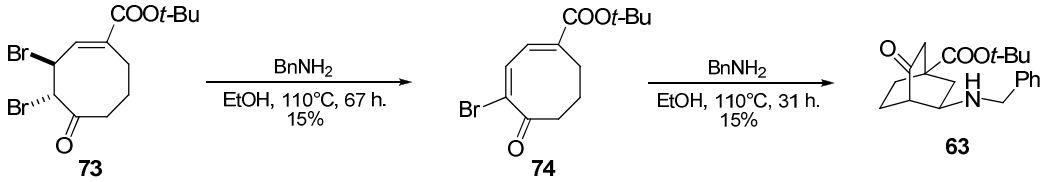
Compound **73** was treated with DBU since these were the only effective conditions for the transformation of compound **56** (previously discussed along this chapter). This reaction achieved compound **65** and **76** with 50% and 37% yield, respectively (Scheme 109).



Scheme 109. Reactivity of compound **73** with DBU

It is surprising to obtain the aromatic isomer **65**, which was previously yielded in reactions were 5-oxo-cycloocta-1,3 dienone **56** was incorporated as starting material. It is not ruled out here a basic mechanism of their formation and as in the previous case the isomer of **65**, compound **75** may be a precursor, which explains the results obtained under the treatment with DBU.

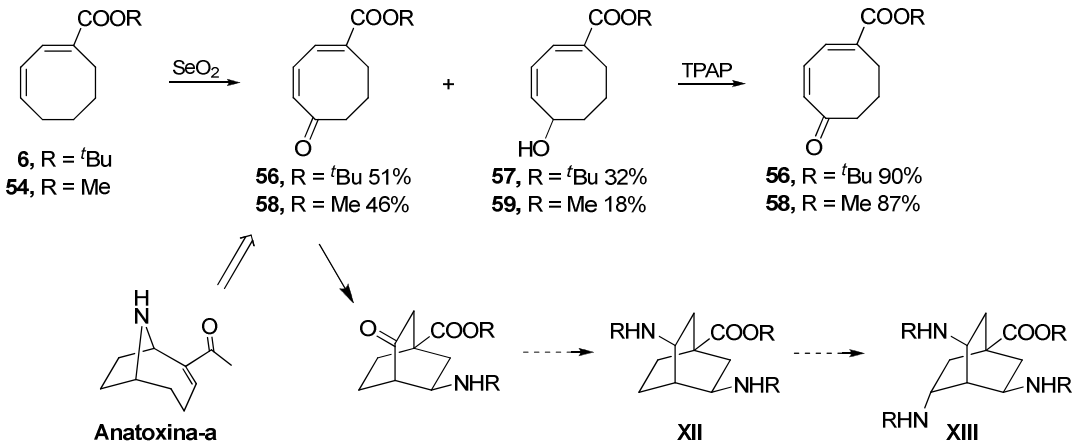
Since the main objective is to observe the reaction of the cyclooctadienones with the functionalized C-4 position by addition of primary amines, it was decided to test the reactivity of the mono-bromide derivative **74** and also for the di-bromide **73** as shown in Scheme 110.



Scheme 110. Reactivity of compounds **75** and **76** with benzylamine

The reaction of compound **73** by addition of benzylamine after purification by CC, only afforded as a known compound the mono-bromide intermediate **74** with low yield (15%). When compound **74** was submitted to react under the same conditions, compound **63** was the only isolated product in 15% yield, instead of the expected derivative with a bromide substituent in C-6 which supports the proposed mechanism and it is difficult to explain the loss of bromine without counting for an extra unsaturation. Taking into account these results, in the future will be convenient the synthesis of derivatives with less labile substituents.

From this chapter we can conclude that the obtention of important intermediates in the synthesis of Anatoxin-*a* with the C-5 position activated was carried out, being **56** and **58** obtained by an allylic oxidation with SeO_2. The yield on **56** and **58** can be improved because they are easily obtained from the alcohols **57** and **59** by TPAP oxidation. These reaction conditions also allow us to make an important contribution to the production of other cyclooctanic derivatives such as *tert*-butyl and methyl 4-oxo-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate, **60** and **61** when **7** and **55** were subjected to react under the same conditions.



Scheme 111.

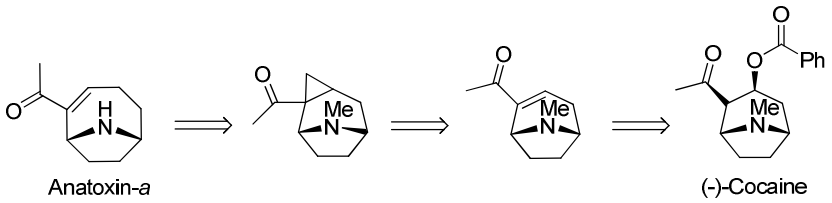
Furthermore, through a complete study of the reactivity of **56** with primary amines, compounds with a bicycle[2.2.2]octane structure were obtained. This fact opens a new and very interesting

research pathway as its functionalization makes possible to achieve intermediates like **XII** or **XIII**. These type of compounds exhibit potential as organocatalysts, particularly derivative **XIII** which presents an own axis of symmetry C3 and could be obtained by the recently methodology reported by White *et al*.[133] of remote methylene functionalization.

[133] Chen, M. S. and White, M. C. *Science* **2007**, *318*, 783-787.

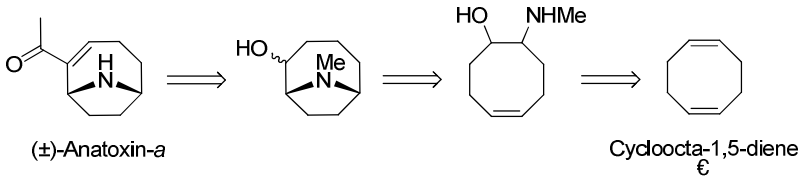
APPROXIMATION TO THE SYNTHESIS OF ANATOXIN-*A*:

Anatoxin-*a* was isolated in 1977 and it was reported by Edwards *et al.*[134] its structure was corroborated by X-Ray diffraction from *N*-acetyl derivative. The first Asymmetric synthesis was performed from tropane alkaloids such as cocaine through ring expansion (Scheme 112). The majority of theses syntheses were published by Edwards` research group.[135] Years later, a more efficient synthesis was performed as well using chlorhydrate of (-) cocaine.[136]



Scheme 112. (-)-Cocaine as starting material in the synthesis of Anatoxin-*a*.

The first total racemic synthesis of anatoxin-*a* was described by Edwards in 1979 using cycloocta-1,5-diene, as shown in Scheme 113.[137]

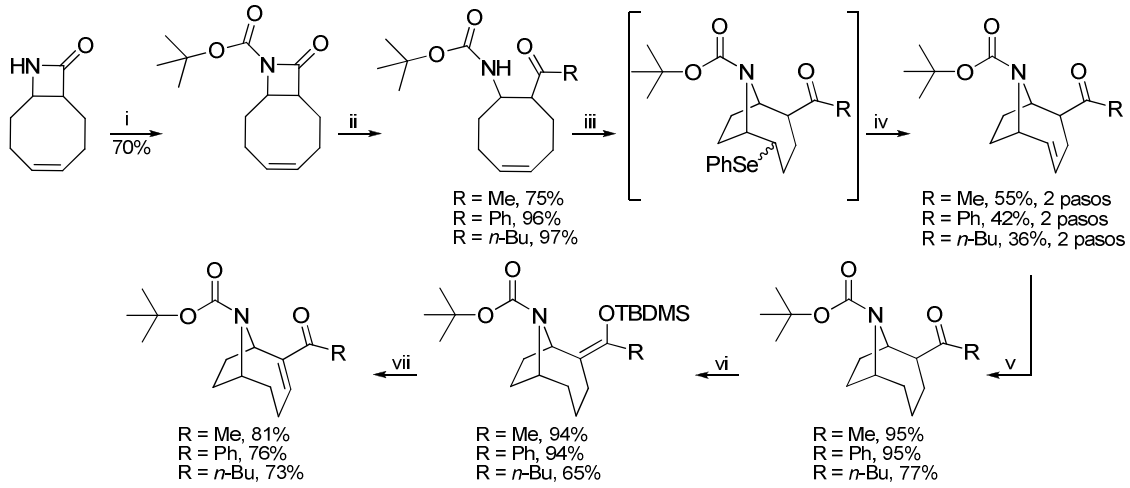


Scheme 113. First racemic synthesis of Anatoxin-*a*

Due to the importance that its synthesis means in the obtention of new adducts with similar biological characteristic as the anatoxin-*a* and the achievement of such as unusual 9-azabicyclo[4.2.1]nonane skeleton, several research groups have been working in its synthesis and therefore exist a large number of articles about this theme. Among these, it can be found different obtention of (±)-Anatoxin-*a*,[138] being relevant to our research group the reported by Parsons in

[134] Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K. *Can. J. Chem.* **1977**, *55*, 1367-1371.
[135] Campbell, H. F.; Edwards, O. E.; Kolt, R.; *Can. J. Chem.* **1977**, *55*, 1372-1379.
[136] Wegge, T. Schwarz, S.; Seitz, G. *Tetrahedron: Asymmetry*, **2000**, *11*, 1405-1410.
[137] Campbell, H. F.; Edwards, O. E.; Elder, J. W.; Kolt, R. *Pol. J. Chem.* **1979**, *53*, 27-37.
[138] (a) Danheiser, R. L.; Morin, J. M. Jr.; Salaski, E. J. *J. Am. Chem. Soc*. **1985**, *107*, 8066-8073. (b) Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron*, **2000**, *56*, 309-315. (c) Roe, S. J.; Stockman, R. A. *Chem. Commun*., **2008**, 3432-3434.

2000, whose synthesis has been achieved through a β-lactam ring opening-transannular cyclization sequence to set up the bridged bicyclic framework of the natural product (Scheme 114).

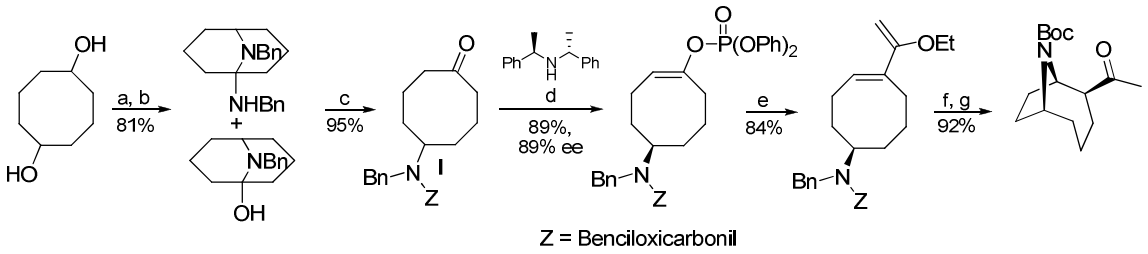


Scheme 114. *Reagents and conditions*: (i) Boc_2O, DMAP, CH_3CN, r.t, 12 h. (ii) MeMgBr, PhMgBr ó *n*-BuMgCl (1.1 eq), -40°C, 1 h, r.t, THF. (iii) PhSeCl, CH_3CN, r.t, 30 min. (iv) H_2O_2, THF, 0°C- r.t (v) H_2, Pd/C, MeOH, 1 h. (vi) Addition of MeOH or BnOH, NaH, THF, r.t, TBDMSCl, 9 h. (vii) 1) PhSeCl, CH_3CN, r.t, 30 min. 2) H_2O_2, THF, 0°C- r.t

This synthesis involves a cycloaddition of chlorosulfonyl isocyanate with cyclooctadiene followed by Boc protection of the resulting β-lactam. Reaction of the latter one with a variety of nucleophiles, followed by selenium-mediated cyclization and oxidation gave the skeleton of anatoxin-*a* bearing various sidechains. The methodology used for the obtention of the last two intermediates (Scheme 114) was reported by Rapoport.[139]

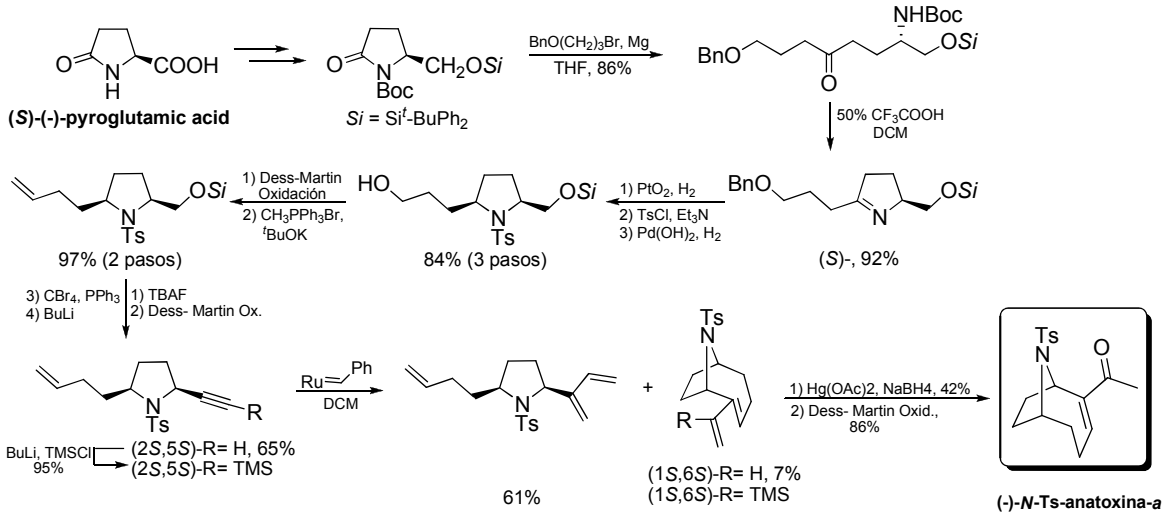
Other examples of enantioselectives synthesis of (+)-Anatoxin-*a* found in literature are: the reported by Somfai *et al*., using *L*-pyroglutamic acid,[140] chirospecific synthesis of conformationally constrained anatoxin analogues,[141] and cyclization of electrophilic allenes.[142]
A formal asymmetric synthesis of (+)-Anatoxin-*a* using an enantioselective deprotonation strategy on an eight-membered ring by Aggarwal *et al*.,[143] is really interesting because used *cis*-1,5-cyclooctanodiol as starting material and it is one of the most concise and efficient (34% overall yield) synthesis reported (Scheme 115). The key steps in this synthesis are the highly enantioselective desymmetrization of the cyclooctanone **I** and a novel cascade reaction to set up the 9-azabicyclo[4.2.1]nonane skeleton.

[139] Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem*. **1989**, *54*, 4654-4660.
[140] Somfai, P. and Åhman, J. *Tetrahedron Letters*, **1992**, *33*, 3791-3794.
[141] Hernandez, A.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 1058-1066.
[142] Mansell, H. L. *Tetrahedron*, **1996**, *52*, 6025-6061.
[143] Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *Angew. Chem. Int. Ed*. **1999**, *38*, 1985-1986.



Scheme 115. *Reagents and conditions*: (a) PDC, DCM, 100%. (b) 1 aq. $PhCH_2NH_2$ (40%), *p*-TsOH (30 mol%), Δ, 2. H_2SO_4 (10%). (c) $PhCH_2$-OCOCl, $Sc(OTf)_3$ (5 mol%), iPr_2Net, MeCN. (d) (*R*,*R*)-NH, HCl, *n*-BuLi (2 eq), $(PhO)_2POCl$, THF, -100°C. (e) $[Pd(PPh_3)_4]$, CH_2=CH(OEt)$SnBu_3$, LiCl, THF, Δ. (f) 45% HBr in AcOH. (g) Pd/C, H_2, MeOH, $(t\text{-}BuCO)_2O$.

Another more recent and interesting contribution to the enantioselective synthesis of (+)-anatoxin-*a* using enyne metathesis was reported by Sato and Mori (Scheme 116).[144]

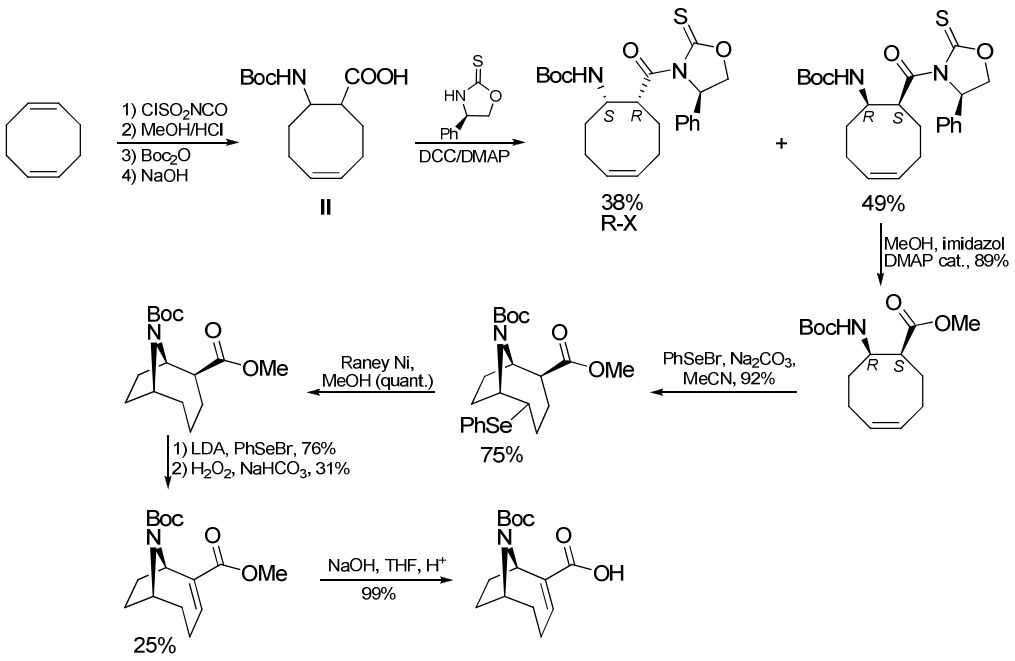


Scheme 116. Synthesis of *N*-tosylanatoxin-*a*

The formal total synthesis of (+)-anatoxin-*a* was accomplished using enyne metathesis as a key step. It was very interesting that (+)-anatoxin-a was synthesized from (*S*)-pyroglutamic acid *via* an unusual inversion of chirality, which is rationalized in terms of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative at the stage of oxymercuration of the diene.

During the development of this research, it was reported the synthesis of anatoxin-*a* analogue by resolution of the amino acid **II** using chiral (*R*)-4-phenyl-oxazolidin-2-thione as derivatizing agent, using cycloocta-1,5-diene as starting material (Scheme 117).[145]

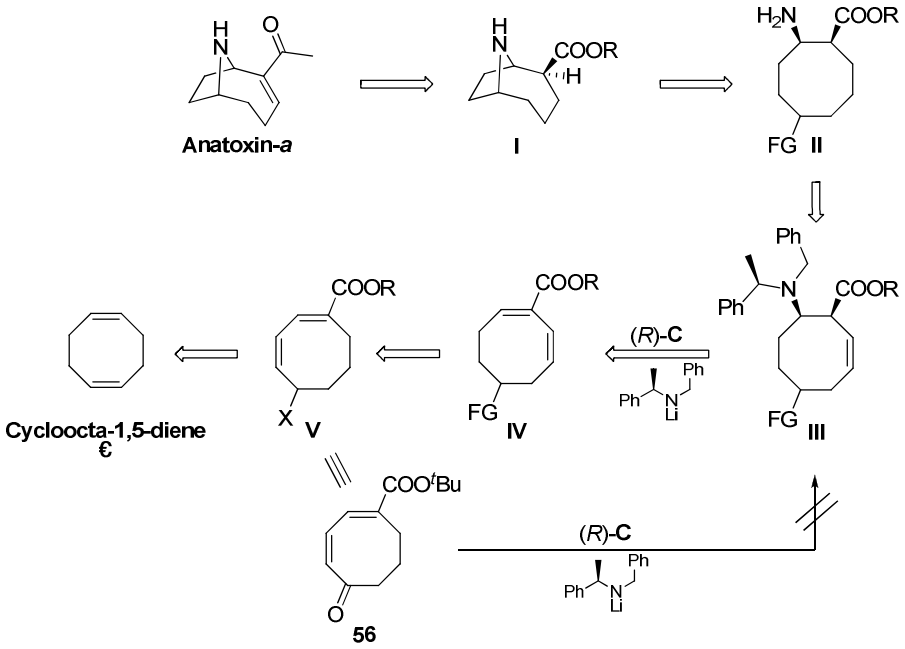
[144] Tomita, T.; Kita, Y.; Kitamura, T.; Sato, Y.; Mori, M. *Tetrahedron*, **2006**, *62*, 10518-10527.
[145] Marc, M.; Outurquin, F.; Renard, P-Y.; Créminon, C.; Franck, X. *Tetrahedron Letters*, **2009**, *50*, 4554-4557.



Scheme 117. Resolution of the racemic mixture of amino acids and approach to the synthesis of anatoxin-*a*

APPROXIMATION TO THE SYNTHESIS OF ANATOXIN-*A*

Retrosynthetic analysis:



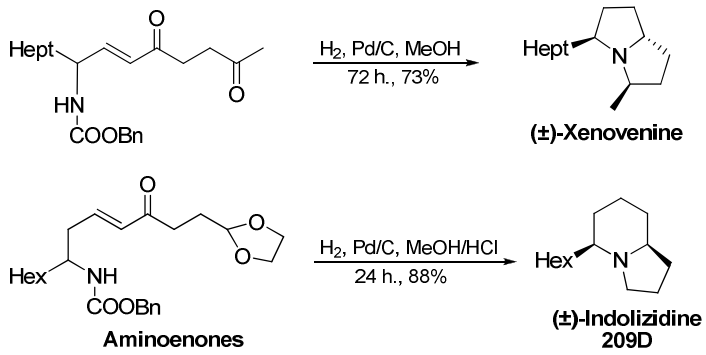
Scheme 118. Retrosynthetic analysis of Anatoxin-*a*

As it can be observed in Scheme 118, the key step in the synthesis of Anatoxin-*a* is the formation of the intermediate **III** where the stereogenic centers have to be generated. This compound is coming from adduct **IV** that itself can be obtained from **V**, which has been prepared in the previous chapter as compound **56**. The study of its reactivity by direct addition of the chiral lithium amide (*R*)-**C** with no results and the addition of different kind of amines which has opened the door to a new and interesting research pathway, bring us back to the point of trying new routes. For example when the carbonyl group in derivative **V** is protected as a dioxolane, it is possible to afford the diene system observed in derivative **IV** away from the quaternary carbon in C-5 position which will not have the stabilization from the carbonyl by conjugation. It will also be interesting to have this 1,7-diene system because we have observed, in previous chapters, that the Michael addition reaction takes place quantitatively for this scaffold unlike with the cycloocta-1,3-diene system.

Our first approach from **III** will be in just one step to perform deprotection of the carbonyl group at C-5, hydrogenolysis of amine protecting groups, intramolecular condensation and a subsequent

reduction. A detailed bibliographic search for intramolecular cyclization throughout condensation of an amine group with a carbonyl group was made. Blechert *et al*., has published an interesting highly selective cross-coupling reaction of *N*-protected allylic and homoallylic amines with α,β-unsaturated ketones and acrylates followed by reductive cyclization as a general approach to the synthesis of mono- and bicyclic-piperidine and pyrrolidine derivatives.[146]

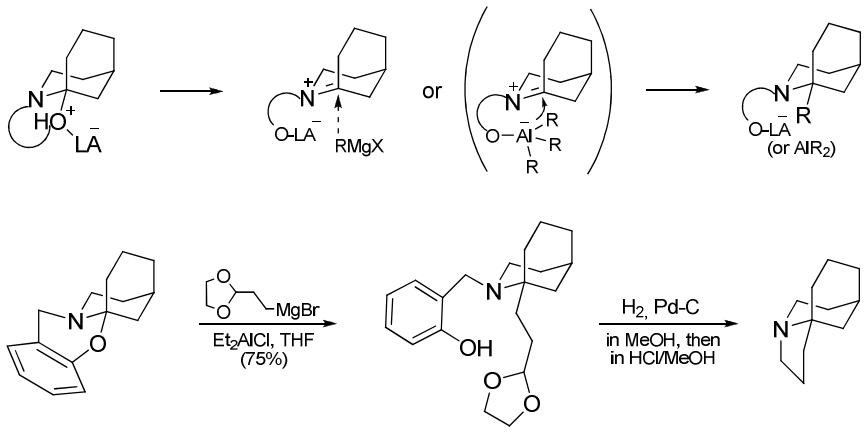
Cross-coupling of *N*-protected allylic and homoallylic amines with enones or acrylates should easily afford aminoenones, which upon catalytic hydrogenation are converted into the saturated *N*-heterocycles in a sequence of double bond reduction, *N*-deprotection and cyclization (Scheme 119).[147] Simple reductive aminations affording piperidines and pyrrolidines are known to proceed *cis*-selectively under the control of the stereocentre adjacent to the nitrogen.[148] In addition, aminoenones containing a second carbonyl group are shown to undergo a further diastereoselective cyclization[149] yielding bicycles like (±)-*Indolizidine* 209D and (±)-*Xenovenine*.



Scheme 119. Synthesis of (±)-Xenovenine and (±)-Indolizidine 209D.

Even when nucleophilic alkylation on anti-Bredt iminium ions to the synthesis of 1-alkylated 2-azabicyclo[3.3.1]nonanes have been described,[150] as shown in Scheme 120, the alternative obtention of the amine **II** (Scheme 118) and the appropriate change of the functional group in this intermediate will give a synthetic versatility to the proposal.

[146] Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Letters*, **2005**, *46*, 43-46.
[147] (a) Davies, S. B.; McKervey, A. M. *Tetrahedron Letters*, **1999**, *40*, 1229-1232. (b) Benetti, S.; Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Synthesis*, **2002**, *3*, 331-338. (c) Boeglin, D.; Heitz, A.; Martinez, J.; Fehrentz, J. A. *Eur. J. Org. Chem*. **2003**, *16*, 3139-3146.
[148] Mota, A. J.; Langlois, N. *Tetrahedron Letters*, **2003**, *44*, 1141-1143 and references cited therein.
[149] Randl, S.; Blechert, S. *J. Org. Chem*. **2003**, *68*, 8879-8882 and references cited therein.
[150] (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem*. **1997**, *62*, 8280-8281. (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Letters*, **2001**, *42*, 3010-3015.



Scheme 120. Nucleophilic alkylation on anti-Bredt iminium ions

In this way compound **56** was subjected to 1,3-dioxolane protection as shown in the following Table.

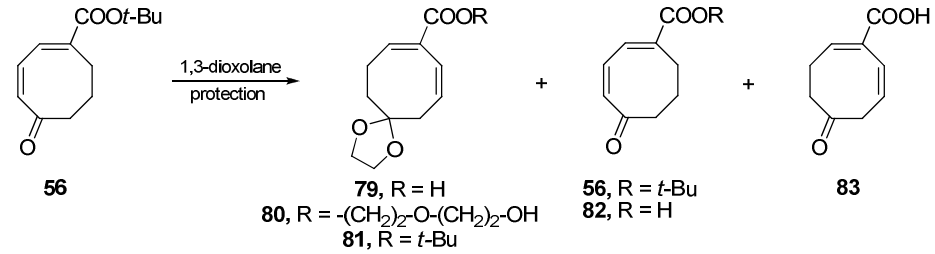


Table 11. 1,3-dioxolane protection of compound **56**. *General reaction conditions*: Benzene, Dean-Stark 110°C.

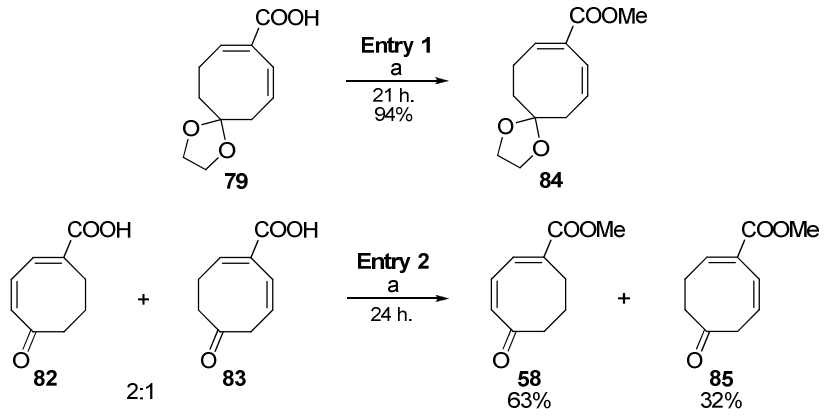
Entry	56 (mmol)	1,2-Ethanediol (mmol)	PTSA (mmol)	t (h.)	Recovery S.M. 56 (%)	79 (%)	80 (%)	81 (%)	82 (%)	83 (%)
1	1.20	12.00	0.06	27	-	21	8	-	-	-
2	0.34	0.70	0.02	24	15[a]	34	-	46[a]	-	-
3	0.54	1.08	0.03	24	13[b]	-	-	38[b]	27	11

[a] Where obtained as a mixture in a 3:1 ratio
[b] Where obtained as a mixture in a 3:1 ratio

Broadly, the desired protected product was achieved in low yield due to ester reaction and formation of by-products. Migration of the conjugate double bond from 1,3 to 1,7 was expected in acid media. In this manner, by using PTSA the double bond could be isomerized to the farthest position from the spiranic centre being *tert*-butyl 5,5-ethylenedioxycyclooct-1,7-diene-1-carboxylate **81** or its respective acid **79** the major products. Under the reaction conditions highlighted in Entry 1, the protected compound was obtained in its acid form and isolated as its ester by treatment with $TMSCHN_2$ as shown in the following Scheme, compound **80** is formed due to the 12 fold excess of 1,2-ethanediol, by reducing the amount of 1,2-ethanediol to 2 eq. and the

reaction time (Entry 2), we obtained the protected product **81** in 46% yield and the protected acid **79** in 34 % yield. In Entry 3, although the conditions were maintained, the reproducibility and control of this protection starts to play an important yield control.

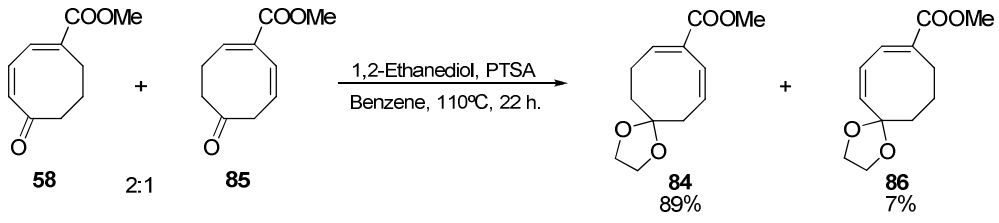
To recover efficiently the above acids, the methyl esters were obtained by treatment with trimethylsilyldiazomethane (Scheme 121).



Scheme 121. *Reagents and conditions:* (a) $TMSCHN_2$, Benzene/H_2O (1:1 v/v), r.t.

Compound **84** was isolated and full characterized showing in its I.R. spectrum the functional groups like C=O at 1723 cm^{-1} and C-O at 1256 cm^{-1} and its ^1H NMR shows the characteristic splitting for its conjugated double bond in 1,7 position at 5.79-5.96 ppm (1H, m, H-7), 6.34 ppm (1H, d, *J* 11, H-8) and 7.02-7.09 ppm (1H, t, *J* 6.6, H-2).

Due to the difficulty of isolating compounds **58** and **85** and taking into account that the protection of the carbonyl group as dioxolane promotes the obtention of compound **84** as a major product, it was decided to make the treatment on this mixture affording the results shown in Scheme 122.

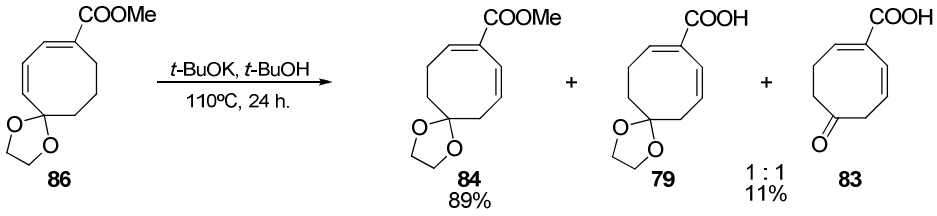


Scheme 122. 1,3-dioxolane protection for the unsaturated methyl esters

Dioxolane protection for the 2:1 ratio mixture of **58** and **85** was nearly quantitative and migration of the double bond is significantly observed obtaining 13:1 ratio mixture of **84** and **86**, respectively.

Deprotection of the ester did not take place being the methyl ester a stable group wherein protection of the carbonyl group can be perform under this conditions. The structure of compound **86** was corroborated by 2D NMR experiments (Table 37), wherein the most important correlations in its COSY spectrum are between H-C-2 at 7.20 ppm (d, *J* 5.2) with H-C-3 at 5.89 ppm (dd, *J* 12.6 and 5.2) and H-C-4 at 5.59 ppm (d, *J* 12.6) with H-C-3.

Considering that the reactivity of the cyclooctadiene is very peculiar, highlighting the trend of double bonds migration in basic medium because of the greater thermodynamic stability as it was observed for Huber *et al*.,[61] compound **86** was set to react under *t*-BuOK (Scheme 123).

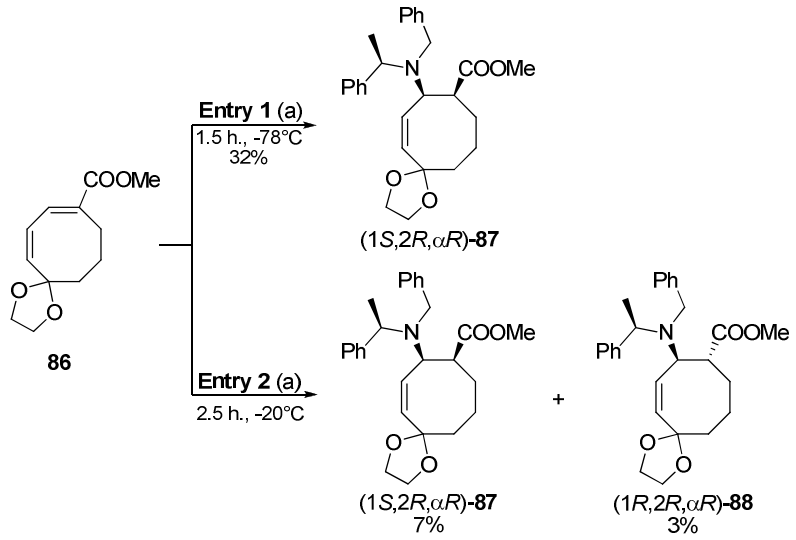


Scheme 123. Isomerization reaction of the double bonds in basic media

In spite that this reaction yields by-products, compound **79** and **83** have got the conjugate unsaturated bond in the optimal position and can be easily esterified, and subsequently protected. This reaction was performed again using freshly sublimed *t*-BuOK and the same results were observed. The isomerization of the double bonds can be performed as well in acid media but exists a high probability of 1,3-dioxolane deprotection.

Assuming that the Michael addition of chiral lithium amides over compounds **86** and **84** is going to behave like in compounds **6** and **7**, this is a hypothesis, because a small change into a molecule may cause a large change in its reactivity. In this manner, to prove the behavior of compound **86** in the addition reaction of (*R*)-**C** is of great importance for further experiments to be developed later (Scheme 124).

Reactivity of the protected cyclooctadiene carboxylates with (*R*)-C:



Scheme 124. *Reagents and conditions:* (a) (*R*)-*N*-benzyl-*N*-α-methylbenzylamine 6 eq., *n*-BuLi 5.8 eq., THF, -78°C.

Comparing the yields achieved in the Michael addition for compound **6** (42%) and compound **86** (32%) can show that the reactivity remains basically the same for the conjugated 1,3-unsaturated ester, incorporation of a functionalized group in C-5 turns to affect the reactivity slightly due to the presence of the 1,3-dioxolane group which is a relatively strong chelating group, unlike the reaction with compound **6** starting material was not isolated in this case. In order to increase the yield, it was decided to raise the temperature at -20°C, but the obtained results are those ones indicated in Scheme 124, it was also the first time that the formation of the *anti* diastereoisomer (1*R*,2*R*,α*R*)-**88** was observed. The two addition products were isolated and fully characterized, mainly emphasizing their different rotation powers being $\mathbf{[\alpha]_D^{20}}$ = +19.3 (*c* 0.15, $CHCl_3$) and $\mathbf{[\alpha]_D^{20}}$ = -1.3 (*c* 0.48, $CHCl_3$), for compounds **87** and **88**, respectively. These diastereoisomers show differences in their ^1H and ^{13}C NMR spectra, for compound **87** at 2.39-2.50 ppm (1H, m, H-1), 3.77 ppm (1H, m, H-2), 52.6 ppm (CH, C-1) and 56.7 (CH, C-2); for compound **88** at 2.68-2.75 ppm (1H, m, H-1), 4.71 ppm (1H, dd, *J* 12.0 and 8.0, H-2), 49.1 (CH, C-1) and 57.7 (CH, C-2).

When the Michael addition is performed over methyl 5,5-ethylenedioxycycloocta-1,7-diene-1-carboxylate **84** as shown in the following Table, the reactions have better yields than those ones performed with compound **86** but unlike the Michael addition carried out with compound **7** this one it is not quantitative, starting material could be observed in the ^1H NMR spectra from the reaction crudes but longer periods of time may reduce the yield (Entry 1).

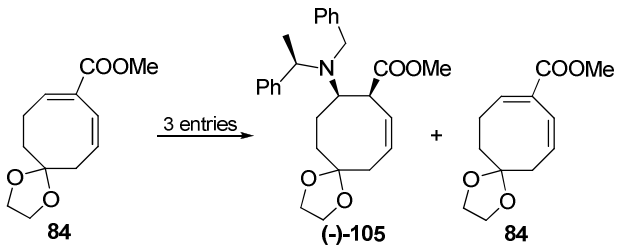


Table 12. Michael addition of (*R*)-**C** to compound **84** at -78°C

Entry	84 (mmol)	(*R*)-C (mmol)	*n*-BuLi 1.6 M. (mmol)	THF (mL)	t (hours)	(-)-108 : 84	Yield (%)
1	0.61	3.70	3.50	1.5	2.5	2.5 : 1	43
2	0.82	4.90	4.80	2.0	2	3 : 1	60
3	0.93	5.60	5.40	2.0	2	3 : 1	50

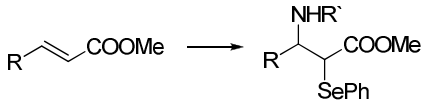
Tandem addition selenylation or hydroxylation reactions:

Due to a retro-Michael reaction observed when (1*S*,2*R*,α*R*)-**13** was purified through silica gel, it can be predicted that the same behavior may be observed for the Michael reaction product **(-)-105** obtained when **84** is submitted to the chiral lithium amide (*R*)-**C** addition. An alternative for achieving isolation of this product could be in situ addition of phenylselenyl chloride, which will be added to the α-position of the unsaturated ester position replacing the α-hydrogen preventing in this manner, elimination of the chiral amide.

Tandem reaction: selenylation addition

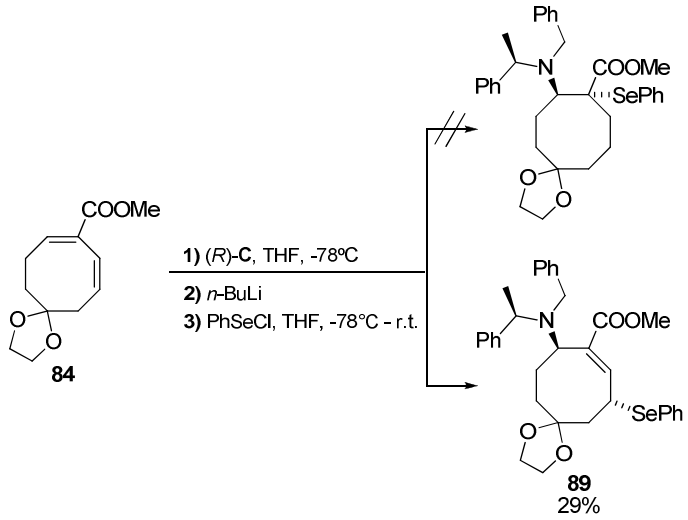
The α-phenylselenyl carbonyl compounds are important bifunctional synthons and α-phenylselenyl aldehydes and ketones have been extensively studied.[151] Parlanti and Piancatelli *et al.*[152] have worked in the direct amino-phenylselenylation of enoates as a route in the synthesis of α-phenylseleno-β-amino esters and β-lactams. They have described that unactivated and deactivated olefins can be rapidly and efficiently functionalized by phenylselenyl chloride, *via* a Lewis acid mediated stereospecific addition; the enhanced reactivity observed in these conditions probably arises from the interaction between the Lewis acid and the chloride anion of the electrophilic reagent.[153]

[151] (a) Lebarillier, L.; Outurquin, F.; Paulmier, C. *Tetrahedron*, **2000**, *56*, 7483-7493. (b) Houllemare, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C. *Synthesis*, **1997**, 101 and references cited therein.
[152] Torchiarolo, G. C.; D`Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Bella, M. *Tetrahedron* **1998**, *54*, 15657-15666.
[153] D`Onofrio, F.; Parlanti, L.; Piancatelli, G. *Tetrahedron Lett*. **1995**, *36*, 1929-1932.



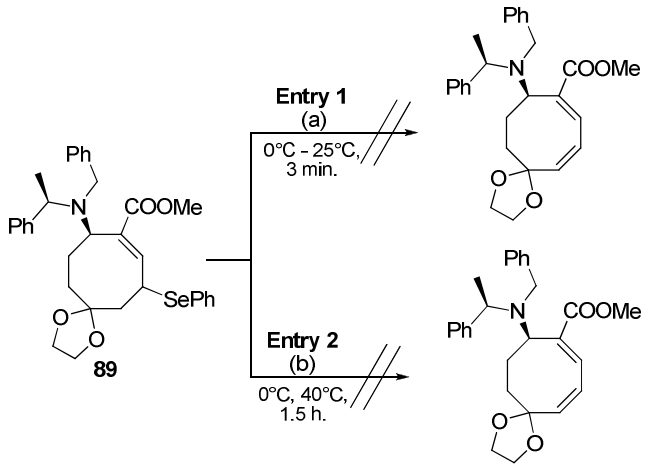
Scheme 125. Applied methodology in the synthesis of α-phenylseleno-β-amino esters

When addition of (*R*)-**C** is performed over **84** at -78°C followed after 1.5 hours by addition of PhSeCl, it is achieved adduct **89** as a reaction product, instead of the selenyl in α-position, probably due to the high steric bulk.



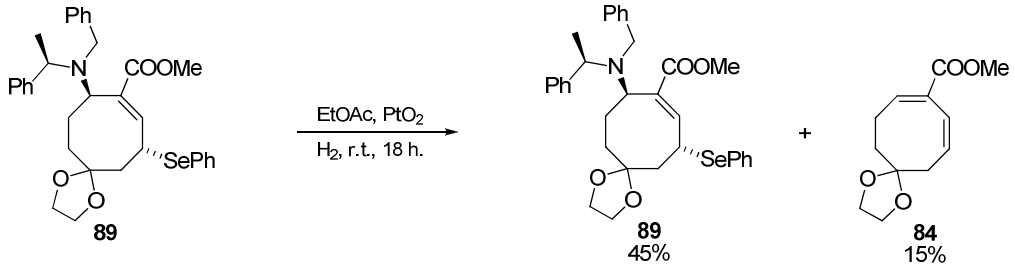
Scheme 126. One-pot α-phenylselenylation

Compound **89** was isolated in 29% yield and the proposed stereochemistry indicated in the previous Scheme is in accordance to the pattern of the tandem reactions of addition and anti α-alkylation, even when in this case the influence is far away. Compound **89** can be an useful intermediate because it can be purified through CC and subsequent elimination of the phenylselenyl group and hydrogenation of the double bonds will afford an important adduct (Scheme 127).



Scheme 127. (a) H_2O_2, THF, 0°C-25°C, 3 min. (b) Pyridine, DCM, H_2O_2, 0°C-40°C, 1.5 h.

Elimination reaction did not take place even when the mixture was refluxed at 40°C for 1.5 hours, probably the elimination of the α-phenylselenyl group to the double bond has to be carried out in stronger conditions For corroborating the influence of the double bond, compound **89** was submitted to hydrogenation but as it can be observed in Scheme 128, it was only recovered starting material and full elimination of the amine and phenylselenyl groups destroying the previously incorporated chirality so for this reason we changed the strategy to incorporate a hydroxy group instead.



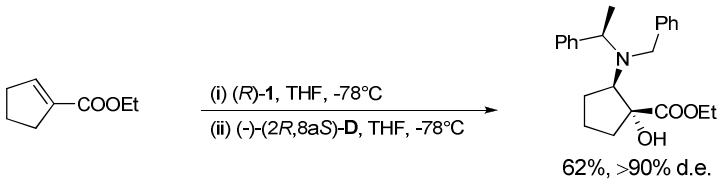
Scheme 128. Hydrogenation reaction of compound **89**

Tandem reaction: hydroxylation addition

The examples found in literature on addition of lithium amides and subsequent hydroxylations of cyclic enoates are not very common. In 2002, Davies *et al.*,[154] reported the conjugated addition and hydroxylation over ethyl 1-cyclopentene-1-carboxylate, achieving the desired product with high diastereoselectivity (>90%, ^{1}H NMR data analysis from the reaction crude) and surprisingly the

[154] Davies, S. G.; Epstein, S. W.; Garner, C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555-1565.

obtention of only one diastereoisomer was yielded in 62% after purification, as shown in Scheme 129.



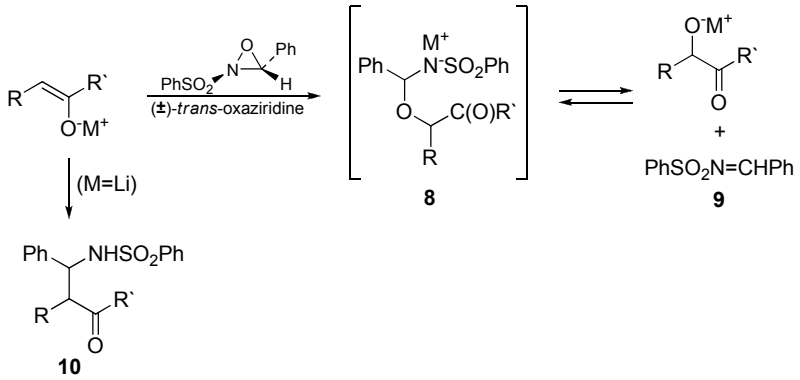
Scheme 129. *Reagents and conditions:* (i) Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv.), THF, -78°C, 2 h. (ii) (-)-(canforsulfonyl)-oxaziridine (2 equiv.), THF, -78°C-r.t

Using the conditions described for the asymmetric synthesis of β-amino-α-hydroxy acids *via* diastereoselective hydroxylation of homochiral β-amino enolates with oxaziridines.[155] It was performed a complete study to search for the best conditions for finding the matched pair when compound **55** was used as a model of starting material to shift later to the more elaborated compound **84** once the optimal conditions are met. This argument is made by the major difficulty of obtaining the latter compound.

Theoretical[156] and experimental[157] studies have suggested a S_N2 type mechanism for the oxygen transfer from *N*-sulfonyloxaziridines to nucleophiles. Although the early part of the reaction coordinate is dominated by the four-electron repulsion of the nucleophiles and the lone pair on oxygen, the "electrophilic" nature of oxaziridines has been attributed to the presence of a low-lying empty Walsh orbitals (LUMO) that rapidly decreases in energy during C-O and N-O bond elongation induced by the attacking nucleophiles. It was concluded that the molecular recognition is steric in origin, dictated by the substituents on the oxaziridine nitrogen and carbon atoms.

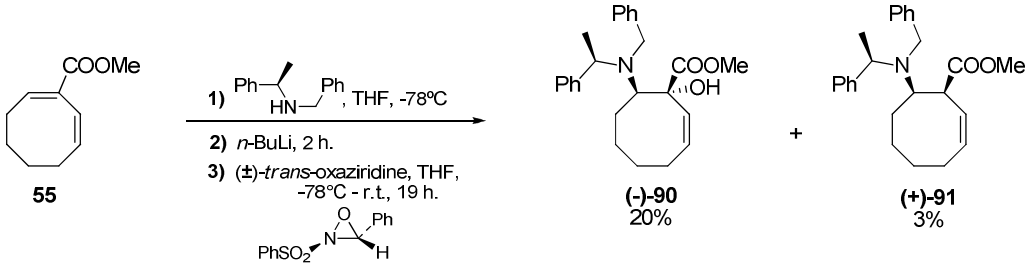
An S_N2 type mechanism has been proposed by Davis *et al*. for the hydroxylation of enolate anions by oxaziridines (Scheme 130).[158] The enolate anion attacks at the oxaziridine oxygen atom to give hemiaminal intermediate **8** which fragments to the sulfonimine **9** and alkoxide. When (±)-2-(phenylsulfonyl)-3-phenyloxaziridine is used, exits evidence implicating **8** in the oxidation of enolates. Oxidation of lithium enolates by the previous (±)-*trans*-oxaziridine gives, in addition to the α-hydroxy carbonyl compound, the imino-aldol product **10** resulting from addition of the enolate to the sulfonimine **9**.

[155] Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans 1*, **1994**, 2373-2384.
[156] (a) Bach, R. D.; Wolber, G. *J. Am. Chem. Soc.* **1984**, *106*, 1410-1415. (b) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem*. **1990**, *55*, 3325-3330.
[157] Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem*. **1986**, *51*, 4240-4245.
[158] Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc*. **1990**, *112*, 6679-6690.



Scheme 130. General mechanism for enolate oxidation with *N*-Sulfonyloxaziridine

For analyzing the stereoselective hydroxylation it is necessary to screen a variety of reagents. Firstly, the reaction has to be performed by addition of the Davis oxaziridine (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine as source of electrophilic oxygen (Scheme 131) to check the diastereoselectivity of the reaction.



Scheme 131. One-pot α-hydroxylation of homochiral β-amino enolate

In this experiment we could confirmed the selectivity as >95% d.e. since the alternative *syn* diastereoisomer could not be identified in the ^{1}H NMR spectrum of the crude product. This reasoning can be evidenced from previous additions of (*R*)-**C** over cyclooctanic unsaturated esters where the stereoselectivity of the product is primarily directed by the chiral amine without having observed the formation of other diastereoisomers, taking into account the importance of the temperature in this kind of addition. Compounds **(-)-90** and **(+)-91** were isolated in 20% and 3% yields and fully characterized being their rotation powers $[\alpha]_D^{20}$ = -15.7 (*c* 1.15, $CHCl_3$) and $[\alpha]_D^{20}$ = +4.7 (*c* 0.64, $CHCl_3$), respectively. The low yield of compound **(+)-91** is probably due to a retro-Michael reaction which takes place during CC purification. For this reason the recovery of starting material (37%). Characteristic signals for compound **(-)-90** are: In I.R. spectrum at 3348 cm^{-1} (O-H), in ^{1}H NMR at 4.94 ppm (1H, s, O*H*) and 5.40-5.48 ppm (2H, m, H-7 and H-8) and in ^{13}C NMR at 76.4 ppm (C, C-1) and 134.5 ppm (CH x 2, C-7 and C-8), this compound also crystallized in a mixture Hex: ether (1:1 v/v) which melting point is 138-140°C and its structure has been confirmed by X-Ray (Fig. 36) as it shows Annexe **F**.

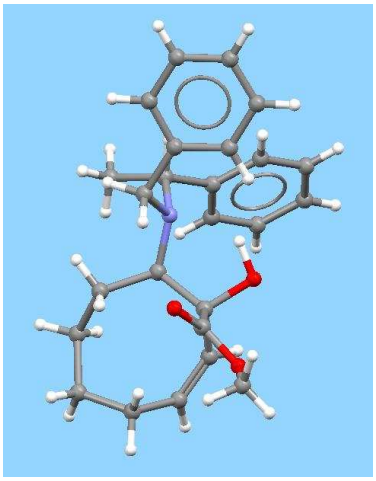
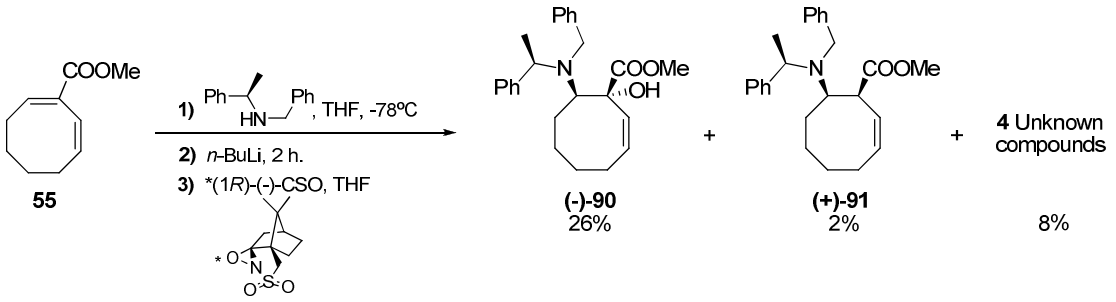


Figure 36. Molecular structure representation of compound **(-)-90**

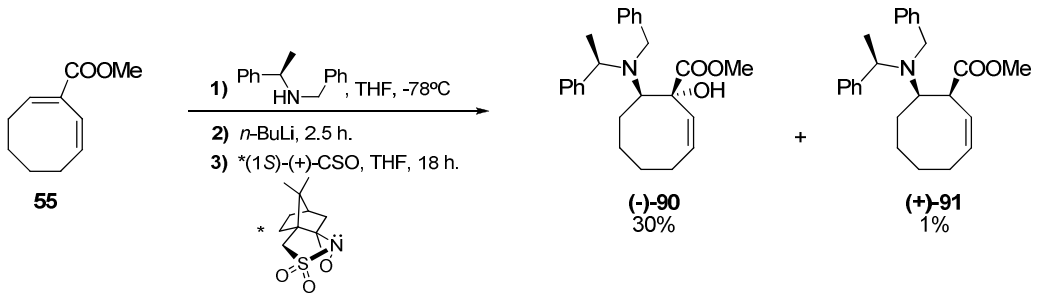
The X-Ray spectroscopy results confirm the proposed structure represented in Scheme 131 confirming the stereochemistry of its three chiral centers as (1*R*,2*R*,α*R*).

Under the same conditions, treatment with (1*R*)-(-)-(10-Camphorsulfonyl) oxaziridine in situ, provides the results shown in Scheme 132, unlike the previous experiment the presence of by-products precluded an accurate assessment. Furthermore, isolation of the hydroxylated product **(-)-90** by flash chromatography was more complicated than before.



Scheme 132. One-pot α-hydroxylation of homochiral β-amino enolate

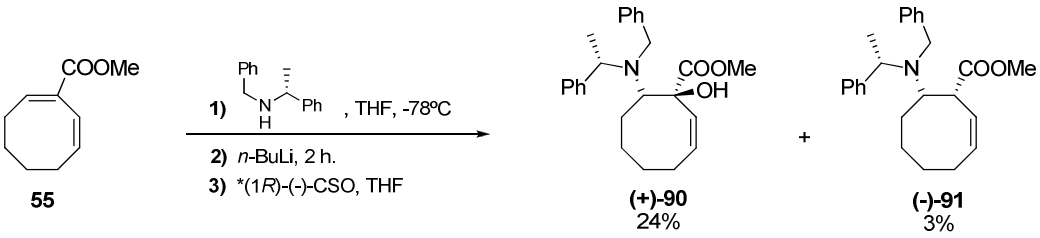
To complete the screen, the last experiment was subjected in situ by addition of (1*S*)-(+)-(10-Camphorsulfonyl) oxaziridine (Scheme 133).



Scheme 133. One-pot α-hydroxylation of homochiral β-amino enolate

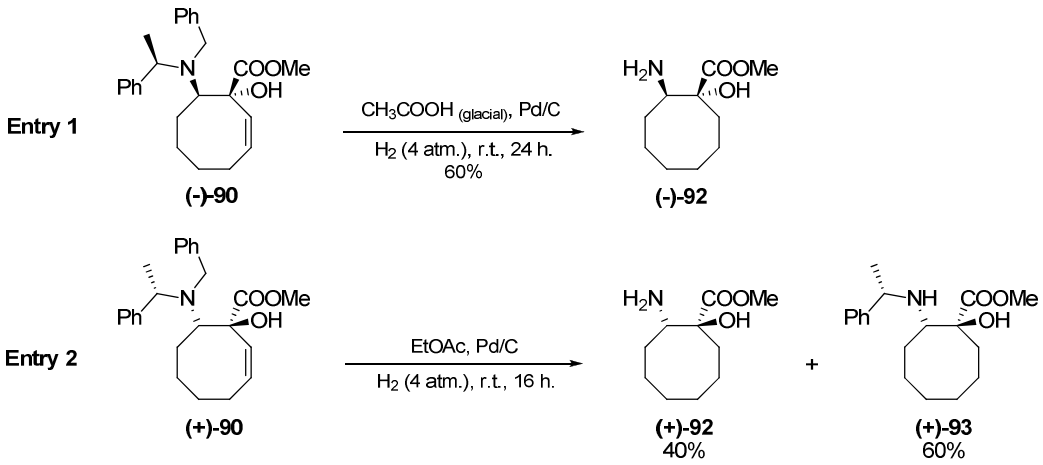
The ^{1}H NMR spectrum from the crude product showed a cleaner reaction in spite of the low yield and purification by CC was performed in a much better way. The selectivity could be confirmed as >95% d.e. from its spectrum. Compound **(-)-90** was pure isolated showing a slight increase in its rotational power $\mathbf{[\alpha]_D^{20}}$ = -17.7 (*c* 1.18, $CHCl_3$).

Interestingly, the corresponding hydroxylation using the antipodal chiral lithium amide (*S*)-**C** by addition of (1*R*)-(-)-(10-Camphorsulfonyl) oxaziridine in situ, led to recover 33% yield of starting material and to afford compound **(+)-90** in 24% yield and its rotation power was measured as $\mathbf{[\alpha]_D^{20}}$ = +28.2 (*c* 0.98, $CHCl_3$). In spite that the rotation power has slightly increased, the ^{1}H NMR from the crude product is not clean and the isolation of the hydroxylated product **(+)-90** by flash chromatography was as well complicated (Scheme 134).



Scheme 134. One-pot α-hydroxylation of homochiral β-amino enolate

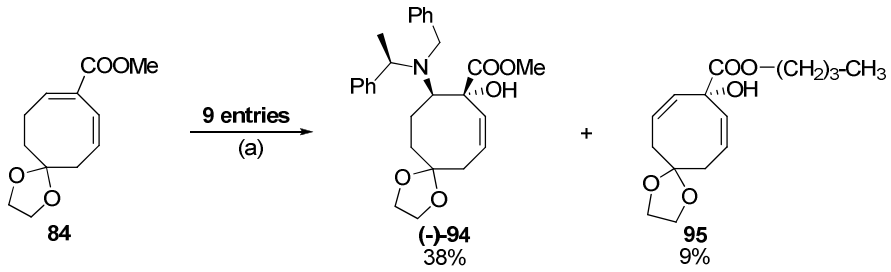
With compounds **(-)-90** and **(+)-90** in hand, we tried the hydrogenation and hydrogenolysis reactions as we have been suggested in the retrosynthetic analysis of Anatoxin-*a*.



Scheme 135. Hydrogenation and hydrogenolysis reactions

In Entry 1, the reaction product **(-)-92** was afforded in 60% yield and successfully characterized. In this procedure the use of glacial acetic acid as a solvent may affect the yield during the extraction because in Entry 2 by addition of ethyl acetate the reaction products yields are quantitative. These entries show us that is viable to perform the hydrogenation and full hydrogenolysis in EtOAc but needs a longer period. In this way, we described the synthesis of β-amino-α-hydroxy cyclooctane carboxylic acid derivatives.

With the best conditions in hand for the one-pot α-hydroxylation of homochiral β-amino enolate **55** we used them for compound **84**.



Scheme 136. *Reagents and conditions:* (a) (*R*)-**C**, *n*-BuLi, THF, -78°C, 2 h, (1*S*)-(+)-CSO/THF, -78°C-r.t 20 h.

After performing 9 entries (Table 21, see experimental part) making different variations on the reagents equivalents the reaction was led to its optimization (Entries 7-9, Table 21) by increasing slightly the reaction product yield **(-)-94**, which crystallized in a mixture of Hex: ether (1:1 v/v) and its structure has been corroborated by X-Ray spectroscopy as shown in Figure 37 (Annexe **G**) confirming the stereochemistry of its three chiral centers as (1*R*,2*R*,α*R*) and the measure of its mp of 158-160°C and its rotation power is $\mathbf{[\alpha]_D^{20}}$ = -5.11 (*c* 0.97; $CHCl_3$).

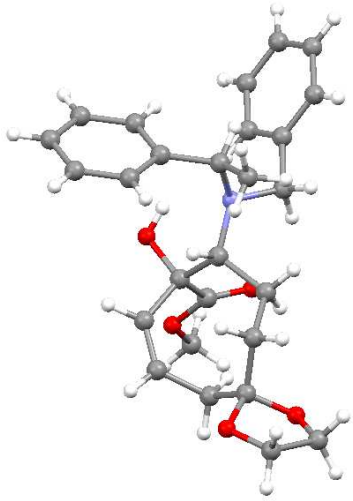


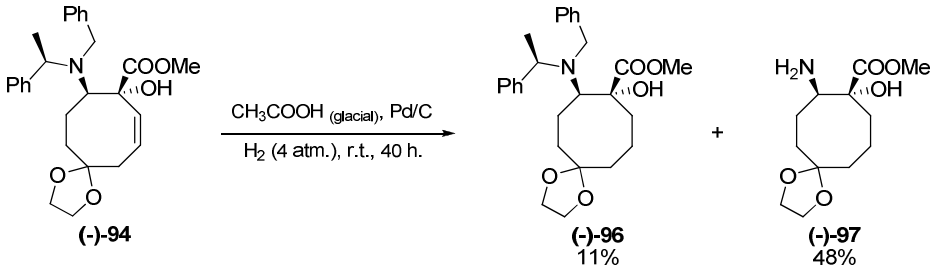
Figure 37. Molecular structure representation of compound **(-)-94**

Regarding to its spectroscopic data, interesting signals in its I.R. spectrum appear at 3427, 1726 and 1224 cm^{-1} accounting for the functionalized groups O-H, C=O and C-O, respectively; by its ^{1}H NMR spectrum we can confirm the addition of the amine at 1.41 (3H, d, *J* 7.0, N(α)*Me*), 3.62-3.65 (1H, d, J_{AB}, 14.0, CH_ACH_BPh), 4.19-4.23 (1H, d, J_{AB}, 14.0, CH_ACH_BPh) and 7.04-7.37 ppm (10H, m, *H*-Ar); the presence of the ester at 3.64 ppm (3H, s, COO*Me*); the 1,3-dioxolane protection at 3.93-3.98 ppm (4H, m, COO(CH_2)$_2$) and the unsaturated system at 5.55-5.61 ppm (2H, H-7 and H-8). By analysis of its ^{13}C NMR spectrum we could establish important signals as 12.0 (CH_3, N(α)*Me*); 52.4 (CH_3, COO*Me*), 64.5 (CH_2, O*C*H$_2$CH$_2$O), 64.9 (CH_2, OCH$_2$*C*H$_2$O), 77.3 (C, C-1), 113.0 (C, C-5), 136.1 (CH x 2, C-7 and C-8) and 174.2 ppm (C, *C*OOMe).

In spite that the by-product at performing this conditions with compound **55** was the Michael addition compound **(+)-91**, in the same reaction with **84** as starting material, a secondary product was isolated and fully characterized as butyl-1-hidroxy-5,5-ethylenedioxycyclooct-2,7-diene-1-carboxylate **95**, showing that the simplicity of its spectra is due to the existence of a symmetry plane in the molecule as shown ^{1}H and ^{13}C NMR spectra at 5.73-5.81 ppm (4H, m, H-2, H-3, H-7 and H-8) and at 130.0 ppm (CH x 2, C-2 and C-3) and 134.4 ppm (CH x 2, C-7 and C-8) assigned to its double unsaturation. The formation of this compound can be explained by reaction with BuO^- present as impurity in *n*-BuLi and Cope elimination by oxidative reaction of the tertiary amine.

Taking into account that the protocol of hydrogenation and hydrogenolysis was developed for compounds **(-)-90** and **(+)-90**, the key step now, before subjecting these reactions is the deprotection of the carbonyl group because it may favour the intramolecular cyclization by condensation with the amine.

Two reactions were performed. The first one by addition of H_2O, PTSA in acetone and stirred at room temperature for 20 hours and the second one refluxed at 50°C for 60 hours. In the two cases the deprotected compound was not yielded. On the other hand, due to the great stabilization that this molecule shows, it could be that the hydrogenation and hydrogenolysis reactions will need a stronger media to afford the desirable product, the reaction was subjected in glacial acetic acid as a solvent, Pd/C (30 % Pd basis) and under H_2 (4 atm.) for 40 hours (Scheme 137).

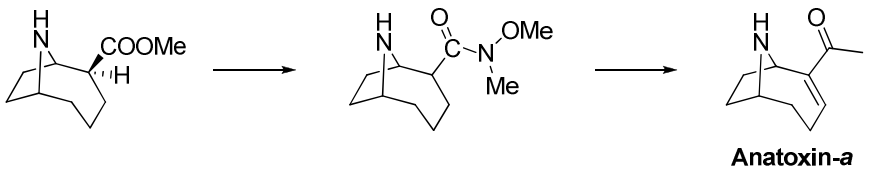


Scheme 137. One pot hydrogenation and hydrogenolysis reaction test.

In spite of a longer reaction time, compound **(-)-96** was achieved in 11% yield. As a confirmation that hydrogenation and hydrogenolysis took place, the adduct **(-)-97** was yielded in 48% and characterized. Its functionalized groups are present in the IR spectrum at 3385 cm^{-1} for O-H and N-H, 1726 cm^{-1} for C=O and 1104-1056 cm^{-1} for C-O-C. Its ^{1}H NMR spectrum is kind of simple but the ^{13}C NMR spectrum show all the 12 carbons present in this structure being the most important the following: 52.6 ppm (CH_3, COO*Me*), 64.1 and 64.8 ppm for (CH_2 x 2 , O*C*H_2*C*H_2O), 77.2 ppm (CH, C-2), 82.2 ppm (C, C-1), 111.4 ppm (C, C-5) and 175.8 ppm (C, *C*OOMe).

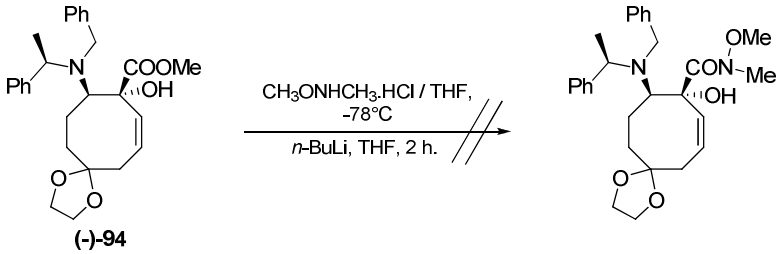
Application of the Weinreb`s amide in earlier derivatives:

One of the processes envisaged in the retrosynthetic Scheme 138 for the synthesis of Anatoxin-*a*, involves the conversion of the ester into the methyl ketone and it is planned to be performed through the Weinreb`s amide.



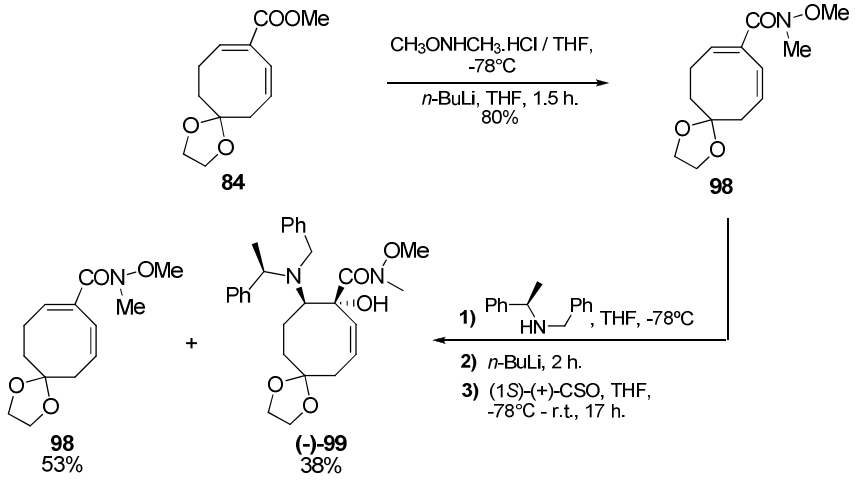
Scheme 138. Weinreb`s amide protocol in the approximation to the synthesis of Anatoxin-*a*

Therefore, it seems appropriate to test the reactivity of this functional group in the initial cyclooctadiene, as it is known preferential reactivity of the conjugate amide to overcome Michael addition avoiding 1,2 addition reactivity. Different experiments were carried out. Firstly, compound **(-)-94** was led to react by previous addition of N,O-dimethylhydroxylamine hydrochloride dissolved in THF and *n*-BuLi (Scheme 139). Unfortunately the reaction product was not yielded perhaps because of steric factors.



Scheme 139. Preparation of the Weinreb´s amide

In a similar manner, the Weinreb`s amide method was carried out for compound **84** affording in this case compound **98** with 80% yield (Scheme140).



Scheme 140. Preparation of the Weinreb´s amide

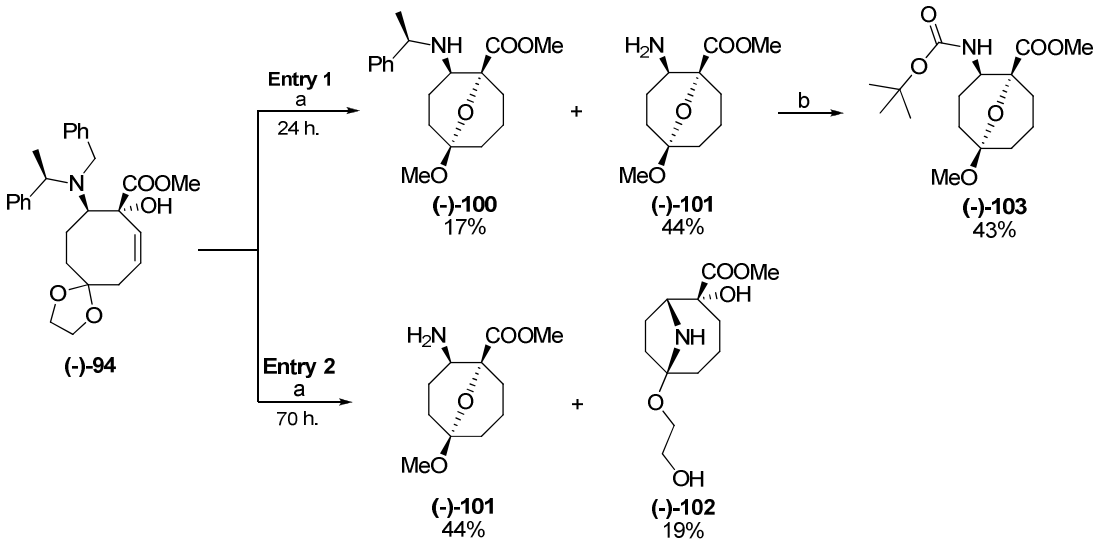
With compound **98** in hand, Michael addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide and subsequent in situ addition of (1*S*)-(+)-(10-Camphorsulfonyl) oxaziridine was carried out. After purification by CC unreacted starting material **98** (53%) was recovered together with reaction product **(-)-99** isolated in 38%, but due to the low quantity isolated it was not fully characterized. In

spite of this, the yield achieved for compound **(-)-99** is good, accounting for the recovery of starting material, and it could also be optimized for exploring further reactivity.

Intramolecular cyclization reactions:

Continuing the development of our planned synthetic route, the intramolecular cyclization is our next step. Synthesis of (±)-Indolizidine 209D showed in previous Scheme 119 resembles ours wherein deprotection of dioxolane has to take place to the formation of an anti-Bredt double bond.[150]

Two experiments were performed for studying the possibility of intramolecular cyclization in compound **(-)-94** under catalytic hydrogenation conditions. As shown in Scheme 141, compound **(-)-94** was dissolved in MeOH and Pd/C (30 % Pd basis) and HCl_c (37%, 8 drops) were added into the system and reacted under H_2 (4 atm.) for 24 hours. This first entry yielded after purification by CC compound **(-)-100** and **(-)-101** in 17% and 44%, respectively. The expected intramolecular cyclization between the deprotected amine and the deprotected carbonyl group did not take place; nevertheless intramolecular cyclization did take place between the hydroxy group and the functionalized C-5 position. These results disclosed interesting issues to be considered, namely: under these conditions both the amine and the 1,3-dioxolane groups were deprotected but the amine need longer reaction period, moreover intramolecular cyclization is possible albeit interference of the hydroxy group in C-1 is observed.

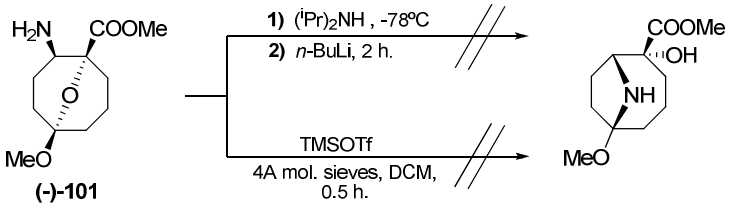


Scheme 141. *Reagents and conditions:* (a) c. HCl, MeOH, Pd/C, H_2 (4 atm.), r.t. (b) Boc_2O, THF, r.t, 3 h.

Compound **(-)-100** was just identified by its ^{1}H NMR spectrum but its structure can be confirmed by the full characterization of compound **(-)-101** (Table 41, see 2D NMR part), which has $[\alpha]_D^{20}$ = -9.85 (*c* 1.02; $CHCl_3$). The functional groups in the IR spectrum are present at 3383 (N-H), 1731 (C=O) and 1068-1041 (C-O-C) cm^{-1} and its structure of 9-oxabicyclo[3.3.1]nonane can be corroborated by its ^{13}C NMR spectrum with the two quaternary carbons in the ring at 81.2 ppm (C, C-1) and 98.0 ppm (C, C-5). On the other hand, by the preparation of the protected derivative **(-)-103** afforded in 43% yield confirms that the nature of the amine is primary, because if this functional group was forming the intramolecular cycle when we carry out its protection with Boc_2O would be tertiary and it can be corroborated by the following signals in its ^{1}H NMR being the most representative at 4.07 ppm (1H, m, H-2) and 4.40 ppm (1H, d, *J* 9.6, N-H).

For studying the behavior of compound **(-)-94** under longer reaction periods, this one was subjected to react under the same conditions for 70 hours. This second Entry yielded after purification by CC compound **(-)-101** and **(-)-102** in 44% and 19%, respectively. Formation of compound **(-)-102** is a great achievement and its structure can be confirmed by analysis of its spectroscopic data. In its I.R. spectrum we can observed the typical vibrational bands of functional groups such as 3375 (N-H, O-H), 1739 (C=O), 1141 and 1037 (C-O-C) cm^{-1}. The most important signals in its ^{1}H NMR spectrum are at 3.68-3.72 (3H, m, H-1 and OCH_2CH_2OH); 3.78 (3H, s, COO*Me*); 3.80-3.85 (2H, m, OCH_2CH_2OH) and its ^{13}C NMR spectrum corroborates the presence of the 12 carbons at 20.0 (CH_2); 24.5 (CH_2 x 2); 32.1 (CH_2 x 2); 52.8 (CH_3, COO*Me*); 63.2 (CH_2, O-CH_2-CH_2-OH); 64.6 (CH_2, O-CH_2-CH_2-OH); 76.6 (CH, C-1); 92.4 (C, C-2); 98.1 (C, C-6); 174.0 (C, *C*OOMe).

Taking into account that compound **(-)-101** may be an intermediate in the formation of derivatives with a nitrogen bridge, encouraged us to perform different kind of reactions to promote the desired intramolecular cyclization by activation of the amine group or/and opening reactions of the intramolecular [3.3.1] ring, with no results.[159]



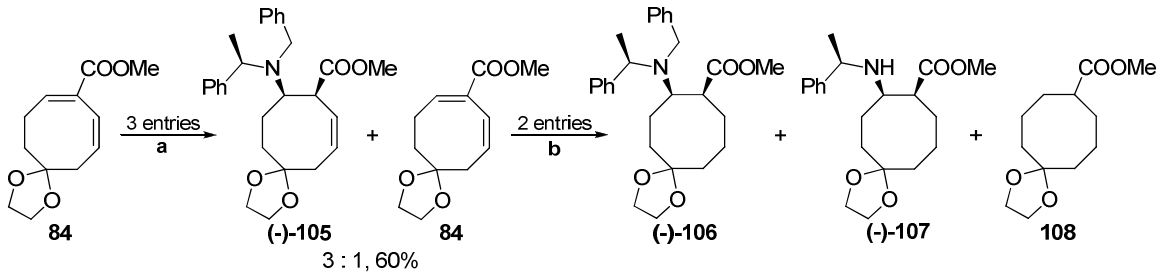
Scheme 142. Test reactions, reactivity of compound **(-)-101**

[159] (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc*. **2001**, *123*, 12510-12517. (b) Sugiura, M.; Kobayashi, S. *Organic Letters* **2001**, *3*, 477-480. (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2008**, *130*, 7198-7199. (d) Furukubo, S.; Moriyama, N.; Onomura, O.; Matsumura, Y. *Tetrahedron Letters* **2004**, *45*, 8177-8181.

To avoid the observed interaction of the α-hydroxy group and to promote intramolecular cyclization of the amine group, compound **(-)-94** was subjected to a protection reaction with methyl chloromethyl ether (MOMCl), affording the protected product **(-)-104** pure after flash chromatography in only 0.3%.

After a careful study of the results obtained so far, we reconsider an alternative and feasible pathway in the synthesis of Anatoxin-*a*. Taking into account the retro-Michael reaction of compound **(-)-105** occurring during purification by CC, the low yields and not viable intermediates obtained in the one-pot α-phenylselenylation and one-pot α-hydroxylation of homochiral β-amino enolates together with the results obtained in the intramolecular cyclization reaction, it was decided to perform the addition of (*R*)-**C** to compound **84** and further continue with the hydrogenation reaction without isolating the Michael adduct **(-)-105**.

As shown previously in Table 12, were performed three entries which crudes` ^{1}H NMR spectra show the ratio mixture of the products from the Michael addition reaching under the best conditions a 3:1 ratio of **(-)-105** and **84** in 60% yield (Table 22, see experimental part). Subsequently, the crudes were subjected to hydrogenation reactions performing two experiments, in the first one, and after 2.5 hours reaction, compounds **(-)-106** and **108** were isolated after CC with 40% and 20% yields, respectively. The second test (Entry 2, Table 13) after 19 hours reaction and purification by flash column chromatography yielded compounds **(-)-106**, **(-)-107** and **108** in 39%, 1% and 13% with a significant general increase.

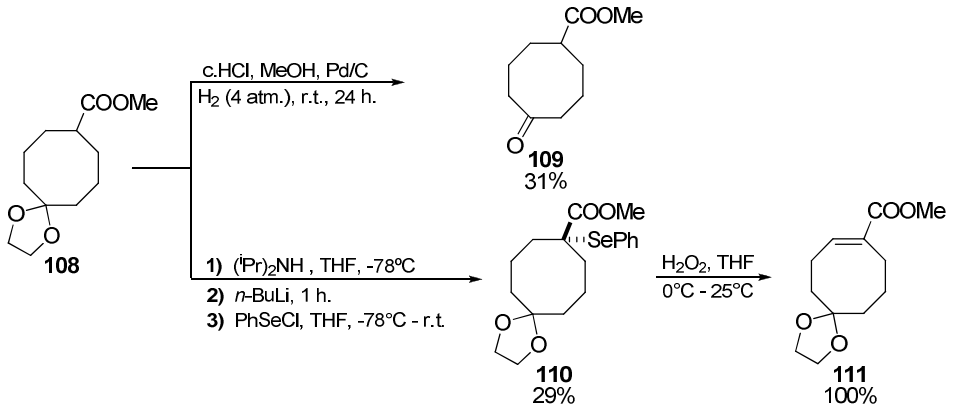


Scheme 143. *Reagents and conditions:* (a) (*R*)-**C**, *n*-BuLi, THF, -78°C, 2 h. (b) EtOAc $_{(dry)}$, PtO_2, H_2, r.t

Table 13. Reaction conditions for protocol **b**

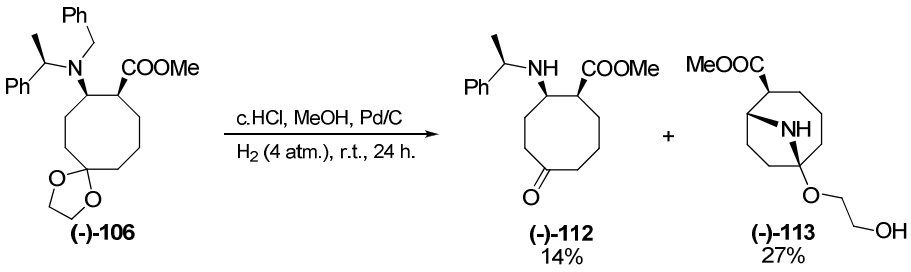
Entry	(-)-105 : 84 (mmol)	EtOAc (mL)	PtO_2 (mmol)	t (hours)	(-)-106 (%)	(-)-107 (%)	108 (%)
1	0.37	15	0.36	2.5	40	-	20
2	0.57	15	0.56	19	39	1	13

The study on the reactivity of compound **108** has helped us to corroborate that deprotection of the 1,3 dioxolane group can be achieved under acid catalytic hydrogenation conditions (Scheme 144). On the other hand, it can be used to regenerated the Michael acceptor by addition of phenylselenyl chloride affording compound **110** in 29% yield followed by elimination of the phenylselenyl group obtaining compound **111** in 100% yield (Scheme 144) whose recovery is important due to the value of this intermediate for performing new Michael addition and because show the way to make the final double bond in Anatoxin-*a* synthesis.



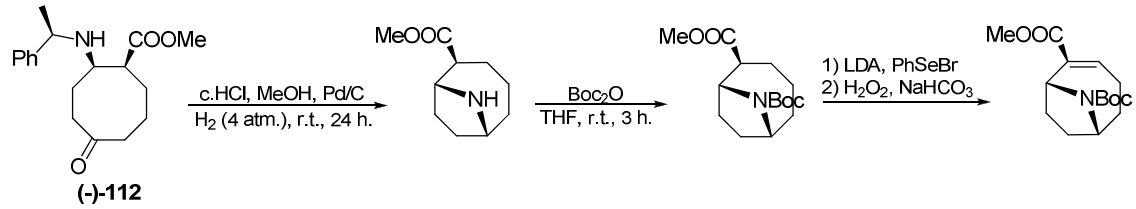
Scheme 144. Reactivity of compound **108**

With compound **(-)-106** in hand, the previous hydrogenolysis, deprotection and intramolecular cyclization reaction was subjected. After 24 hours reaction, it yielded compound **(-)-112** and **(-)-113** in 14% and 27%, respectively.



Scheme 145. Hydrogenolysis, deprotection and intramolecular cyclization reaction

These two compounds are highly advanced intermediates in the synthesis of Anatoxin-*a*. Methyl (1*S*,2*R*,α*R*)-2-*N*-α-methylbenzylamino-5-oxocyclooctane-1-carboxylate **(-)-112** could be subjected to react under the same conditions to form probably the methyl 9-azabicyclo[4.2.1]nonane-2-carboxylate which by protection of the amine with Boc_2O and addition-elimination of phenylselenyl bromide we will led to the unsaturated bicyclic ring.



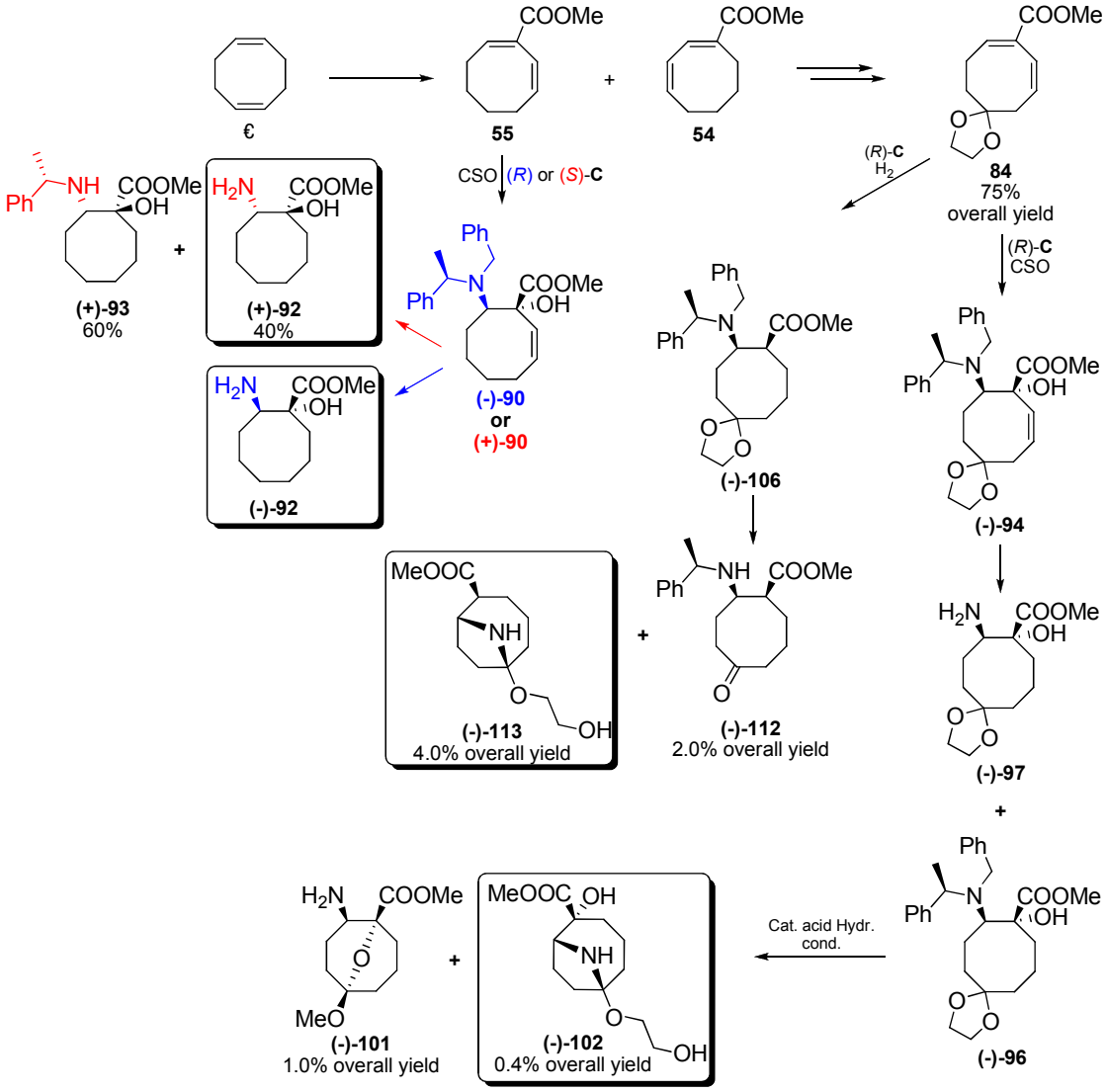
Scheme 146. Possible route to follow from adduct **(-)-112**.

The main objective of this work was the synthesis of Anatoxin-*a* but the obtention of similar adducts is of great importance in the study of its activity to trace human and nonhuman nicotinic acetylcholine receptors.

In conclusion in this chapter we have reached several goals, that there are shown in the general scheme 147. Firstly, the preparation and optimization of the synthetic procedure that yields compound **84** obtained after 2 steps from cycloocta-1,3-diene carboxylate in 75% overall yield. Product **84** represents derivative **IV** in the proposed retrosynthetic scheme of Anatoxin-*a*.

The study of the reactivity of compound **55**, to find appropriate conditions for the diastereoselective hydroxylation of homochiral β-amino enolates with oxaziridines afforded in reasonable yields the two products: methyl (1*R*,2*R*)- and (1*S*,2*S*)-1-hydroxy-2-amino-cyclooctanecarboxylates, **(-)-92** and **(+)92**, respectively, which can be further converted into their respective functionalized cyclooctanic β-amino acids enriching our adducts library.

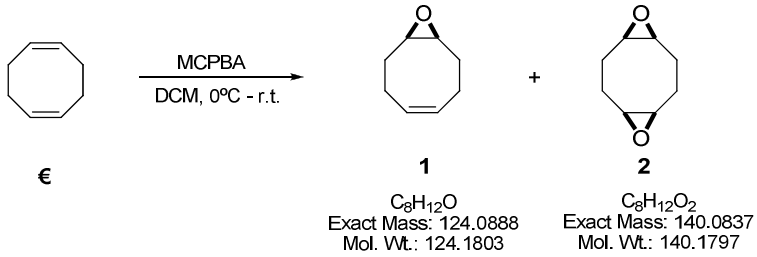
Through application of the aforementioned conditions to compound **84**, adduct **(-)-94** was obtained which provides **(-)-101** and **(-)-102** in 5.0% and 2.1% yield, respectively. These are interesting functionalized bicycles derivatives. In addition, their obtention made us redirect the synthesis pathway towards the direct addition of (*R*)-**C** to compound **84** wherein the intermediate **(-)-106** was isolated and through catalytic acid hydrogenation compounds **(-)-112** and **(-)-113** were afforded in 6.3% and 12.2% yield, respectively, being the two of them highly advanced synthons of Anatoxin-*a* synthesis.



Scheme 147. Obtention of highly potential synthons for the synthesis of Anatoxin-*a*

1. Asymmetric synthesis of (1*S*,2*R*)-2-aminocyclooctanecarboxylic acid:

***Synthesis of 1,2-epoxicycloocta-5-ene 1*:**

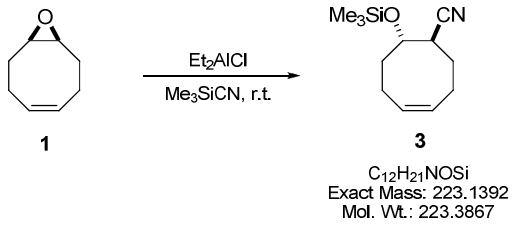


Comercial available 1,5-cyclooctadiene (10.00 g, 92.60 mmol) was dissolved in DCM (150 mL), and stirred at 0ºC, MCPBA (18.50 g, 107.20 mmol) was added slowly and the solution was stirred for 1.5 hours at r.t.. The reaction mixture was quenched with $Na_2S_2O_{3\,(sat.)}$ (15 mL), extracted with DCM (3 x 80 mL), washed with H_2O, $NaHCO_{3\,(sat.)}$ and $Na_2S_2O_{3\,(sat.)}$. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained a mixture of **1** and **2** (8.61 g). Fractional microdistillation vacuum was performed to give the following compounds:

Monoepoxide **1** (≈ 15 mm Hg, 65ºC) as a colourless oil (17.97 g, 72%). **IR υ_{max} (neat)**: 3050 (C-H), 2955, 1655 (C=C), 1229 (C-O), 936, 862 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.90-2.25 (6H, m, H-3, H-8, H-4α and H-7α), 2.30-2.55 (2H, m, H-4β and H-7β), 3.02 (2H, m, H-1 and H-2), 5.52 (2H, m, H-5 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 23.5 (CH_2, C-3 and C-8), 28.0 (CH_2, C-4 and C-7), 56.4 (CH, C-1 and C-2), 128.7 (CH, C-5 and C-6). ***m/z* (CI^+) (rel. intensity):** 124 (M, 2), 95 (14), 80 (100), 67 (100), 54 (37).
[Lit., (Davies S.G. and Whitham G. H. *Journal Chemical Society Perkin II* **1975**, pp 861-863) **^{13}C NMR (22.6 MHz; $CDCl_3$):** δ 23.7 (C-4 and C-7) [a]; 28.3 (C-3 and C-8) [a]; 56.5 (C-1 and C-2); 128.9 (C-5 and C-6)].[a] Ambiguous assignment, may be interchanged.

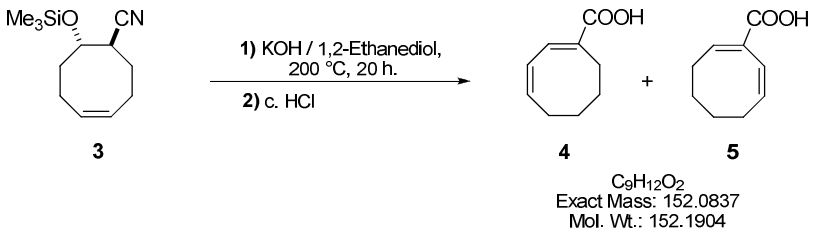
Diepoxide **2** (remaining of the distillation) as a yellow oil (8.65 g, 22%). **IR υ_{max} (neat)**: 3050 (C-H), 2920 (C-H), 1258 (C-O), 912, 828 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.80-2.10 (8H, m, H-3, H-4, H-7, H-8), 2.90 (4H, m, H-1, H-2, H-5, H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.9 (CH_2, C-3, C-4, C-7, C-8), 55.1 (CH, C-1, C-2, C-5, C-6). ***m/z* (EI^+) (rel. intensity):** 140 (M, 1), 122 (1), 112 (2), 96 (8), 79 (34), 67 (80), 55 (100).
[Lit., (Davies S.G. and Whitham G. H. *Journal Chemical Society Perkin II* **1975**, pp 861-863) **^{13}C NMR (22.6 MHz; $CDCl_3$):** δ 22.0 (C-3, C-4, C-7 and C-8); 56.0 (C-1 and C-2)].

Synthesis of (1R*,2R*,5Z)-2-trimethylsilyloxi-cycloocta-5-enecarbonitrile 3:



In a dried flask under Ar atmosphere was added Et_2AlCl (1.0 M in heptane, 2.30 mL, 2.00 mmol) followed by the addition of Me_3SiCN (7.50 mL, 56.00 mmol), the resulting solution was stirred for 30 min. at r.t. After via cannula compound **1** (5.72 g, 46.00 mmol) was added slowly into the system and stirred for other 30 min. The crude was poured on a mixture of NaOH 3M. and ice (200 mL), extracted with Et_2O, washed with NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified for full characterization by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) but purification can be avoided. It was obtained compound **3** as a pale yellow oil (10.3 g, 100%). **IR υ_{max} (neat)**: 3017 (C-H), 2951, 2241 (C≡N), 1653 (C=C), 1251 (C-O), 1096, 1071 (Si-O), 843 (Si-C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 0.17 (9H, s, *Me*$_3$SiO), 1.66 (2H, m, H-3), 1.87 (2H, m, H-8), 2.01 (2H, m, H-4), 2.23 (2H, m, H-7), 3.03 (1H, ddd, *J* 11.7, 7.9 and 3.9, H-1), 3.90 (1H, td, *J* 7.9 and 3.4, H-2), 5.56 (1H, dt, *J* 7.0 and 2.7, H-6), 5.73 (1H, dt, *J* 10.8 and 7.0, H-5). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 0.8 (3 x CH_3, *Me*$_3$SiO), 22.7 (CH_2, C-8), 23.8 (CH_2, C-3), 28.8 (CH_2, C-7), 35.9 (CH_2, C-4), 37.6 (CH, C-1), 71.6 (CH, C-2), 121.5 (C, *C*≡N), 127.2 (CH, C-6), 131.2 (CH, C-5). ***m/z* (CI$^+$) (rel. intensity):** 223 (MH^+, 1), 208 (50), 195 (3), 180 (6), 167 (3), 152 (10), 126 (16), 116 (21), 101 (47), 80 (23), 73 (100), 59 (48).

***Synthesis of cycloocta-1,3 and 1, 7-dienecarboxylic acid 4 and 5 respectively*:**



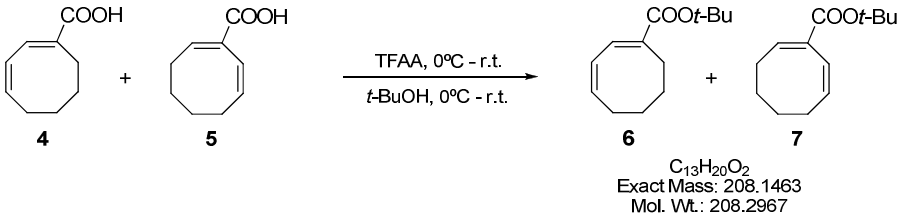
Compound **3** (24.61 g, 110.00 mmol) was dissolved in a mixture of KOH (28.50 g) and 1,2-Ethanediol (469 mL) previously prepared and the resulting solution was refluxed at 200 ºC for 20 hours. After, the system was cooled down and H_2O (330 mL) was added. The crude was extracted with Et_2O (3 x 200 mL) and the aqueous phase was treated with HCl c. reaching pH acid, this solution was extracted with Et_2O (3 x 100 mL), washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4,

filtered and concentrated *in vacuo*. It was obtained a brown oil (16.44 g, 98%) that contains a mixture of **4** and **5** (1:1). Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) was performed for full characterization.

Compound **4**: **IR υ_{max} (neat):** 3600 (O-H), 2958 (C-H), 2934, 1684 (C=O), 1622 (C=C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.56 (4 H, m, H-6 and H-7), 2.21 (2H, m, H-5), 2.50 (2H, m, H-8), 5.85 (2H, m, H-3 and H-4), 7.28 (1H, m, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.5 (CH_2, C-7), 25.6 (CH_2, C-6), 25.8 (CH_2, C-5), 29.8 (CH_2, C-8), 124.0 (CH, C-4), 131.0 (C, C-1), 136.8 (CH, C-3), 139.3 (CH, C-2), 173.0 (C, *C*OOH). ***m/z* (EI$^+$) (rel. intensity):** 153 (MH^+, 32), 136 (26), 124 (10), 107 (74), 89 (72), 77 (100), 69 (32), 63 (25), 1 (57). **HRMS (Cl$^+$) *m/z* calcd. for $C_9H_{12}O_2$:** 152.0837; **found** 152.0827; **Δ** = -6.6 ppm.

Compound **5: IR υ_{max} (neat):** 3600 (O-H), 3021 (C-H), 2930, 1690 (C=O), 1622 (C=C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.25 (2H, m, H-5), 1.48 (2H, m, H-4), 2.13 (2H, m, H-6), 2.31 (2H, m, H-3), 5.88 (1H, dt, *J* 11.3 and 7.2, H-7), 6.13 (1H, d, *J* 11.3, H-8), 7.08 (1H, t, *J* 8.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 22.6 (CH_2, C-5), 25.5 (CH_2, C-4), 28.2 (CH_2, C-6), 28.4 (CH_2, C-3), 122.5 (CH, C-7), 129.3 (C, C-1), 133.9 (CH, C-8), 144.9 (CH, C-2), 171.2 (C, *C*OOH). ***m/z* (CI$^+$) (rel. intensity):** 152 (MH^+, 10), 135 (9), 107 (41), 89 (36), 77 (100), 63 (23), 1 (56). **HRMS (Cl$^+$) *m/z* calcd. for $C_9H_{12}O_2$:** 152.0837; **found** 152.0833; **Δ** = -2.6 ppm.

***Synthesis of tert-butyl cycloocta-1,3 and 1,7-dienecarboxylate 6 and 7 respectively*:**

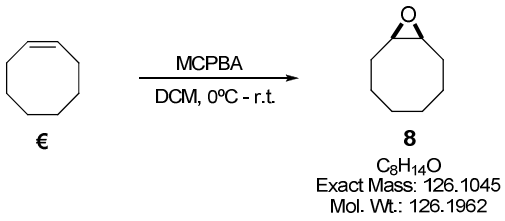


In a flask was measured a mixture of the acids **4** and **5** (5.11 g, 33.60 mmol) and TFAA (9 mL, 64 mmol) was added at 0 ºC, after the system was stirred at r.t. for 15 min. The temperature was again cooled down to 0ºC and *t*-BuOH (11 mL, 110 mmol) was added into the system and stirred for 4 h. The reaction mixture was quenched with NaOH (10%, 50 mL), extracted with Et_2O, washed with NaOH 1M. and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained as a crude a brown oil (7.08 g) that contains a mixture of **6** and **7** (1:1). Through acidulation of the aqueous phase with HCl c. and extraction with DCM it could be recovered mixture of the acids that did not react (1.58 g). Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (98:2-70:30 v/v) gave a mixture of **6** and **7** (1:1, 4.35 g, 79%) and the following compounds:

1,3-cyclooctadiene ester **6** as a pale yellow oil (2.65g, 48%), **IR υ_{max} (neat):** 2932 (C-H), 1709 (C=O), 1368 (C=C),1155 (C-O) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.43 (9H, s, COOC(CH_3)$_3$), 1.43-1.52 (4H, m, H-6 and H-7); 2.06 (2H, m, H-5), 2.33 (2H, m, H-8), 5.69 (2H, m, H-3 and H-4), 6.92 (1H, d, *J* 2.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.9 (CH_2, C-6), 24.1 (CH_2, C-7), 26.3 (CH_2, C-8), 28.2 (CH_3 x 3, COOC(CH_3)$_3$), 29.8 (CH_2, C-5), 79.9 (C, COOC(CH_3)$_3$), 124.5 (CH, C-4), 133.6 (C, C-1), 135.4 (CH, C-3), 135.7 (CH, C-2), 166.0 (C, COOC(CH_3)$_3$). ***m/z* (CI^+) (rel. intensity):** 152 (MH^+-56, 36), 135 (13), 123 (6), 107 (35), 93 (5), 79 (32), 77 (13), 57 (100). **HRMS (MH^+) *m/z* calcd. for $C_{13}H_{20}O_2$:** 208.1463; **found** 208.1444; **Δ** = -9.1 ppm.

1,7-cyclooctadiene ester **7** as a pale yellow oil (1.70 g, 31%), **IR υ_{max} (neat):** 2930 (C-H), 1717 (C=O), 1456, 1368 (C=C), 1159 (C-O) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.49 (9H, s, COOC(CH_3)$_3$), 2.11 (4H, m, H-4 and H-5), 2.24 (4H, m, H-3 and H-6), 5.80 (1H, dt, *J* 11.2 and 7.2, H-7), 6.09 (1H, d, *J* 11.2, H-8), 6.85 (1H, t, *J* 8.0, H-2).**^{13}C NMR (50 MHz; $CDCl_3$):** δ 22.4 (CH_2, C-4), 22.9 (CH_2, C-5), 28.2 (CH_3 x 3, COOC(CH_3)$_3$), 28.3 (CH_2, C-6), 28.4 (CH_2, C-3), 80.1 (C, COOC(CH_3)$_3$), 123.7 (CH, C-7), 131.8 (C, C-1), 132.8 (CH, C-8), 141.3 (CH, C-2), 166.6 (C, COOC(CH_3)$_3$). ***m/z* (CI^+) (rel. intensity):** 208 (MH^+, 1), 152 (31), 135 (12), 123 (6), 107 (32), 92 (12), 79 (41), 67 (13), 57 (100). **HRMS (MH^+) *m/z* calcd. for $C_{13}H_{20}O_2$:** 208.1463; **found** 208.1458; **Δ** = -2.4 ppm.

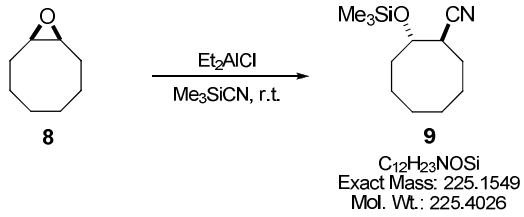
Synthesis of cyclooctane oxide 8:



Comercial available cis-cyclooctene 95% from Aldrich (3.00 g, 27.00 mmol) was dissolved in 30 mL of DCM and the system was stirred and cooled down at 0ºC. MCPBA (5.31 g, 30.80 mmol) was added slowly and the solution was stirred for 1.5 hours leaving the system to reach r.t. The reaction mixture was quenched with 10 mL of $Na_2S_2O_{3\ (sat.)}$, extracted with DCM (3 x 30 mL), washed with H_2O, $NaHCO_{3\ (sat.)}$ and $Na_2S_2O_{3\ (sat.)}$. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained monoepoxide **8** as a colourless to white solid (3.28 g, 100%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.17 (4H, m, H-5 and H-6); 1.58 (4H, m, H-4 and H-7), 2.17 (4H, m, H-3 and H-8); 2.92 (2H, m, H-1 and H-2).

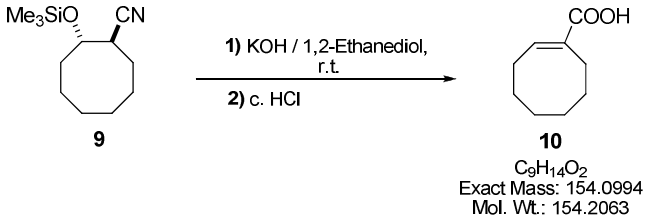
[Lit., (Paulson D. R.; Tang F.Y.H.; Moran G. F.; Murray A. S.; Pelka B. P. And Vasquez E. M. *J. Org. Chem*. **1975**, *40* (2), 184-186) **^{13}C NMR (50 MHz; $CDCl_3$):** δ 55.1 (C-1)].

Synthesis of (1R*,2R*)-2-trimethylsilyloxi-cycloocta-carbonitrile 9:



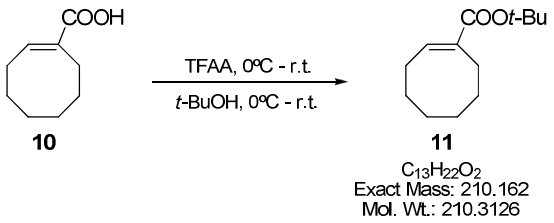
Following previous procedure, it was added Et_2AlCl (0.80 mL, 0.80 mmol) followed by the addition of Me_3SiCN (2.50 mL, 18.00 mmol). Via cannula compound **8** (1.90 g, 15.00 mmol) was added slowly and the system was stirred for other 3 hours. The crude was poured on a mixture of NaOH 3M. and ice (50 mL), extracted with Et_2O, washed with NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. The residue can be purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5-70:30 v/v). It was obtained compound **9** (0.68 g, 20%). **^{1}H NMR (400 MHz; $CDCl_3$):** δ 0.14 (9H, s, *Me*$_3$SiO), 1.17-1.99 (12H, m), 2.10-2.20 (1H, ddd, *J* 12.2, 7.8 and 2.6, H-1), 2.85-2.95 (1H, dd, *J* 7.8 and 4.4, H-2).

***Synthesis of cycloocta-1-enecarboxylic acid 10*:**



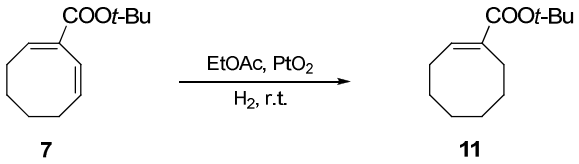
Compound **9** (0.68 g, 3.00 mmol) was dissolved in a mixture of KOH (0.80 g) and 1,2-Ethanediol (14 mL) previously prepared and the resulting solution was refluxed at 200 ºC for 20 hours. After, the system was cooled down and it was added H_2O (50 mL). The crude was extracted with Et_2O (3 x 30 mL) and the aqueous phase was treated with HCl c. reaching pH acid, this solution was extracted with Et_2O (3 x 30 mL), washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained compound **10** (0.39 g, 85%) which was characterized as its *tert*-butyl ester.

***Synthesis of tert-butyl cycloocta-1-enecarboxylate 11*:**



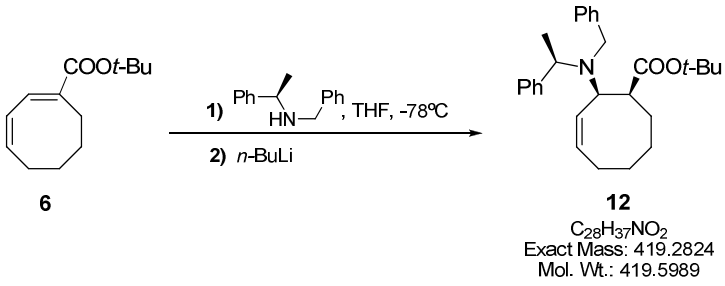
Following previous procedure, compound **10** (0.23 g, 1.50 mmol) and TFAA (0.4 mL, 3.0 mmol) was added at 0 ºC, after the system was stirred at r.t. for 15 min. The temperature was again cooled down to 0ºC and *t*-BuOH (0.5 mL, 5.2 mmol) was added into the system and stirred for 4 h. The reaction mixture was quenched with NaOH (10%, 10 mL), extracted with Et_2O, washed with NaOH 1M. and NaCl $_{(sat)}$, dried over Na_2SO_4 and concentrated *in vacuo*. Through acidulation of the aqueous phase with HCl c. and extraction with DCM it could be recovered cyclooctenecarboxylic acid **10** (15%). Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (98:2-70:30 v/v) gave the unsatured ester **11** (253 mg, 80%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.48 (9H, s, COOC(CH_3)$_3$), 1.55 (4H, m, H-5 and H-6), 2.24 (4H, m, H-4 and H-7), 2.41 (4H, m, H-3 and H-8), 6.88 (1H, t, *J* 8.4, H-2).**^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.9 (CH_2, C-5); 25.5 (CH_2, C-6); 26.1 (CH_2, C-4); 26.8 (CH_2, C-7); 28.4 (3 x CH_3, COOC(CH_3)$_3$), 29.3 (CH_2, C-3); 29.4 (CH_2, C-8); 79.9 (C, COOC(CH_3)$_3$), 135.0 (C, C-1); 141.3 (CH, C-2), 167.3 (C, COOC(CH_3)$_3$).

***Synthesis of tert-butyl cycloocta-1-enecarboxylate 11 by hydrogenation of compound 7*:**



In a dry flask was measured compound **7** (270.0 mg, 1.3 mmol) and dissolved in 20 mL of EtOAc, after it was added PtO_2 (147.0 mg, 0.7 mmol). The reaction system was purged with H_2 and stirred under H_2 atmosphere at r.t. for 30 min. It was obtained compound **11** (263mg, 97%).

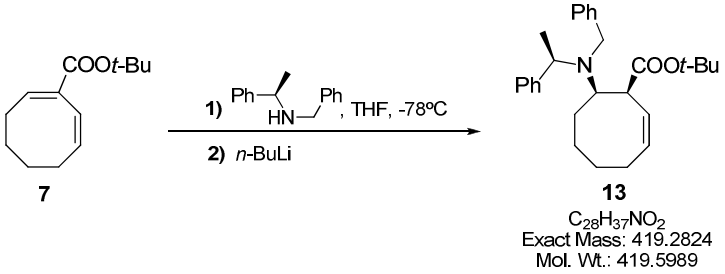
Synthesis of tert-butyl (1S,2R,αR,3Z)-2-N-benzyl-N-α-methylbenzylamino-cycloocta-3-enecarboxylate 12:



In a dry flask and under Ar atmosphere was added the chiral amine (4.1 mL, 19.6 mmol) and dissolved in THF (15 mL). After, the system was cooled down to -78ºC and *n*-BuLi (1.6 M., 11.4 mL, 18.3 mmol) was added and stirred for 15 min., after warmed it up to 0ºC for other 15 min. The system was cooled down to -78ºC again and compound **6** (805 mg, 3.86 mmol) was added and stirred for 6 hours. The reaction mixture was quenched with NH_4Cl $_{(sat)}$ (5 mL), extracted with

EtOAc, washed with H_2O and NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. After the crude was diluted in DCM and washed with Citric acid 10% and $NaHCO_3$, dried, filtered and evaporated under reduce pressure. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (98:2-90:10 v/v) afforded starting material **6** (531 mg, 42%) and compound **12** (705 mg, 42%), $\mathbf{[\alpha]_D^{26}}$ = +98.0 (*c* 1.2, $CHCl_3$); **IR υ_{max} (neat):** 2932 (C-H), 1700 (C=O), 1653 (C=C), 1559, 1493, 1368, 1248 (C-O), 1030, 783 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.37 (9H, m, COOC(CH_3)$_3$); 1.45 (3H, d, *J* 6.8, C(α)*Me*); 1.20-1.65 (4H, m, H-6 and H-7); 1.22 (1H, m, H-8$_A$); 1.62 (1H, m, H-8$_B$); 1.92 (1H, m, H-5$_A$); 2.08 (1H, m, H-5$_B$); 2.50 (1H, m, H-1); 3.85 (1H, m, H-2); 3.85 (1H, AB, J_{AB} 17.1, NCH_ACH$_B$Ph); 4.10 (1H, AB, J_{AB} 17.1, NCH$_A$CH_BPh); 4.25 (1H, q, *J* 6.8, C*H*(α)); 5.80 (1H, m, H-4); 6.05 (1H, m, H-3); 7.30 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 13.2 (CH_3, C(α)*Me*); 25.8 (CH_2, C-6); 27.5 (CH_2, C-7); 27.9 (CH_3 x 3, COOC(CH_3)$_3$); 30.1 (CH_2, C-8); 30.6 (CH_2, C-5); 51.7 (CH_2, N-*C*H_2); 53.5 (CH, C-1); 54.7 (CH, *C*H(α)); 56.5 (CH, C-2); 80.0 (C, COO*C*(CH_3)$_3$); 126.5-129.9 (CH x 10, Ar); 128.0 (CH, C-4), 129.6 (CH-C-3); 141.9 (C, C$_{ipso}$); 144.1 (C, C$_{ipso}$); 174.9 (C, *C*OOC(CH_3)$_3$). ***m/z* (CI$^+$) (rel. intensity):** 419 (MH^+, 19), 258 (21), 205 (8), 172 (11), 136 (6), 105 (100), 77 (33). **HRMS (Cl$^+$) *m/z* calcd. for $C_{28}H_{37}NO_2$:** 419.2824; **found** 419.2843; **Δ** = 4.5 ppm. **$C_{28}H_{37}NO_2$ requires** C, 80.2; H, 8.9; N, 3.3; **found** C, 80.0; H, 8.5; N, 3.2%.

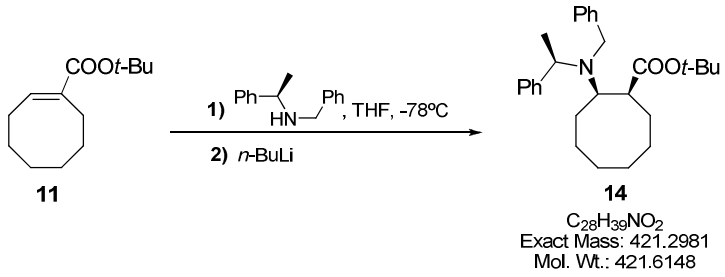
Synthesis of tert-butyl (1S,2R,αR,7Z)-2-N-benzyl-N-α-methylbenzylamino-cycloocta-7-enecarboxylate 13:



Following general procedure for the Michael addition reaction, it was added the chiral amine (3.14 g, 14.00 mmol), dissolved in THF (20 mL) and at -78ºC *n*-BuLi (1.6 M, 7.4 mL, 12.0 mmol) was added, stirred for 15 min, and after for other 15 min at 0°C. At -78ºC compound **7** (942 mg, 4 mmol) was added and stirred for 1.5 hours. The reaction mixture was quenched with NH_4Cl $_{(sat)}$ (5 mL), extracted with EtOAc, washed with H_2O and NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. After the crude was dissolved in DCM and washed with Citric acid 10% and $NaHCO_3$, dried, filtered and evaporated under reduce pressure. It was obtained compound **13** (1.72 g, 100%) that can be used without further purification or by crystallization from a mixture of Hex/Et_2O. **mp** 119ºC, $\mathbf{[\alpha]_D^{26}}$ = -4.7 (*c* 0.96, $CHCl_3$); **IR υ_{max} (neat):** 2939 (C-H), 1717 (C=O), 1651 (C=C), 1541,

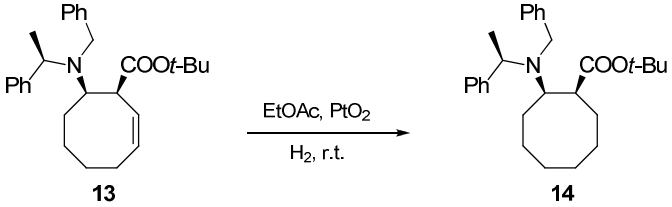
1493, 1456, 1368, 1248 (C-O), 1155, 1030, 783 (=C-H), 750, 700 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.17 (3H, d, *J* 7.0, C(α)*Me*); 1.56 (9H, m, COOC(CH_3)$_3$); 1.65-1.75 (4H, m, H-4 and H-5); 1.90-2.10 (5H, m, H-1, H-3 and H-6); 3.61 (1H, d, J_{AB} 15.2, NCH_ACH_B); 3.65 (1H, m, H-2); 3.77 (1H, d, J_{AB} 15.2, NCH_ACH_B); 4.08 (1H, q, *J* 7.0, C(α)*H*); 5.74 (1H, m, H-7); 5.85 (1H, t, *J* 10.1, H-8); 7.26 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.7 (CH_3, C(α) *Me*); 26.3 (CH_2); 27.3 (CH_2); 27.5 (CH_2); 28.4 (CH_3 x 3, COOC(CH_3)$_3$); 30.2 (CH_2); 48.1 (CH, C-1); 50.8 (CH_2, N-CH_2); 63.2 (CH, *C*H(α)); 65.8 (CH, C-2); 80.5 (C, COO*C*(CH_3)$_3$); 126.4 (CH); 128.6 (CH), 126.5 – 128.3 (CH x 10, *o, m, p-Ph*); 143.2 (C, C_{ipso}); 144.0 (C, C_{ipso}); 173.1 (C, *C*OOC(CH_3)$_3$). ***m/z* (CI^+) (rel. intensity):** 420 (MH^+, 70), 258 (22), 154 (52), 105 (100). **HRMS (Cl^+) *m/z* calcd. for $C_{28}H_{37}NO_2$:** 419.2824; **found** 419.2819; **Δ** = -1.2 ppm. **$C_{28}H_{37}NO_2$ requires** C, 80.2; H, 8.9; N, 3.3; **found** C 79.9; H, 8.5; N, 3.1%. **R-X:** See annexe A.

Synthesis of tert-butyl (1S,2R,αR)-2-N-benzyl-N-α-methylbenzylamino-cyclooctanecarboxylate 14:



Following general procedure for the Michael addition, compound **11** (500.0 mg, 2.4 mmol) was dissolved in THF (2 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.8 mmol) was dissolved in THF (10 mL) and *n*-BuLi (1.6 M., 3.6 mL, 5.7 mmol) were set to react. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (9:1-7:3 v/v) gave (1*S*,2*R*,α*R*)-**14** (152 mg, 15%).

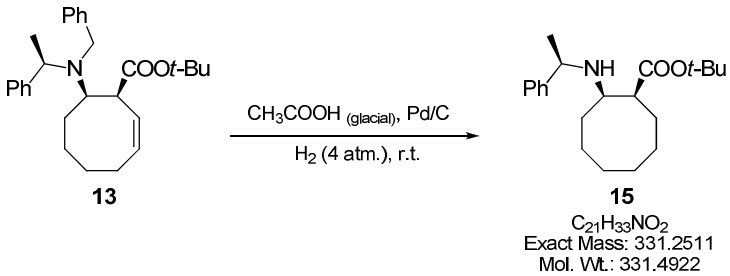
***Synthesis of tert-butyl (1S,2R,αR)-2-N-benzyl-N-α-methylbenzylamino-cyclooctanecarboxylate 14 by hydrogenation of compound 13*:**



Following general procedure for a hydrogenation reaction, (1*S*,2*R*,α*R*,7*Z*)-**13** (338.0 mg, 0.8 mmol) in EtOAc (20 mL), PtO_2 (93.0 mg, 0.4 mmol) was stirred under H_2 atmosphere at r.t. for 3 hours

gave crude (1*S*,2*R*,α*R*)-**14** (261 mg, 77%) and 23% of starting material was recovered. This compound was purified by crystallization from a mixture of Hex/Et_2O. **mp** 110ºC, $\mathbf{[\alpha]_D^{26}}$ = +109 (*c* 1.0, $CHCl_3$); **IR υ_{max} (neat):** 2970, 2927 and 2852 (C-H), 1719 (C=O), 1455, 1370, 1148 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.26 (3H, d, *J* 7.0, C(α)-*Me*); 1.41 (9H, s, COOC(CH_3)$_3$); 1.57-1.62 (8H, m, H-4, H-5, H-6, H-7); 2.24 (2H, m, H-8); 2.50 (2H, m, H-3); 3.12 (1H, m, H-1); 3.15 (1H, m, H-2); 3.85 (1H, d, J_{AB} 14.0, N-CH_ACH$_B$); 3.90 (1H, d, J_{AB} 14.0, N-CH$_A$CH_B); 3.96 (1H, q, *J* 6.5, N-C(α)*H*). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 17.0 (CH_3, C(α)*Me*); 24.3 (CH_2, C-6); 26.1 (CH_2 x 2 , C-5, C-7); 28.2 (CH_3 x 3, COOC(CH_3)$_3$); 28.3 (CH_2, C-4); 29.5 (CH_2, C-8); 29.6 (CH_2, C-3); 49.7 (CH, C-1); 51.6 (CH_2, N-CH_2); 54.8 (CH, C-2); 58.7 (CH, *C*H(α)); 80.2 (C, COO*C*(CH_3)$_3$); 126.5 (CH, *o*-Ph); 126.8 (CH, *o*-Ph); 128.0 (CH, *m*-Ph) 128.2 (CH, *m*-Ph); 128.2 (CH, *p*-Ph); 128.2 (CH, *p*-Ph); 143.2 (C, C_{ipso}); 145.3 (C, C_{ipso}); 176.3 (C, *C*OOC(CH_3)$_3$). **HRMS (Cl^+) *m/z* calcd. for $\mathbf{C_{28}H_{40}NO_2}$ $\mathbf{[M+H]^+}$:** 422.3054; **found** 422.3039; **Δ** = -3.5 ppm. **$C_{28}H_{39}NO_2$ requires** C, 79.8; H, 9.3; N, 3.3; **found** C 80.1; H, 9.5; N, 3.0%. **R-X:** See annexe B.

Synthesis of tert-butyl (1S,2R,αR)-2-N-α-methylbenzylamino-cyclooctanecarboxylate 15:



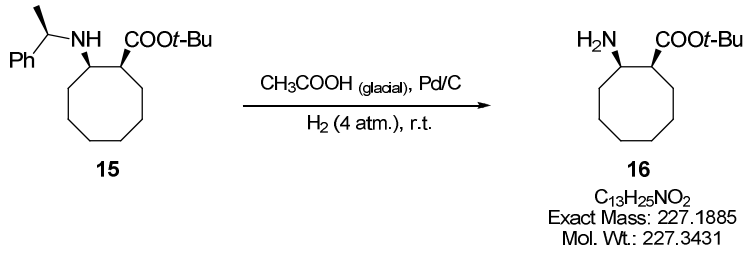
13 **15**

$C_{21}H_{33}NO_2$
Exact Mass: 331.2511
Mol. Wt.: 331.4922

In a dried vial for hydrogenation compound **13** (67.0 mg, 0.2 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in glacial acetic acid (3 mL), Pd/C (10 % Pd basis, 35 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After, filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2-1:1 v/v) gave (1*S*,2*R*,α*R*)-**15** (12 mg, 23%). **IR υ_{max} (neat):** 3374 (N-H), 2973, 2924 and 2856 (C-H), 1723 (C=O), 1452, 1367, 1151 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.34 (3H, d, *J* 6.2, C(α)-*Me*); 1.49 (9H, s, COOC(CH_3)$_3$); 1.20-1.70 (10H, m); 1.80-1.95 (2H, m); 2.75 (1H, m, H-1); 2.95 (1H, m, H-2); 3.90 (1H, m, N-C(α)*H*); 7.26 (5H, m, *H*-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.6 (CH_3, C(α)-*Me*); 24.8 (CH_2, C-6); 25.5 (CH_2, C-5); 26.0 (CH_2 , C-7); 27.1 (CH_2 C-4); 27.5 (CH_2, C-8); 28.4 (CH_3 x 3, COOC(CH_3)$_3$); 32.3 (CH_2, C-3); 46.7 (CH, C-1); 54.3 (CH, *C*(α)); 55.4 (CH, C-2); 80.5 (C, COO*C*(CH_3)$_3$); 126.9 (CH x 2, *o*-Ph); 127.1 (CH x 2, *m*-Ph); 128.5 (CH, *p*-Ph); 146.5 (C, C_{ipso});

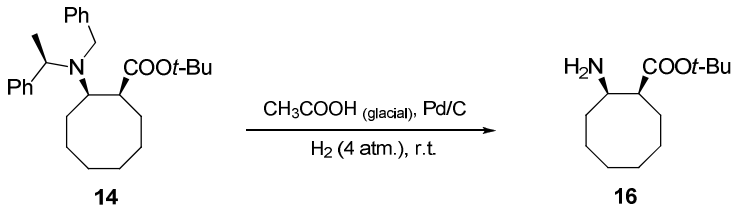
174.9 (C, *C*OOC(CH_3)$_3$). **HRMS (ESI) *m/z* calcd. for $C_{21}H_{34}NO_2$ $[M+H]^+$:** 332.2584; **found** 332.2572; **Δ** = -3.6 ppm.

Synthesis of tert-butyl (1S,2R)-2-amino-cyclooctanecarboxylate 16:



Following general procedure for a hydrogenolysis reaction, compound **15** (11.00 mg, 0.03 mmol) was measured, dissolved in glacial acetic acid (1 mL) and Pd/C (10 % Pd basis, 33 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After, filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (7:3-1:1 v/v) gave (1*S*,2*R*)-**16** (4.3 mg, 57%).

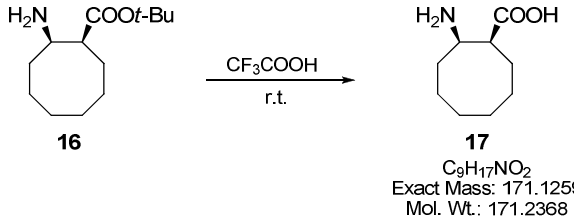
Synthesis of tert-butyl (1S,2R)-2-amino-cyclooctanecarboxylate 16 by hydrogenolysis of compound (1S,2R,αR)-14:



In a dried vial for hydrogenation compound **14** (67.0 mg, 0.2 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in glacial acetic acid (4 mL), Pd/C (10 % Pd basis, 34 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (7:3-1:1 v/v) gave (1*S*,2*R*)-**16** (45 mg, 100%). $[\alpha]_D^{26}$= -11.2 (*c* 1.2, $CHCl_3$), **IR υ_{max} (neat):** 3375 (N-H), 2922 and 2847 (C-H), 1724 (C=O), 1464, 1370, 1153 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.43 (9H, s, COOC(C*H*$_3$)$_3$; 1.53-1.65 (6H, m, H-5, H-6, H-7); 1.75-1.90 (6H, m, H-4 ,H-8, H-3); 2.62 (1H, m, H-1); 3.27 (1H, m, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 23.6 (CH_2, C-6); 23.8 (CH_2, C-5); 25.9 (CH_2, C-7); 26.7 (CH_2, C-4); 28.2 (CH_2, C-8); 28.3 (CH_3 x 3, COOC(*C*H$_3$)$_3$); 33.8 (CH_2, C-3); 47.6 (CH, C-1); 51.7 (CH, C-2); 80.4

(C, COO*C*$(CH_3)_3$); 175.6 (C, *C*OOC$(CH_3)_3$). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{26}NO_2$ $[M+H]^+$:** 228.1958; **found** 228.1941; **Δ** = -7.4 ppm.

Synthesis of (1S,2R)-2-amino-cyclooctanecarboxylic acid 17 by hydrolysis of the β-amino ester (1S,2R)-16:

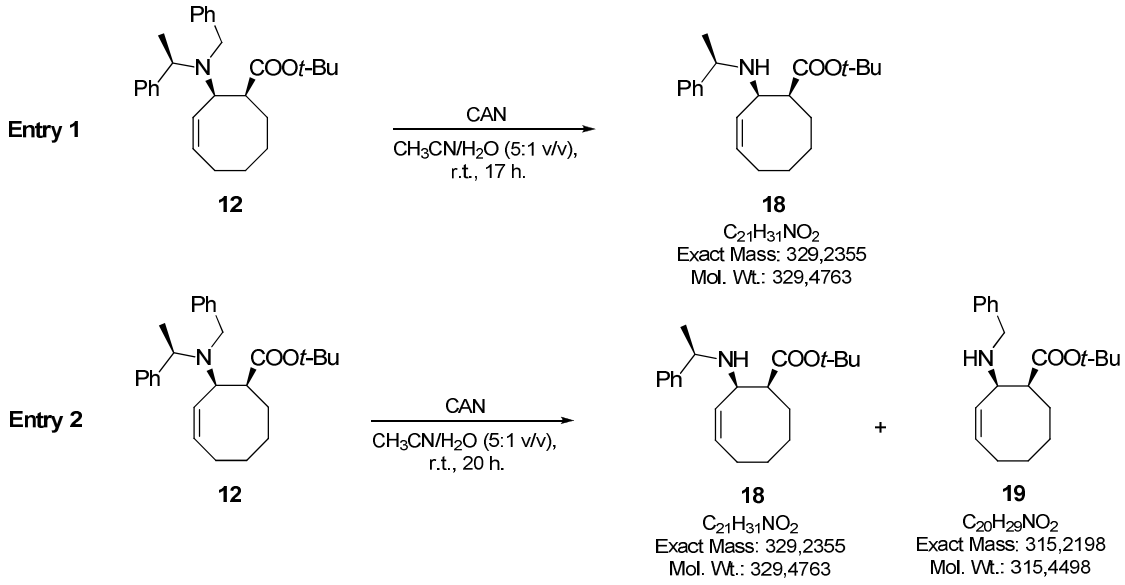


The β-amino ester (1*S*,2*R*)-**16** (34.0 mg, 0.2 mmol) was dissolved in CF_3COOH (0.5mL, 7.0 mmol) and stirred for 1.5 hours at r.t. The solution was concentrated *in vacuo* and dissolved in HCl 1 M. (1.0 mL), organic impurities were washed with EtOAc. Purification by Ion-exchange resin DOWEX 50 x 8-200 gave (1*S*,2*R*)-**17** (29 mg, 100%). $\mathbf{[\alpha]_D^{26}}$**=** -16.5 (*c* 0.7, H_2O). **^{1}H NMR (400 MHz; D_2O)**: δ 1.49-1.52 (4H, m, H-5, H-6); 1.60-1.74 (4H, m, H-4, H-7); 1.86-1.88 (4H, m, H-3, H-8); 3.04 (1H, ddd, *J* 8.5, 5.0 and 3.0, H-1); 3.73 (1H, ddd, *J* 9.0, 6.3 and 3.0, H-2). **^{13}C NMR (50 MHz; D_2O):** δ 23.0 (CH_2, C-5); 24.4 (CH_2, C-6); 25.0 (CH_2, C-4); 25.7 (CH_2, C-7); 26.5 (CH_2, C-8); 28.7 (CH_2, C-3); 42.7 (CH, C-1); 50.9 (CH, C-2); 177.6 (C, C-9). **HRMS (ESI) *m/z* calcd. for $C_9H_{17}NO_2$ $[M+H]^+$:** 172.1332; **found** 172.1336; **Δ** = 2.3 ppm.

[Lit.,(Forró, E. and Fülöp, F. *Org. Lett*. **2003**, 5, 1209-1212) β-amino acid (1*R*,2*S*)-**17** $\mathbf{[\alpha]_D^{25}}$**=** +17.8 (*c* 0.4, H_2O)].

1.1 Reactivity of *tert*-butyl (1*S*,2*R*,α*R*,3*Z*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cycloocta-3-ene carboxylate 12:

Elimination reaction of benzyl alpha in compound 12:



Procedure:

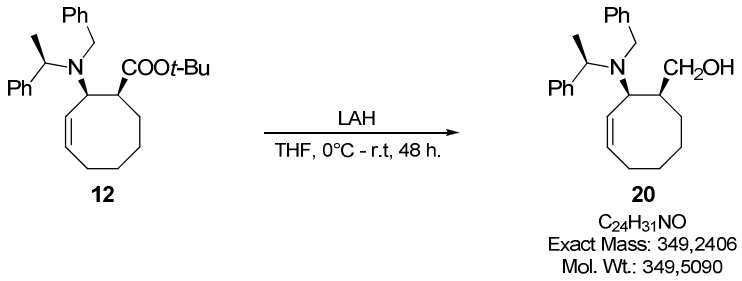
Entry 1:

Compound **12** (68.00 mg, 0.16 mmol) was dissolved in a mixture of AcCN/H_2O (5:1 v/v, 5 mL) and Ammonium cerium (IV) nitrate (0.53 mg, 0.96 mmol) was added, the system was purged with Ar and stirred for 17 hours at r.t. under inert atmosphere. The reaction mixture was quenched with $NaHCO_{3\ (sat.)}$ (10 mL), the double of mixture solvent volume used, it was stirred for 15 min, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded *tert*-butyl (1*S*,2*R*,α*R*,3*Z*)-2-*N*-α-methylbenzylamino-cycloocta-3-ene carboxylate **18** (50.1 mg, 95%), **IR υ_{max} (neat):** 3374 (N-H), 2974 and 2927 (C-H), 1721 (C=O), 1452, 1367 (C-O), 1150, 701 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.31 (3H, d, *J* 6.5, C(α)*Me*); 1.44 (9H, s, $COOC(CH_3)_3$); 1.10-1.28 (1H, m, H-7_B); 1.28-1.35 (1H, m, H-6_B); 1.55-1.85 (4H, m, H-6_A, H-7_A and H-8); 1.85-2.10 (2H, m, H-5_A and H-5_B); 2.81-2.85 (1H, m, H-1); 3.68-3.72 (1H, dd, *J* 8.8 and 5.1, H-2); 3.95-4.00 (1H, q, *J* 6.5, C*H*(α)); 5.51-5.55 (1H, t, *J* 10.5, H-3); 5.70-5.77 (1H, dd, *J* 10.5 and 8.0, H-4); 7.22-7.35 (5H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 23.6 (CH_3, C(α)*Me*); 25.7 (CH_2, C-6); 27.2 (CH_2, C-5); 28.1 (CH_3 x 3, $COOC(CH_3)_3$); 28.6 (CH_2, C-7); 29.8 (CH_2, C-8); 50.9 (CH, C-1); 52.4 (CH, C-2); 54.7 (CH, *C*H(α)); 80.1(C, $COOC(CH_3)_3$); 126.6, 126.7 and 128.3 (CH x 5, Ph); 130.0 (CH, C-4); 132.8 (CH, C-3); 145.9 (C, C_{ipso}); 173.6 (C, $COOC(CH_3)_3$). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{21}H_{32}NO_2$:** 330.2428; **found** 330.2436; **Δ** = 2.4 ppm.

Entry 2:

Compound **12** (89.30 mg, 0.21 mmol) was dissolved in a mixture of AcCN/H_2O (5:1 v/v, 6 mL) and Ammonium cerium (IV) nitrate (0.53 mg, 0.96 mmol) was added, the system was purged with Ar and stirred for 20 hours at r.t. under inert atmosphere. The reaction mixture was quenched with $NaHCO_{3\ (sat.)}$ (12 mL), stirred for 15 min, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded compound **18** (44.6 mg, 65%) and *tert*-butyl (1*S*,2*R*,α*R*,3*Z*)-2-benzylamino-cycloocta-3-ene carboxylate **19** (10.2 mg, 14%). **IR υ_{max} (neat):** 3375 (N-H), 2928 and 2851 (C-H), 1720 (C=O), 1145, 848 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.45 (9H, s, COOC(CH_3)$_3$); 1.46-2.09 (8H, m, H-5, H-6, H-7 and H-8); 2.81 (1H, m, H-1); 3.73 (1H, m, H-2); 3.75 (1H, d, *J* 13.1, N-CH_2); 3.89 (1H, d, *J* 13.1, N-CH_2); 5.66 (1H, t, *J* 10.4, H-3); 5.84 (1H, dd, *J* 10.4 and 8.4, H-4); 7.21-7.34 (5H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 25.6 (CH_2, C-7); 27.3 (CH_2, C-6); 28.3 (CH_3 x 3, COOC(CH_3)$_3$); 28.9 (CH_2, C-8); 30.0 (CH_2, C-5); 51.8 (CH_2, CH_2(N)); 52.3 (CH, C-1); 54.9 (CH, C-2); 80.6 (C, COO*C*(CH_3)$_3$); 127.1 (CH x 2, C-3, C-4); 128.5 (CH x 5, Ph); 131.6 (C, C_{ipso}); 173.9 (C, *C*OOC(CH_3)$_3$).**HRMS $[M+H]^+$ *m/z* calcd. for $C_{20}H_{30}NO_2$:** 316.2271; **found** 316.2287; **Δ** = 5.1 ppm.

Reduction of the tert-butyl group with Lithium Aluminium Hydride in compound 12:



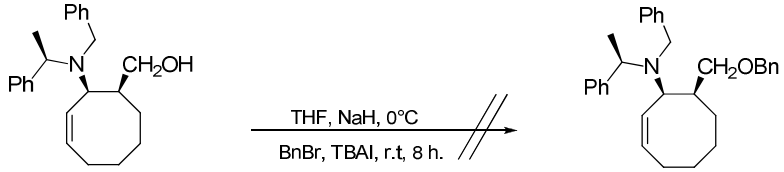
12 **20**

$C_{24}H_{31}NO$
Exact Mass: 349,2406
Mol. Wt.: 349,5090

In a dried flask with Ar atmosphere, compound **12** (82.5 mg, 0.2 mmol) was added and dissolved in THF (3 mL). The reaction system was stirred at 0°C and $LiAlH_4$ (23.0 mg, 0.6 mmol) was added. After, the reaction mixture was stirred at r.t. for 48 hours. The reaction was quenched with a mixture of EtOAc/H_2O (1:1 v/v, 2mL) and filtered through a sintered glass funnel layered with 1 cm of celite and 0.5 cm silice. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded (1*S*,2*R*,α*R*,3*Z*)-2-*N*-(benzyl-*N*-α-methylbenzylamino)-cycloocta-3-enyl-methanol **20** (38.6 mg, 55%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.46 (3H, d, *J* 7.0, C(α)*Me*); 1.50-2.30 (6H, m, H-6, H-7 and H-8); 2.46-2.48 (2H, m, H-5); 3.48 (1H, CH_AH_B, J_{AB} 15.3, CH_2-N); 3.32-3.40 (1H, dd, *J* 21.2 and 9.2, H-1); 3.53 (1H, m, H-2); 3.92 (1H, dd, *J* 9.7 and 3.2, CH_2-OH);); 3.94 (1H, CH_AH_B, J_{AB} 15.3, CH_2-N); 4.59 (1H, q, *J* 6.9, C(α)*H*)); 5.50 (1H, t, *J*

10.3, H-3); 5.72 (1H, dd, *J* 18.4 and 10.3, H-4); 7.30 (10H, m, H-Ar). **HRMS [M+H]$^+$ *m/z* calcd. for $C_{24}H_{32}NO$:** 350.2478; **found** 350.2461; **Δ** = - 4.8 ppm.

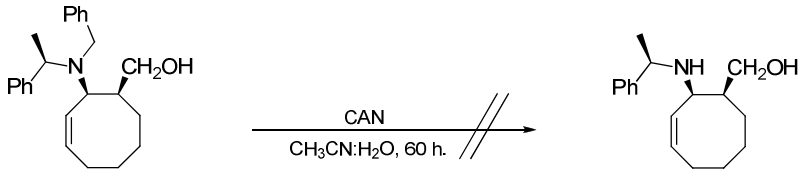
Protective reaction of the alcohol group in compound 20:



20

In a dried flask under Ar atmosphere, compound **20** (38.60 mg, 0.11 mmol) was added and dissolved in THF (2 mL). The reaction system was stirred at 0°C and NaH (5.20 mg, 0.13 mmol) previously dissolved in a minimum quantity of THF was added. After, at r.t. BnBr (0.03 mL, 0.22 mmol) and TBAI (4.10 mg, 0.01 mmol) were added and the reaction mixture was stirred for 8 hours. The system was quenched with H_2O at 0°C and extracted with EtOAc. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

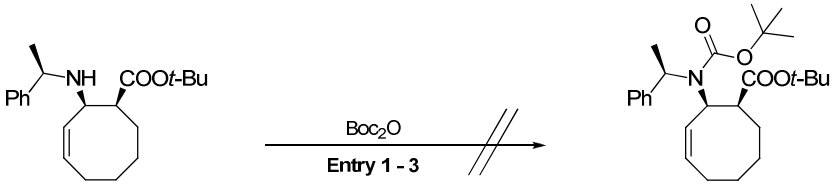
Elimination reaction of the benzyl group in the chiral amine fragment in compound 20:



20

Under Ar atmosphere compound **20** (20.20 mg, 0.06 mmol) was dissolved in a mixture of AcCN/H_2O (5:1 v/v, 3.6 mL) and CAN (0.13 mg, 0.24 mmol) was added into the system. The reaction mixture was stirred at r.t. for 60 hours. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Protective reaction of the secondary amine in compound 18:



18 **R.P.**

Table 14.

Entry	18 (mg, mmol)	THF (mL)	Reaction conditions	Time (hours)	R.P. %
1	34.80, 0.11	2.5	Boc_2O (24.00 mg, 0.11 mmol), r.t	70	-
2	34.80, 0.11	2.5	Boc_2O (24.00 mg, 0.11 mmol), 110°C.	24	-
3	24.30, 0.07	1.0	1) NaHMDS 0.6 M. (0.27 mL, 0.16 mmol), r.t. 2) Boc_2O (16.20 mg, 0.07 mmol).	10	-
4	31.10, 0.10	1.5	1) Boc_2O (46.00 mg, 0.21 mmol). 2) NaHMDS 0.6 M. (0.48 mL, 0.29 mmol), r.t.	2	-

Procedure:

Entry 1 and 2:

Under Ar Atmosphere compound **18** (34.80 mg, 0.11 mmol) was dissolved in THF (2.5 mL), Boc_2O (24.00 mg, 0.11 mmol) was added previously dissolved in a minimum quantity of THF and the reaction system was stirred at r.t. for 70 hours. After, the reaction mixture was quenched with $NaHCO_3$ 5% (12 mL), extracted with EtOAc, washed with $NaCl_{(sat.)}$ and K_2CO_3 10%, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude showed the presence of starting material, for this reason it was submitted in the same reactions conditions as at r.t. but being refluxed at 110°C., the protected product was not obtained.

Entry 3:

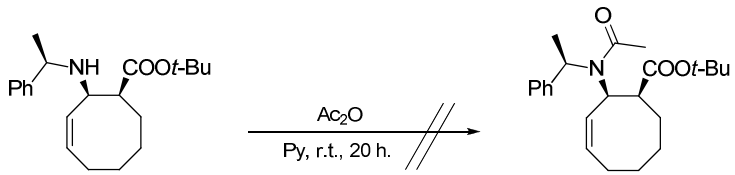
Compound **18** (24.30 mg, 0.07 mmol) in THF (1 mL) was added Sodium bis-(trimethylsilyl)-amide (0.6 M., 0.27 mL, 0.16 mmol) at r.t. After 15 min., a solution of di-*tert*-butyl dicarbonate (16.20 mg, 0.07 mmol) in THF (1 mL) was added and the reaction was stirred for 10 hours. After, THF was removed by rotary evaporation, followed by portioning between 5 mL of HCl 0.1 M. and 2 mL of EtOAc. A small amount of product may remain in the HCl layer at this point can be removed by treatment of the HCl layer with 2 mL of $NaHCO_{3\ (sat.)}$ followed by extraction with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ^1H NMR spectrum of the crude showed that the protected product was not obtained but maybe the formation of a β-lactam was instead.

Entry 4:

To avoid the formation of the β-lactam, compound **18** (31.10 mg, 0.10 mmol) was dissolved in THF (1.5 mL) and a solution of di-*tert*-butyl dicarbonate (46.00 mg, 0.21 mmol) in THF (1.5 mL)

was added. After 15 min, Sodium bis-(trimethylsilyl)-amide (0.6 M., 0.48 mL, 0.29 mmol) was added and the system was stirred at r.t. for 2 hours. The work up consisted in the remove of THF by rotary evaporation, followed by portioning between 6 mL of HCl 0.1 M. and 3 mL of EtOAc. A small amount of product may remain in the HCl layer at this point can be removed by treatment of the HCl layer with 3 mL of $NaHCO_{3\ (sat.)}$ followed by extraction with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ^1H NMR spectrum of the crude showed that the protected product was not obtained.

Acetylation reaction of the secondary amine with acetic anhydride in compound 18:



18

Compound **18** (21.50 mg, 0.06 mmol) was dissolved in Pyridine (0.04 mL) and acetic anhydride (0.04 mL, 0.42 mmol) was added. The reaction mixture was stirred at r.t. for 20 hours. The system was quenched with ice, extracted with EtOAc, washed with HCl 2M., H_2O, $NaHCO_3$ 5% and $NaCl_{(sat)}$, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude showed the presence of starting material.

Acetylation reaction of the secondary amine with chloride acetate in compound 18:

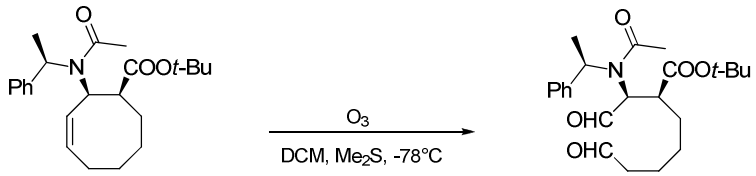
18 **21**

$C_{23}H_{33}NO_3$
Exact Mass: 371,2460
Mol. Wt.: 371,5130

Compound **18** (22.00 mg, 0.07 mmol) was dissolved in THF (1 mL), triethylamine (0.03 mL, 0.20 mmol) and chloride acetate (0.01 mL, 0.20 mmol) were added at 0°C and the system was stirred for 1 hour at this temperature. After, the reaction system was stirred for other 17 hours at r.t. The reaction mixture was quenched with EtOAc/H_2O (1:1 v/v, 2 mL), extracted with EtOAc, washed with H_2O and $NaCl_{\ (sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded starting material **18** (5.50 mg, 25%) and *tert*-butyl (1*S*,2*R*,α*R*,3*Z*)-2-*N*-acetamido-*N*-α-methylbenzylamino-cycloocta-3-enecarboxylate **21** (18.40 mg, 74%), **IR υ_{max} (neat):** 2977 and

2848 (C-H), 1716 (C=O),1660 and 1630 (C=O), 1443, 1143, 735 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.25 (9H, s, COOC(CH_3)$_3$); 1.67 (3H, d, *J* 6.9, C(α)*Me*); 1.68 (3H, s, CO*Me*); 1.25-1.46 (2H, m, H-6); 1.79-2.00 (4H, m, H-7 and H-8); 2.05-2.20 (1H, m, H-5$_A$); 2.20-2.35 (1H, m, H-5$_B$); 2.52 (1H, m, H-1); 5.15 (1H, m, H-2); 5.32 (1H, m, CH(α)); 5.81 (1H, dd, *J* 10.4 and 8.1, H-4); 6.30 (1H, t, *J* 10.2, H-3); 7.34 (5H, m, H-Ar); δ_C (50 MHz; $CDCl_3$) 19.4 (CH_3, C(α)*Me*); 24.4 (CH_3, CO-*Me*); 25.8 (CH_2); 26.9 (CH_2); 28.1 (CH_3 x 3, COOC(CH_3)$_3$); 30.2 (CH_2); 30.6 (CH_2); 51.9 (CH, C-1); 52.3 (CH, C-2); 54.4 (CH, C*H*(α)); 80.1 (C, COO*C*(CH_3)$_3$); 126.9, 127.8 and 128.6 (CH x 5, Ph); 127.3 (CH, C-4); 130.8 (CH, C-3); 141.9 (C, C_{ipso}); 171.6 (C, *C*OMe); 173.8 (C, *C*OOC(CH_3)$_3$). **HRMS [M+Na] *m/z* calcd. for $C_{23}H_{33}NO_3Na$:** 394.2353; **found** 394.2352; **Δ** = -0.3 ppm.

Ozonolysis reaction of compound 21:

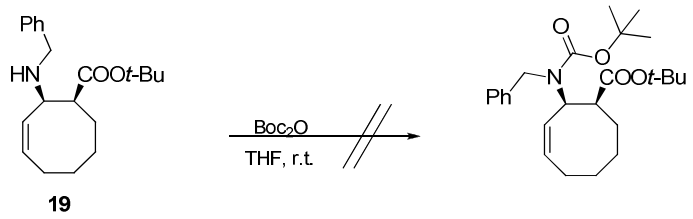


21 **22**

$C_{23}H_{33}NO_5$
Exact Mass: 403,2359
Mol. Wt.: 403,5118

Under Ar atmosphere compound **21** (17.90 mg, 0.05 mmol) was dissolved in DCM (1 mL), the reaction system was stirred at -78°C and the reaction mixture was purged and bubbled with O_3 until a blue colouration was observed (approximately 5 min.), after dimethyl sulfide (54.00 mg, 0.87 mmol) was added and stirred for a while. The system was warm up until r.t. and evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude showed the cleavage of the alkene and the formation of (2*S*,3*S*,α*R*)-2-(*N*-acetamido-*N*-α-methylbenzylamino)-3-*tert*-butoxy carbonyl-octanedial **22** (20.40 mg, 100%), **IR υ_{max} (neat):** 2966-2851 (C-H), 1716 (C=O), 1643 (C=O), 1145, 790 701 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 0.5-1.25 (6H, m, H-4, H-5, H-6); 1.41 (9H, s, COOC(CH_3)$_3$); 1.66 (3H, d, *J* 6.5, C(α)*Me*); 1.68 (3H, s, COMe); 2.21 (2H, m, H-7); 2.99 (1H, m, H-3); 3.78 (1H, dd, *J* 6.0 and 1.8, H-2); 5.23 (1H, q, *J* 6.5, C *H*(α)); 7.38 (5H, m, H-Ar); 9.46 (1H, C*H*O); 9.64(1H, d, *J* 1.8, C*H*O). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 18.4 (CH_3, C(α)*Me*); 21.8 (CH_2); 22.4 (CH_3, CO-*Me*); 26.3 (CH_2); 28.2 (CH_3 x 3, COOC(*C*H_3)$_3$); 29.0 (CH_2); 43.7 (CH_2, C-7); 44.7 (CH, C-3); 57.8 (CH, C-2); 63.4 (CH, *C*H(α)); 81.2 (C, COO*C*(CH_3)$_3$); 128.8 and 129.1(CH x 5, Ph); 139.0 (C, C_{ipso}); 171.0 (C, *C*OMe); 173.9 (C, *C*OOC(CH_3)$_3$); 198.9 (C, *C*HO, C-8); 202.6 (C, *C*HO, C-1).

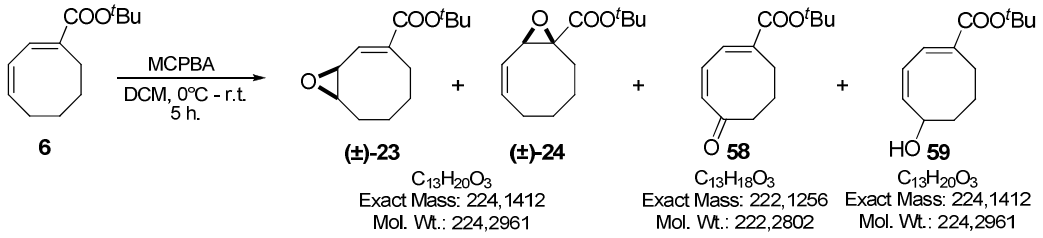
Protective reaction of the secondary amine with Boc_2O in compound 19:



Under Ar atmosphere compound **19** (4.00 mg, 0.01 mmol) was dissolved in THF (1 mL), Boc_2O (2.80 mg, 0.01 mmol) was added previously dissolved in a minimum quantity of THF and the reaction system was stirred at r.t. for 24 hours. The ^{1}H NMR spectrum of the crude showed that the protected product was not obtained.

1.2 Reactivity of *tert*-butyl cycloocta-1,3-dienecarboxylate 6:

Epoxidation reaction of compound 6:



Following previous procedure, compound **6** (623.8 mg, 3.0 mmol) was dissolved in DCM (30 mL), and stirred at 0ºC, MCPBA (568.5 mg, 3.3 mmol) was added slowly and the solution was stirred for 5 hours at r.t.. The reaction mixture was quenched with $Na_2S_2O_{3\,(sat.)}$ (10 mL), extracted with DCM (3 x 80 mL), washed with H_2O, $NaHCO_{3\,(sat.)}$ and $Na_2S_2O_{3\,(sat.)}$. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (99:1-70:30 v/v) gave recovery of starting material (93.6 mg, 15%) and the following compounds:

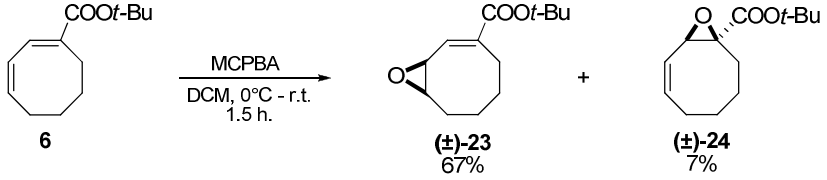
(±) (1*E*,3*R**,4*S**) *tert*-butyl cycloocta-1,2-diene carboxylate 3,4 oxide **23** (450 mg, 67%), **IR υ_{max} (neat):** 2976 and 2938 (C-H), 1701 (C=O), 1468, 1653 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.49 (9H, s, COOC(CH_3)$_3$; 1.40-1.80 (5H, m, H-5$_A$, H-6 and H-7); 2.10 (1H, ddd, *J* 9.2, 8.0 and 4.0, H-5$_B$); 2.22 (1H, dd, *J* 13.6 and 10.4, H-8$_A$); 2.55 (1H, dd, *J* 14.4 and 8.0, H-8$_B$); 3.20 (1H, ddd, *J* 12.0, 4.0 and 3.6, H-4); 3.56 (1H, d, *J* 3.6, H-3); 6.72 (1H, s, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.5 (CH_2, C-6); 27.5 (CH_2 x 2, C-7 and C-5); 28.0 (CH_3 x 3, COOC(CH_3)$_3$); 28.2 (CH_2, C-8); 54.0 (CH, C-4); 58.6 (CH, C-3); 80.7 (C, COO*C*(CH_3)$_3$); 132.2 (CH, C-2); 137.7 (C, C-1); 166.3 (C, *C*OOC(CH_3)$_3$). ***m/z* (CI$^+$) (rel. intensity):** 168 (MH$^+$, 5), 152 (4), 139 (2), 123 (63), 107 (9), 95 (16), 79 (22), 67 (19), 57 (100).

(±)-(1*R**,2*S**,3*Z*) *tert*-butyl cycloocta-3,4-diene carboxylate 1,2 oxide **24** (47 mg, 7%), **IR υ_{max} (neat):** 2932 (C-H), 1732 (C=O), 1468, 1248, 963, 843 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.50-2.40 (8H, m, H-5, H-6, H-7, H-8); 1.48 (9H, s, COOC(CH_3)$_3$; 3.80 (1H, s, H-2); 5.54 (1H, d, *J* 11.6, H-3); 5.79 (1H, dd, *J* 11.6 and 7.0, H-4). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 25.1 (CH_2, C-7); 25.4 (CH_2, C-6); 27.6 (CH_2, C-8); 27.9 (CH_3 x 3, COOC(CH_3)$_3$); 29.2 (CH_2, C-5); 58.3 (CH, C-2); 62.6 (C, C-1); 81.9 (C, COO*C*(CH_3)$_3$); 121.7 (CH, C-4); 134.6 (CH, C-3); 169.2 (C, *C*OOC(CH_3)$_3$).

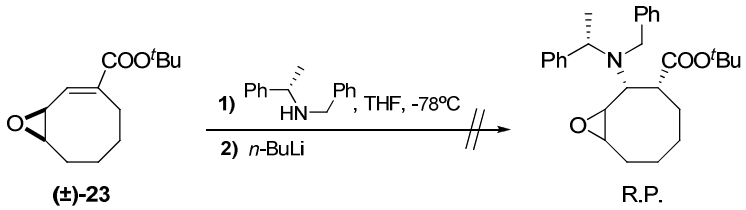
(1E,3Z) tert-butyl 5-oxo-cycloocta-1,3-dienecarboxylate **58** as a pale yellow oil (27 mg, 4%), **IR υ_{max} (neat):** 2976 and 2868 (C-H), 1707 (C=O), 1663 (C=C), 1456, 1370, 1292 (C-O), 1252, 1157cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.52 (9H, s, COOC(CH_3)$_3$); 2.10 (2H, q, *J* 6.6 and 13.4, H-7); 2.50 (2H, t, *J* 6.6, H-8); 2.57 (2H, t, *J* 6.6, H-6); 6.03 (1H, d, *J* 12.6, H-4); 6.57 (1H, dd, *J* 5.5 and 12.6, H-3); 7.26 (1H, d, *J* 5.5, H-2). **^{13}C RMN (50 MHz; $CDCl_3$):** δ 26.3 (CH_2, C-7); 28.0 (CH_3 x 3, COOC(CH_3)$_3$); 31.8 (CH_2, C-8); 38.5 (CH_2, C-6); 81.4 (C, COO*C*(CH_3)$_3$); 133.6 (CH, C-4); 134.7 (CH, C-2); 135.8 (CH, C-3); 140.1 (C, C-1); 165.5 (C, *C*OOC(CH_3)$_3$); 205.2 (C, C-5). ***m/z* (Cl^+) (rel. intensity):** 222 (M^+, 5) 205 (3), 186 (5), 166 (19), 149 (19), 121 (22), 94(13), 77 (26), 57 (100).

(1*E*,3*Z*) *tert*-butyl 5-hydroxycycloocta-1,3-dienecarboxylate **59** as a brown yellow oil (47 mg, 7%), **IR υ_{max} (neat):** 3412 (O-H), 2934 (C-H), 1705 (C=O), 1624 (C=C), 1250 (C-O) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.50 (9H, s, COOC(CH_3)$_3$); 1.8-1.9 (4H, m, H-6 and H-7); 2.74 (2H, dd, *J* 8.2 and 13.2, H-8); 4.36 (1H, dd, *J* 8.2 and 9.6, H-5); 5.89 (1H, dd, *J* 8.2 and 11.6, H-4); 6.09 (1H, dd, *J* 4.2 and 11.6, H-3); 7.08 (1H, d, *J* 4.2, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 22.4 (CH_2, C-7); 27.0 (CH_2, C-6); 27.4 (CH_2, C-8); 28.3 (CH_3 x 3, COOC(CH_3)$_3$); 80.9 (C, COO*C*(CH_3)$_3$); 85.1 (CH, C-5); 125.6 (CH, C-4); 134.8 (CH, C-3); 135.6 (CH, C-2); 135.9 (C, C-1); 166.9 (C, *C*OOC(CH_3)$_3$).

This epoxydation reaction was performed again in the same conditions but for a shorter period to give rise to the monoepoxide (1*E*,3*R**,4*S**) *tert*-butyl cycloocta-1,2-diene carboxylate 3,4 oxide (±)-**23** (67%) together with S.M. (23%) and (1*R**,2*S**,3*E*) *tert*-butyl cycloocta-3,4-diene carboxylate 1,2 oxide (±)-**24** (7%).

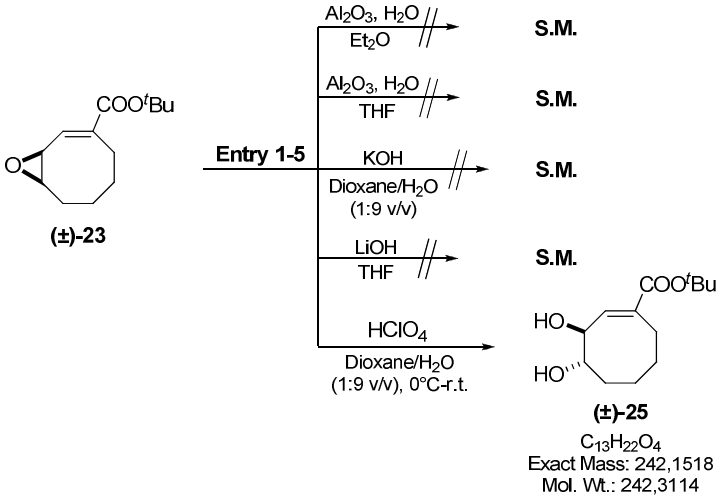


Addition of lithium (S)-N-benzyl-N-α-methylbenzylamide to compound (±)-**23*:***



Following general procedure for the Michael addition reaction, compound (±)-**23** (24.50 mg, 0.11 mmol) was dissolved in THF (1 mL), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (34.60 mg, 0.16 mmol) in THF (1 mL) and *n*-BuLi (1.6 M, 0.10 mL, 0.15 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2.0 hours. The reaction was quenched by addition of NH_4Cl $_{(sat.)}$ Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v–70:10 v/v) gave recovery of starting material (±)-**23**.

Epoxide ring opening reaction:



Procedure:

Entry 1:

To a solution of Al_2O_3 (1.20 g) in Et_2O (1 mL) was added H_2O (0.12 mL) and under Ar atmosphere was stirred for 20 min. After, compound (±)-**23** (24.7 mg, 0.11 mmol) was added and the reaction system was stirred for 18 hours. After this time, MeOH (2.5 mL) was added; the solution was filtered through Celite and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 2:

A solution of Al_2O_3 (1.45 g) in THF (1.8 mL) and H_2O (0.12 mL) was refluxed at 50°C. After, compound (±)-**23** (24.7 mg, 0.11 mmol) was added and the reaction system was refluxed for 12

hours and other 4 hours at 80°C. After this time, MeOH (2.5 mL) was added; the solution was filtered through Celite and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 3:

To compound (±)-**23** (18.8 mg, 0.08 mmol) was added a solution of KOH in dioxane/H_2O (1:9 v/v, 2.7 M., 7.2 mL), the reaction system was stirred at r.t for 3.5 hours. After this time, the reaction crude was extracted with DCM, washed with H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

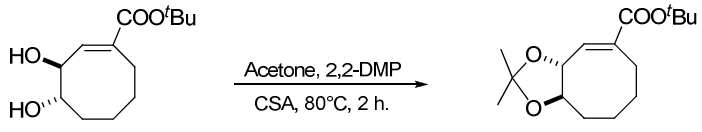
Entry 4:

Compound (±)-**23** (17.00 mg, 0.08 mmol) was dissolved in THF (3mL) and LiOH (3M., 0.05 mL) was added. The reaction system was stirred at r.t for 216 hours. The reaction crude was extracted with DCM, washed with H2O, dried, filtered and evaporated under reduce pressure. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 5:

To compound (±)-**23** (352.5 mg, 1.6 mmol) was added a solution of $HClO_4$ in dioxane/H_2O (1:9 v/v, 60%, 3.2 mL) at 0°C. The reaction system was stirred at r.t for 9.5 hours. After this time, H_2O was added; the reaction crude was extracted with EtOAc, washed with $NaHCO_{3\ (sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2-6:4 v/v) afforded starting material (±)-**23** (70.5 mg, 20%) and (±) (3*R**,4*R**,*E*) *tert*-butyl 3,4-dihydroxycycloocta-1-ene carboxylate **25** (240 mg, 62%). **IR υ_{max} (neat):** 3422 (O-H), 2930 (C-H), 1707 (C=O), 1653 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.48 (9H, s, COOC(CH_3)$_3$; 1.65 (2H, m, H-6); 1.92 (2H, m, H-7); 2.12 (2H, dt, *J* 12.8 and 3.6, H-5); 2.61 (2H, dt, *J* 7.2 and 3.6, H-8); 3.50 (1H, dt, *J* 8.8 and 3.6, H-4); 4.30 (1H, dd, *J* 8.8 and 6.8, H-3); 6.67 (1H, d, *J* 6.8, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.4 (CH_2, C-7); 25.6 (CH_2, C-6); 27.2 (CH_2, C-5); 28.3 (CH_3 x 3, COOC(*C*H_3)$_3$); 32.4 (CH_2, C-8); 74.4 (CH, C-4); 75.3 (CH, C-3); 80.8 (C, COO*C*(CH$_3$)$_3$); 133.9 (C, C-1); 140.7 (CH, C-2); 166.1 (C, *C*OOC(CH$_3$)$_3$). **HRMS (Cl^+) *m/z* calcd. for $C_{13}H_{22}O_4$:** 242.1518; **found** 242.1508; **Δ** = -4.1 ppm. ***m/z* (CI^+) (rel. intensity):** 242 (M, 1), 204 (16), 186 (48), 141 (8), 123 (17), 105 (10), 95 (9), 79 (14), 58 (100).

Protection reaction of compound (±)-**25*:***

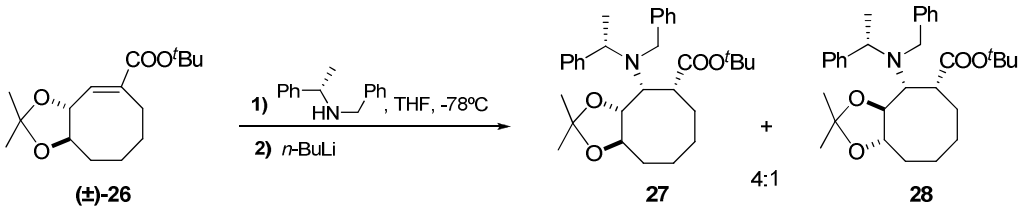


(±)-25 **(±)-26**

$C_{16}H_{26}O_4$
Exact Mass: 282,1831
Mol. Wt: 282,3752

Compound (±)-**25** (158.00 mg, 0.65 mmol) was dissolved in acetone (10 mL) and 2,2-DMP (10 mL) and CSA (catalytic amount) were added. The reaction system was purged with Ar and under inert atmosphere it was refluxed at 80°C and stirred for 2 hours. After, the reaction mixture was extracted with Et_2O, washed with $NaHCO_{3\ (sat.)}$, $NaCl_{\ (sat.)}$ and H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2 – 1:1 v/v) gave (±) *tert*-butyl 3,4-isopropilidendioxicycloocta-1-en-carboxylate **26** (184 mg, 100%). **IR υ_{max} (neat):** 2936 and 2866 (C-H), 1709 (C=O), 1458, 1370, 1238, 1163, 1067 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.42 (3H, s, CC*H*$_3$); 1.43 (3H, s, CC*H*$_3$); 1.48 (9H, s, COOC(C*H*$_3$)$_3$; 1.57 (4H, m, H-6 and H-7); 2.15 (2H, m, H-5); 2.65 (2H, m, H-8); 3.48 (1H, dd, *J* 8.4 and 3.0, H-4); 4.40 (1H, dd, *J* 8.4 and 6.0, H-3); 6.78 (1H, d, *J* 6.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.2 (CH_2, C-7); 24.6 (CH_2, C-6); 26.9 (CH_3 x 2, C(*C*H$_3$)$_2$); 27.8 (CH_2 x 2, C-5 and C-8); 28.1 (CH_3 x 3, COOC(*C*H$_3$)$_3$); 79.7 (C, COO*C*(CH$_3$)$_3$); 80.4 (CH, C-4); 81.4 (CH, C-3); 108.3 (C, *C*Me$_2$); 133.6 (C, C-1); 137.6 (CH, C-2); 165.6 (C, *C*OOC(CH$_3$)$_3$). **HRMS (Cl^+) *m/z* calcd. for $C_{16}H_{26}O_4$:** 282.1831; **found** 282.1825; **Δ** = -2.1 ppm. ***m/z* (CI^+) (rel. intensity):** 282 (MH^+, 1), 267 (2), 226 (9), 209 (3), 168 (54), 151 (29), 121 (43), 77 (37), 57 (100).

Michael addition of lithium (S)-N-benzyl-N-α-methylbenzylamide to compound (±)-***26:***



(±)-26 **27** **28**

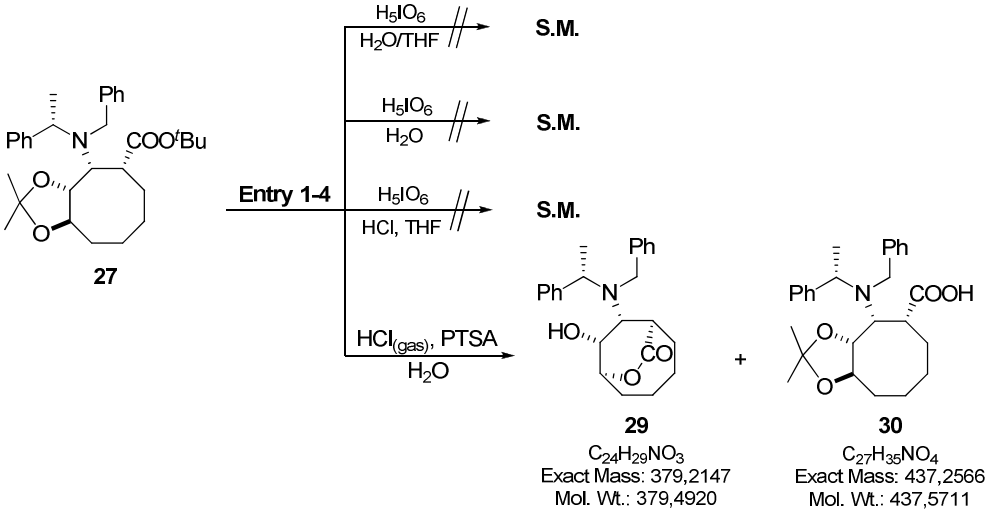
$C_{31}H_{43}NO_4$
Exact Mass: 493,3192
Mol. Wt.: 493,6774

Following general procedure for the Michael addition reaction, compound (±)-**26** (188.6 mg, 0.6 mmol) in THF (2 mL), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (592.8 mg, 2.8 mmol) in THF (8 mL) and *n*-BuLi (1.6 M., 1.7 mL, 2.6 mmol). After the addition of the unsaturated compound, the reaction was stirred for 2 hours. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/DCM (6:4 – 1:1 v/v) gave recovery of starting material (±)-**26** (55 mg, 33%)

and (1*S*,2*R*,3*S*,4*S*,α*S*) *tert*-butyl 2-(*N*-benzyl-*N*-α-methylbenzylamino)-3,4-isopropilidendioxicyclooctane carboxylate **27** (107 mg, 36%), which was full characterized and (1*S*,2*R*,3*R*,4*R*,*αS)* *tert*-butyl 2-(*N*-benzyl-*N*-α-methylbenzylamino)-3,4-isopropilidendioxicyclooctane carboxylate **28** (27 mg, 9%).

(1*S*,2*R*,3*S*,4*S*,α*S*)-**27**: **IR υ_{max} (neat):** 2980 and 2930 (C-H), 1734 (C=O), 1456, 1368, 1148 (C-O), 1055, 700 and 667 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.15 (3H, d, *J* 8.0, C(α)*Me*); 1.40 (3H, s, C*Me*$_2$); 1.41 (3H, s, C*Me*$_2$); 1.50 (9H, s, COOC(C*H*$_3$)$_3$; 1.20-1.72 (6H, m, H-6, H-7 and H-8); 1.80-2.00 (2H, m, H-5); 2.60 (1H, ddd, *J* 12.0, 8.0 and 4.0, H-1); 3.40 (1H, t, *J* 8.0, H-2); 3.61 (1H, ddd, *J* 12.0, 8.0 and 4.0, H-4); 3.90 (1H, t, *J* 8.0, H-3); 4.02 (2H, CH_AH_B, CH_2-N); 4.47 (1H, q, *J* 8.0, CH(α)); 7.40 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.1 (CH_2, C-6); 22.2 (CH_3, C(α)*Me*); 24.0 (CH_2, C-7); 25.4 (CH_2, C-5); 26.8 (CH_3, CMe_2); 27.2 (CH_3, CMe_2); 29.3 (CH_3 x 3, COOC(*C*H$_3$)$_3$); 31.6 (CH_2, C-8); 49.1 (CH, C-1); 52.1 (CH_2, CH_2-N); 60.6 (CH, CH(α)); 63.5 (CH, C-2); 79.7 (C, COO*C*(CH$_3$)$_3$); 81.1 (CH, C-3); 81.2 (CH, C-4); 106.5 (C, *C*Me$_2$); 126.1-129.0 (CH x 10, H-Ar); 143.8 (C, C_{ipso}); 145.7 (C, C_{ipso}); 173.5 (C, *C*OOC(CH$_3$)$_3$). **HRMS (Cl^+) *m/z* calcd. for $C_{31}H_{43}NO_4$:** 493.3192; **found** 493.3226; **Δ** = 6.9 ppm. ***m/z* (CI^+) (rel. intensity):** 493 (MH^+, 4), 435 (4), 316 (6), 288 (15), 274 (32), 190 (10), 153 (14), 105 (100), 77 (95).

Isopropilidendioxi-opening reaction:



Procedure:

Entry 1:

Compound **27** (18.70 mg, 0.04 mmol) was dissolved in THF (1.5 mL) and a solution of H_5IO_6 (21.6 mg, 0.1 mmol) in H_2O (0.5 mL) was added. The reaction system was stirred at r.t for 48 hours. The work up of the reaction was performed by extraction with EtOAc; the crude was

washed with $Na_2S_2O_3$ 5% and $NaHCO_3$ 5%, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 2:

To compound **27** (18.70 mg, 0.04 mmol) was added a solution of H_5IO_6 (43.0 mg, 0.2 mmol) in H_2O (0.5 mL). The reaction system was stirred at r.t for 12 hours. The work up of the reaction was performed by extraction with EtOAc; the crude was washed with $Na_2S_2O_3$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 3:

Compound **27** (18.70 mg, 0.04 mmol) was dissolved in THF (1 mL), after HCl 2M. (1 mL) and H_5IO_6 (43.0 mg, 0.2 mmol) were added. The reaction system was stirred at r.t for 4.5 hours. The work up of the reaction was performed by extraction with EtOAc; the crude was washed with $Na_2S_2O_3$ 5% and $NaHCO_3$ 5%, dried, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 4:

Under Ar atmosphere, compound **27** (45.20 mg, 0.09 mmol) was dissolved in MeOH (5 mL) and a catalytic amount of PTSA was added, after $HCl_{(gas)}$ was passed for 2 min. The reaction system was stirred at r.t for 4 hours. The crude was extracted with DCM, washed with $NaHCO_3$ 10% and H_2O, dried, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2-6:4 v/v) afforded recovery of starting material **27** (2.0 mg, 5%) and the following compounds:

(1*R*,6*S*,9*R*,10*S*,*αS*)-9-(*N*-benzyl-*N*-α-methylbenzylamino)-10-hydroxy-7-oxabicyclo[4.2.2]decan-8-one **29** (19.3 mg, 57%). $[\alpha]_D^{20}$ +28.4 (*c* 0.89, $CHCl_3$); **IR υ_{max} (neat):** 2926 and 2857 (C-H), 1728 (C=O), 1454, 1371, 1217 (C-O), 1074, 754 and 700 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.20-1.30 (2H, m, H-4); 1.43 (3H, d, *J* 6.8, C(α)*Me*); 1.50-1.70 (2H, m, H-3); 1.82 (1H, m, H-5_A); 1.91 (1H, m, H-5_B); 2.02 (1H, m, H-2_A); 2.20 (1H, m, H-2_B); 3.05 (1H, m, H-1); 3.09 (1H, dd, *J* 9.2 and 2.1, H-9); 3.79 and 3.84 (2H, CH_AH_B, *J* 14.4, CH_2-N); 3.94 (1H, dd, *J* 9.2 and 5.6, H-10); 3.97 (1H, q, *J* 6.8, CH(α)); 4.63 (1H, td, *J* 5.6 and 2.8, H-6); 7.38 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 13.1 (CH_3, C(α)*Me*); 22.7 (CH_2, C-4); 24.6 (CH_2, C-3); 28.9 (CH_2, C-5); 33.8 (CH_2, C-2); 41.8 (CH, C-1); 50.3 (CH_2, CH_2-N); 55.7 (CH, CH(α)); 59.1 (CH, C-9); 68.3 (CH, C-10); 77.9 (CH, C-6); 127.4-128.7 (CH x 10, H-Ar); 139.5 (C, C_{ipso}); 143.8 (C, C_{ipso}); 174.8 (C, *C*OO). **HRMS (Cl^+) *m/z* calcd. for $C_{24}H_{29}NO_3$:** 379.2147; **found** 379.2191; **Δ** = 11.6 ppm. ***m/z***

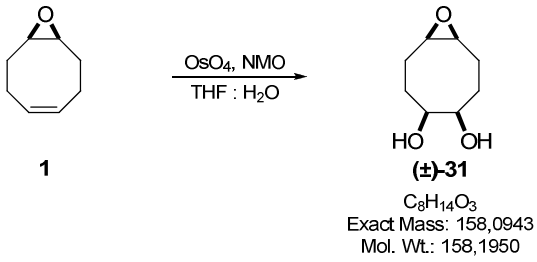
(CI$^+$) (rel. intensity): 282 (MH^+, 1), 267 (2), 226 (9), 209 (3), 168 (54), 151 (29), 121 (43), 77 (37), 57 (100).

(1*R*,2*R*,3*S*,4*S*,*αS*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-3,4-isopropilidendioxicyclooctane carboxylic acid **30** (12.5 mg, 32%). **IR υ_{max} (neat):** 3400, 2930 and 2859 (C-H), 1726 and 1711 (C=O), 1462, 1379, 1256 (C-O), 1065, 756, 731 and 700 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.30 (3H, d, *J* 6.8, C(α)*Me*); 1.48 (3H, s, C*Me*$_2$); 1.58 (3H, s, C*Me*$_2$); 1.60-1.70 (4H, m, H-6 and H-7); 1.88-2.08 (2H, m, H-5); 2.18-2.40 (3H, m, H-1 and H-8); 3.30 (1H, dd, *J* 10.0 and 8.0, H-2); 3.67 (1H, m, H-4); 4.10 (1H, t, *J* 8.0, H-3); 4.10-4.30 (2H, m, CH_2-N); 4.47 (1H, q, *J* 8.0, CH(α)); 7.40 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 14.1 (CH_3, C(α)*Me*); 22.1 (CH_2, C-6); 23.2 (CH_2, C-7); 26.6 (CH_3, CMe_2); 27.2 (CH_3, CMe_2); 29.5 (CH_2, C-5); 31.4 (CH_2, C-8); 42.6 (CH, C-1); 62.7 (CH, C-2); 62.7 (CH, CH(α)); 68.4 (CH_2, CH_2-N); 80.2 (CH, C-4); 80.5 (CH, C-3); 107.4 (C, *C*Me_2); 127.4-131.1 (CH x 10, H-Ar); 132.6 (C, C_{ipso}); 141.7 (C, C_{ipso}); 176.6 (C, *C*OOH).

2. Approximation to the synthesis of Tashiromine:

2.1. Reactivity of 1,2-epoxicycloocta-5-ene 1:

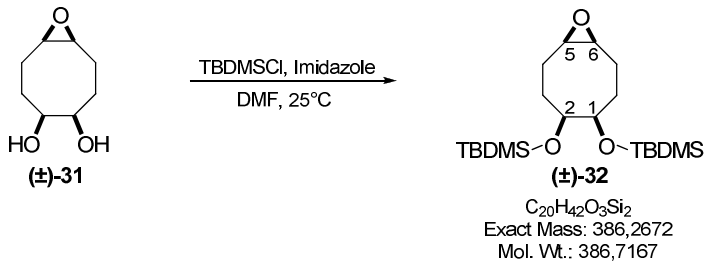
Cis-hydroxylation:



1 **(±)-31**

$C_8H_{14}O_3$
Exact Mass: 158,0943
Mol. Wt.: 158,1950

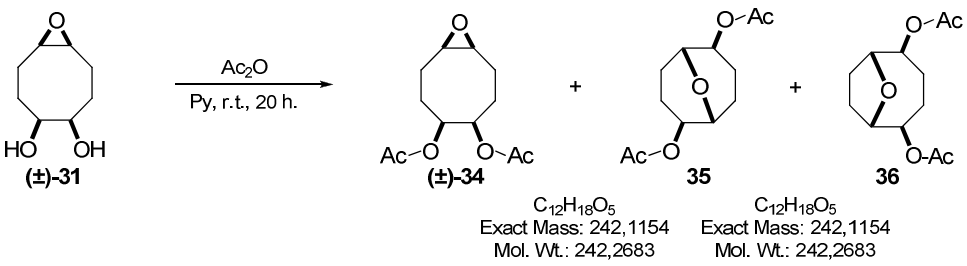
Compound **1** (200.0 mg, 1.6 mmol) was dissolved in a mixture of THF/H_2O (1:1 v/v, 4 mL), OsO_4 (0.04 mL, 4.20 mmol) and NMO (568.0 mg, 4.2 mmol) were added to the system at 0°C. The solution was allowed to warm to 25°C and stirred for 22 hours before being cooled to 0°C. Excess $Na_2S_2O_4$ was added. After filtration, the solution was concentrated under reduced pressure and transferred to a liquid – liquid extractor and continuously extracted with EtOAc for 24 hours, then with DCM for 72 hours. The combined organic phases were dried and evaporated under reduced pressure. Purification of the residue by silica gel for flash column chromatography (pore 60Å. 40-63 µm) DCM/MeOH (95:5 v/v) gave the epoxydiol (±)-**31** (185 mg, 73%) as a white solid. Due to its polarity, it was protected and full characterized as 4,5 *tert*-butyldimethylsilyloxy (±)-**32**.



In a flask was added compound (±)-**31** (368.0 mg, 2.3 mmol), TBDMSCl (879.0 mg, 5.8 mmol), imidazole (790.0 mg, 11.6 mmol) and DMF (0.5 mL). The reaction mixture was stirred at r.t. for 20 hours. The solution was diluted with water and DCM. The aqueous layer was extracted with DCM (4x), dried and evaporated under reduced pressure to give a clear oil. Purification of the residue by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (9:1-7:3 v/v) (1*R**,2*S**,5*R**,6*S**)-1,2-bis-(*tert*-butyldimethylsilyloxy)-5,6-epoxicyclooctane (±)-**32** (841 mg, 94%). **IR υ_{max} (neat):** 2954, 2928 and 2859 (C-H), 1476, 1256 (Si-Me_2), 1048 (Si-O), 831 and 782 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; 85°C, d_8-toluene):** δ 0.11 (6H, s, Si(CH_3)$_2$; 0.15 (6H, s, Si(CH_3)$_2$; 1.00 (18H, s, (C(CH_3)$_3$) x 2); 1.50-1.92 (8H, m, H-3, H-4, H-7 and H-8); 2.64-2.71 (2H, m, H-5 and H-6); 4.01-4.05 (2H, m, H-1 and H-2). **^{13}C NMR (50 MHz; 85°C, d_8-toluene):** δ -4.9 (CH_3 x 2, Si(*C*H_3)$_2$); -4.7(CH_3 x 2, Si(*C*H_3)$_2$); 18.1 (C x 2, (Si*C*(Me_3) x 2); 22.7 (CH_2 x 2); 25.9 (CH_3 x 6, (SiC(*C*H_3)$_3$); 31.2 (CH_2 x 2); 54.4 (CH x 2, C-5 and C-6); 77.4 (CH x 2, C-1 and C-2). **HRMS [M+Na] *m/z* calcd. for $C_{20}H_{42}O_3Si_2Na$:** 409.2565; **found** 409.2558; **Δ** = -1.7 ppm.

[Lit., (Hodgson D.M.; Cameron I.D.; Christlieb M.; Green R. Lee G.P. and Robinson L.A. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2161-2174.) (1*R**,4*S**,5*R**,8*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]nonane **^{1}H NMR (500 MHz; 85°C, d_8-toluene):** δ 0.04 (6H, s, Si(CH_3)$_2$; 0.15 (6H, s, Si(CH_3)$_2$; 0.94 (18H, s, (C(*Me*$_3$)$_3$) x 2); 1.49-1.89 (8H, m, C(2)H_2, C(3)H_3, C(6)H_6 and C(7)H_7); 2.61-2.64 (2H, m, C(1)H_1 and C(8)H_8); 3.95-3.98 (2H, m, C(4)H_4 and C(5)H_5). **^{13}C NMR (125 MHz; 85°C, d_8-toluene):** δ -4.9 (CH_3 x 2, Si(*C*H_3)$_2$); -4.6 (CH_3 x 2, Si(*C*H_3)$_2$); 18.2 (C x 2, (Si*C*(CH_3)$_3$); 22.8 (CH_2 x 2); 26.0 (CH_3 x 6, (SiC(*C*H_3)$_3$); 31.3 (CH_2 x 2); 54.5 (CH x 2, *C*O*C*); 77.6 (CH x 2, *C*OSi)].

Acetylation reaction of compound (±)-**31*:***



Under Ar atmosphere compound (±)-**31** (51.3 mg, 0.3 mmol) was dissolved in Pyridine (0.2 mL) and acetic anhydride (0.2 mL, 2.0 mmol) was added. The reaction mixture was stirred at r.t. for 19 hours. The system was quenched with ice, extracted with EtOAc, washed with HCl 2M., H_2O, $NaHCO_3$ 5% and NaCl $_{(sat)}$, filtered and concentrated *in vacuo*. Purification of the residue by silica gel for flash column chromatography (pore 60Å. 40-63 µm) DCM/MeOH (99:1-90:10 v/v) gave the following compounds:

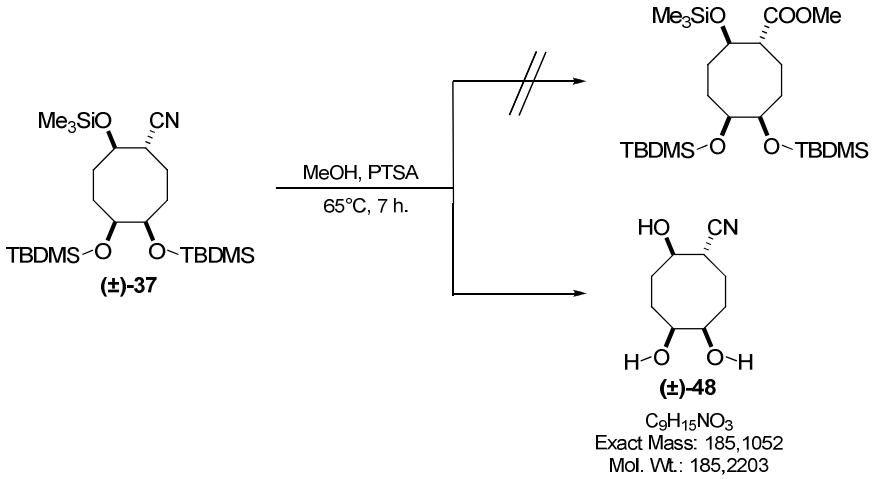
(1*R**,2*S**,5*R**,6*S**)-1,2-diacetoxy-5,6-epoxicyclooctane (±)-**34** (40 mg, 55%). **IR υ_{max} (neat):** 2938 (C-H), 1733 (C=O), 1365, 1249 and 1224 (C-O), 1019 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.38-2.16 (8H, m, H-3, H-4, H-7 and H-8); 2.06 (6H, s, (OCO*Me*) x 2); 2.95-3.01 (2H, m, H-5 and H-6); 5.08-5.14 (2H, m, H-1 and H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.8 (CH_3 x 2, (*Me*$COO)_2$); 22.1 (CH_2 x 2, C-3 and C-8); 26.4 (CH_2 x 2, C-4 and C-7); 54.2 (CH x 2, C-5 and C-6); 76.1 (CH x 2, C-1 and C-2); 167.0 (C x 2, Me*C*OO). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{18}O_5Na$:** 265.1046; **found** 265.1048; **Δ** = 0.8 ppm.

1:1 ratio mixture of 9-oxabicyclo[3.3.1]nonane-2,6-diyl diacetate **35** and 9-oxabicyclo[2.4.1]nonane-2,5-diyl diacetate **36** (20 mg, 28%). **IR υ_{max} (neat):** 2950 C-H), 1721 (C=O), 1368 and 1237 (C-O), 1013 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.41-2.27 (16H, m, H-3, H-4, H-7, H-8 and H-3`, H-4`, H-7`, H-8`); 2.03 (3H, s, CO*Me*); 2.06 (3H, s, CO*Me*`); 4.31-4.38 (2H, dd, *J* 9.6 and 3.0, H-1 and H-5 from [3.3.1]); 4.48 (1H, m, H-1 and H-6 from [2.4.1]); 4.67-4.74 (1H, dd; *J* 5.0 and 4.0, H-2 and H-6 from [3.3.1]); 4.94-4.98 (1H, p, *J* 4.7, H-2 and H-5 from [2.4.1]). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.4 (CH_3, CO*Me*); 21.5(CH_3, CO*Me*); 24.1 (CH_2, C-4); 24.6 (CH_2, C-8); 24.8(CH_2, C-3); 30.2 (CH_2, C-7)); 73.9(CH x 2, C-1 and C-5); 78.9 (CH x 2, C-1 and C-6); 79.0 (CH x 2, C-2 and C-6); 82.3 (CH, C-2 and C-5); 170.2 (C, *C*OMe); 171.0 (C, *C*OMe`). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{18}O_5Na$:** 265.1046; **found** 265.1040; **Δ** = -2.3 ppm.
[Lit., (Duthaler, R. O.; Wicker, K.; Ackermann, P. And Ganter, C. *Helvetica Chimica Acta* **1972**, Vol. *55*, Fasc. 5, 1809-1827) 9-oxabicyclo[3.3.1]nonane-2,6-diyl diacetate **35**, **IR:** 1730, 1468, 1368, 1250, 1132, 1100, 1042, 1022, 971, 897. **NMR**: 1.40-2.50 (m, H2-C(3), -C(4), -C(7), -C(8)); 2.10 (s, H_3COO-C(2), -C(6)); 3.95 (m ($W\frac{1}{2}$ ca. 11) H-C(1), -C(5)); 4.74 (t, $J_{2,3}^{endo} = J_{2,3}^{exo}$ (bzw. $J_{6,7}^{endo} = J_{6,7}^{exo}$) = 4 [zusätzl. Aufspaltung durch $J_{1,2}$ (bzw. $J_{5,6}$) ca. 2)] H-C(2), -C(6).
9-oxabicyclo[2.4.1]nonane-2,5-diyl diacetate **36**, **I.R:** 1728, 1479, 1452, 1433, 1372, 985, 973, 904. **NMR:** 1.50-2.60 (m, H2-C(3), -C(4), -C(7), -C(8)); 2.25 (s, H_3COO-C(2), -C(5); 4.78 (m ($W\frac{1}{2}$ ca. 14) H-C(1), -C(6), 5.25 (m ($W\frac{1}{2}$ ca. 13) H-C(2), -C(5)].

Epoxide opening reaction in compound (±)-**32*:***

In a dried flask under Ar atmosphere was added Et_2AlCl (0.16 mL, 0.16 mmol) followed by the addition of Me_3SiCN (0.40 mL, 3.00 mmol), the resulting solution was stirred for 30 min. at r.t. After via cannula compound (±)-**32** (456.00 mg, 1.18 mmol) was added slowly and the system was stirred for other 68 hours. The crude was poured on a mixture of NaOH 3M. and ice, extracted with Et_2O, washed with NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. The residue was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (98:2-90:10 v/v) gave (±) (1*R**,2*R**,5*S**,6*R**)-5,6-bis-(*tert*-butyldimethylsilyloxy)-2-(trimethylsilyloxy)-cyclooctane-carbonitrile **37** (473 mg, 81%), **IR υ_{max} (neat):** 2958, 2926 and 2860 (C-H), 2240 (C≡N), 1244 (C-O), 1076 (Si-O), 840 and 780 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.06 (9H, s, Si(C*H*$_3$)$_3$); 0.07 (6H, s, Si(C*H*$_3$)$_2$); 0.16 (6H, s, Si(C*H*$_3$)$_2$); 0.89 (18H, s, (C(C*H*$_3$)$_3$) x 2); 1.40-2-05 (8H, m, H-3, H-4, H-7 and H-8); 2.18-2.39 (1H, m, H-2); 2.98-3.05 (1H, m, H-1); 3.78-3.95 (2H, m, H-5 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ -4.8 (CH_3 x 3, Si(*C*H$_3$)$_3$); -4.6 (CH_3 x 2, Si(*C*H$_3$)$_2$); -4.3(CH_3 x 2, Si(*C*H$_3$)$_2$); 18.4 (C x 2, Si*C*(Me$_3$)); 26.1 (CH_3 x 6, (SiC(*Me*$_3$) x 2); 30.9 (CH_2 x 4); 38.9 (CH, C-1); 74.3 (CH, C-2); 76.6 (CH, C-5); 77.0 (CH, C-6); 122.8 (C, *C*N). **HRMS [M+Na] *m/z* calcd. for $C_{24}H_{51}NO_3Si_3Na$:** 508.3069; **found** 508.3073; **Δ** = 0.8 ppm.

Direct formation of the ester reaction from nitrile group:

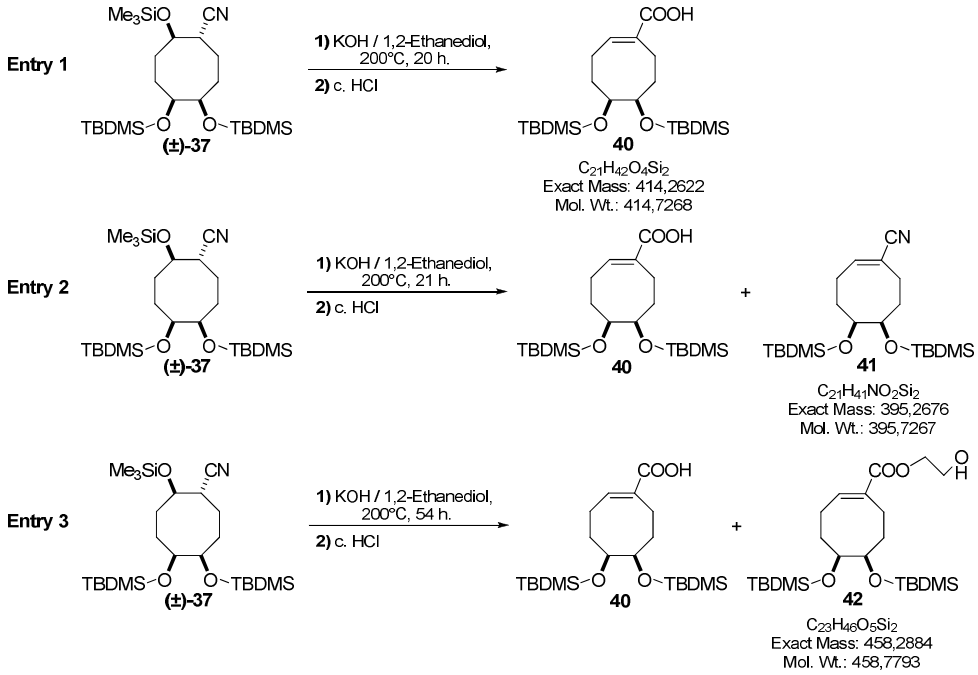


Compound (±)-**37** (114.00 mg, 0.23 mmol) was dissolved in MeOH (3 mL) and PTSA (46.00 mg, 0.24 mmol) was added and the reaction system was stirred and refluxed at 65°C for 7 hours. The reaction was quenched with H_2O dissolving the ammonium salts. The organic layer was washed with $NaHCO_{3\ (sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude (88 mg) showed the deprotection of the alcohol groups and due to its polarity and therefore difficulty to purify the crude was subjected to a protection reaction of the diols for full characterization.

(±)-48 **(±)-49**
$C_{12}H_{19}NO_3$
Exact Mass: 225,1365
Mol. Wt.: 225,2842

Compound (±)-**48** (88.00 mg, 0.47 mmol) was dissolved in acetone (5 mL) and 2,2-DMP (5 mL) and CSA (catalytic amount) were added. The reaction system was refluxed at 80°C and stirred for 16 hours. After, the reaction mixture was extracted with Et_2O, washed with $NaHCO_{3\ (sat.)}$, $NaCl_{\ (sat.)}$ and H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (7:3 – 1:1 v/v) gave the racemic mixture of compound (±) (1*R**,2*R**,5*S**,6*R**)-5,6-isopropilidendioxicycloocta-2-hydroxy-1-carbonitrile **49** (27 mg, 28%), **IR υ_{max} (neat):** 3444 (O-H), 2987 and 2942 (C-H), 2243 (C≡N), 1217 (C-O), 1078, 1058, 1033 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.31 (3H, s, CH_3); 1.39 (3H, s, CH_3); 1.61-2.05 (6H, m, H-3, H-4 and H-7); 2.18-2.41 (2H, m, H-8); 2.72-2.89 (1H, ddd, *J* 12.0, 6.0 and 2.0, H-1); 3.59-3.73 (1H, m, H-2); 3.99-4.22 (2H, m, H-5 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 23.3 (CH_2, C-3); 25.3 (CH_3); 28.1 (CH_3); 28.9 (CH_2, C-8); 30.1 (CH_2, C-4); 32.2 (CH_2, C-7); 38.8 (CH, C-1); 70.6 (CH, C-2); 76.9 (CH, C-5); 78.8 (CH, C-6); 107.2 (C, *C*$(Me)_2$); 120.8 (C, *C*N). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{19}NO_3Na$:** 248.1257; **found** 248.1255; **Δ** = -0.8 ppm.

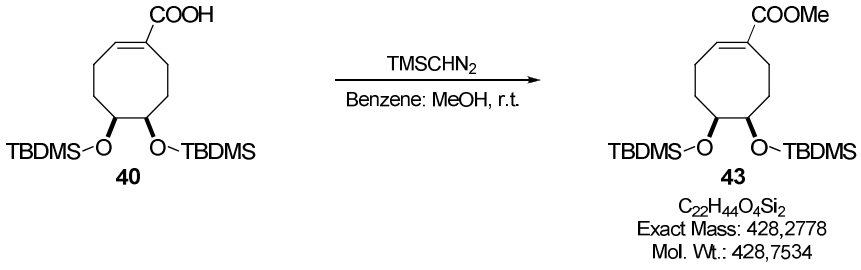
Hydrolysis reaction of the nitrile group in compound (±)-**37*:***



Procedure:

Entry 1:

Following general procedure for the hydrolysis of the nitrile group, compound (±)-**37** (166.0 mg, 0.3 mmol) was dissolved in a mixture of KOH (103.0 mg, 1.8 mmol) and 1,2-Ethanediol (2 mL), the resulting solution was refluxed at 200 ºC for 20 hours. After, the system was cooled down and it was added H_2O. The crude was extracted with Et_2O and the aqueous phase was treated with HCl c. reaching pH acid, this solution was extracted with Et_2O, washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (95:5 v/v) – EtOAc (100 v/v) gave (*E*)-5,6-bis(*tert*-butyldimethylsilyloxy)cycloocta-1-ene carboxylic acid **40** as a white solid (73.0 mg, 59%). Due to difficulty in its purification it was full characterized as its methyl ester **43**.



Under Ar atmosphere compound **40** (48.00 mg, 0.12 mmol) was dissolved in a mixture of Benzene/MeOH (1:1 v/v, 1 mL) and $TMSCHN_2$ 2.0 M (0.07 mL, 0.14 mmol) was added. The

reaction system was stirred at r.t. for 4 hours. After, the solution was evaporated under reduced pressure. The residue was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (95:5 v/v) gave (*E*)-methyl 5,6-bis(*tert*-butyldimethylsilyloxy)cycloocta-1-enecarboxylate **43** (41.0 mg, 80%); **IR υ_{max} (neat):** 2951, 2930 and 2860 (C-H), 1727 (C=O), 1255 (C-O), 1054 (Si-O), 833 and 777 (Si-C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 0.11 (6H, s, Si(CH_3)$_2$); 0.15 (6H, s, Si(CH_3)$_2$); 1.02 (18H, s, (C(CH_3)$_3$) x 2); 1.50-1.56 (1H, m, H-4$_B$); 1.76-1.89 (1H, m, H-3$_B$, H-4$_A$, H-8$_B$); 1.90-1.95 (1H, m, H-7$_B$); 2.08-2.10 (1H, m, H-7$_A$); 2.45-2.51 (1H, m, H-8$_A$); 2.63-2.75 (1H, m, H-3$_A$); 3.49 (3H, s, COO*Me*); 3.89-3.94 (2H, m, H-5 and H-6); 6.91 (1H, t, *J* 8.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ -4.9 (CH_3 x 2, Si(*C*H_3)$_2$); -4.6 (CH_3 x 2, Si(*C*H_3)$_2$); 18.2 (C x 2, (Si*C*(Me$_3$)); 20.8 (CH_2, C-8) 21.2 (CH_2, C-3); 25.9 (CH_3 x 6, (SiC(*Me*$_3$) x 2); 34.2 (CH_2, C-4); 34.4 (CH_2, C-7); 50.7 CH_3, COO*Me*); 77.7 (CH x 2, C-5 and C-6); 134.6 (C, C-1); 141.3 (CH, C-2); 167.1 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{22}H_{44}O_4Si_2Na$:** 451.2670; **found** 451.2678; **Δ** = 1.8 ppm.

Entry 2:

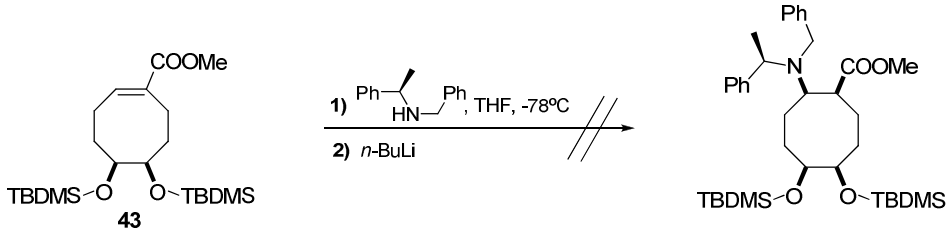
Following previous procedure, compound (±)-**37** (457.0 mg, 0.9 mmol) was dissolved in a mixture of KOH (241.0 mg) and 1,2-Ethanediol (4 mL) and refluxed at 200 ºC for 21 hours. After, the system was cooled down and it was added H_2O, the crude was extracted with Et_2O and the aqueous phase was treated with HCl c. pH acid, this solution was extracted with Et_2O, washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1 – 7:3 v/v) gave the carboxylic acid **40** (133.0 mg, 37%) and (*E*)-5,6-bis(*tert*-butyldimethylsilyloxy)cycloocta-1-enecarbonitrile **41** (100 mg, 28%); **IR υ_{max} (neat):** 2954, 2927 and 2862 (C-H), 2218 (C≡N), 1258 (C-O), 1071 (Si-O), 836 and 775 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.10 (6H, s, Si(CH_3)$_2$); 0.13 (6H, s, Si(CH_3)$_2$); 0.99 (18H, s, (C(CH_3)$_3$) x 2); 1.37-1.90 (4H, m, H-4 and H-7); 2.42-2.81 (4H, m, H-3 and H-8); 3.87-3.94 (2H, m, H-5 and H-6); 6.17 (1H, t, *J* 8.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ -5.04 (CH_3 x 2, Si(*C*H_3)$_2$); -4.99 (CH_3 x 2, Si(*C*H_3)$_2$); 18.1(C x 2, (Si*C*(Me$_3$)); 22.3 (CH_2); 24.1 (CH_2); 25.9(CH_3 x 6, (SiC(*Me*$_3$) x 2); 33.4 (CH_2); 33.8 (CH_2); 76.3 (CH, C-5); 76.7 (CH, C-6); 116.2 (C, *C*N); 118.6 (C, C-1); 146.2 (CH, C-2). **HRMS [M+Na] *m/z* calcd. for $C_{21}H_{41}NO_2Si_2Na$:** 418.2568; **found** 418.2555; **Δ** = -3.1 ppm.

Entry 3:

Following previous procedure, compound (±)-**37** (164.0 mg, 0.3 mmol) was dissolved in a mixture of KOH (90.0 mg) and 1,2-Ethanediol (2 mL) and refluxed at 200 ºC for 54 hours. After, the system was cooled down and it was added H_2O, the crude was extracted with Et_2O and the

aqueous phase was treated with HCl c. pH acid, this solution was extracted with Et_2O, washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 – 80:20 v/v) gave the carboxylic acid **40** (66.0 mg, 47%) and (*E*)-2-hydroxyethyl 5,6-bis(*tert*-butyldimethylsilyloxy)cycloocta-1-enecarboxylate **42** (20 mg, 14%)**, IR υ_{max} (neat):** 3449 (O-H), 2951, 2928 and 2862 (C-H), 1720 (C=O), 1257 (C-O), 1060 (Si-O), 832 and 774 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.01 (6H, s, Si(CH_3)$_2$); 0.06 (6H, s, Si(CH_3)$_2$); 0.89 (18H, s, (C(CH_3)$_3$) x 2); 1.04-2.18 (4H, m, H-4 and H-3); 2.24-2.42 (2H, m, H-7); 2.51-2.84 (2H, m, H-8); 3.60-.3.98 (2H, m, CH_2CH_2OH); 4.18-4.37 (2H, m, CH_2CH_2OH); 6.68-7.11 (1H, t, *J* 7.8, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ -4.97 (CH_3 x 2, Si(*C*H_3)$_2$); -4.70 (CH_3 x 2, Si(*C*H_3)$_2$); 18.1 (C x 2, Si*C*(Me$_3$)); 21.0 (CH_2); 22.7 (CH_2); 25.8 (CH_3 x 6, (SiC(*Me*$_3$) x 2); 33.8 (CH_2); 34.0 (CH_2); 61.6 (CH_2, CH_2CH_2OH); 66.1(CH_2, CH_2CH_2OH); 77.0 (CH x 2, C-5 and C-6); 134.0 (C, C-1); 142.7 (CH, C-2); 167.7 (C, *C*OO). **HRMS [M+Na] *m/z* calcd. for $C_{23}H_{46}O_5Si_2Na$:** 481.2776; **found** 481.2762; **Δ** = -2.9 ppm.

Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 43:



Procedure:

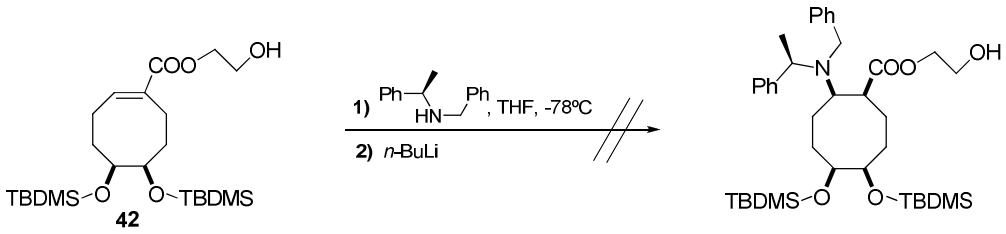
Entry 1:

Following general procedure for the Michael addition reaction, compound **43** (28.00 mg, 0.07 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.02 mL, 0.10 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.06 mL, 0.10 mmol). After the addition of the unsaturated compound, the reaction was stirred for 2 hours. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (9:1-7:3 v/v) gave recovery of starting material (17 mg).

Entry 2:

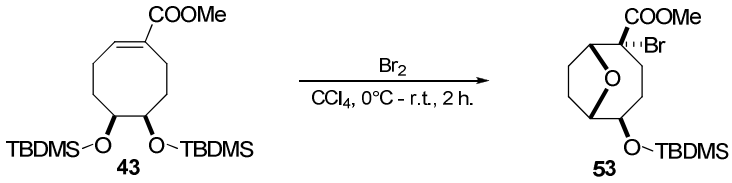
Following previous procedure, compound **43** (17.00 mg, 0.04 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.03 mL, 0.16 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.10 mL, 0.16 mmol). After the addition of the unsaturated compound, the reaction was stirred for 3 hours. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (9:1-7:3 v/v) gave recovery of starting material (15 mg).

Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 42:



Following previous procedure, compound **42** (19.60 mg, 0.04 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.04 mL, 0.18 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.11 mL, 0.17 mmol). After the addition of the unsaturated compound, the reaction was stirred for 3 hours. The ^{1}H NMR spectrum of the crude (18 mg) showed recovery of starting material.

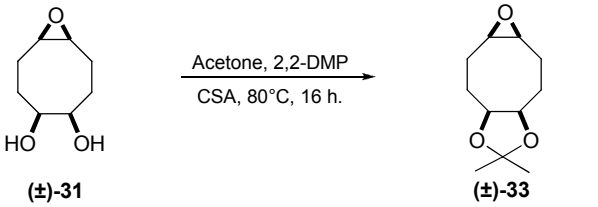
Bromination reaction of compound 43:



$C_{16}H_{29}BrO_4Si$
Exact Mass: 392,1018
Mol. Wt.: 393,3886

Compound **43** (27.00 mg, 0.06 mmol) was dissolved in CCl_4 (10 mL) and the reaction system was stirred and cooled down to 0°C. After, Br_2 (0.01 mL, 31 mmol) was added and stirred for 30 min, the ice bath was removed and stirred for 2 hours at r.t. The reaction mixture was evaporated under reduced pressure. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (9:1 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave the supposable dibromide compound as a single spot in TLC (24 mg, 68%). When the characterization was performed for this fraction, it was observed than in ^{1}H and ^{13}C NMR spectroscopy the double bond signal vanished but due to the number of signals present in the spectrums the proper assignation could not be achieved and the HRMS results are also inconsistent because only mass peaks are observed for compounds containing single bromine being probably compound **53** the obtained product under this conditions. **IR υ_{max} (neat):** 2951, 2928 and 2857 (C-H), 1741 (C=O), 1258 (C-O), 1093 (Si-O), 1048 (C-Br), 842 (Si-C), 771 (C-Br) cm^{-1}. **HRMS [M+Na] *m/z* calcd. for $C_{16}H_{29}O_4SiBrNa$:** 415.0911; **found** 415.0915; **Δ** = -1.0 ppm.

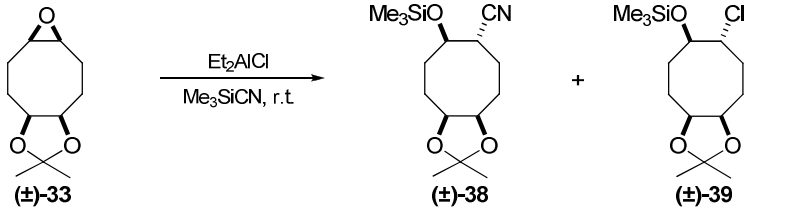
Protection reaction of compound (±)-**31*:***



(±)-31 **(±)-33**
$C_{11}H_{18}O_3$
Exact Mass: 198,1256
Mol. Wt.: 198,2588

Compound (±)-**31** (107.50 mg, 0.68 mmol) was dissolved in acetone (8 mL) and 2,2-DMP (8 mL) and CSA (catalytic amount) were added, the system was refluxed at 80°C and stirred for 16 hours. After work up was performed, purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) DCM/MeOH (98:2 – 95:5 v/v) gave (±)-5,6-isopropilidendioxi-1,2-epoxy-cyclooctane **33** (131 mg, 97%), **IR υ_{max} (neat):** 2987 and 2930 (C-H), 1214 (C-O), 1055, 870 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.33 (3H, s, C*H*$_3$); 1.45 (3H, s, C*H*$_3$); 1.65-1.81 (4H, m, H-3 and H-8); 1.95-2.16 (4H, m, H-4 and H-7); 3.02-3.08 (2H, m, H-1 and H-2); 4.24-4.29 (2H, m, H-5 and H-6) . **^{13}C NMR (50 MHz; $CDCl_3$):** δ 23.1 (CH_2 x 2); 25.1 (CH_2 x 2); 25.4 (CH_3); 27.9 (CH_3); 55.4 (CH x 2, C-1 and C-2); 77.1 (CH x 2, C-5 and C-6); 106.8 (C, *C*$(Me)_2$). **HRMS [M+Na] *m/z* calcd. for $C_{11}H_{18}O_3Na$:** 221.1148; **found** 221.1155; **Δ** = 3.2 ppm.

Epoxide opening reaction in compound (±)-**33*:***



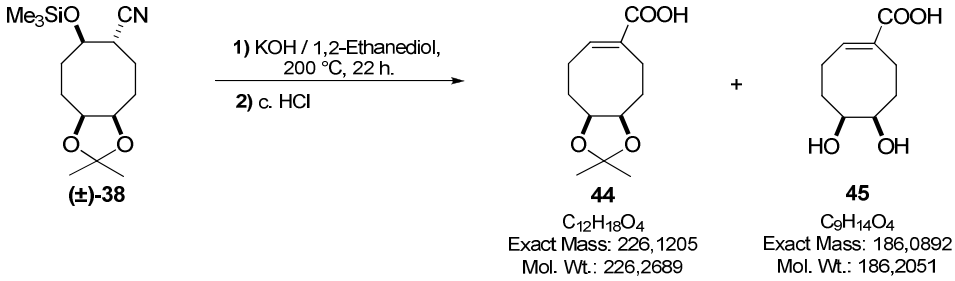
(±)-33 **(±)-38** **(±)-39**
$C_{15}H_{27}NO_3Si$
Exact Mass: 297,1760
Mol. Wt.: 297,4653
$C_{14}H_{27}ClO_3Si$
Exact Mass: 306,1418
Mol. Wt.: 306,9009

In a dried flask under Ar atmosphere was added Et_2AlCl (1.0 M., 0.14 mL, 0.14 mmol) followed by the addition of Me_3SiCN (0.46 mL, 3.40 mmol), the resulting solution was stirred for 30 min. at r.t. After, via cannula compound(±)-**33** (254.00 mg, 1.28 mmol) was added slowly and the system was stirred for other 18 hours. The crude was poured on a mixture of NaOH 3M. and ice, extracted with Et_2O, washed with NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. The residue was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) DCM/MeOH (10:0-9:1 v/v) gave the following compounds:

(±)-(1*R**,2*R**,5*S**,6*R**)-5,6-isopropilidendioxi-2-trimethylsilyloxy-1-carbonitrile cyclooctane **38** (333 mg, 88%), **IR υ_{max} (neat):** 2986 and 2951 (C-H), 2241 (C≡N), 1257 (C-O), 1102 (Si-O), 879 and 844 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.16 (9H, s, OSi*Me*$_3$); 1.38 (3H, s, C*Me*$_2$); 1.39 (3H, s, C*Me*$_2$); 1.46-2.33 (8H, m, H-3, H-4, H-7 and H-8); 2.74-2.92 (1H, m, H-1); 3.45-3.83 (1H, H-2); 4.01-4.32 (2H, m, H-5 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 0.20 (CH_3 x 3, OSi*Me*$_3$); 23.4 (CH_2); 25.3 (CH_3, C*Me*$_2$); 28.1(CH_2); 28.2 (CH_3, C*Me*$_2$) ; 29.8 (CH_2); 32.5(CH_2) ; 38.9 (CH, C-2); 71.4 (CH, C-1); 77.5 (CH, C-5); 78.7 (CH, C-6); 107.1 (C, *C*Me$_2$); 121.0 (C, *C*N). **HRMS (Na) *m/z* calcd. for $C_{15}H_{27}NO_3SiNa$:** 320.1652; **found** 320.1650; **Δ** = -0.6 ppm.

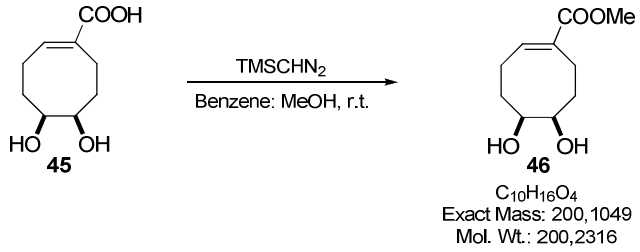
(±)-(1*R**,2*R**,5*S**,6*R**)-5,6-isopropilidendioxicycloocta-2-trimethylsilyloxy-1-chloride **39** (47.5 mg, 12%), **IR υ_{max} (neat):** 2982 and 2955 (C-H), 1257 (C-O), 1099 and 1052 (Si-O), 840 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.13 (3H, s, SiO*Me*); 1.33 (3H, s, C*Me*$_2$); 1.42 (3H, s, C*Me*$_2$); 1.55-2.39 (8H, m, H-3, H-4, H-7 and H-8); 3.89-4.03 (2H, m, H-1 and H-2); 4.10-4.25 (2H, m, H-5 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$)**: δ 0.42 (CH_3 x 3, OSi*Me*$_3$); 23.3 (CH_2); 25.8 (CH_3, C*Me*$_2$); 27.1 (CH_2); 28.5 (CH_3, C*Me*$_2$) ; 28.8 (CH_2); 30.5(CH_2) ; 66.8 (CH, C-2); 76.6 (CH, C-1); 77.2 (CH x 2, C-5 and C-6); 107.4 (C, *C*Me$_2$). **HRMS (Na) *m/z* calcd. for $C_{14}H_{27}O_3SiCl$:** 329.1310; **found** 329.1300; **Δ** = -3.0 ppm.

Hydrolysis reaction of the nitrile group in compound (±)-**38*:***



Following general procedure for the hydrolysis of the nitrile group, compound (±)-**38** (380.0 mg, 1.3 mmol) was dissolved in a mixture of KOH (337.0 mg) and 1,2-Ethanediol (5.5 mL) and refluxed at 200 ºC for 22 hours. After, the system was cooled down and H_2O was added. The crude was extracted with Et_2O and the aqueous phase was treated with HCl c. reaching pH acid, this solution was extracted with Et_2O, washed with H_2O and NaCl $_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*, gave a crude (65 mg) which was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (7:3 v/v) gave the expected unsaturated carboxylic acid **44** (9.2 mg, 3%) whose characterization was not performed due to the presence of impurities. Unsatisfied for the low quantity obtained in the first extraction, the possibility of deprotection in the reaction product is high, for this reason other extractions were performed in

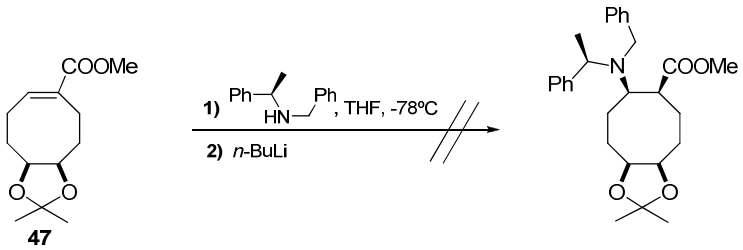
different solvents. Using *n*-butanol was observed in its ^{1}H NMR spectrum the presence of the deprotected carboxylic acid **45** (190 mg, 65%), which was esterified and protected again for full characterization.



Following general procedure for the esterification of acids, compound **45** (178.50 mg, 0.96 mmol) was dissolved in a mixture of Benzene/MeOH (1:1 v/v, 4 mL) and $TMSCHN_2$ 2.0 M (0.60 mL, 1.20 mmol) was added. The reaction system was stirred at r.t. for 4 hours, the reaction crude was used in a protection reaction:

Following general procedure for the protection of the diol, compound **46** (190.00 mg, 0.95 mmol) was dissolved in acetone (10 mL) and 2,2-DMP (10 mL) and CSA (catalytic amount) were added, refluxed at 80°C and stirred for 5 hours. After work up was performed, purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl 5,6-isopropilidendioxicycloocta-1-en-carboxylate **47** (46 mg, 21%), **IR υ_{max} (neat):** 2990 and 2950 (C-H), 1711 (C=O), 1214 (C-O), 1061 and 1039 (C-O-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.30 (3H, s, C*Me*$_2$); 1.44 (3H, s, C*Me*$_2$); 1.95-2.63 (8H, m, H-3, H-4,H-7 and H-8); 3.73 (3H, s, COO*Me*); 4.10-4.20 (2H, m, H-5 and H-6); 6.96-7.02 (1H, dt, *J* 5.4 and 2.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 22.1 (CH_2); 24.3 (CH_2); 25.6 (CH_3, C*Me*$_2$); 28.3 (CH_3, C*Me*$_2$); 28.5 (CH_2); 28.6 (CH_2); 52.2 (CH_3, COO*Me*); 77.9 (CH,C-5); 78.3 (CH, C-6); 106.8 (C, *C*Me$_2$); 133.0 (C, C-1); 141.7 (CH, C-2); 168.5 (C, *C*OOMe).

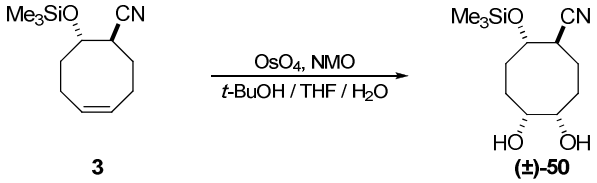
Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 47:



Following general procedure for the Michael addition, compound **47** (6.20 mg, 0.03 mmol) was dissolved in THF (0.5 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.02 mL, 0.09 mmol) was dissolved in THF (0.5 mL) and *n*-BuLi (1.6 M., 0.05 mL, 0.08 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2.5 hours at -78°C. The ^{1}H NMR spectrum of the crude (12 mg) showed recovery of starting material.

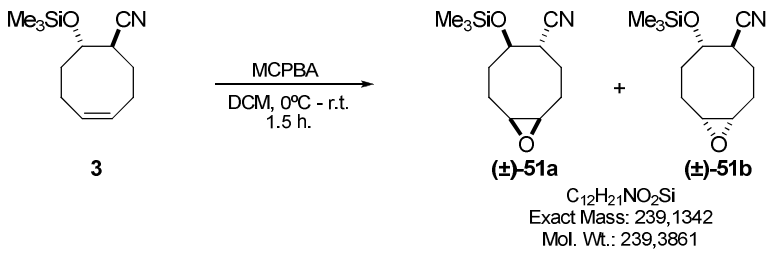
2.2. Reactivity of 2-trimethylsiloxi-cycloocta-5-ene-1-carbonitrile 3:

Cis-hydroxylation reaction of compound 3:



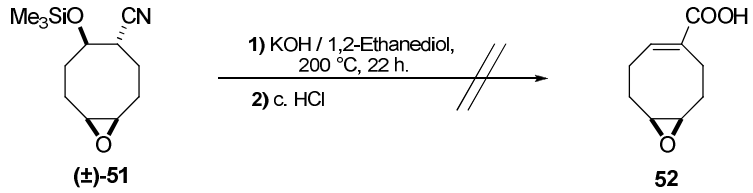
Compound **3** (119.6 mg, 0.5 mmol) was dissolved in a mixture of *t*-BuOH/THF/H_2O (7:2:1, v/v, 4 mL), OsO_4 (0.03 mL, 3.20 mmol) and NMO (184.0 mg, 1.3 mmol) were added to the system at 0°C. The solution was allowed to warm to 25°C and stirred for 15 hours before being cooled to 0°C. The reaction was quenched with $Na_2SO_{3\ (sat.)}$ and stirred for 30 min. Extracted with EtOAc, washed with $Na_2S_2O_3$ 10%, HCl 2M. and H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude (1.8 mg) showed the presence of the reaction product (±)-**50**. Due to the low quantity liquid – liquid extraction could not be carry out but it should be performed for these kinds of polar compounds.

Epoxidation reaction of compound 3:



Compound **3** (49.10 g, 0.22 mmol) was dissolved in DCM (5 mL) and cooled down to 0ºC with previous stirring of the system, MCPBA (45.60 g, 0.26 mmol) was added slowly and the solution was stirred for 1.5 hours at r.t. The reaction mixture was quenched with $Na_2S_2O_{3\ (sat.)}$, extracted with DCM, washed with H_2O, $NaHCO_{3\ (sat.)}$ and $Na_2S_2O_{3\ (sat.)}$. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained 52.8 mg of crude which was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (95:5-80:20 v/v) gave starting material **3** (1.0 mg, 2%) and the racemic mixture in 1:1 ratio: (±)-(1*R*,2*S*)-5,6-epoxi-2-(trimethylsilyloxy)cyclooctane-1-carbonitrile **51** (49.0 mg, 98%). **IR υ_{max} (neat):** 2954 (C-H), 2218 (C≡N), 1252 (C-O), 1096 (Si-O), 879 and 844 (Si-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 0.14 (18H, s, (OSi*Me*$_3$) x 2); 1.25-2.28 (16H, m, H-3, H-4, H-7, H-8, H-3`, H-4`, H-7`and H-8`); 2.81-3.08 (6H, m, H-1, H-5, H-6, H-1`, H-5`and H-6`); 3.95-4.02 (1H, m, H-2); 4.04-4.21 (1H, ddd, *J* 8.0, 3.0, 1.0, H-2`). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.8 (CH_2); 22.6 (CH_2`); 23.9 ($CH_2$); 25.0 ($CH_2$`); 26.2 (CH_2); 26.5 (CH_2`); 31.9 ($CH_2$); 33.4 ($CH_2$`); 36.4 (CH, C-1); 36.8 (CH, C-1`); 54.4 (CH, C-5); 55.0 (CH, C-5`); 55.1 (CH, C-6); 55.7 (CH, C-6`); 69.6 (CH, C-2); 70.0 (CH, C-2`); 120.2 (C, CN); 121.0 (C, C`N). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{21}NO_2SiNa$:** 262.1234; **found** 262.1228; **Δ** = -2.3 ppm.

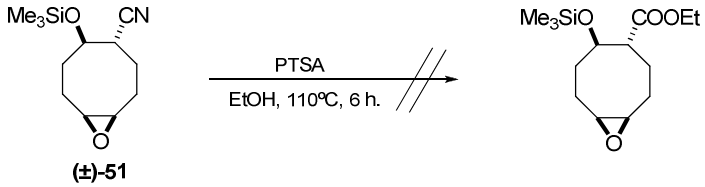
Hydrolysis reaction of the nitrile group in compound (±)-**51*:***



(±)-51 **52**

Racemic mixture of (±)-**51** (102.9 g, 0.4 mmol) was dissolved with a mixture of KOH (112 mg) and 1,2-Ethanediol (1.8 mL) previously prepared and the resulting solution was refluxed at 200 ºC for 22 hours. After the system was cooled down and H_2O (2 mL) was added. The crude was extracted with Et_2O and the aqueous phase was treated with HCl c. reaching pH acid, this solution was extracted with Et_2O, washed with H_2O and $NaCl_{\ (sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained 15 mg of crude that by ^{1}H NMR resonance showed a lot of signals and because of the low quantity and presence of impurities it could not be purified.

Alcoholysis reaction of the nitrile to ester in compound (±)-**51*:***



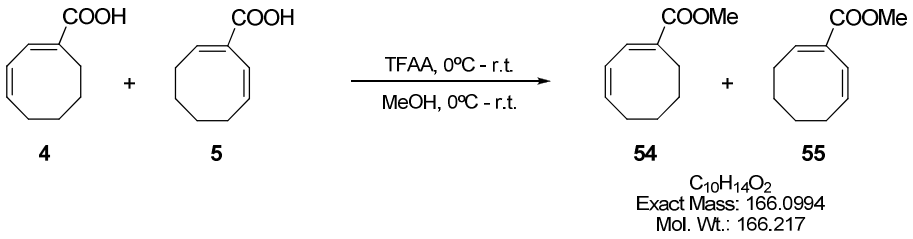
(±)-51

Compound (±)-**51** (112.60 mg, 0.47 mmol) was dissolved in EtOH (3 mL) and PTSA (91.00 mg, 0.47 mmol) was added. The system was stirred and refluxed at 110ºC for 6 hours. The reaction mixture was quenched by the addition of H_2O (1.5 mL), which caused the separation in two layers. The organic layer which contained the ester was washed with $NaHCO_{3\,(sat.)}$ and dried over Na_2SO_4. Purification of the residue by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5-0:100 v/v) gave a fraction that by I.R. showed characteristics signals for O-H and C≡N groups but due to the low quantity it could not be purified again for full characterization.

3. Synthesis and reactivity of (1*E*,3*Z*) *tert*-butyl and methyl 5-oxo-cycloocta-1,3-diene carboxylate:

3.1 Preparation of starting materials:

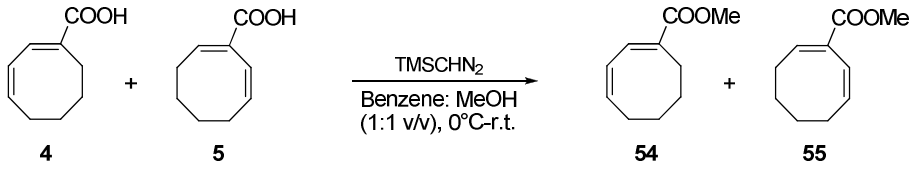
***Synthesis of methyl cycloocta-1,3 and 1,7-dienecarboxylates 54 and 55, respectively*:**



In a flask was measured a mixture of the acids **4** and **5** (0.98 g, 6.44 mmol) and it was added TFAA (1.71 mL, 12.30 mmol) at 0 ºC, after the system was stirred at r.t. for 15 min. The temperature was again cooled down to 0ºC and MeOH (0.53 mL, 21.00 mmol) was added into the system and stirred for 4 h. The reaction mixture was quenched with NaOH (10%, 15 mL), extracted with Et_2O, washed with NaOH 1M. and $NaCl_{\,(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. It was obtained a brown oil (749.40 mg, 70%) that contains a mixture of **54** and **55** (1:1). Through acidulation of the aqueous phase with HCl c. and extraction with DCM it could be recovered mixture of the acids that did not react (116.50 mg, 12%). Purification by silica gel for flash column chromatography of the ester mixture (pore 60Å. 40-63 µm) Hex/Et_2O (98:2-80:20 v/v) was performed, it was obtained the following compounds:

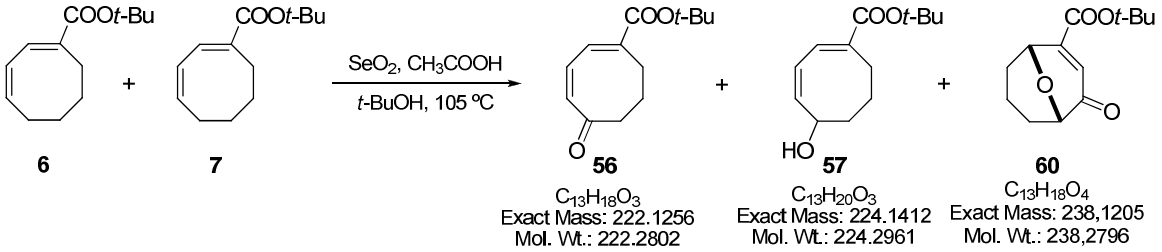
Methyl cycloocta-1,3-dienecarboxylate **54** (characterization of a pure fraction, 156 mg), **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.54-1.56 (4H, m, H-6 and H-7); 2.18-2.21 (2H, m, H-5); 2.47-2.53 (2H, m, H-8); 3.76 (3H, s. COO*Me*); 5.83-5.87 (2H, m, H-3 and H-4); 7.15 (1H, m, H-2).

Methyl cycloocta-1,7-dienecarboxylate **55** (characterization of a pure fraction, 181 mg), **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.43-1.58 (4H, m, H-4 and H-5); 2.07-2.16 (2H, m, H-6); 2.23-2.33 (2H, m, H-3); 3.75 (3H, s, COO*Me*); 5.78-5.91 (1H, m, H-7); 6.09-6.14 (1H, d, *J* 11.0, H-8); 6.94-7.02 (1H, t, *J* 8.2, H-2).



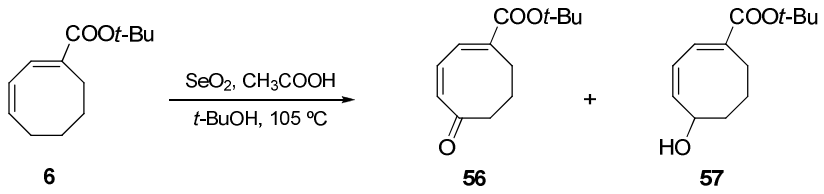
Under Ar atmosphere the mixture of compounds **4** and **5** (6.80 g, 44.7 mmol) was dissolved in a mixture of Benzene/MeOH (1:1 v/v, 1 mL) and $TMSCHN_2$ 2.0 M (26.0 mL, 50.0 mmol) was added. The reaction system was stirred at r.t. for 21 hours. After, the solution was evaporated under reduced pressure. The 1:1 crude mixture of the esters was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (99:1 v/v) – $CHCl_3$/MeOH (9:1 v/v). It was recovered 3.84 g (56%) in total from different fractions containing the esters **54** and **55**.

Oxidation of the 1:1 ratio mixture of compounds 6 and 7:



The unsaturated 1:1 ratio mixture of the esters **6** and **7** (1.40 g, 6.70 mmol) was dissolved in *t*-BuOH (30 mL), a mixture of SeO_2 (6.00 g, 54.10 mmol) and glacial acetic acid (1.5 mL) was added. The reaction system was stirred and refluxed at 105ºC for 5 hours. The reaction time depends on the quantity, for this reason TLC must be carried out. After, the system was cooled down and *t*-BuOH was evaporated under reduced pressure, the crude was poured into a mixture of water/ice, extracted with Et_2O, filtered through celite and concentrated *in vacuo*. It was obtained a crude mixture (2.42 g) which was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Ether (95:5- 8:2 v/v) gave compound **56** (769 mg, 52%), compound **57** (257 mg, 17%) and compound **60** (250 mg, 10%). For optimization of the reaction and study of the reaction products, this reaction was carried out separately for every ester.

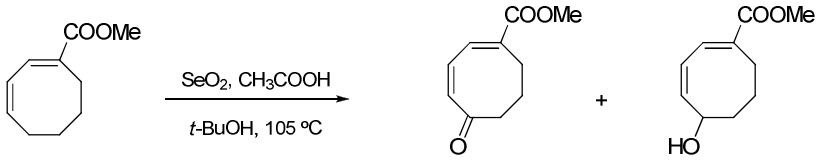
Synthesis of (1E,3Z) tert-butyl 5-oxo-cycloocta-1,3-dienecarboxylate 56:



6 **56** **57**

Unsaturated ester **6** (1.88 g, 9 mmol) was dissolved in *t*-BuOH (39 mL), a mixture of SeO_2 (8.65 g, 78.00 mmol) and glacial acetic acid (1.5 mL) was added. The reaction system was stirred and refluxed at 105ºC for 5.5 hours. The reaction time depends on the quantity, for this reason TLC must be carried out. After, the system was cooled down and *t*-BuOH was evaporated under reduced pressure, the crude was poured into a mixture of water/ice, extracted with Et_2O, filtered through celite and concentrated *in vacuo*. It was obtained a mixture of **56** and **57** (2.91 g) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1- 8:2 v/v) gave the following compounds which were previously full characterized: Compound **56** as a pale yellow oil (1.02 g, 51%) and (1*E*,3*Z*) *tert*-butyl 5-hydroxycycloocta-1,3-dienecarboxylate **57** as a brown yellow oil (0.64 g, 32%).

Synthesis of (1E,3Z)-methyl 5-oxo-cycloocta-1,3-dienecarboxylate 58:



54 **58** **59**

$C_{10}H_{12}O_3$
Exact Mass: 180.0786
Mol. Wt.: 180.2005

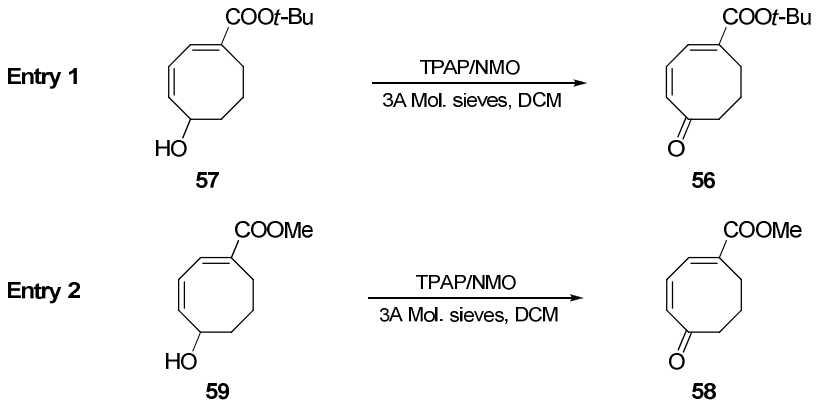
$C_{10}H_{14}O_3$
Exact Mass: 182.0943
Mol. Wt.: 182.2164

Unsaturated ester **54** (267.0 mg, 1.6 mmol) was dissolved in *t*-BuOH (7 mL), a mixture of SeO_2 (1.5 g, 14.0 mmol) and glacial acetic acid (0.13 mL) was added. The reaction system was stirred and refluxed at 105ºC for 5.0 hours. After, the system was cooled down and *t*-BuOH was evaporated under reduced pressure, the crude was poured into a mixture of water/ice, extracted with Et_2O, filtered through celite and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-8:2 v/v) gave the following compounds:

(1*E*,3*Z*)-methyl 5-oxo-cycloocta-1,3-dienecarboxylate **58** (134.00 mg, 46%), **^{1}H NMR (200 MHz; $CDCl_3$):** δ 2.04-2.18 (2H, q, *J* 7.0 and 13.6, H-7); 2.52-2.61 (4H, m, H-6 and H-8); 3.82 (3H, s, COO*Me*); 6.03-6.09 (1H, d, *J* 12.8, H-4); 6.54-6.64 (1H, dd, *J* 5.8 and 12.8, H-3); 7.36-7.39 (1H, d, *J* 5.6, H-2).

(1*E*,3*Z*)-methyl 5-hydroxycycloocta-1,3-dienecarboxylate **59** (53.00 mg, 18%), **^{1}H NMR (200 MHz; $CDCl_3$):** 1.20-1.97 (4H, m, H-6 and H-7); 2.70-2.77 (2H, m, H-8); 4.06-4.17 (1H, dd, *J* 5.8 and 8.8, H-5); 5.76-5.84 (1H, dd, *J* 4.0 and 11.8, H-4); 5.95-6.06 (1H, dd, *J* 3.0 and 11.8, H-3); 7.16-7.18 (1H, d, *J* 4.0, H-2).

Oxidation reaction of compounds 57 and 59:



Procedure:

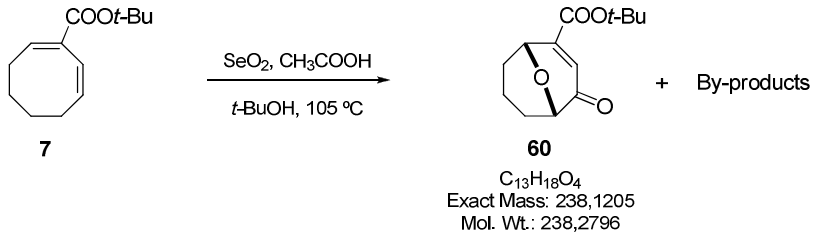
Entry 1:

Compound **57** (180.0 mg, 0.8 mmol) was dissolved in DCM (6 mL) and 3A molecular sieves previously activated, NMO (380.0 mg, 2.8 mmol) and TPAP (catalytic amount) were added into the system, under Ar atmosphere the reaction was stirred for 2 hours at r.t. After, the residue was filtered through celite/silica gel column passing abundant DCM and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-8:2 v/v) gave compound **56** (161.0 mg, 90%).

Entry 2:

Compound **59** (53.0 mg, 0.3 mmol) was dissolved in DCM (2.5 mL) and 3A molecular sieves previously activated, NMO (122.0 mg, 0.9 mmol) and TPAP (catalytic amount) were added into the system, under Ar Atmosphere the reaction was stirred for 8 hours at r.t. After, the residue was filtered through celite/silica gel column passing abundant DCM and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-8:2 v/v) gave compound **58** (47.0 mg, 87%).

Oxidation reaction of compound 7 with Selenium dioxide:



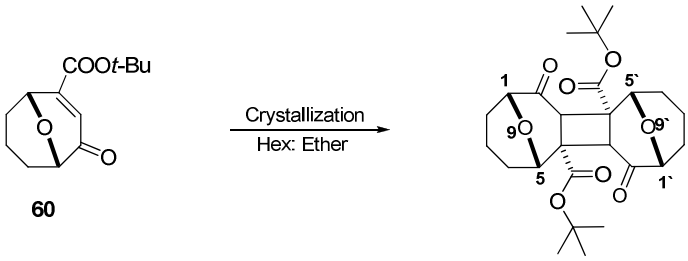
7

60

$C_{13}H_{18}O_4$
Exact Mass: 238,1205
Mol. Wt.: 238,2796

Unsaturated ester **7** (316.20 mg, 1.52 mmol) was dissolved in *t*-BuOH (7 mL), a mixture of SeO_2 (1.5 g, 14.0 mmol) and glacial acetic acid (0.13 mL) was added. The reaction system was stirred and refluxed at 105ºC for 5.0 hours. After, the system was cooled down and *t*-BuOH was evaporated under reduced pressure, the crude was poured into a mixture of water/ice, extracted with Et_2O, filtered through celite and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-80:20 v/v) gave 11% of by-products which were not identified due to quantity and *tert*-butyl 4-oxo-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate **60** (104.10 mg, 29%) which was allowed to crystallize in a mixture Hexane/Et_2O (1:1, v/v). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.52 (9H, s, COOC(CH_3)$_3$); 1.68 (2H, m, H-7); 1.71-2.08 (4H, m, H-6, H-8); 4.23 (1H, d, *J* 4.8, H-5); 4.87 (1H, d, *J* 5.2, H-1); 6.87 (1H, s, H-3). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 14.7 (CH_2, C-7); 25.0 (CH_2, C-6); 26.2 (CH_2, C-8); 27.9 (CH_3 x 3, COOC(CH_3)$_3$); 68.4 (CH, C-1); 75.7 (CH, C-5); 82.9 (C, COOC(CH_3)$_3$); 131.7 (CH, C-3); 150.3 (C, C-2); 163.4 (C, COOC(CH_3)$_3$); 199.2 (C, C-4). **HRMS [M+Na] *m/z* calcd. for $C_{13}H_{18}O_4Na$:** 261.1097; **found** 261.1101; **Δ** = 1.5 ppm.

Crystallization product of compound 60:



60

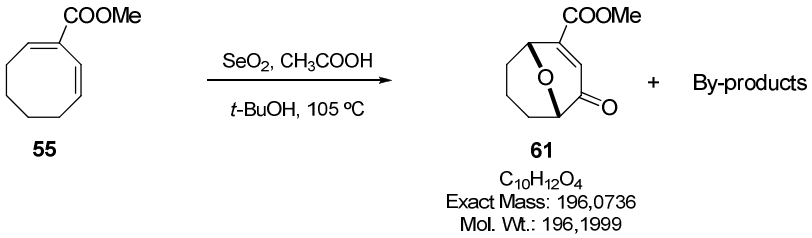
62

$C_{26}H_{36}O_8$
Exact Mass: 476,2410
Mol. Wt.: 476,5592

Compound **60** was dissolved in a mixture of Hex/Et_2O (1:1 v/v) and it was leave for a period in conditions of crystallization, it afforded the compound dimer **62**, (1*R**,5*S**,1`*R*\*,5`*S**)-dimethyl 6,12-dioxohexadecahydro-1,5:7,11-diepoxycyclobuta[1,2:3,4]di[8]annulene-6b,12b-dicarboxylate, **mp** 171–172 ºC, **IR υ_{max} (neat):** 2947 (C-H), 1718 (C=OO*t*-Bu), 1699 (C=O), 1458, 1370, 1262 (C-O), 1159, 1045 and 1024 cm^{-1}.**^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.51 (CH_3 x 6, COOC(*Me*)$_3$ and

COOC(*Me*)$_3$`); 1.48-1.65 (4H, m, H-7 and H-7`); 1.75-1.97 (8H, m, H-6, H-8, H-6`and H-8`); 3.93 (2H, s, H-3 and H-3`); 4.18 (2H, d, *J* 4.0, H-1 and H-1`); 4.25 (2H, d, *J* 5.3, H-5 and H-5`). **$^{13}$C NMR (50 MHz; $CDCl_3$):** δ 16.8 ($CH_2$ x 2, C-7 and C-7`); 27.1 (CH_2 x 2, C-6 and C-6`); 27.9 ($CH_3$ x 6, COOC$(CH_3)_3$ and COOC$(CH_3)_3$`); 29.1 (CH_2 x 2, C-8 and C-8`); 51.6 (C x 2, C-4 and C-4`); 54.6 (CH x 2, C-3 and C-3`); 74.5 (CH x 2, C-5 and C-5`); 77.2 (CH x 2, C-1 and C-1`); 83.1 (C x 2, COO*C*$(CH_3)_3$ and COO*C*`$(CH_3)_3$); 169.4 (C x 2, *C*OO$(CH_3)_3$ and *C*`OO$(CH_3)_3$); 211.3 (C x 2, C-2 and C-2`). ***m/z* (CI$^+$) (rel. intensity):** 420 (MH^+, 70), 258 (22), 154 (52), 105 (100). **HRMS [M+Na] *m/z* calcd. for $C_{26}H_{36}O_8Na$:** 499.2302; **found** 499.2301; **Δ** = -0.2 ppm. **R-X:** See annexe C.

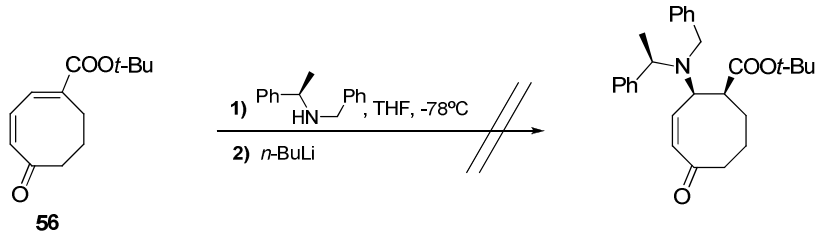
Oxidation reaction of compound 55 with Selenium dioxide:



Following previous procedure, unsaturated ester **55** (173.0 mg, 1.0 mmol) was dissolved in *t*-BuOH (4 mL), a mixture of SeO_2 (1.0 g, 8.7 mmol) and glacial acetic acid (0.1 mL) was added. The reaction system was stirred and refluxed at 105ºC for 5.0 hours. After, the system was cooled down and *t*-BuOH was evaporated under reduced pressure, the crude was poured into a mixture of water/ice, extracted with Et_2O, filtered through celite and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 μm) Hex/EtOAc (98:2-80:20 v/v) gave 11% of by-products which were not identified due to quantity and compound **61** (22.30 mg, 11%) which was allowed to crystallize in a mixture Hexane/Et_2O (1:1, v/v). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.66 (2H, H-7); 1.85-2.10 (4H, H-6, H-8); 3.85 (3H, COO*Me*); 4.25 (1H, d, *J* 5.4, H-5); 4.91 (1H, d, *J* 5.0, H-1); 6.95 (1H, H-3).

3.2. Reactivity of (1*E*,3*Z*) *tert*-butyl 5-oxo-cycloocta-1,3-diene carboxylate:

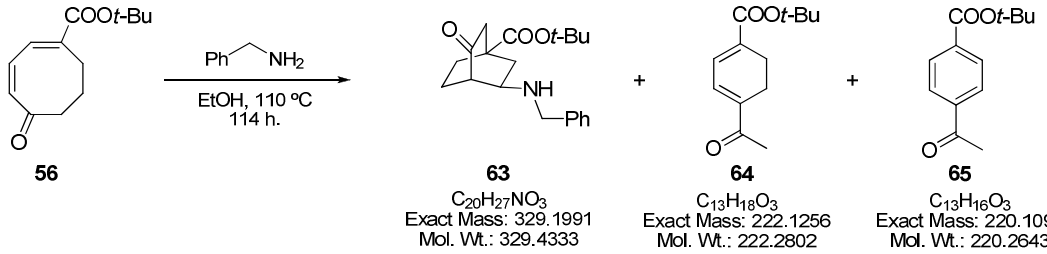
Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide:



56

Following general procedure for the Michael addition, compound **56** (40.0 mg, 0.18 mmol) was dissolved in THF (2 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.09 g, 0.43 mmol) was dissolved in THF (3 mL) and *n*-BuLi (1.6 M., 0.26 mL, 0.41 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2.5 hours at -78°C. The ^{1}H NMR spectrum of the crude showed recovery of starting material.

Addition of benzylamine:



56

63
$C_{20}H_{27}NO_3$
Exact Mass: 329.1991
Mol. Wt.: 329.4333

64
$C_{13}H_{18}O_3$
Exact Mass: 222.1256
Mol. Wt.: 222.2802

65
$C_{13}H_{16}O_3$
Exact Mass: 220.1099
Mol. Wt.: 220.2643

Compound **56** (197.0 mg, 0.9 mmol) was dissolved in EtOH (15 mL) and Bn-NH_2 (0.16 mL, 1.40 mmol) was added. The system was stirred and refluxed at 110ºC for 114 hours. After the reaction system was cooled down and evaporated under reduced pressure. It gave a mixture (297 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-7:3 v/v) gave the following compounds:

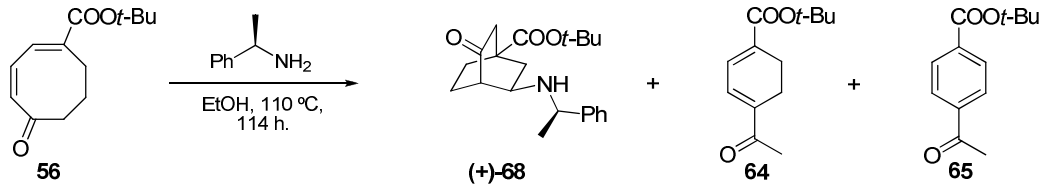
tert-butyl 3-benzylamino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate **63** as a pale yellow oil (123 mg, 42%), **IR υ_{max} (neat):** 2974 and 2875 (C-H), 1724 (C=O), 1455, 1370, 1261 (C-O), 1162, 1073 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.43 (9H, s, COO(CH_3)$_3$); 1.40-1.69 (1H, m, H-2$_A$); 1.70-1.90 (4H, m, H-8 and H-7); 2.23 (1H, ddd, *J* 3.3, 9.2, 12.2, H-2$_B$); 2.35 (1H, dd, *J* 3.3, 18.3, H-6$_A$); 2.52 (1H, m, H-4); 2.55 (1H, dd, *J* 3.3, 18.3, H-6$_B$); 3.17 (1H, dt, *J* 3.3, 9.2, H-3); 3.70 and 3.80 (2H, S_{AB}, *J* 13.2, NH-CH_2-Ph); 7.21-7.32 (5H, m, Ph). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.3 (CH_2, C-8); 27.2 (CH_2, C-7); 27.9 (CH_3 x 3, COOC(*C*H_3)$_3$); 45.6 (CH_2, C-6); 43.5 (C, C-1); 36.8 (CH_2, C-2); 47.0 (CH, C-4); 54.0 (CH, C-3); 50.6 (HN-*C*H_2-Ph); 80.8 (C, COO*C*(CH$_3$)$_3$) 127.0-

128.0 (CH x 5, *Ph*); 139.7 (C, C_{ipso}); 173.8 (C, *C*OOC$(CH_3)_3$), 213.0 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{20}H_{28}NO_3$ [M+H]$^+$:** 330.2069; **found** 330.2049; **Δ** = -6.1 ppm.

tert-butyl 4-acetylcyclohexa-1,3-diene carboxylate **64** (45.10 mg, 23%), **IR υ_{max} (neat):** 2970 and 2870 (C-H), 1724 (C=O), 1252 (C-O), 1167, 1073 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.49 (9H, s, COOC-(C*H*$_3$)$_3$); 2.34 (3H, s, C*H*$_3$); 2.46-2.48 (2H, m, H-5); 2.46-2.48 (2H, m, H-6); 6.94 (1H, S.AB, *J* 6.0, H-3); 7.02 (1H, S.AB, *J* 6.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.4 (CH_2, C-5); 21.8 (CH_2, C-6); 25.4 (CH_3); 28.0 (CH_3 x 3, COOC(*C*H$_3$)$_3$); 80.9 (C, COO*C*(CH$_3$)$_3$); 138.3 (CH, C-3); 130.8 (CH, C-2); 136.0 (C, C-1); 140.3 (C, C-4); 165.7 (C, *C*OOC$(CH_3)_3$); 196.6 (C, *C*O-Me). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{18}O_3$ [M+Na]:** 245.1154; **found** 245.1145; Δ = -3.7 ppm.

tert-butyl 4-acetylbenzoate **65** (8.75 mg, 5%), **IR υ_{max} (neat):** 2932 (C-H), 1713 (C=O), 1693 (C=O), 1291 (C-O), 1164, 1117, 849, 769 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.61 (9H, s, COOC-(C*H*$_3$)$_3$); 2.64 (3H, s, C*H*$_3$); 7.98 (2H, S.AB, *J* 8.6, H-3 and H-5); 8.07 (2H, S.AB, *J* 8.6, H-2 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 26.8 (CH_3, CO*C*H$_3$); 28.1 (CH_3 x 3, COOC(*C*H$_3$)$_3$); 81.7 (C, COO*C*(CH$_3$)$_3$); 128.0 (CH x 2, C-3 and C-5); 129.6 (CH x 2, C-2 and C-6); 135.8 (C, C-1); 139.8 (C, C-4); 164.8 (C, *C*OOC$(CH_3)_3$); 197.6 (C, *C*O-Me).

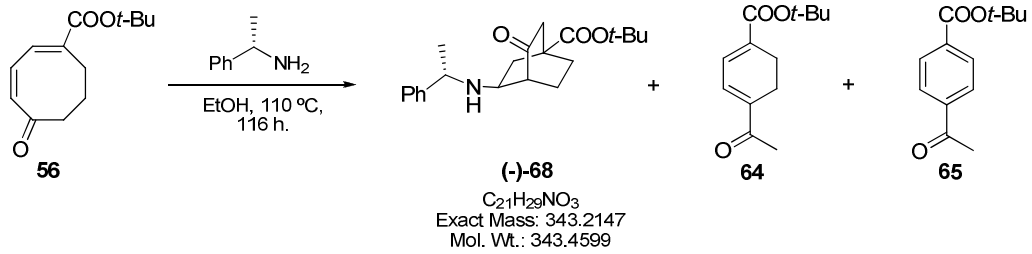
Addition of (R)-N-α-methylbenzylamine:



Compound **56** (182.10 mg, 0.82 mmol) was dissolved in EtOH (15 mL) and *D*(+)-alpha-methylbenzyl-amine (99% *e.e.*, 0.17 mL, 1.31 mmol) was added. The system was stirred and refluxed at 110ºC for 114 hours. After the reaction system was cooled down and evaporated under reduced pressure. It gave a mixture (254 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) afforded starting material **56** (10.10 mg, 7%), compound **64** (66.00 mg, 39%), compound **65** (4.70 mg, 3%) and *tert*-butyl (1*S*,3*R*,4*S*,α*R*)-3-*N*-α-methylbenzylamino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate **(+)-68** as a pale yellow oil (90.00 mg, 34%), crystallized in a 1:1 (v/v) mixture of Hex/EtOAc, **mp** 108–109 ºC, $[\alpha]_D^{20}$= +32.7 (*c* 0.90, $CHCl_3$), **IR υ_{max} (neat):** 2970 and 2870 (C-H), 1724 (C=O), 1450 (N-H), 1370, 1252 (C-O), 1167, 1073 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.25-1.28 (3H, d, *J* 6.6, CH_3(α)); 1.40 (9H, s, COO(C*H*$_3$)$_3$); 1.60-1.76 (5H, m, H-2a, H-7 and H-8); 2.23 (1H, ddd, *J* 3.3,

9.2, 12.2, H-2b); 2.35 (1H, dd, *J* 3.3, 15.3, H-6a); 2.52 (1H, m, H-4); 2.55 (1H, dd, *J* 3.3, 15.3, H-6b); 2.85-2.96 (1H, td, *J* 3.3, 9.2, H-3); 3.85 (1H, q, *J* 6.6, CH(α)); 7.21-7.32 (5H, m, *Ph*). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.3 (CH_2, C-8); 25.1 (CH_3, HC-*C*H_3-Ph); 27.2 (CH_2, C-7); 27.9 (CH_3 x 3, COOC(*C*H_3)$_3$); 36.7 (CH_2, C-2); 43.7 (C, C-1); 45.6 (CH_2, C-6); 46.9 (CH, C-4); 54.0 (CH, C-3); 50.6 (CH, NH-*C*H-Ph); 80.8 (C, COO*C*(CH$_3$)$_3$); 127.0-128.0 (CH x 5, *Ph*); 139.7 (C, C_{ipso}); 173.8 (C, *C*OOC(CH$_3$)$_3$), 213.0 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}NO_3$ $[M+H]^+$:** 344.2226; **found** 344.2207; **Δ** = -5.5 ppm. **R-X:** See annexe D.

Addition of (S)-N-α-methylbenzylamine:



Compound **56** (195.40 mg, 0.88 mmol) was dissolved in EtOH (15 mL) and (*S*)-(-)-alpha-methylbenzyl-amine 99+% (99% *e.e*., 0.18 mL, 1.41 mmol) was added. The system was stirred and refluxed at 110ºC for 116 hours. After the reaction system was cooled down and evaporated under reduced pressure. It gave a mixture (263 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) afforded starting material **56** (1.11 mg, 1%), compound **64** (113.12 mg, 53%), compound **65** (5.58 mg, 3%) and *tert*-butyl (1*R**,3*S**,4*R**,α*S*)-3-*N*-α-methylbenzylamino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate **(-)-68** as a pale yellow oil (115.00 mg, 39%); $[\alpha]_D^{20}$ = -31.8 (*c* 0.99, $CHCl_3$).

Addition of (S)-N-α-methylbenzylamine in the presence and absence of light:

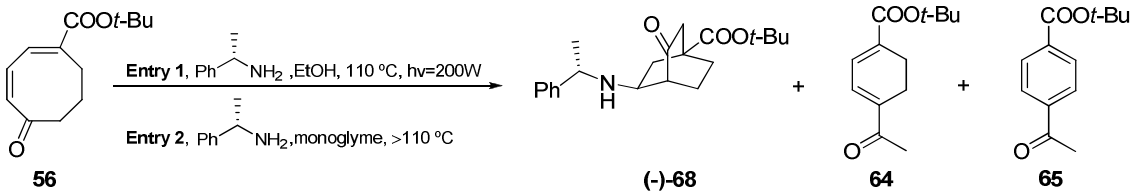
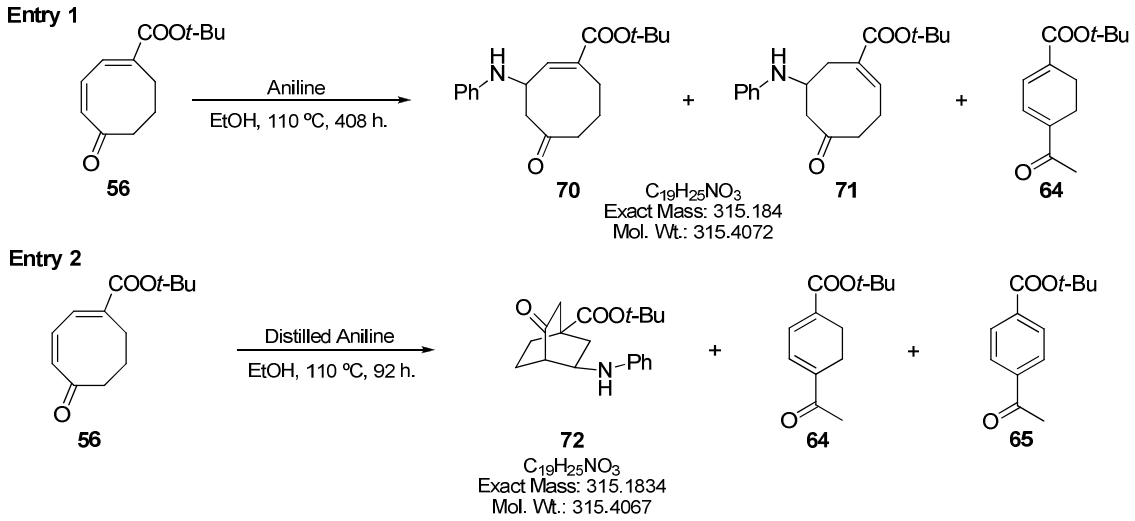


Table 15.

Entry	56 (mg, mmol)	(*S*)-amine (mg, mmol)	Solvent (mL)	Time (h.)	56%	(-)-68%	64%	65%
1 200W	110.0, 0.5	73.0, 0.6	EtOH (10)	45	7	23	58	1
2 isolated	107.0, 0.5	73.0, 0.6	Monoglyme (18)	96	0	30	62	1

Following general procedure for the protection reaction of the carbonyl group, compound **56** was dissolved and (*S*)-amine was added. A system was refluxed in the presence of a lamp (200W) at 110ºC and the other system was completed light isolated and refluxed at > 110ºC. Reaction systems were concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) were performed for every entry.

Addition of phenylamine:



Procedure:

Entry 1:

Following previous procedure, compound **56** (111.00 mg, 0.50 mmol) was dissolved in EtOH (10 mL) and aniline (58.00 mg, 0.60 mmol) was added. The system was stirred and refluxed at 110ºC for 408 hours. After the reaction system was cooled down and evaporated under reduced pressure. It gave a crude (75 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) afforded starting material **56** (14.00 mg, 12%), **64** (4.00 mg, 9%) and the following compounds:

(*E*) *tert*-butyl 5-oxo-3-phenylaminocycloocta-1-ene carboxylate **70** as a pale yellow oil (46.00 mg, 30%). **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.46 (9H, s, COOC(CH_3)$_3$); 1.60 (1H, m, H-7b); 1.98 (1H, m, H-7a); 2.31 (1H, m, H-8a); 2.46 (1H, m, H-6a); 2.59 (1H, t, *J* 12.1, H-4a); 2.64 (1H, m, H-6b); 2.87 (1H, m, H-8b); 3.08 (1H, dd, *J* 4.4 and 12.1, H-4b); 4.72 (1H, ddd, *J* 4.2, 8.5, 12.1, H-3); 6.60 (2H, d, *J* 9.4, H-2` and H-6`); 6.70 (1H, d, *J* 8.5, H-2); 6.78 (1H, t, *J* 8.2, H-4`); 7.21 (2H, t, *J* 8.8, H-3`and H-5`). **$^{13}$C NMR (50 MHz; $CDCl_3$):** δ 24.9 ($CH_2$, C-7); 27.0 ($CH_2$, C-8); 28.0 ($CH_3$ x 3, COOC($CH_3$)$_3$ ); 41.2 ($CH_2$, C-6); 49.0 (CH, C-3); 53.4 ($CH_2$, C-4); 81.0 (C, COO*C*($CH_3$)$_3$); 113.3 (2 x CH, C-2` and C-3`); 118.5 (CH, C-4`); 129.4 (CH x 2, C-5`and C-6`); 134.4 (C, C-1); 144.0

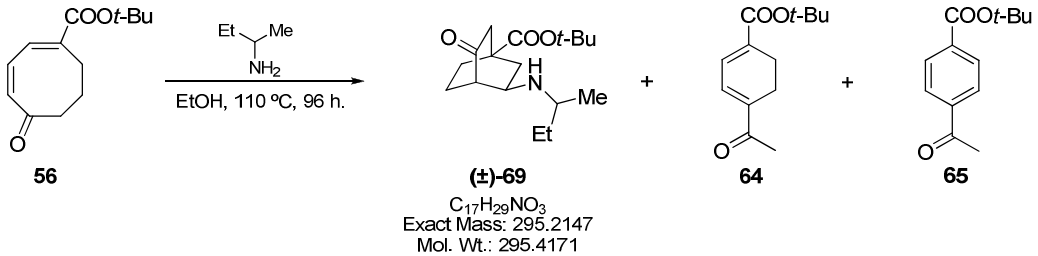
(CH, C-2); 146.0 (C, C_{ipso}); 165.0 (C, *C*OOC$(CH_3)_3$); 210.0 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{19}H_{26}NO_3$ [M+H]$^+$:** 316.1907; **found** 316.1903; **Δ** = -1.3 ppm.

(*E*) *tert*-butyl 5-oxo-7-phenylaminocycloocta-1-ene carboxylate **71** (11.00 mg, 9%) . **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.46 (9H, s, COOC(C*H*$_3)_3$); 1.98 (2H, m, H-3); 2.31 (1H, m, H-8a); 2.87 (1H, m, H-8b); 2.46 (1H, m, H-4a); 2.59 (1H, m, H-6a); 2.64 (1H, m, H-4b); 3.08 (1H, m, H-6b); 4.72 (1H, m, H-7); 6.60 (2H, d, *J* 7.7, H-2` and H-6`); 6.70 (1H, dd, *J* 7.8, 17.7, H-2); 6.78 (1H, t, *J* 7.3, H-4`); 7.21 (2H, t, *J* 7.3, H-3`and H-5`). **$^{13}$C NMR (50 MHz; $CDCl_3$):** δ 26.6 ($CH_2$, C-7); 28.0 ($CH_3$ x 3, COOC(*C*$H_3)_3$ ); 29.6 ($CH_2$, C-2); 38.0 ($CH_2$, C-6); 45.8 (CH, C-3); 50.5 ($CH_2$, C-4); 81.2 (C, COO*C*$(CH_3)_3$); 113.3 (CH x 2, C-2` and C-6`); 118.2 (CH, C-4`); 129.4 (CH x 2, C-3` and C-5`); 134.4 (C, C-1); 136.5 (CH, C-8); 146.0 (C, C_{ipso}); 173.4 (C, *C*OOC$(CH_3)_3$); 212.9 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{19}H_{25}NO_3$ Na:** 338.1726; **found** 338.1738; **Δ** = 3.5 ppm.

Entry 2:

Following general procedure for the protection reaction of the carbonyl group, compound **56** (81.00 mg, 0.40 mmol) was dissolved in EtOH (9 mL) and distilled aniline (50.00 mg, 0.50 mmol) was added. The system was stirred and refluxed at 110ºC for 92 hours. After the reaction system was cooled down and evaporated under reduced pressure. It gave a crude (75 mg) that was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2- 70:30 v/v) afforded 14:1 ratio mixture of compounds **64** and **65** (48.00 mg, 45%) and *tert*-butyl 3-phenylamino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate **72** as a pale yellow oil (7.00 mg, 3%). . **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.43 (9H, s, COO(C*H*$_3)_3$); 1.40-1.60 (1H, m, H-2_A); 1.70-1.90 (4H, m, H-7 and H-8); 2.23 (1H, ddd, *J* 2.9, 6.0, 12.2, H-2_B); 2.35 (1H, dd, *J* 3.3, 15.3, H-6_A); 2.52 (1H, d, *J* 9.2, H-3); 2.55 (1H, dd, *J* 3.3, 11.3, H-6_B); 3.17 (1H, dt, *J* 3.3, 9.2, H-4); 6.60 (2H, d, *J* 9.4, H-2` and H-6`); 6.78 (1H, t, H-4`); 7.21 (2H, t, H-3` and H-5`).

Addition of (±)-sec-butyl amine:



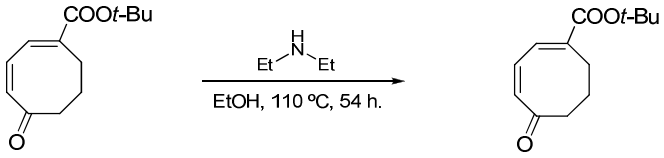
56 **(±)-69** **64** **65**

$C_{17}H_{29}NO_3$
Exact Mass: 295.2147
Mol. Wt.: 295.4171

Following general procedure for the protection reaction of the carbonyl group, compound **56** (64.00 mg, 0.30 mmol) was dissolved in EtOH (6 mL) and *sec*-butyl amine (31.00 mg, 0.40 mmol) was added. The system was stirred and refluxed at 110ºC for 96 hours. After the reaction system

was cooled down and evaporated under reduced pressure. It gave a mixture (72 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2- 80:20 v/v) afforded starting material **56** (9.00 mg, 14%), compounds **64** and **65** (22.00 mg, 39%) and *tert*-butyl 3-(*sec*-butylamino)-5-oxo-bicyclo[2.2.2]octane-1-carboxylate (±)-**69** as a pale yellow oil (13.00 mg, 18%), **IR υ_{max} (neat):** 2967 and 2931 (C-H), 1724 (C=O), 1368, 1253 (C-O),1162 cm^{-1} . **^{1}H NMR (400 MHz; $CDCl_3$):** δ 0.83-0.87 (3H, td, *J* 7.4 and 1.8, CH_3`); 0.97-0.99 (3H, dd, *J* 7.4 and 2.7, CH`and CH_2`); 1.44 (9H, s, COOC(CH_3)$_3$); 1.40-1.60 (1H, m, H-2a); 1.76-1.78 (4H, m, H-8 and H-7); 2.23-2.25 (1H, ddd, *J* 3.3, 9.2, 12.2, H-2b); 2.26 (1H, dd, *J* 3.3, 15.3, H-6a); 2.35 (1H, dd, *J* 9.2 and 3.3, H-4); 2.45 (1H, dd, *J* 3.3, 15.3, H-6b); 2.40-2.65 (1H, td, *J* 3.3, 9.2, H-3); 3.50-3.51 (1H, m, NH-CH`). **$^{13}$C NMR (50 MHz; $CDCl_3$):** δ 10.1 ($CH_3$, C-3`); 19.6 (CH_3, C-1``); 20.3 (CH_2, C-8); 20.6 (CH_2, C-2`); 27.2 ($CH_2$, C-7 ); 28.0 ($CH_3$ x 3, COOC($CH_3$)$_3$); 37.9 ($CH_2$, C-2); 43.5 (C, C-1); 45.6 ($CH_2$, C-6); 46.9 (CH, C-4); 50.5 (CH, C-1`); 52.0 (CH, C-3); 80.8 (C, COOC(CH_3)$_3$); 173.9 (C, COOC(CH_3)$_3$), 213.4 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{17}H_{30}NO_3$ $[M+H]^+$:** 296.2220; **found** 296.2223; **Δ** = 1.0 ppm.

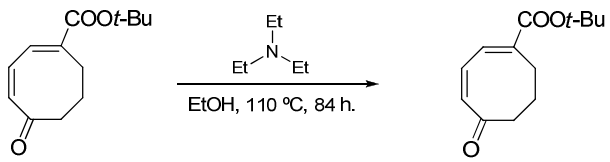
Addition of diethylamine:



56 **56**

Following general procedure for the protection reaction of the carbonyl group, compound **56** (20.00 mg, 0.09 mmol) was dissolved in EtOH (5 mL) and diethylamine (13.00 mg, 0.20 mmol) was added. The system was stirred and refluxed at 110ºC for 54 hours. After the reaction system was cooled down and evaporated under reduced pressure. It afforded starting material **56** (20.00 mg).

Addition of triethylamine:



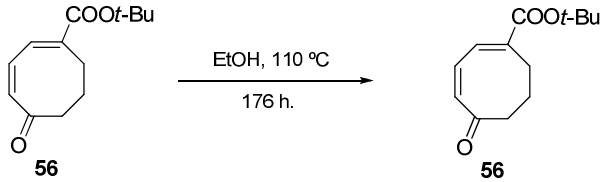
56 **56**

Following general procedure for the protection reaction of the carbonyl group, compound **56** (20.00 mg, 0.09 mmol) was dissolved in EtOH (5 mL) and triethylamine (22.00 mg, 0.20 mmol) was added. The system was stirred and refluxed at 110ºC for 84 hours. After the reaction system

was cooled down and evaporated under reduced pressure. It afforded starting material **56** (20.00 mg).

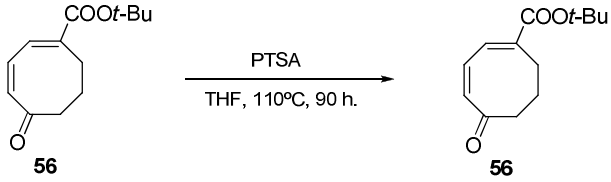
3.3 Stability tests of (1*E*,3*Z*) *tert*-butyl 5-oxo-cycloocta-1,3-diene carboxylate in different mediums:

Refluxed in Ethanol:



Compound **56** (20.00 mg, 0.09 mmol) was dissolved in EtOH (5 mL). The system was stirred and refluxed at 110ºC for 176 hours. After the reaction system was cooled down and evaporated under reduced pressure. It afforded starting material **56** (20.00 mg).

Addition of p-Toluenesulfonic acid:

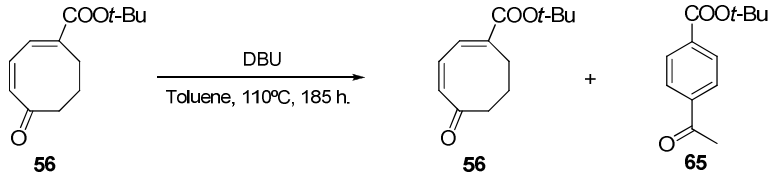


Compound **56** (20.00 mg, 0.09 mmol) was dissolved in THF (5 mL) and PTSA (25.00 mg, 0.13 mmol) was added. The system was stirred and refluxed at 110ºC for 90 hours. After the reaction system was cooled down and evaporated under reduced pressure. It afforded starting material **56** (20.00 mg).

Addition of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone:

Compound **56** (11.00 mg, 0.05 mmol) was dissolved in benzene (8 mL) and DDQ (43.00 mg, 0.20 mmol) was added. The system was stirred and refluxed at 110ºC for 62 hours. After the reaction system was cooled down and evaporated under reduced pressure. It afforded starting material **56** (11.00 mg).

Addition of 1,8-Diazabicyclo [5.4.0] undec-7-ene:



Unsaturated ester **56** (8.00 mg, 0.04 mmol) was dissolved in Toluene (5 mL) and DBU (12.00 mg, 0.08 mmol) was added. The reaction system was stirred and refluxed at 110ºC for 185 hours and followed by TLC. The system was cooled down, extracted with DCM, washed with $NaHCO_3$, dried, filtered and concentrated *in vacuo*. It was obtained 2 mg of crude that by ^1H NMR spectroscopy showed starting material **56** and compound **65** in a 2:1 relation respectively.

3.4 Reactivity of the reaction products of (1*E*,3*Z*) *tert*-butyl 5-oxo-cycloocta-1,3-diene carboxylate:

Dehydrogenation reactions:

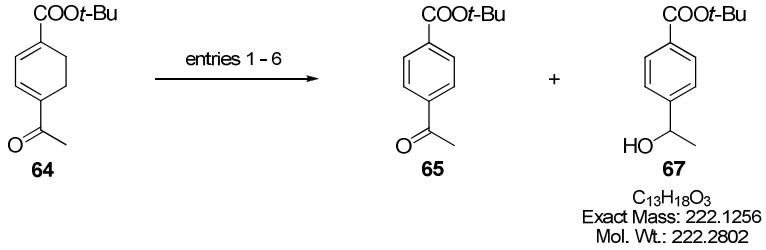


Table 16.

Entry	64 (mg, mmol)	Reaction conditions	Solvent	% 64	% 65	% 67
1	58.00, 0.26	SeO_2 (60.00 mg, 0.54 mmol), 110ºC, 138 h.	EtOH (10 mL)	60	40	-
2	22.00, 0.10	SeO_2 (44.00 mg, 0.39 mmol), 2 drops CH_3COOH, 105ºC, 15 h.	*t*-BuOH (10 mL)	Decomposition of starting material		
3	11.00, 0.05	DDQ (12.60 mg, 0.06 mmol), 90ºC, 20 h.	Benzene (6 mL)	41	52	-
4	28.50, 0.13	DDQ (43.00 mg, 0.19 mmol), 95ºC, 62 h.	Benzene (8 mL)	31	50	-
5	13.30, 0.06	DBU (16.50 mg, 0.11 mmol), 110ºC, 20 h.	Toluene (5 mL)	7	64	13
6	3.34, 0.02	Br_2 (5.00 mg, 0.03 mmol), 0°C - r.t., 2 h.	CCl_4 (2 mL)	-	100	-

Procedure:

Entry 1:

Compound **64** (58.00 mg, 0.26 mmol) was dissolved in EtOH (5 mL) and SeO_2 (60.00 mg, 0.54 mmol) was added previously dissolved in EtOH (5 mL). The reaction system was stirred and refluxed at 110ºC for 138 hours and followed it by TLC and analyzing aliquots by ^{1}H NMR to control the formation of compound **65**. After 66 hours reflux, it was observed the major yield of **65** after this time the signals of both **64** and **65** decreased and it was observed the formation of other compounds with structures no common to ours. The reaction mixture was poured into a mixture of H_2O (50 mL) neutralized with $NaHCO_3$. Deposited selenium was removed through Celite filtration, washed and extracted with CCl_4, filtered and concentrated *in vacuo*. It was obtained 58 mg of crude whose purification was tried by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-80:20 v/v).

Entry 2:

Compound **64** (22.00 mg, 0.10 mmol) was dissolved in *t*-BuOH (10 mL) and it was added a mixture of SeO_2 (44.00 mg, 0.39 mmol) and CH_3COOH glacial (1.5 mL). The reaction system was stirred and refluxed at 105ºC for 15 hours and followed it by TLC. After this time *t*-BuOH was evaporated and the crude was poured into a mixture of H_2O/ice (25 mL), extracted with Et_2O, filtered through Celite and concentrated *in vacuo*. It was obtained 53 mg that both by TLC and ^{1}H NMR showed the decomposition of the starting material.

Entry 3:

Compound **64** (11.00 mg, 0.05 mmol) was dissolved in PhH (6 mL) and it was added DDQ (12.60 mg, 0.06 mmol). The reaction system was stirred and refluxed at 90ºC for 20 hours under Ar atmosphere. The reaction mixture was concentrated *in vacuo* and purification by silica gel for column chromatography (pore 60Å. 40-63 µm) was performed to remove DDQ excess. It was obtained 8 mg of crude whose ^{1}H NMR spectrum showed compound **64** and **65** (52%) in 1:0.74 relation.

Entry 4:

Compound **64** (28.50 mg, 0.13 mmol) was dissolved in PhH (8 mL) and it was added DDQ (43.00 mg, 0.19 mmol). The reaction system was stirred and refluxed at 95ºC for 62 hours under Ar atmosphere. The reaction mixture was concentrated *in vacuo* and purification by silica gel for column chromatography (pore 60Å. 40-63 µm) was performed to remove DDQ excess. It was obtained 24 mg of crude whose ^{1}H NMR spectrum showed compound **64** and **65** (50%) in 0.75:1 relation.

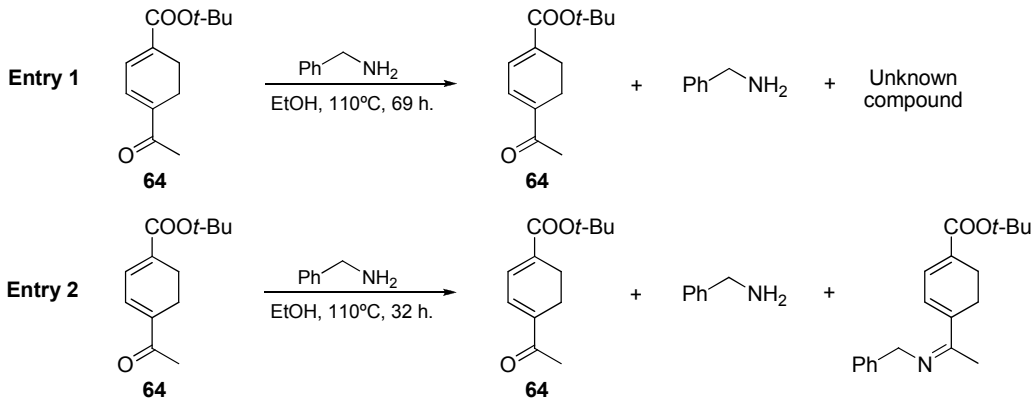
Entry 5:

Compound **64** (13.30 mg, 0.06 mmol) was dissolved in toluene (5 mL) and it was added DBU (16.50 mg, 0.11 mmol). The reaction system was stirred and refluxed at 110ºC for 20 hours. The reaction mixture diluted in DCM and HCl 10%, extracted with DCM, washed with $NaHCO_{3\ (sat.)}$, dried over Na_2SO_4 and concentrated *in vacuo*. It gave 13 mg of a mixture purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) obtaining compound **64** (0.50 mg, 7%), compound **65** (4.00 mg, 64%) and *tert*-butyl 4-(1-hydroxyethyl)benzoate **67** (0.80 mg, 13%), **IR υ_{max} (neat):** 3410 (O-H), 2974 (C-H), 1716 (C=O), 1373, 1295 (C-O), 1164, 852 and 778 (*p*-Ph), 709, 662 cm^{-1} . **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.44 (3H, d, CH-C*H*$_3$); 1.61 (9H, s, COOC(C*H*$_3$)$_3$); 4.98 (1H, q, HO-C*H*-CH$_3$); 7.42 (2H, S.AB, *J* 8.6, H-3 and H-5); 7.88 (2H, S.AB, *J* 8.6, H-2 and H-6). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 25.6 (CH$_3$, CH-*C*H$_3$) 28.4 (CH$_3$ x 3, COOC(*C*H$_3$)$_3$); 70.3 (CH, OH-*C*H-CH$_3$); 81.2 (C, COO*C*(CH$_3$)$_3$); 125.0 (CH x 2, C-3 and C-5); 129.9 (CH x 2, C-2 and C-6); 131.8 (C, C-4); 150.6 (C, C-1); 166.0 (C, *C*OOC(CH$_3$)$_3$). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{18}O_3Na$:** 245.1148; **found** 245.1166; **Δ** = 7.3 ppm.

Entry 6:

Compound **64** (3.34 mg, 0.02 mmol) was dissolved in CCl_4 (2 mL) the system was cooled down at 0°C and it was added Br_2 (5.00 mg, 0.03 mmol). The reaction system was stirred for 15 min. at 0°C and after at r.t. for 2 hours. The reaction mixture was diluted in DCM (20mL) and washed with HCl 2M., $NaHCO_{3\ (sat.)}$, H_2O and $NaCl_{\ (sat.)}$, dried over Na_2SO_4 and concentrated *in vacuo*. It afforded compound **65** (3.00 mg, 100%)

Addition of benzylamine:



Procedure:

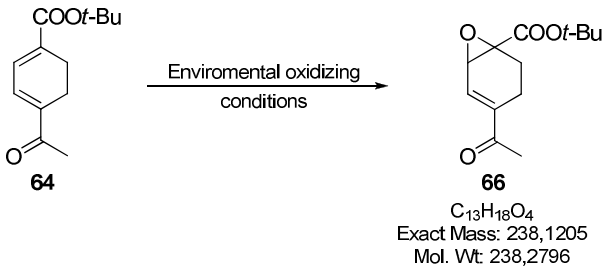
Entry 1:

Compound **64** (48.00 mg, 0.22 mmol) was dissolved in EtOH (5 mL) and it was added benzylamine (29.00 mg, 0.27 mmol). The reaction system was stirred and refluxed at 110ºC for 69 hours and followed it by TLC. The reaction mixture was cooled down and concentrated *in vacuo*. It was obtained 68 mg of crude whose purification was carried out by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (99:1- 70:30 v/v) gave starting material **64** (7.00 mg, 14%), benzylamine (24 mg) and an unknown compound that it could not be characterized.

Entry 2:

Compound **64** (89.5 mg, 0.40 mmol) was dissolved in EtOH (10 mL) and it was added benzylamine (0.07 mL, 0.64 mmol). The reaction system was stirred and refluxed at 110ºC for 32 hours and followed it by TLC. The reaction mixture was cooled down and concentrated *in vacuo*. It was obtained 98 mg of crude which ^{1}H NMR spectrum (R-300) showed the presence of starting material and the unknown compound, due that this compound cannot be isolated after purification by silica gel for flash column chromatography. It is proposed the formation of the imine which can be easily deprotected during purification.

Spontaneous oxidation of compound 64:



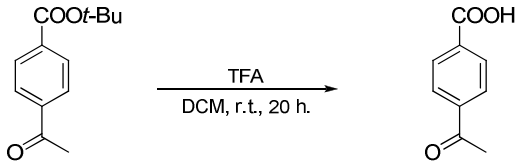
64 **66**

$C_{13}H_{18}O_4$
Exact Mass: 238,1205
Mol. Wt: 238,2796

Union of fractions (100 mg) that were stored during months from different reactions containing *tert*-butyl 5-oxo-cycloocta-1,3-dienecarboxylate **56** to be purified from compound **64** and **65** (148 mg) was performed. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (99:1-60:40 v/v) afforded also *tert*-butyl 4-acetyl-1,2-epoxi-cyclohex-3-ene-1-carboxylate **66** (13 mg); **IR υ_{max} (neat):** 2974 and 2920 (C-H), 1716 (C=O), 1373, 1295 (C-O), 1164, 852, 778, 709 cm^{-1} . **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.49 (9H, s, COOC(CH_3)$_3$); 1.95 (1H, m, H-6a); 1.96 (1H, m, H-5a); 2.32 (3H, s, COCH_3) 2.43 (1H, m, H-6b); 2.72 (1H, m, H-5b); 3.62 (1H, d, *J* 4.0, H-2); 6.89 (1H, dd, *J* 2.5 and 4.0, H-3). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 18.4 (CH_2, C-5); 21.1 (CH_2, C-6); 25.3 (CH_3, COCH_3); 28.1 (COOC(CH_3)$_3$); 52.0 (CH, C-2); 61.6 (C, C-1);

82.6 (C, COO*C*$(CH_3)_3$); 131.9 (CH, C-3); 143.7 (C, C-4); 168.0 (C, *C*OOC$(CH_3)_3$); 197.2 (C, *C*OCH_3). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{18}O_4Na$:** 261.1097; **found** 261.1103; **Δ** = 2.3 ppm.

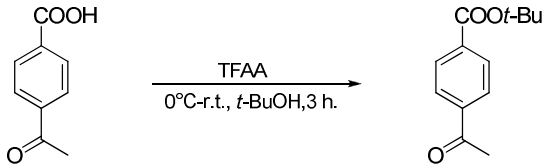
Deprotection reaction of the tert-butyl group in compound 65:



65

Compound **65** (10.00 mg, 0.05 mmol) was dissolved in DCM (2 mL) and it was added TFA (0.30 mL, 4.00 mmol). The reaction system was stirred at r.t. under Ar atmosphere for 20 hours. After, solvent and reagent were evaporated. The ^{1}H NMR spectrum of the crude showed the deprotected product (11.00 mg, 100%), which could be corroborated by comparison with its commercially available one.

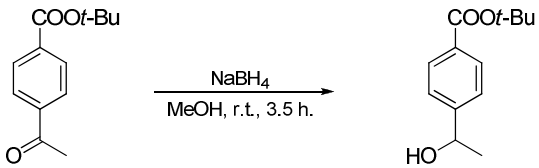
Esterification reaction of 4-acetylbenzoic acid comercial available:



€ **65**

To corroborate the proposed structure of compound **65**, it was used as a starting material 4-acetylbenzoic acid (98%) comercial available from Aldrich (100.00 mg, 0.61 mmol), TFAA (0.20 mL, 0.63 mmol) was added at 0°C. The reaction system was stirred for 15 min. and leaved it to reach r.t. After, at 0°C it was added *t*-BuOH (0.20 mL, 3.46 mmol). The reaction mixture was stirred for 3 hours, quenched with NaOH 10% (20 mL), extracted with Et_2O, washed with NaOH 1M. and $NaCl_{(sat)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum from the crude (75 mg, 56%) showed the formation of the proposed compound **26**, **^{1}H NMR (200 MHz; $CDCl_3$):** attached.

Reduction reaction of the carbonyl group in compound 65:



65 **67**

Compound **65** (11.00 mg, 0.05 mmol) was dissolved in MeOH (2mL) and $NaBH_4$ (1.00 mg, 0.03 mmol) was added. The reaction system was stirred at r.t. for 3.5 hours. After, the mixture was quenched with H_2O and some drops of HCl 2M., extracted with EtOAc, washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The ^1H NMR spectrum of the crude showed the formation of compound **67** (12.00 mg, 100%).

Hidrogenolysis reactions of tert-butyl-(benzylamino)-5-oxo-bicyclo[2.2.2]octane-1-carboxylate:

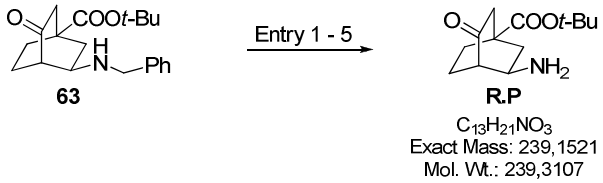


Table 17.

Entry	63 (mg, mmol)	Reaction conditions	Solvent	63%	R.P.%
1	12.60, 0.04	6.20 mg Pd/C, H_2 (4 atm.), 24 hours.	$CH_3COOH_{glacial}$ (1mL)	-	35 (Identified by I.R and ^1H NMR, no pure)
2	48.00, 0.15	19.40 mg Pd/C, H_2 (4 atm.), 24 hours.	$CH_3COOH_{glacial}$ (2mL)	25	Polymeric specie
3	24.00, 0.07	11.00 mg $Pd(OH)_2/C$, H_2 (4 atm.), 24 hours.	EtOAc (2mL)	100	-
4	21.50, 0.07	11.00 mg Pd/C, H_2 (4 atm.), 24 hours.	EtOAc (2mL)	79	-
5	17.00, 0.05	10.00 mg Pd/C, H_2 (4 atm.), 24 hours.	EtOH (2mL)	88	-

Procedure:

Entry 1:

In a dried vial for hydrogenation compound **63** (12.60 mg, 0.04 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in glacial acetic acid (1 mL), Pd/C (10 % Pd basis, 6.20 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2-1:1 v/v) gave (1*R*,4*R*) *tert*-butyl 3-amino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate **R.P** (3.00 mg, 35%). Due to its polarity, impurities and low quantity, it could not be fully characterized but the deprotection of the amine can be observed

in its **IR υ_{max} (neat):** 3386 (N-H), 2924 and 2853 (C-H), 1727 (C=O), 1460, 1260 (C-O), 1162, and 1072 cm^{-1}.

Entry 2:

Following general procedure for a hydrogenolysis reaction, compound **63** (48.00 mg, 0.15 mmol) was added, dissolved in glacial acetic acid (2 mL), Pd/C (10 % Pd basis, 19.40 mg) was added and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1- 1:1 v/v) gave compound **63** (12.00 mg, 25%) and a polymeric specie (15 mg) characteristic because of the wide signals in its **^{1}H NMR** spectrum and corroborated by mass spectroscopy.

Entry 3:

Compound **63** (24.00 mg, 0.07 mmol) was added, dissolved in EtOAc (2 mL), $Pd(OH)_2/C$ (20 % Pd basis, 11.00 mg) was added and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed recuperation of starting material **63** (24.00 mg, 100%).

Entry 4:

Compound **63** (21.50 mg, 0.07 mmol) was added, dissolved in EtOAc (2 mL), Pd/C (10 % Pd basis, 11.00 mg) was added and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed recuperation of starting material **63** (17.00 mg, 79%).

Entry 5:

In a dried vial for hydrogenation compound **63** (17.00 mg, 0.05 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in EtOH (2 mL), Pd/C (10 % Pd basis, 10.00 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed recuperation of starting material **63** (15.00 mg, 88%).

Reactions of tert-butyl-(1S,3R,4S,αR)- and (1S,3S,4S,αS)-3-N-α-methylbenzylamino-5-oxo-bicyclo[2.2.2]octane-1-carboxylate (+) and (-)-68 respectively with benzylamine:

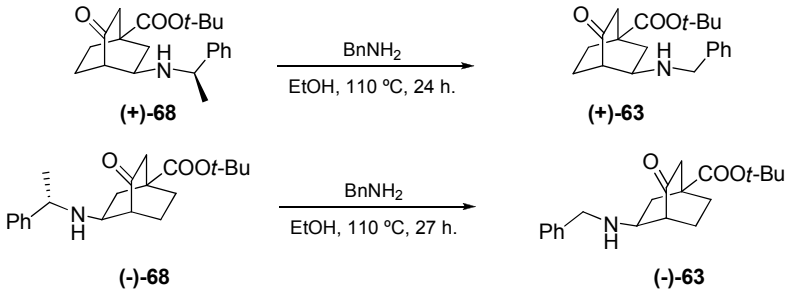


Table 18.

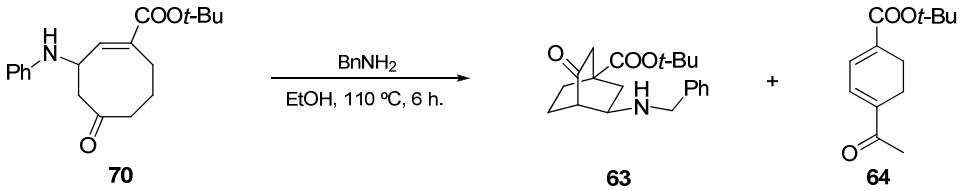
Entry	Starting material (mg, mmol)	Reaction conditions	Solvent	S.M. (mg, %)	63 (mg, %)	Rotation Power
1	**(+)-68** (23.00, 0.07)	$BnNH_2$ (10.00 mg, 0.10 mmol)	EtOH (5 mL)	**(+)-68** (4.00, 17%)	**(+)-63** (15.00, 82%)	$[\alpha]_D^{20}$= + 0.20 (*c* 0.58, $CHCl_3$)
2	**(-)-68** (27.00, 0.08)	$BnNH_2$ (15.00 mg, 0.14 mmol)	EtOH (6 mL)	-	**(-)-63** (22.11, 84%)	$[\alpha]_D^{20}$= - 3.30 (*c* 0.84, $CHCl_3$)

Procedure:

Entry 1 and 2:

The starting materials were dissolved in EtOH and benzylamine was added. The systems were stirred and refluxed at 110ºC for 24 and 27 hours, respectively. After the reaction systems were cooled down and evaporated under reduced pressure. It gave 30.00 mg (entry 1) and 41.00 mg (entry 2) of crude. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded as it shown in the table X compounds (+)-24 in 82% yield and (-)-24 in 84% yield and their rotation powers, respectively.

Addition of benzylamine to (E) tert-butyl 5-oxo-3-(phenylamino)-cycloocta-1-enecarboxylate 70:

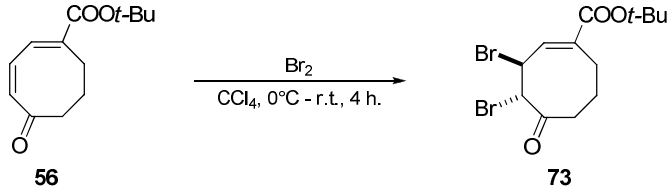


Following general procedure for the protection reaction of the carbonyl group, compound **70** (11.00 mg, 0.04 mmol) was dissolved in EtOH (2 mL) and benzylamine (6.00 mg, 0.06 mmol) was added. The system was stirred and refluxed at 110ºC for 6 hours. After the reaction system was

cooled down and evaporated under reduced pressure. It gave a mixture (14 mg) purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded compound **63** (6.00 mg, 53%) and compound **64** (3.80 mg, 47%).

3.5 Synthesis of (1*E*,3*E*) *tert*-butyl-4-bromo-5-oxo-cycloocta-1,3-diene carboxylate:

Bromination reaction of compound 56:

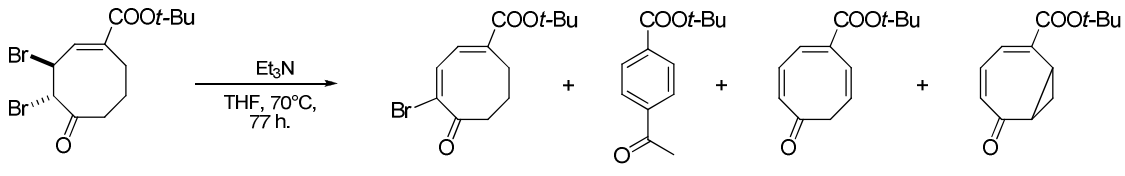


56 **73**

$C_{13}H_{18}Br_2O_3$
Exact Mass: 379,9623
Mol. Wt.: 382,0882

Compound **56** (27.00 mg, 0.12 mmol) was dissolved in CCl_4 (10 mL) and the reaction system was stirred and cooled down at 0°C. After, Br_2 (0.01 mL, 31 mmol) was added and stirred for 30 min, the ice bath was removed and stirred for 4 hours at r.t. The reaction mixture was dissolved in DCM (20 mL), washed with HCL 2M., $NaHCO_3$ $_{(sat.)}$, H_2O and $NaCL$ $_{(sat.)}$; dried over Na_2SO_4, filtered and concentrated *in vacuo*. It afforded (3*R**,4*R**,*E*) *tert*-butyl 3,4-dibromo-5-oxo-cycloocta-1-enecarboxylate **73** (43.00 mg, 91%), $\mathbf{[\alpha]_D^{20}}$**=** -0.33 (*c* 0.61, $CHCl_3$) which crystallizes in Hex/EtOAc (1:1 v/v), **mp** 161–162 ºC, **IR** $\mathbf{\upsilon_{max}}$ **(neat):** 2976 and 2930 (C-H) , 1712 (C=O), 1449 (C=C), 1369, 1292 (C-O), 1253, 1159, 1127, 1110 (C-Br) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.47 (9H, s, $COOC(CH_3)_3$); 2.00-3.02 (6H, m, H-6, H-7, H-8); 4.23 (1H, d, *J* 11.2, H-4); 5.01 (1H, dd, *J* 11.2 and 9.6, H-3); 6.80 (1H, d, *J* 9.6, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 27.1 (CH_2, C-7); 27.8 (CH_2, C-8); 28.2 (CH_3 x 3, $COOC(CH_3)_3$); 37.8 (CH_2, C-6); 46.8 (CH); 60.4 (CH); 82.2 (C, $COOC(CH_3)_3$); 137.5 (CH, C-2); 138.1 (C, C-1); 164.7 (C, $COOC(CH_3)_3$); 202.0 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{18}Br_2O_3$ [M+Na):** 402.9515; **found** 402.9543; **Δ** = 6.9 ppm. **R-X:** See annexe E.

Dehydrobromination reaction of compound 73:



73 **74** **65** **75** **76**

$C_{13}H_{17}BrO_3$
Exact Mass: 300,0361
Mol. Wt.: 301,1763

$C_{13}H_{16}O_3$
Exact Mass: 220,1099
Mol. Wt.: 220,2643

$C_{13}H_{16}O_3$
Exact Mass: 220,1099
Mol. Wt.: 220,2643

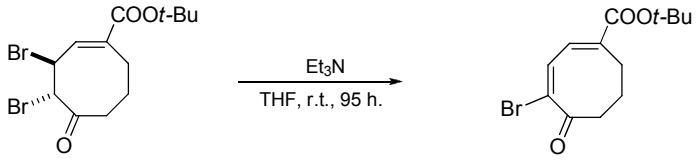
Compound **73** (13.00 mg, 0.03 mmol) was dissolved in THF (5 mL) and stirred at r.t. It was added triethylamine (5.00 mg, 0.05 mmol) and the reaction was followed by TLC for 24 hours. During this period it was not observed other spot diferent to the starting material so a reflux system was coupled and the reaction mixture was stirred at 70°C, after 77 hours reaction, it was observed by TLC three spots. At this point, it was added 1 equivalent of triethylamine and the system was refluxed for other 48 hours. After solvent and triethylamine excess were evaporated under reduced pressure. It gave a mixture (20 mg) that it was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5-70:30 v/v) afforded compound **65** (0.30 mg, 3%) and the following compounds:

(1*E*,2*E*) *tert*-butyl-4-bromo-5-oxo-cycloocta-1,3-dienecarboxylate **74** (3.00 mg, 18%), **IR υ_{max} (neat):** 2914 (C-H), 1707 (C=O), 1678 (C=O), 1457 (C=C), 1365, 1153, 1114, 872, 781 (C-Br) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.52 (9H, s, COOC(CH_3)$_3$), 2.15 (2H, m, H-7); 2.48 (2H, t, *J* 10.0, H-8); 2.70 (2H, t, *J* 10.0, H-6); 7.11 (1H, d, *J* 15.0, H-3); 7.40 (1H, d, *J* 10.0, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 26.9 (CH_2, C-7); 28.3 (CH_3 x 3, COOC(CH_3)$_3$); 32.9 (CH_2, C-8); 38.1(CH_2, C-6); 82.1 (C, COO*C*(CH_3)$_3$); 130.2 (C, C-1); 134.0 (CH, C-2); 138.5 (CH, C-3); 141.1 (C, C-4); 165.5 (C, *C*OOC(CH_3)$_3$); 197.3 (C, C-5). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{17}BrO_3$ [M+Na]:** 323.0253; **found** 323.0236; **Δ** = -5.3 ppm.

tert-butyl 5-oxo-cycloocta-1,3,7-trienecarboxylate **75** (2.00 mg, 19%), **IR υ_{max} (neat):** 2925 (C-H), 1783 (C=O), 1709 (C=O), 1385, 1369, 1279, 1257, 1160, 1093 (C=C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.55 (9H, s, COOC(CH_3)$_3$), 2.95-3.07 (2H, m, H-6); 5.87 (1H, q, *J* 10.2, H-7); 6.65 (1H, d, *J* 13.2, H-4); 6.68 (1H, d, *J* 10.2, H-8); 6.84 (1H, dd, *J* 12.2 and 7.2, H-3); 7.41 (1H, d, *J* 7.2, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 28.2 (CH_3 x 3, COOC(CH_3)$_3$); 43.7 (CH_2, C-6); 82.2 (C, COO*C*(CH_3)$_3$); 128.4 (CH, C-7); 129.8 (CH, C-8); 130.5 (C, C-1); 132.1 (CH, C-4); 135.8 (CH, C-3); 141.1 (CH, C-2); 173.8 (C, *C*OOC(CH_3)$_3$); 205.8 (C, C-5).

tert-butyl 6-oxo-bycicle[5.1.0]octa-2,4-diene-2-carboxylate **76** (1.00 mg, 10%), **IR υ_{max} (neat):** 3020 (C-H), 1694 (C=O), 1655 (C=O), 1280 (C-O), 1163, 1061 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.54 (9H, s, COOC(CH_3)$_3$), 1.60 (1H, ddd, *J* 4.6, 6.3 and 7.2, H-8a); 1.99 (1H, ddd, *J* 4.6, 9.0 and 13.5, H-8b); 2.55 (1H, ddd, *J* 1.5, 6.3 and 9.0, H-7); 2.72 (1H, ddd, *J* 1.5, 6.3 and 9.0, H-1); 6.13 (1H, d , *J* 12.5, H-5); 6.41 (1H, dd, *J* 7.8 and 12.5, H-4); 6.86 (1H, d, *J* 7.8, H-3). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 14.1 (CH_2, C-8); 23.4 (CH, C-1); 28.1 (CH_3 x 3, COOC(CH_3)$_3$); 44.4 (CH, C-7); 82.0 (C, COO*C*(CH_3)$_3$); 127.2 (CH, C-3); 131.4 (CH, C-5); 131.7 (CH, C-4); 141.1 (C, C-2); 165.6 (C, *C*OOC(CH_3)$_3$); 198.4 (C, C-6). **HRMS (ESI) *m/z* calcd. for $C_{13}H_{16}O_3$ [M+Na]:** 243.0992; **found** 243.0998; **Δ** = 1.9 ppm.

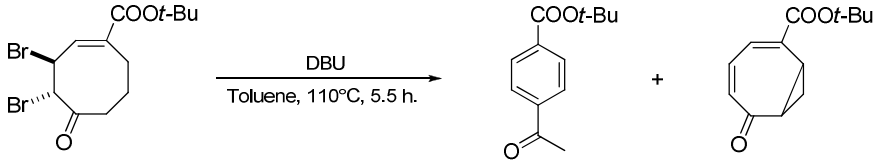
Optimization of the Dehydrobromination reaction:



73 **74**

Compound **73** (21.00 mg, 0.06 mmol) was dissolved in THF (5 mL) and triethylamine (23.00 mg, 0.20 mmol) was added. It was coupled to the reaction mixture flask a $CaCl_2$ trap and the system was stirred for for 95 hours at r.t. After solvent and triethylamine excess were evaporated under reduced pressure. It was obtained a crude (16 mg) that it was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-7:3 v/v) afforded compound **74** (14 mg, 83%).

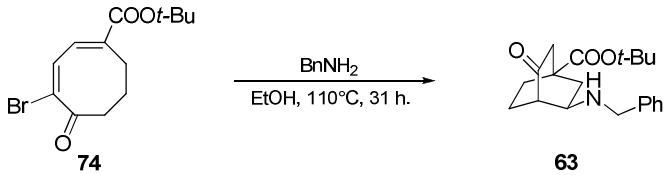
Addition of of 1,8-Diazabicyclo[5.4.0]undec-7-ene:



73 **65** **76**

Compound **73** (21.00 mg, 0.06 mmol) was dissolved in toluene (5 mL) and DBU (96.00 mg, 0.60 mmol) was added. The reaction system was stirred at 110°C for 5.5 hours. After, the reaction mixture was diluted with DCM and HCl 10%, extracted with DCM, washed with $NaHCO_{3\ (sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. It gave a mixture (17 mg) that it was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5-70:30 v/v) afforded the recovery of starting material **73** (10.00 mg, 48%), compound **65** (3.00 mg, 23%) and compound **76** (2.00 mg, 15%).

Reaction of (1E,3E) tert-butyl-4-bromo-5-oxo-cycloocta-1,3-dienecarboxylate 74 with benzylamine:

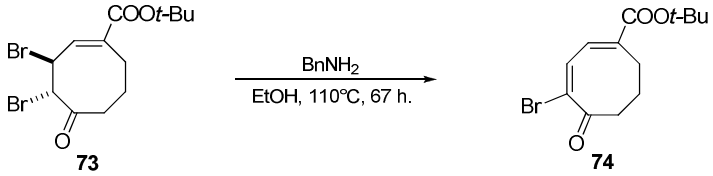


74 **63**

Compound **74** (14.00 mg, 0.05 mmol) was dissolved in EtOH (5 mL) and it was added benzylamine (14.00 mg, 0.13 mmol). The reaction system was stirred at 110°C for 31 hours. After, solvent and benzylamine excess were evaporated under reduced pressure. It was obtained a crude

(34 mg) which presents the posibility of a salt formation, for this reason it was dissolved in Et_2O, cooled down at 0°C and filtered through a sintered glass funnel layered with 1 cm of celite. The combined organic extracts were washed with $NaHCO_{3\,(sat.)}$, dried over Na_2SO_4 and concentrated *in vacuo*. It gave a crude (24 mg) that it was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) afforded compound **63** (2.00 mg, 15%).

Reaction of tert-butyl-3,4-dibromo-5-oxo-cycloocta-1-enecarboxylate 73 with benzylamine:

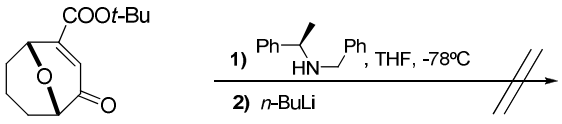


73 **74**

Compound **73** (16.00 mg, 0.04 mmol) was dissolved in EtOH (5 mL) and it was added benzylamine (7.00 mg, 0.06 mmol). The reaction system was stirred at 110°C for 67 hours. After, solvent and benzylamine excess were evaporated under reduced pressure. It was obtained a crude (24 mg) which presents the posibility of a salt formation, for this reason it was dissolved in Et_2O, cooled down at 0°C and filtered through a sintered glass funnel layered with 1 cm of celite. The combined organic extracts were washed with $NaHCO_{3\,(sat.)}$, dried over Na_2SO_4 and concentrated *in vacuo*. It gave a crude (13 mg) that it was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2-70:30 v/v) afforded compound **74** (2.00 mg, 15%).

3.6 Reactivity of *tert*-butyl 4-oxo-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate 60:

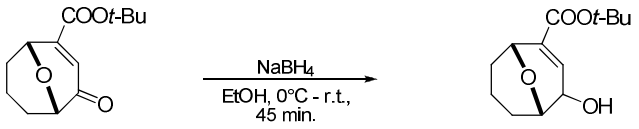
Addition of (R)-N-benzyl-N-α-methylbenzylamine:



60

Following general procedure for the Michael addition reaction, compound **60** (35.20 mg, 0.15 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.06 mL, 0.27 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.15 mL, 0.24 mmol). After 3 hours reaction it was not observed any change in the TLC, for this reason the reaction was quenched with NH_4CL (2mL) and worked it up recovering starting material.

Reduction reaction of compound 60 with Sodium borohydride:

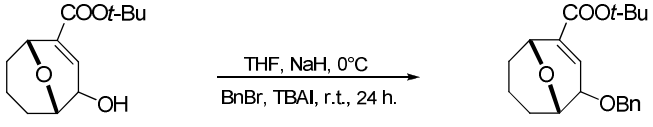


60 **77**

$C_{13}H_{20}O_4$
Exact Mass: 240,1362
Mol. Wt.: 240,2955

Compound **60** (24.00 mg, 0.10 mmol) was dissolved in EtOH (2mL) and $NaBH_4$ (1.50 mg, 0.04 mmol) was added at 0°C. The reaction system was stirred at r.t. for 45 min.. After, the mixture was quenched with H_2O and some drops of HCl 2M., extracted with EtOAc, washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-6:4 v/v) gave *tert*-butyl 4-hydroxy-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate **77** (24.0 mg, 100%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.45 (9H, s, COOC(CH_3)$_3$); 1.66 -2.02 (6H, H-6, H-7 and H-8); 2.54 (1H, broad singlet, H-4); 4.05 (1H, t, *J* 5.2, H-5); 4.62 (1H, dd, *J* 6.2, 4.4, H-1); 6.96 (1H, d, *J* 2.6,H-3).**^{13}C NMR (50 MHz; $CDCl_3$):** δ 15.2 (CH_2, C-7); 24.1 (CH_2, C-8); 27.8 (CH_2, C-6); 28.3 (CH_3 x 3, COOC(CH_3)$_3$); 66.0 (CH, C-5); 67.4 (CH, C-1); 69.8 (CH, C-4); 81.3 (C, COO*C*(CH_3)$_3$); 134.2 (C, C-2); 140.6 (CH, C-3); 164.1 (C, *C*OOC(CH_3)$_3$

Protective reaction of the alcohol group in compound 77:



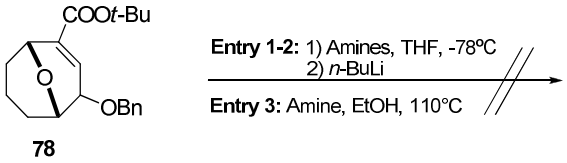
77 **78**

$C_{20}H_{26}O_4$
Exact Mass: 330,1831
Mol. Wt.: 330,4180

In a dried flask under Ar atmosphere, compound **77** (24.20 mg, 0.10 mmol) was added and dissolved in THF (3 mL). The reaction system was stirred at 0°C and NaH (4.80 mg, 0.12 mmol) previously dissolved in a minimum quantity of THF was added. After, at r.t. BnBr (0.02 mL, 0.20 mmol) and TBAI (3.70 mg, 0.01 mmol) were added and the reaction mixture was stirred for 24 hours. The system was quenched with H_2O at 0°C and extracted with EtOAc. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5-70:30 v/v) gave *tert*-butyl 4-benzyloxy-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate **78** (24.4 mg, 74%). **IR υ_{max} (neat):** 2936 (C-H), 1706 (C=O), 1167 (C-O), 1045 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.47 (9H, s, COOC(CH_3)$_3$); 1.66-2.04 (6H, H-6, H-7 and H-8); 4.17 (1H, t, *J* 5.8, H-1); 4.38 (1H, m, H-5); 4.42 (1H, m, H-4); 4.60 (2H, s, CH_2Ph); 7.06 (1H, d, *J* 2.6, H-3); 7.35 (5H, H-Ar). **^{13}C**

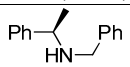
NMR (50 MHz; $CDCl_3$): δ 15.4 (CH_2, C-7); 24.9 (CH_2, C-8); 27.7 (CH_2, C-6); 28.3 (CH_3 x 3, COOC(CH_3)$_3$); 67.6 (CH, C-1); 68.4 (CH, C-5); 71.7 (CH_2, CH_2Ph); 72.6 (CH, C-4); 81.1 (C, COOC(CH_3)$_3$); 127.9, 128.1 and 128.7 (CH x 5, Ph) ; 134.4 (C, C-2); 138.1(C, C_{ipso}); 138.4 (CH, C-3); 164.1(C, COOC(CH_3)$_3$. **HRMS [M+Na] *m/z* calcd. for $C_{20}H_{26}O_4Na$:** 353.1723; **found** 353.1718; **Δ** = -1.4 ppm.

Addition of (±)-α-Methyl-benzylamine and (R)-N-benzyl-N-α-methylbenzylamine to compound 78:



78

Table 19.

Entry	78 (mg, mmol)/ solvent	Amine (mg, mmol) / solvent	*n*-BuLi 1.6 M. (mL, mmol)	T. (°C)	t .(h.)	S.M. (%)
1	20.70, 0.06 THF (1mL)	 13.20 mg, 0.11 mmol THF (1 mL)	0.06, 0.10	-78	2	100
2	21.00, 0.06 THF (1 mL)	 23.20 mg, 0.11 mmol THF (1 mL)	0.06, 0.10	-78	3.5	100
3	21.00, 0.06 EtOH (3 mL)	 13.20 mg, 0.11 mmol	-	110	36	100

Procedure:

Entry 1:

Following general procedure for the Michael addition, compound **78** (20.70 mg, 0.06 mmol) was dissolved in THF (1 mL), (±)-α-Methyl-benzylamine (13.20 mg, 0.11 mmol) was dissolved in THF (1 mL) and *n*-BuLi (1.6 M., 0.06 mL, 0.10 mmol) were set to react at -78°C. After 2 hours reaction it was not observed any change in the TLC, for this reason the reaction mixture was quenched with NH_4CL (2mL) and worked it up recovering starting material.

Entry 2:

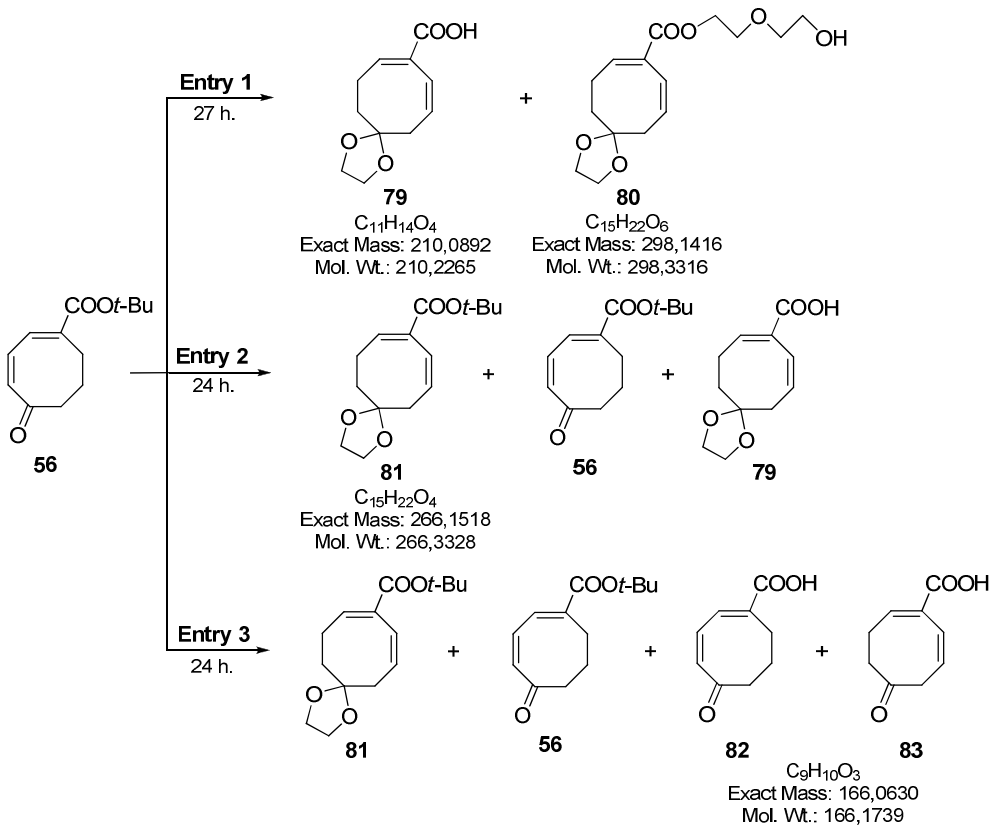
Following general procedure for the Michael addition, compound **78** (21.00 mg, 0.06 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (23.20 mg, 0.11 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.06 mL, 0.10 mmol) were set to react. After 3.5 hours reaction it was not observed any change in the TLC, for this reason the reaction mixture was quenched with NH_4CL (2mL) and worked it up recovering starting material.

Entry 3:

Following general procedure for the protection reaction of the carbonyl group, compound **78** (21.00 mg, 0.06 mmol) was dissolved in EtOH (3 mL) and (±)-α-Methyl-benzylamine (12.40 mg, 0.10 mmol) was added. The system was stirred and refluxed at 110ºC for 36 hours. After the reaction system was cooled down and evaporated under reduced pressure, it afforded the recovery of starting material.

4. Approximation to the synthesis of Anatoxin-*a*:

Protective reaction of the carbonyl group in compound 56:



Procedure:

Entry 1:

Using a Dean-Stark apparatus, compound **56** (266.0 mg, 1.2 mmol) was dissolved in Benzene. 1,2-Ethanediol (0.7 mL, 12.0 mmol) and PTSA (11.40 mg, 0.06 mmol) were added and the reaction system was stirred and refluxed at 110°C for 27 hours. After, the solution was evaporated under reduced pressure, dissolved in Et_2O, washed with NaOH 10% and H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Due to the reduction of the ester signal in the ^{1}H NMR spectrum of the crude, the inorganic layer was treated with HCl c. reaching pH acid, extracted with DCM, washed with H_2O, dried and concentrated, the ^{1}H NMR spectrum from the inorganic layer showed the presence of 5,5-ethylenedioxycycloocta-2,7-diene-1-carboxylic acid **79** (52 mg, 21%) which was fully characterized by its methyl ester **84** added below.

The crude extracted from the organic layer was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1-0:10 v/v) gave 2-hydroxyethoxy-ethyl 5,5-ethylenedioxycycloocta-2,7-diene-1-carboxylate **80** (27 mg, 8%), **IR υ_{max} (neat):** 3498 (O-H), 2951 and 2878 (C-H), 1716 (C=O), 1257 (C-O), 1129, 1064 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 2.24-2.46 (6H, m, H-3, H-4, H-6); 3.58-3.63 (2H, m, CH_CCH_DOH); 3.66-3.80 (4H, m, $COOCH_ACH_BOCH_C$); 3.90-4.02 (4H, m, OCH_2CH_2O); 4.24-4.38 (2H, m, $COOCH_ACH_B$); 5.77-5.96 (1H, m, H-7); 6.26-6.39 (1H, d, *J* 10, H-8); 7.01-7.13 (1H, t, *J* 8, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 26.0 (CH_2, C-3); 31.6 (CH_2, C-4); 36.6 (CH_2, C-6); 62.0 (CH_2, CH_CCH_DOH); 64.1 (CH_2, CH_CCH_D); 64.7 (CH_2 x 2, OCH_2CH_2O); 69.4 (CH_2, $COOCH_ACH_B$); 72.5 (CH_2, $COOCH_ACH_B$); 108.3 (C, C-5); 126.8 (CH, C-7); 128.8 (C, C-1); 129.5 (CH, C-8); 143.6 (CH, C-2); 167.4 (C, COO). **HRMS [M+Na] *m/z* calcd. for $C_{15}H_{22}O_6$:** 321.1308; **found** 321.1309; **Δ** = -0.3 ppm.

Entry 2:

Following general procedure for the protection of the carbonyl group as a dioxolane, compound **56** (76.40 mg, 0.34 mmol) was dissolved in Benzene. 1,2-Ethanediol (0.04 mL, 0.70 mmol) and PTSA (3.80 mg, 0.02 mmol) were added, the reaction system was refluxed at 110°C for 24 hours. After, the solution was evaporated under reduced pressure, dissolved in EtOAc, washed with $NaHCO_3$ 6%, H_2O and NaCl $_{(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude (47 mg, ≈ 61%) showed the presence of starting material and *tert*-butyl 5,5-ethylenedioxycycloocta-1,7-diene-1-carboxylate **81** in a relation 1:3 respectively.

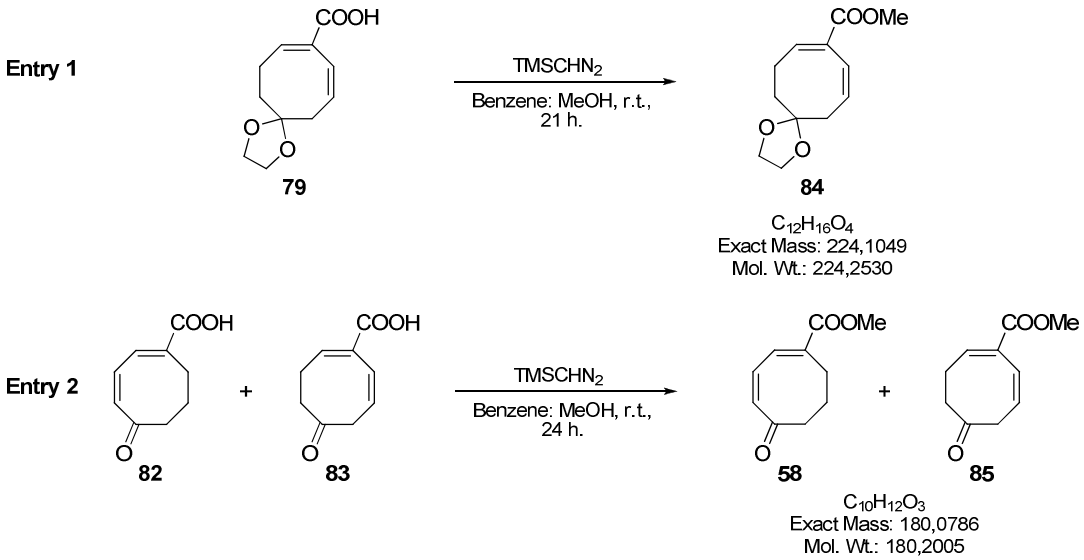
The inorganic layer was treated with HCl c. reaching pH acid, extracted with DCM, washed with H_2O, dried and concentrated under reduced pressure, gave the acid **79** (20 .1 mg, 34%).

Entry 3:

Following general procedure for the protection of the carbonyl group as a dioxolane, compound **20** (120.00 mg, 0.54 mmol) was dissolved in Benzene. 1,2-Ethanediol (0.06 mL, 1.08 mmol) and PTSA (5.70 mg, 0.03 mmol) were added, the reaction system was refluxed for 24 hours. After, the solution was evaporated under reduced pressure, dissolved in EtOAc, washed with $NaHCO_3$ 6%, H_2O and NaCl $_{(sat.)}$, dried, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude (61.40 mg, ≈ 51%) showed the presence of starting material and the protected ester **81** in a relation 1:3 respectively.

The inorganic layer was treated with HCl c. reaching pH acid, extracted with DCM, washed with H_2O, dried and concentrated gave a mixture of the carboxylic acids **82** and **83** (30.0 mg, 38%), this crude was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (1:1 v/v) – $CHCl_3$/MeOH (9:1 v/v) and gave 5-oxo-cycloocta-1,3-diene carboxylic acid previously identified and full characterized as its *tert*-butyl or methyl ester and 5-oxo-cycloocta-1,7-diene carboxylic acid **83** (9 mg, 11%), **IR υ_{max} (neat):** 2932 (C-H), 1708 (C=O), 1249 (C-O), 1037 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 2.59 (2H, m, H-3); 3.18 (2H, d, *J* 7.4, H-6); 3.76 (2H, m, H-4); 6.01 (1H, m, H-7); 6.36 (1H, d, *J* 11, H-8); 7.33 (1H, t, *J* 7.2, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 26.2 (CH_2, C-3); 38.1 (CH_2, C-4); 44.2 (CH_2, C-6); 126.9 (CH, C-7); 128.1 (CH, C-8); 134.8 (C, C-5); 143.7 (CH, C-2); 168.5 (C, C-1); 206.7 (C, *C*OOH). **HRMS (Cl^+) *m/z* calcd. for $C_9H_{10}O_3$:** 189.0522; **found** 189.0516; **Δ** = -3.2 ppm.

Esterification reaction of the mixtures containing the acids:



Procedure:

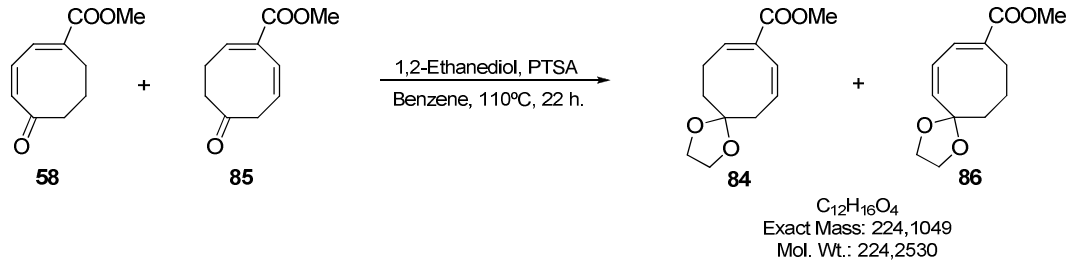
Entry 1:

Under Ar atmosphere compound **79** (18.10 mg, 0.09 mmol) was dissolved in a mixture of Benzene/MeOH (1:1 v/v, 1 mL) and $TMSCHN_2$ 2.0 M (0.05 mL, 0.10 mmol) was added. The reaction system was stirred at r.t. for 21 hours. After, the solution was evaporated under reduced pressure. The residue was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl 5,5-ethylenedioxycycloocta-1,7-diene-1-carboxylate **84** (18.3 mg, 94%), **IR υ_{max} (neat):** 2951 (C-H), 1723 (C=O), 1430, 1256 (C-O), 1065 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.78-1.85 (2H, m, H-3); 2.35-2.49 (4H, m, H-4 and H-6); 3.75 (3H, s, COO*Me*); 3.93-4.01 (4H, m, O*C*H_2*C*H_2O); 5.79-5.96 (1H, m, H-7); 6.34 (1H, d, *J* 11, H-8); 7.02-7.09 (1H, t, *J* 6.6, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 25.9 (CH_2, C-3); 31.6 (CH_2, C-4); 36.6 (CH_2, C-6); 52.2 (CH_3, COO*Me*); 64.7 (CH_2 x 2, O*C*H_2*C*H_2O); 108.3 (C, C-5); 126.9 (CH, C-7); 128.8 (C, C-1); 129.4 (CH, C-8); 143.3 (CH, C-2); 167.9 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{16}O_4Na$:** 247.0941; **found** 247.0946; **Δ** = 2.0 ppm.

Entry 2:

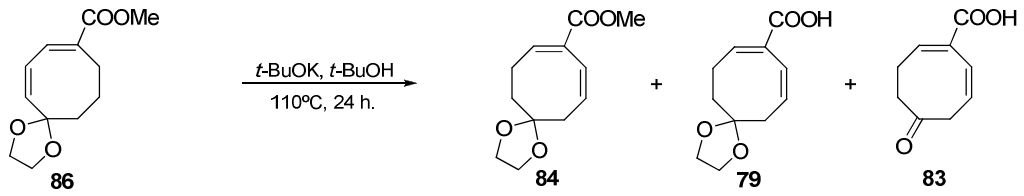
Under Ar atmosphere a mixture of the acids **82** and **83** (12.90 mg, 0.08 mmol) was dissolved in a mixture of Benzene/MeOH (1:1 v/v, 1 mL) and $TMSCHN_2$ 2.0 M (0.1 mL, 0.16 mmol) was added. The reaction system was stirred at r.t. for 24 hours. After, the solution was evaporated under reduced pressure. The residue was purified by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl 5-oxo-cycloocta-1,3-diene-1-carboxylate **58** (8 mg, 63%) and Methyl 5-oxo-cycloocta-1,7-diene-1-carboxylate **85** (4 mg, 32%), **IR υ_{max} (neat):** 2947 (C-H), 1708 (C=O), 1438, 1264 (C-O), 1056 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 2.47-2.63 (4H, m, H-3 and H-4); 3.16 (2H, d, *J* 7.4, H-6); 3.77 (3H, s, COO*Me*); 5.92-6.02 (1H, m, H-7); 6.34 (1H, d, *J* 11, H-8); 7.19-7.26 (1H, t, *J* 6.8, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 26.0 (CH_2, C-3); 38.3 (CH_2, C-4); 44.2 (CH_2, C-6); 52.1 (CH_3, COO*Me*); 127.4 (CH, C-7); 127.9 (CH, C-8); 130.8 (C, C-5); 141.7 (CH, C-2); 166.8 (C, C-1); 206.9 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{10}H_{12}O_3Na$:** 203.0678; **found** 203.0667; **Δ** = -5.4 ppm.

Protective reaction of the carbonyl group in a mixture containing the unsaturated methyl-5-oxo-esters:



Following general procedure for the protection reaction of the carbonyl group as a dioxolane, a mixture of the esters **58** and **85** (14.50 mg, 0.07 mmol) was dissolved in Benzene. 1,2-Ethanediol (0.01 mL, 0.13 mmol) and PTSA (0.62 mg, 0.01 mmol) were added, the reaction system was refluxed for 22 hours. After, the solution was evaporated under reduced pressure, dissolved in EtOAc, washed with $NaHCO_3$ 6%, H_2O and NaCl $_{(sat.)}$, dried, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude (15.7 mg) showed the presence of the two protected ester **84** and **86** in relation 13:1 respectively. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 – 90:10 v/v) gave the unsaturated ester 1,7-**84** (14.0 mg, 89%) and Methyl 5,5-ethylenedioxycycloocta-1,3-diene-1-carboxylate **86** (1.0 mg, 7%), **IR υ_{max} (neat):** 2951 and 2882 (C-H), 1713 (C=O), 1272 and 1223 (C-O), 1098 and 1042 (C-O-C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.72 (4H, m, H-6 and H-7); 2.45 (2H, m, H-8); 3.75 (3H, s, COO*Me*); 3.94-4.04 (4H, m, O*C*H_2*C*H_2O); 5.59 (1H, d, *J* 12.6, H-4); 5.89 (1H, dd, *J* 12.6 and 5.2, H-3); 7.20 (1H, d, *J* 5.2, H-2). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.3 (CH_2, C-7); 25.3 (CH_2, C-8); 31.1 (CH_2, C-6); 52.2 (CH_3, COO*Me*); 65.0 (CH_2 x 2, O*C*H_2*C*H_2O); 108.7 (C, C-5); 124.5 (CH, C-3); 133.6 (C, C-1); 134.6 (CH, C-4); 136.6 (CH, C-2); 167.8 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{16}O_4Na$:** 247.0941; **found** 247.0938; **Δ** = -1.2 ppm.

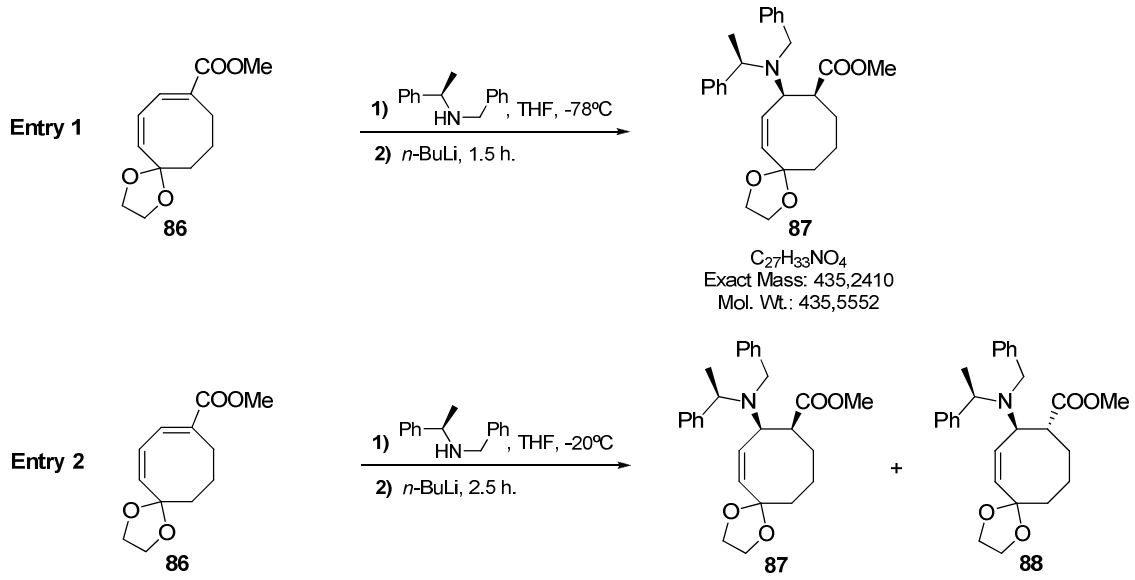
Migration reaction of the double bond:



Compound **86** (25.00 mg, 0.11 mmol) was dissolved in *t*-BuOH (5 mL) and *t*-BuOK (7.11 mg, 0.06 mmol) was added. The reaction system was stirred and refluxed at 110°C for 24 hours. After the *t*-BuOH was evaporated under reduced pressure, diluted in DCM and washed with H_2O and NaCl $_{(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo* gave the crude (22 mg, 89%)

which showed in its ^{1}H NMR spectrum compound **84.** Due to the high possibility of deprotection, the inorganic layer was acidified with HCl c. and extracted with DCM; it was observed in its ^{1}H NMR spectrum of the crude the presence of the acids **79** and **83** in a 1:1 mixture (3 mg, 11%).This reaction was submitted again using *t*-BuOK (sublimated). It was observed the same results in contrast to a slight increase in the amount of the hydrolysis products.

Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 86:



Procedure:

Entry 1:

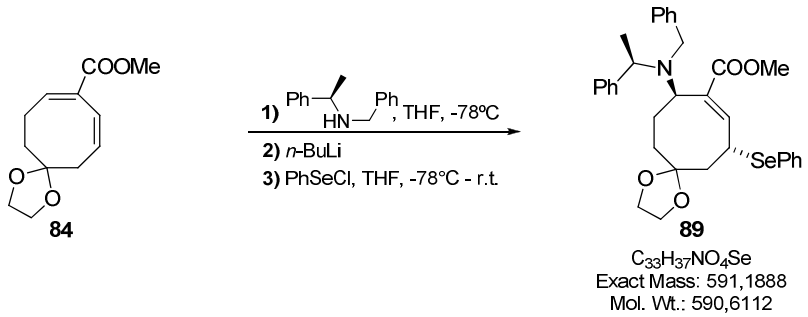
Following general procedure for the Michael addition reaction, compound **86** (35.00 mg, 0.16 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.20 mL, 0.96 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.60 mL, 0.93 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred at -78°C for 1.5 hours. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino 5,5-ethylenedioxycycloocta-3-ene-1-carboxylate **87** (22.5 mg, 32%), $[\alpha]_D^{20}$ = +19.3 (*c* 0.15, $CHCl_3$); **IR υ_{max} (neat):** 2932 and 2877 (C-H), 1726 (C=O), 1163 and 1072 (C-O-C), 701 (C-H, Ph) cm^{-1}. **^{1}H NMR (100 MHz; $CDCl_3$):** δ 1.35 (3H, d, *J* 6.6, C(α)*Me*); 1.43-1.75 (6H, m, H-6, H-7 and H-8); 2.39-2.50 (1H, m, H-1); 3.52 (3H, s, COO*Me*); 3.77 (1H, m, H-2); 3.64 (1H, AB, J_{AB} 17.1, NCH_ACH_BPh); 3.84 (1H, AB, J_{AB} 17.1, NCH_ACH_BPh); 4.03 (4H, m, OCH_2CH_2O); 4.52 (1H, q, *J* 5.4, C(α)*H*); 5.73 (1H, d, *J* 12.2, H-4); 6.04 (1H, dd, *J* 12.2 and 10.0, H-3); 7.20-7.49 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 12.1 (CH_3, N(α)*Me*); 20.2 (CH_2, C-7); 29.7 (CH_2, C-8); 41.0 (CH_2, C-6); 51.8 (CH_3, COO*Me*); 52.1 (CH_2, N-*C*H_2); 52.6 (CH, C-1); 54.3 (CH, N(α)*C*H); 56.7 (CH, C-2); 64.0 (CH_2, O*C*H_2CH_2O);

65.2 (CH_2, OCH_2CH_2O); 109.7 (C, C-5); 128.0, 128.4, 128.5 and 128.6 (CH x 10, Ar); 131.6 (CH, C-4); 133.8 (CH, C-3); 142.0 (C, C_{ipso}, CH_2Ph); 144.0 (C, C_{ipso}, CH*Ph*); 176.0 (C, *C*OOMe). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{27}H_{34}NO_4$:** 436.2482; **found** 436.2464; **Δ** = -4.1 ppm.

Entry 2:

Following previous general procedure, compound **86** (121.00 mg, 0.54 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.70 mL, 3.24 mmol) in THF (2 mL) and *n*-BuLi (1.6 M., 2.00 mL, 3.13 mmol) were set to react. After the addition of the unsaturated compound, the reaction was stirred at -20°C for 2.5 hours. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl (1*S*,2*R*,α*R*) carboxylate **87** (17.0 mg, 7%) and Methyl (1*R*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino 5,5-ethylenedioxycycloocta-3-ene-1-carboxylate **88** (6.0 mg, 3%), $[\alpha]_D^{20}$ = -1.3 (*c* 0.48, $CHCl_3$); **IR υ_{max} (neat):** 2927 (C-H), 1727 (C=O), 1445, 1381 (C-O), 1099 (C-OC) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.36 (3H, d, *J* 6.6, C(α)*Me*); 1.43-1.85 (6H, m, H-6, H-7 and H-8); .2.68-2.75 (1H, m, H-1); 3.35 (3H, s, COO*Me*); 3.62-3.84 (2H, m, NCH_ACH_BPh); 4.03 (4H, m, OCH_2CH_2O); 4.33 (1H, q, *J* 6.8, C(α)*H*); 4.71 (1H, dd, *J* 12.0 and 8.0, H-2); 5.70-5.91 (2H, m, H-4 and H-3); 7.14-7.44 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 13.6 (CH_3, N(α)*Me*); 18.5 (CH_2, C-7); 27.1 (CH_2, C-8); 39.0 (CH_2, C-6); 49.1 (CH, C-1); 50.7 (CH_2, N-*C*H_2); 51.4 (CH_3, COO*Me*); 54.1 (CH, N(α)*C*H); 57.7 (CH, C-2); 64.3 (CH_2, OCH_2CH_2O); 65.3 (CH_2, OCH_2CH_2O); 109.3 (C, C-5); 126.7-129.3 (CH x 10, Ar); 130.9 (CH, C-4); 133.6 (CH, C-3); 141.1 (C, C_{ipso}, CH_2Ph); 143.9 (C, C_{ipso}, CH*Ph*); 175.1 (C, *C*OOMe). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{27}H_{34}NO_4$:** 436.2482; **found** 436.2503; **Δ** = 4.8 ppm.

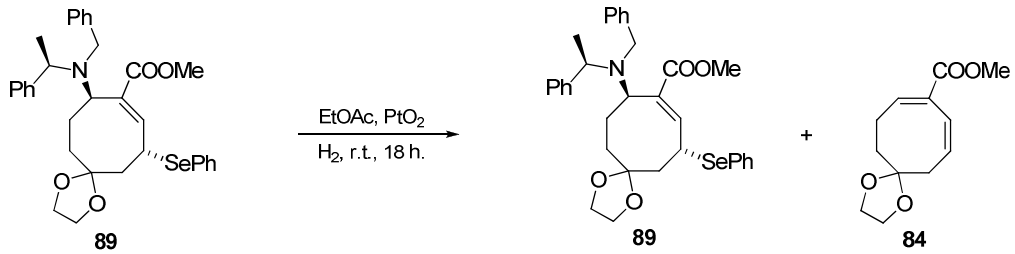
Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 84 and addition of phenylselenyl chloride in situ:



Following general procedure for the Michael addition reaction, compound **84** (48.00 mg, 0.21 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.14 mL, 0.69 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.40 mL, 0.63 mmol) were added. After the addition of the unsaturated

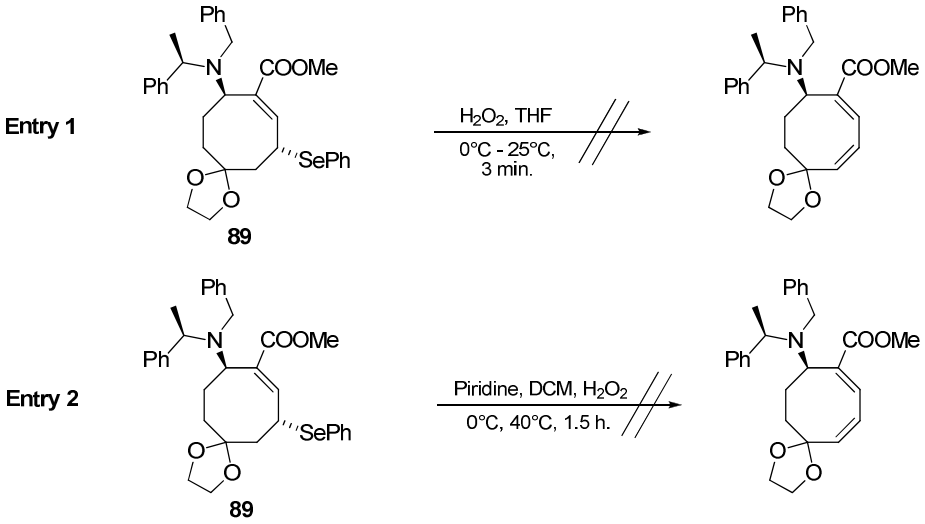
compound, the reaction was stirred for 2 hours and PhSeCl (132.00 mg, 0.69 mmol) was added, previously dissolved in THF (1 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred until the system reached r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave Methyl (2*R*,7*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino 5,5-ethylenedioxy 7-phenylselenylcycloocta-8-ene-1-carboxylate **89** (34.1 mg, 29%); **IR υ_{max} (neat):** 2948 (C-H), 1720 (C=O), 1449, 1279 (C-O), 1147 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.38 (3H, d, *J* 6.8, N(α)*Me*); 1.50-1.75 (2H, m, H-6); 1.75-1.90 (3H, m, H-3 and H-4a); 2.01-2.05 (1H, dt, *J* 13.3 and 2.1, H-4b); 3.66-3.70 (1H, m, H-7); 3.65-3.90 (6H, m, N-CH_2 and OCH_2CH_2O); 3.74 (3H, s, COO*Me*); 3.95-4.05 (1H, m, H-2); 3.99-4.07 (1H, q, *J* 6.6, CH(α)); 6.32 (1H, d, *J* 9.3, H-8); 7.17-7.52 (15H, m, *H*-Ar) **^{13}C NMR (50 MHz; $CDCl_3$):** δ 15.9 (CH_3, N(α)*Me*); 27.6 (CH_2, C-4); 34.5 (CH, C-7); 35.1 (CH_2, C-6); 47.9 (CH_2, C-3); 51.1 (CH_2, N-*C*H_2); 51.8 (CH_3, COO*Me*); 57.1 (CH, N(α)*C*H); 58.3 (CH, C-2); 63.7 (CH_2, OCH$_2$*C*H$_2$O); 65.2 (CH_2, O*C*H$_2$CH$_2$O); 110.2 (C, C-5); 126.4-129.3 (CH x 10, Ar); 128.3 (C, C-1); 135.3 (CH x 5) 136.9(C, C_{ipso}, CHSe*Ph*) ; 138.8 (CH, C-8); 143.1 (C, C_{ipso}, CH_2*Ph*); 143.4 (C, C_{ipso}, CH*Ph*); 168.6 (C, *C*OOMe). **HRMS [M+H]$^+$ *m/z* calcd. for $C_{33}H_{38}NO_4Se$:** 592.1961; **found** 592.1938; **Δ** = -3.9 ppm.

Hydrogenation reaction of compound 89:



In a dry flask was measured compound **89** (33.30 mg, 0.06 mmol) and dissolved in EtOAc (4 mL), after it was added PtO_2 (12.70 mg, 0.06 mmol). The reaction system was purged with H_2 and stirred under H_2 atmosphere at r.t. for 18 hours. Purification by silica gel for flash column chromatography (60Å. 40-63 µm) Hex/EtOAc (9:1 – 7:3 v/v) gave recovery of starting material (15 mg, 45%) and the unsaturated ester **84** (2 mg, 15%).

Elimination reaction of the fragment –SePh:



Procedure:

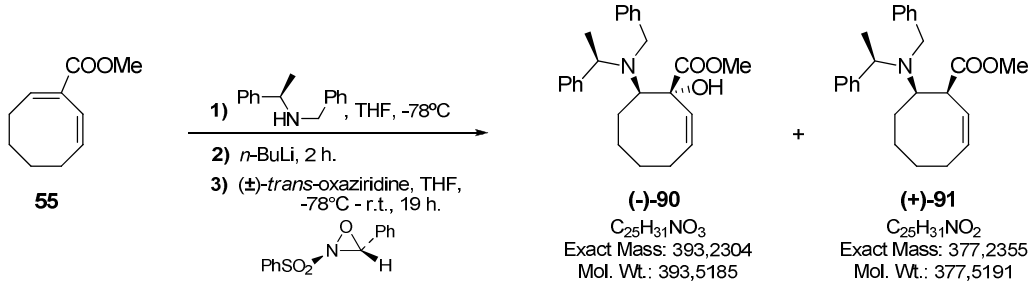
Entry 1:

Under Ar atmosphere, compound **89** (15.7 mg, 0.03 mmol) in THF (1.5ml) at 0°c was added dropwise H_2O_2 (30% w/v aq., 0.01 mL). The resulting yellow solution was stirred at 0°C for 3 min., the ice-water bath was removed and the reaction was stirred at 25°C for another 10 min, diluted with Et_2O and washed with $NaHCO_{3\,(sat.)}$ and $NaCl_{\,(sat.)}$. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude (11.4 mg) showed the recovery of starting material.

Entry 2:

Compound **89** (11.40 mg, 0.02 mmol) was dissolved in DCM (4 mL) at 0°C; Pyridine (0.01 mL, 0.04 mmol) and H_2O_2 (30% w/v aq., 0.04 mL) were added. The ice-water bath was removed and the system was refluxed at 40°C for 1.5 hours. After, the reaction mixture was diluted with H_2O and extracted with DCM, washed with $NaHCO_{3\,(sat.)}$ and $NaCl_{\,(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ^1H NMR spectrum of the crude (12.0 mg) showed the recovery of starting material.

Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 55 and addition* of (±)-trans-2-(*phenylsulfonyl)-3-phenyloxaziridine in situ:



Following general procedure for the Michael addition reaction, compound **55** (105.00 mg, 0.63 mmol) in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.27 mL, 1.30 mmol) in THF (1 mL) and *n*-BuLi (1.6 M., 0.63 mL, 1.01 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2 hours and (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (303.00 mg, 1.30 mmol) was added, previously dissolved in THF (1 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 19 hours, reaching r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave recovery of starting material (39 mg, 37%) and the following compounds:

Methyl (1*R*,2*R*,α*R*)-1-hydroxy-2-*N*-benzyl-*N*-α-methylbenzylamino-cycloocta-7-ene-1-carboxylate **(-)-90** (47 mg, 20%); crystallized in a mixture Hex: ether (1:1 v/v) **mp** 138-140°C**;** $\mathbf{[\alpha]_D^{20}}$ = -15.7 (*c* 1.15, $CHCl_3$); **IR υ_{max} (neat):** 3348 (O-H), 2932 and 2858 (C-H), 1728 (C=O), 1454, 1222 (C-O), 1099, 751 and 697 (=C-H) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.41 (3H, d, *J* 7.0, N(α)*Me*); 1.42-1.62 (3H, m); 1.83-2.38 (5H, m); 3.06-3.12 (1H, dd, *J* 11.0, H-2); 3.59-3.62 ($1H_A$, d, J_{AB} 13.0, N-CH_2); 3.65 (3H, s, COO*Me*); 3.95-4.09 (1H, q, *J* 7.0, C(α)*H*); 4.27-4.34 ($1H_B$, d, J_{AB} 13.0, N-CH_2); 4.94 (1H, s, O*H*); 5.40-5.48 (2H, m, H-7 and H-8); 7.04-7.37 (10H, m, H-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 12.0 (CH_3, N(α)*Me*); 24.5 (CH_2, C-4); 24.8 (CH_2, C-5); 25.3 (CH_2, C-3); 26.1 (CH_2, C-6); 51.7 (CH_2, N-*C*H_2); 52.4 (CH_3, COO*Me*); 57.8 (CH, N(α)*C*H); 64.8 (CH, C-2); 76.4 (C, C-1); 127.4-129.3 (CH x 10, Ar); 134.5 (CH x 2, C-7 and C-8); 140.8 (C, C_{ipso}, CH_2*Ph*); 142.7 (C, C_{ipso}, CH*Ph*); 174.7 (C, *C*OOMe). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{25}H_{32}NO_3$:** 394.2377; **found** 394.2369; **Δ** = -2.0 ppm. **R-X**: See annexe F.

Methyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cycloocta-7-ene-1-carboxylate **(+)-91** (7 mg, 3%); $\mathbf{[\alpha]_D^{20}}$ = +4.7 (*c* 0.64, $CHCl_3$); **IR υ_{max} (neat):** 3028, 2928 and 2847 (C-H), 1735 (C=O), 1168, 774, 751 and 705 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.27 (3H, d, *J* 7.0, C(α)*Me*);

1.57-2.17 (8H, m, H-3, H-4, H-5 and H-6); 3.35 (3H, COO*Me*); 3.43 (1H, NCH_ACH_B); 3.54 (1H, m, H-2); 3.64 (1H, NCH_ACH_B); 3.67 (1H, m, H-1); 3.87 (1H, C(α)*H*); 5.80 (1H, m, H-7); 6.03 (1H, t, *J* 10.1, H-8); 7.19-7.42 (10H, m, H-Ar). **^{13}C NMR (50 MHz; CDCl$_3$):** δ 15.9 (CH_3, C(α)*Me*); 26.4 (CH_2); 28.3 (CH_2); 29.8 (CH_2); 47.0 (CH, C-1); 51.7 (CH_3, COO*Me*); 52.2 (CH_2, N-*C*H_2); 58.5 (CH, *C*H(α)); 62.3 (CH, C-2); 126.4–129.2 (10 x CH, *o*, *m*, *p*-*Ph*); 129.4 (CH); 131.6 (CH); 141.7 (C, C_{ipso}); 144.3 (C, C_{ipso}); 173.8 (C, *C*OOC$(CH_3)_3$). **HRMS [M+Na] *m/z* calcd. for $C_{25}H_{31}NO_2Na$:** 400.2247; **found** 400.2252; **Δ** = 1.2 ppm.

Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 55 and addition of (1R)-(-)-(10-Camphorsulfonyl) oxaziridine in situ :

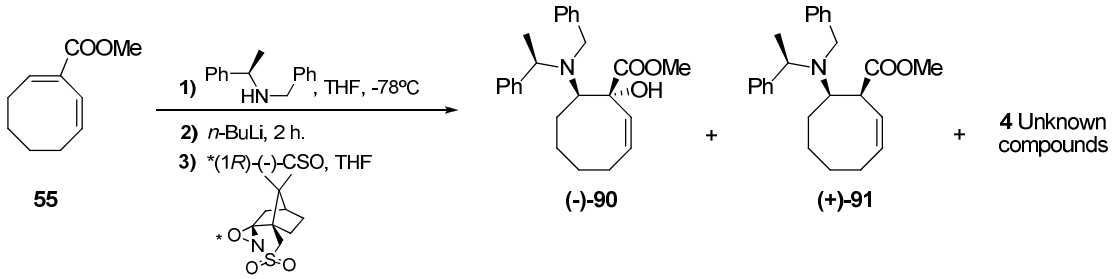


Table 20.

Entry	55 (mg, eq)	(*R*)-amide (mL, eq)	*n*-BuLi (mL, eq)	(1*R*)-(-)-CSO (mg, eq)	t (h.)	55 (%)	(-)-90 (%)	(+)-91 (%)	4 U. C. (%)
1	85.0, 1.0	0.21, 1.8	0.55, 1.6	229.0, 1.8	12	0	26	2	7 (FL-F3)* 1 (FL-F7)*
2	72.0, 1.0	0.20, 2.0	0.43, 1.6	197.0, 2.0	22	15	9	0	5
3	88.0, 1.0	0.23, 2.0	0.53, 1.6	252.0, 2.0	21	0	12	5	6

*^{1}H, ^{13}C NMR, IR and MS spectrums of these fractions have been attached in the CD (spectroscopy part) and they can be found with the fraction name appears in the table.

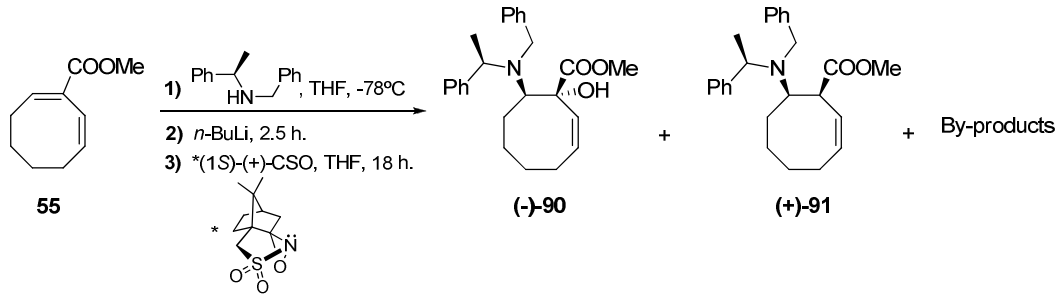
Procedure:

Entry 1-3:

Following general procedure for the Michael addition reaction, compound **55** was dissolved in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine in THF (1 mL) and *n*-BuLi were added. After the addition of the unsaturated compound, the reaction was stirred for 2 hours and (1*R*)-(-)-(10-Camphorsulfonyl) oxaziridine was added, previously dissolved in THF (1 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred respectively for every entry,

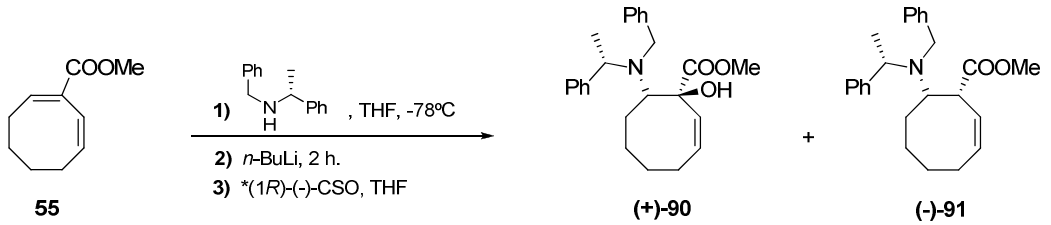
reaching r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 v/v) – $CHCl_3$/MeOH (9:1 v/v) were performed for every entry affording the corresponding compounds and yields as shown in the previous table X.

Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 55 and addition of (1S)-(+)-(10-Camphorsulfonyl) oxaziridine : in situ



Following general procedure for the Michael addition reaction, compound **55** (145.30, 0.87 mmol) was dissolved in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.38 mL, 1.80 mmol) in THF (4 mL) and *n*-BuLi (1.6 M, 0.88 mL, 1.4 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2.5 hours and (1*S*)-(+)-(10-Camphorsulfonyl) oxaziridine (412.00 mg, 1.8 mmol) was added, previously dissolved in THF (4 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 18 hours reaching r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (98:2 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave compound **(-)-90** (102 mg, 30%); $\mathbf{[\alpha]_D^{20}}$ = -17.7 (*c* 1.18, $CHCl_3$) and compound **(+)-91** (3.6 mg, 1%) and by-products (2%).

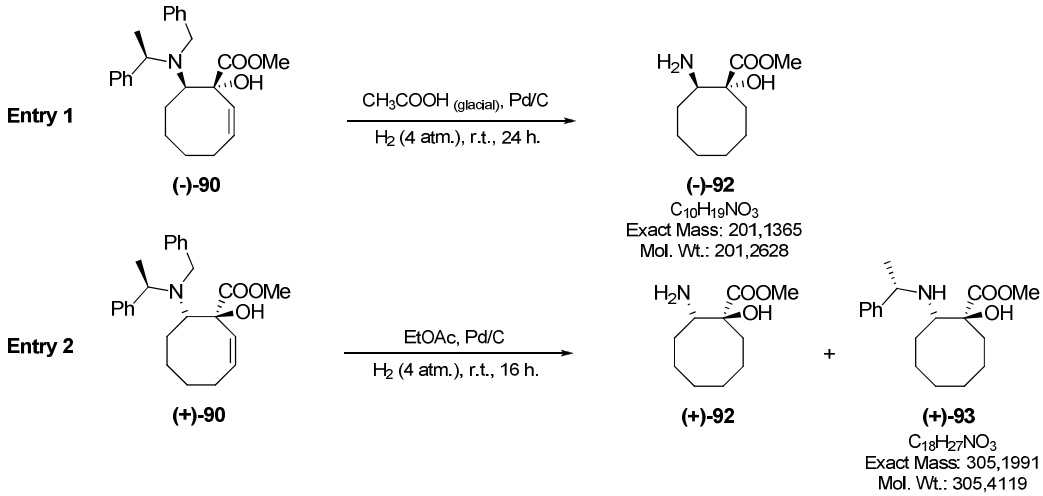
Michael Addition of lithium (S)-N-benzyl-N-α-methylbenzylamide to compound 55 and addition of (1R)-(-)-(10-Camphorsulfonyl) oxaziridine in situ:



Following general procedure for the Michael addition reaction, compound **55** (156.20 mg, 0.94 mmol) was dissolved in THF (2 mL), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.42 mL, 2.0 mmol) in THF (4 mL) and *n*-BuLi. (1.6 M, 1.0 mL, 1.6 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2 hours and (1*R*)-(-)-(10-Camphorsulfonyl) oxaziridine (459.0 mg, 2.0 mmol) was added, previously dissolved in THF (4 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 12 hours, reaching r.t.

Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/Et_2O (99:1 v/v) – $CHCl_3$/MeOH (8:2 v/v) gave recovery of staring material (52 mg, 33%), compound **(+)-90** (91 mg, 24%); $[\alpha]_D^{20}$ = +28.2 (*c* 0.98, $CHCl_3$) and compound **(-)-91** (11 mg, 3%).

Hydrogenolysis reaction of compounds* (+) *and* (-)-90*:



Procedure:

Entry 1:

In a dried vial for hydrogenation compound **(-)-90** (35.50 mg, 0.09 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in glacial acetic acid (2 mL), Pd/C (30 % Pd basis, 5.30 mg) was added into the system and connected under H_2 (4 atm.) for 24 h. After filtration through Celite (eluent DCM) was performed, the organic layer was washed with $NaHCO_{3\,(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) $CHCl_3$/MeOH (95:5-80:20 v/v) gave methyl (1*S*,2*R*)-1-hydroxy-2-amino-cyclooctanecarboxylate **(-)-92** (11 mg, 60%). **IR υ_{max} (neat):** 3364 (O-H), 3298 (N-H), 2920 (C-H), 1731 (C=O), 1450, 1218 (C-O), 1145 cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.35-1.40 (2H, m, H-5); 1.40-1.56 (4H, m, H-4 and H-6); 1.56-1.84 (6H, m, H-3, H-7 and H-8); 3.72 (1H, m, H-2); 3.79 (3H, s, COO*Me*). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.7 (CH_2, C-5); 25.9 (CH_2, x 2, C-4 and C-6); 29.3 (CH_2 x 3, C-3, C-7 and C-8); 52.6 (CH_3, COO*Me*); 63.8 (CH, C-2); 77.4 (C, C-1); 176.0 (C, *C*OOMe). **HRMS $[M+H]^+$ *m/z* calcd. For $C_{10}H_{20}NO_3$:** 202.1438; **found** 202.1439; **Δ** = 0.5 ppm.

Entry 2:

In a dried vial for hydrogenation compound **(+)-90** (19.50 mg, 0.05 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in EtOAc (1 mL), Pd/C (30 % Pd basis, 4.00 mg) was added into the system and connected under H_2 (4 atm.) for 16 h. After filtration

through Celite (eluent DCM and MeOH) was performed, the organic layer was evaporated under reduced pressure, diluted in DCM and washed with $NaHCO_{3\,(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2-0:10 v/v) - $CHCl_3$/MeOH (8:2 v/v) gave compound **(+)-92** (4.0 mg, 40%) and methyl (1*S*,2*S*)-1-hydroxy-2-*N*-α-methylbenzylamino-cyclooctanecarboxylate **(+)-93** (9.2 mg, 60%).

Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 84 and addition of (1S)-(+)-(10-Camphorsulfonyl) oxaziridine in situ:

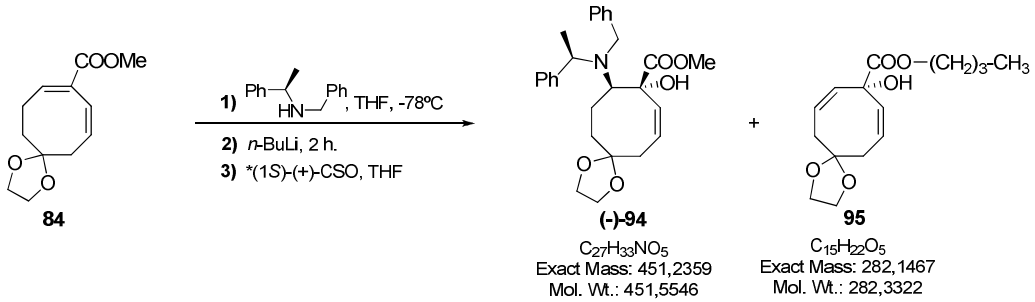


Table 21.

Entry	84 (mg/THF(mL))	(*R*)-amide (mL, eq) /THF (mL)	*n*-BuLi (mL, eq)	(1*S*)-(+)-CSO (mg, eq)/THF (mL)	t (h.)	(-)-94 (%)	95 (%)
1	59.0 / 1.0	(0.13, 2.0) / 2.0	0.34, 1.8	(137.4, 2.0) / 2.0	18	14	5
§2	58.0 / 1.0	(0.13, 2.0) / 1.5	0.34, 1.8	(137.0, 2.0) / 1.5	19	2	3
3	48.0 / 1.0	(0.13, 3.0) / 1.5	0.40, 2.8	(137.4, 2.0) / 1.5	20	15	4
4	113.0 / 1.5	(0.31, 3.0) / 1.4	1.10, 2.8	(344, 3.0) / 1.5	17	20	8
5	176.0 / 2.0	(0.52, 3.0) / 3.0	1.44, 2.8	(573.0, 3.0) / 3.0	19	8	2
6	120.0 / 1.5	(0.34, 3.0) / 1.5	0.94, 2.8	(366.0, 3.0) / 1.5	20.5	19	12
7	120.0 / 1.5	(0.34, 3) / 1.5	0.94, 2.8	(344.0, 2.8) / 2.8	17	38	9
8	120.0 / 1.5	(0.34, 3) / 1.3	0.94, 2.8	(321.0, 2.6) / 2.6	20	38	9
9	120.0 / 1.5	(0.34,3) / 1.3	0.94, 2.8	(272.0, 2.2) / 2.2	20	38	9

§ Temperature - 40°C

Procedure:

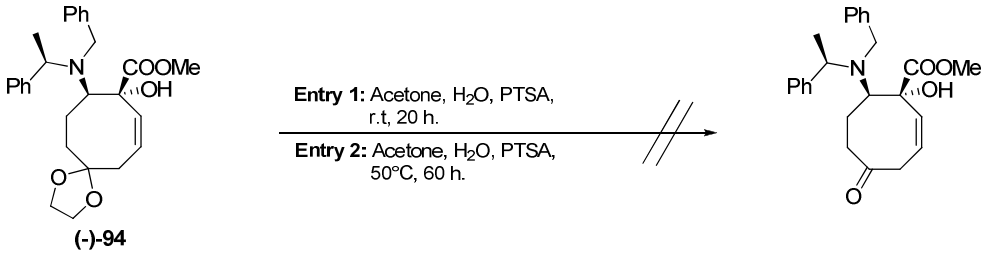
Entry 1-9:

Following general procedure for the Michael addition reaction, compound **84** was dissolved in THF, (*R*)-*N*-benzyl-*N*-α-methylbenzylamine in THF and *n*-BuLi (1.6 M) were added. After the addition of the unsaturated compound, the reaction was stirred for 2.5 hours and (1*S*)-(+)-(10-Camphorsulfonyl) oxaziridine was added, previously dissolved in THF and transferred under Ar atmosphere into the system, the reaction mixture was stirred reaching r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5 v/v) – $CHCl_3$/MeOH (9:1 v/v) gave the following compounds:

Methyl (1*R*,2*R*,α*R*)-1-hydroxy-2-*N*-benzyl-*N*-α-methylbenzylamino-5,5-ethylenedioxycycloocta-7-ene-1-carboxylate **(-)-94**; crystallized in a mixture Hex: ether (1:1 v/v) **mp** 158-160°C; $\mathbf{[\alpha]_D^{20}}$ = -5.11 (*c* 0.97; $CHCl_3$); **IR υ_{max} (neat):** 3427 (O-H), 2970 and 2943 (C-H), 1726 (C=O), 1224 (C-O), 1123, 1100 and 1059 (C-O-C), 756 and 707 (=C-H) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.41 (3H, d, *J* 7.0, N(α)*Me*); 1.76-3.16 (6H, m, H-3, H-4 and H-6); 3.62-3.65 (1H, d, J_{AB}, 14, CH_ACH_BPh); 3.64 (3H, s, COO*Me*); 3.93-3.98 (4H, m, OCH_2CH_2O) and CH(α)); 4.19-4.23 (1H, d, J_{AB}, 14, CH_ACH_BPh); 5.49 (1H, t, *J* 13.2, H-2); 5.55-5.61 (1H, ddd, *J* 11.6, 4.1 and 2.2, H-7); 7.05-7.08, d, *J* 11.6, H-8); 7.04-7.37 (10H, m, *H*-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 12.0 (CH_3, N(α)*Me*); 22.4 (CH_2, C-4); 34.9 (CH_2, C-3); 35.4 (CH_2, C-6); 51.6 (CH_2, N-*C*H_2); 52.4 (CH_3, COO*Me*); 57.9 (CH, N(α)*C*H); 64.5 (CH, C-2); 64.5 (CH_2, O*C*$H_2$$CH_2$O); 64.9 ($CH_2$, OCH_2*C*H_2O); 77.3 (C, C-1); 113.0 (C, C-5); 126.8-129.4 (CH x 10, Ar); 136.1 (CH x 2, C-7 and C-8); 140.5 (C, C_{ipso}, CH_2*Ph*); 142.5 (C, C_{ipso}, CH*Ph*); 174.2 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $\mathbf{C_{27}H_{33}NO_5Na}$:** 474.2251; **found** 474.2230; **Δ** = -4.4 ppm. **R-X:** See annexe G.

Butyl-1-hidroxy-5,5-ethylenedioxycycloocta-2,7-diene-1-carboxylate **95**; **IR υ_{max} (neat):** 3464 (O-H), 2958 and 2868 (C-H), 1726 (C=O), 1213 (C-O), 1067 and 1041 (C-O-C) cm^{-1}. **^{1}H NMR (400; $CDCl_3$):** δ 0.92 (3H, t, *J* 7.4, $(CH_2)_3$CH_3); 1.33-1.38 (2H, m, $(CH_2)_2$-CH_2-CH_3); 1.61-1.65 (2H, q, *J* 6.6, -CH_2-CH_2-CH_2CH_3); 2.65-2.67 (4H, dd, *J* 8.4, 6.1, H-4 and H-6); 3.98 (4H, s, -O(CH_2)$_2$O-); 4.18-4.21 (2H, t, *J* 6.6, COO-CH_2-); 5.73-5.81 (4H, m, H-2, H-3, H-7 and H-8). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 13.8 (CH_3, $(CH_2)_3$CH_3); 19.2 (CH_2); 30.7 (CH_2); 34.0 (CH_2 x 2, C-4 and C-6); 64.8 (CH_2 x 2, O*C*H_2*C*H_2O); 66.8 (CH_2, COO*C*H_2-); 75.4 (C, C-1); 112.5 (C, C-5); 130.0 (CH x 2, C-2 and C-8); 134.4 (CH x 2, C-3 and C-7); 174.9 (C, *C*OO-). **HRMS [M+Na] *m/z* calcd. for $\mathbf{C_{15}H_{22}O_5Na}$:** 419.2824; **found** 419.2819; **Δ** = -1.2 ppm.

Deprotected reaction of the 1,3-dioxolane group in compound* (-)-94*:



Procedure:

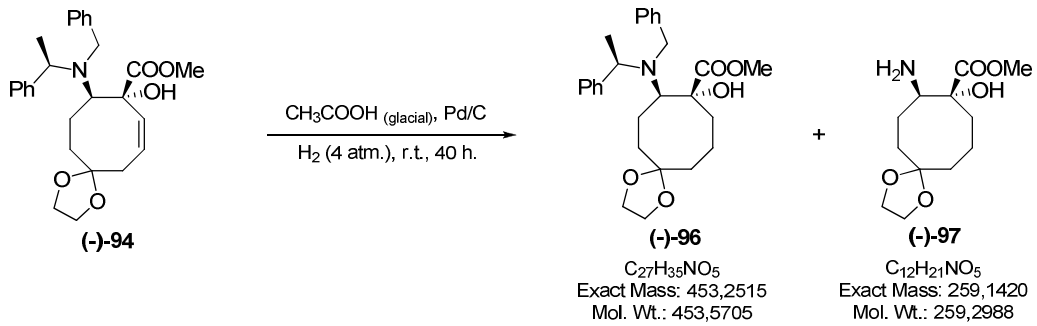
Entry 1:

Compound **(-)-94** (6.30 mg, 0.01 mmol) was dissolved in acetone (1 mL), H_2O (3 drops) and *p*-Toluene sulfonic acid (catalytic amount) were added. The reaction mixture was stirred at r.t. for 20 hours. After, the residue was diluted in EtOAc, washed with $NaHCO_3$ (5%) and NaCl $_{(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Entry 2:

Compound **(-)-94** (6.30 mg, 0.01 mmol) was dissolved in acetone (5 mL), H_2O (6 drops) and *p*-Toluene sulfonic acid (catalytic amount) were added. The reaction mixture was stirred and refluxed at 50°C for 60 hours. After, the residue was diluted in EtOAc, washed with $NaHCO_3$ (5%) and NaCl $_{(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. ^{1}H NMR spectrum of the crude (1.2 mg) showed no reaction product or starting material, for this reason the inorganic layer was acidified reaching pH = 6 and extracted with DCM. The ^{1}H NMR spectrum of the crude from the inorganic layer (2.0 mg) showed decomposition of the starting material and also the hydrolysis of the ester.

Hydrogenolysis reaction of compound* (-)-94*:

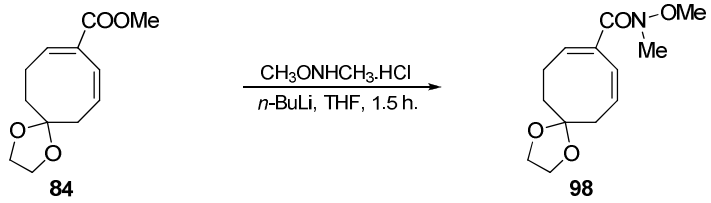


In a dried vial for hydrogenation compound **(-)-94** (19.30 mg, 0.04 mmol) was added and connected to a high vacuum for 1h. After it was dissolved in glacial acetic acid (1 mL), Pd/C (30 % Pd basis, 3.0 mg) was added into the system and connected under H_2 (4 atm.) for 40 hours. After

filtration through Celite (eluent CH_3Cl/MeOH 8:2 v/v) was performed, the organic layer was evaporated under reduced pressure, diluted in DCM, washed with $NaHCO_{3\,(sat.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (8:2 v/v) - $CHCl_3$/MeOH (8:2 v/v) gave the following compounds, due to the low amount, full characterization could not be performed for Methyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-1-hydroxy-5,5-ethylenedioxycyclooctane 1-carboxylate **(-)-96** (2.0 mg, 11%).

Methyl (1*S*,2*R*)-1-hydroxy-2-amino-5,5-ethylenedioxycyclooctane-1-carboxylate **(-)-97** (5.0 mg, 48%). **IR υ_{max} (neat):** 3385 (O-H and N-H), 2943 and 2880 (C-H), 1726 (C=O), 1224 (C-O), 1104 and 1056 (C-O-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.68-2.05 (10H, m, H-3, H-4, H-6, H-7 and H-8); 3.2-3.4 (2H, broad singlet, N*H*$_2$); 3.79 (3H, s, COO*Me*); 3.88-3.94 (5H, m, H-2 and OC*H*$_2$C*H*$_2$O). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 17.5 (CH_2); 32.7 (CH_2); 35.0 (CH_2); 35.7 (CH_2); 38.5 (CH_2); 52.6 (CH_3, COO*Me*); 64.1 (CH_2, O*C*H$_2$CH$_2$O); 64.8 (CH_2, OCH$_2$*C*H$_2$O); 77.2 (CH, C-2); 82.2 (C, C-1); 111.4 (C, C-5); 175.8 (C, *C*OOMe).

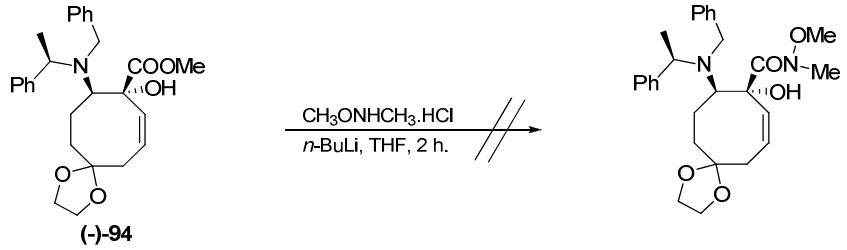
Weinreb ketone synthesis in compound 84:



Under Ar atmosphere, N,O-dimethylhydroxylamine hydrochloride (179.00 mg, 1.80 mmol) was dissolved in THF (3 mL). At -78°C *n*-BuLi (1.6 M., 2.25 mL, 3.60 mmol) was added and the reaction system was stirred for 15 min. and at r.t. for other 15 min. After, the reaction system was cooled down to -78°C and the unsaturated ester **84** (43.00 mg, 0.19 mmol) was added, previously dissolved in THF (1 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 1.5 hours. The reaction was quenched with $NH_4Cl_{\,(sat.)}$ (2 mL), extracted with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) $CHCl_3$/MeOH (98:2 v/v) gave the carboxamide **98** (40.4 mg, 80%). **IR υ_{max} (neat):** 2935 and 2888 (C-H), 1653 (C=O), 1373 (C-O), 1116 and 1047 (C-O-C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.73-1.84 (2H, m, H-4); 2.29-2.47 (4H, m, H-3 and H-6); 3.19 (3H, s, N*Me*); 3.59 (3H, s, NO*Me*); 3.90-4.00 (4H, m, OC*H*$_2$C*H*$_2$O); 5.74-5.85 (1H, ddd, *J* 11.0, 8.3 and 8.3, H-7); 6.14-6.21 (2H, m, H-2 and H-8). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 25.5

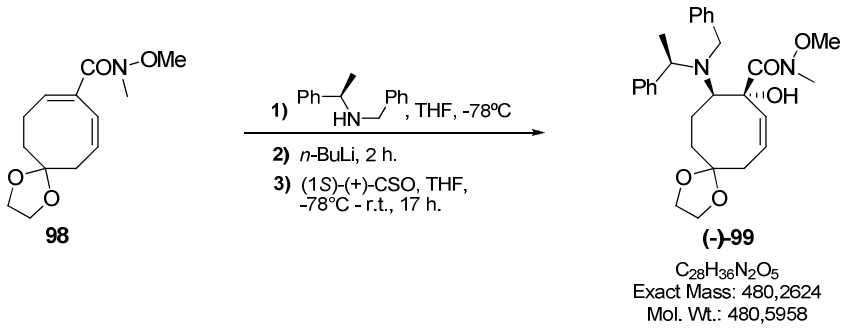
(CH_2, C-4); 31.8 (CH_2, C-3); 33.8 (CH_3, N*Me*); 36.8 (CH_2, C-6); 61.3 (CH_3, NO*Me*); 64.6 (CH_2 x 2, O*C*H_2*C*H_2O); 108.5 (C, C-5); 129.0 (CH, C-7); 129.6 (CH, C-8); 133.2 (C, C-1); 135.1 (CH, C-2); 171.0 (C, *C*ON). **HRMS [M+Na] *m/z* calcd. for $C_{13}H_{19}NO_4Na$:** 276.1206; **found** 276.1223; **Δ** = 6.2 ppm.

Weinreb ketone synthesis in compound* (-)-94*:



N,O-dimethylhydroxylamine hydrochloride (30.00 mg, 0.30 mmol) was dissolved in THF (1 mL), *n*-BuLi (1.6 M., 0.34 mL, 0.54 mmol) was added. After, the unsaturated hydroxy-ester **(-)-94** (15.00 mg, 0.03 mmol) was added, previously dissolved in THF (0.5 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 2 hours. The reaction was quenched with NH_4Cl $_{(sat.)}$, extracted with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR spectrum of the crude showed the recovery of starting material.

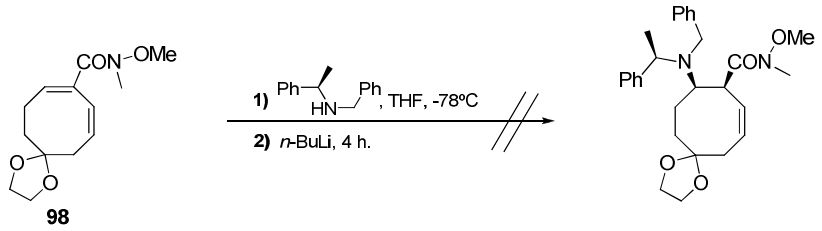
Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 98 and addition of (1S)-(+)-(10-Camphorsulfonyl) oxaziridine in situ:



Following general procedure for the Michael addition reaction, compound **98** (30.00 mg, 0.12 mmol) was dissolved in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.10 mL, 0.36 mmol) in THF (1 mL) and *n*-BuLi. (1.6 M, 0.2 mL, 0.34 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 2 hours and (1*S*)-(+)-(10-Camphorsulfonyl) oxaziridine (82.0 mg, 0.36 mmol) was added, previously dissolved in THF (1 mL) and transferred under Ar atmosphere into the system, the reaction mixture was stirred for 17 hours, reaching r.t. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (6:4

v/v) – $CHCl_3$/MeOH (1:1 v/v) gave recovery of starting material **98** (16.1 mg, 53%) and compound **(-)-99** (9.0 mg, 38%). Due to its low quantity and presence of impurities it could not be purified again for full characterization.

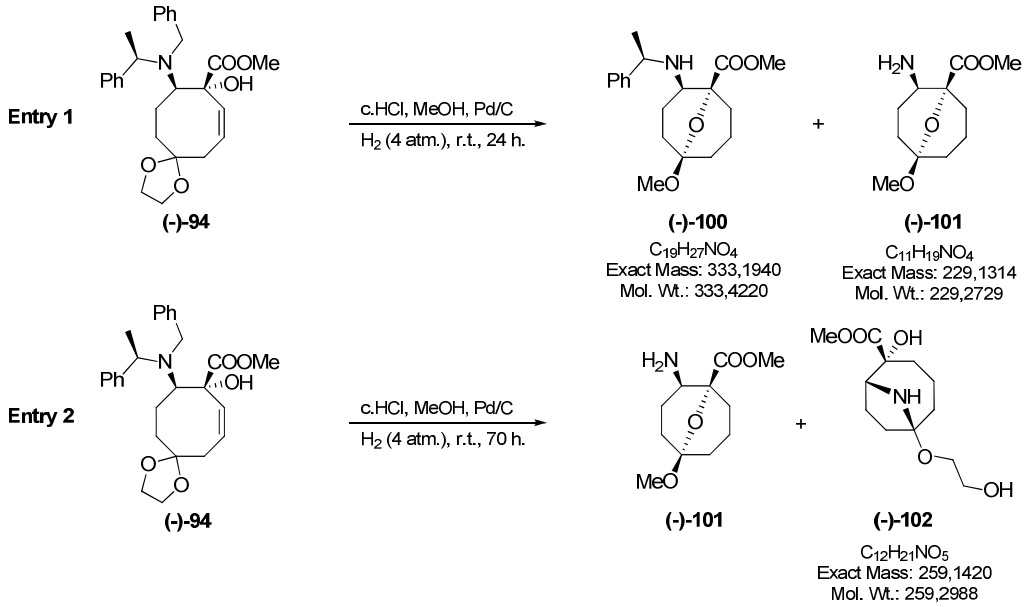
Michael Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 98:



98

Following the general procedure, compound **98** (16.10 mg, 0.06 mmol) was dissolved in THF (1 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.04 mL, 0.20 mmol) in THF (1 mL) and *n*-BuLi. (1.6 M, 0.11 mL, 0.18 mmol) were added. After the addition of the unsaturated compound, the reaction was stirred for 4 hours. ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Hydrogenolysis, deprotection and intramolecular cyclization reaction of compound* (-)-94*:



(-)-94

(-)-100

$C_{19}H_{27}NO_4$
Exact Mass: 333,1940
Mol. Wt.: 333,4220

(-)-101

$C_{11}H_{19}NO_4$
Exact Mass: 229,1314
Mol. Wt.: 229,2729

(-)-94

(-)-101

(-)-102

$C_{12}H_{21}NO_5$
Exact Mass: 259,1420
Mol. Wt.: 259,2988

Procedure:

Entry 1:

Compound **(-)-94** (102.0 mg, 0.23 mmol) was measured and dissolved in MeOH (10 mL), Pd/C (30 % Pd basis, 20.5 mg) and HCl c. (37%, 8 drops) were added into the system and connected under H_2 (4 atm.) for 24 hours. After filtration through Celite (eluents EtOAc and MeOH) was performed and the combined organic extracts evaporated, diluted in DCM, washed with NaOH

1M., dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) EtOAc, DCM, $CHCl_3$, $CHCl_3$/MeOH (1:1 - 0:10 v/v) gave the following compounds:

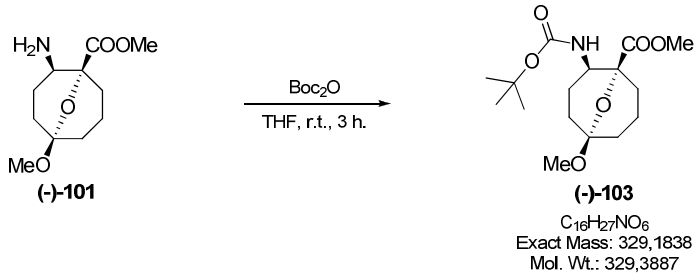
Methyl (1*S*,2*R*,5*R*,α*R*)-2-*N*-α-methylbenzylamino-5-methoxy-9-oxabicyclo[3.3.1]nonane-1-carboxylate **(-)-100** (11.8 mg, 17%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.25 (3H, d, *J* 6.6, C(α)-*Me*); 1.36-2.24 (10H, m, H-3, H-4, H-6, H-7 and H-8); 3.15 (1H, m, H-2); 3.17 (3H, s, COO*Me*); 3.67 (1H, q, *J* 6.6, C*H*(α)); 3.80 (3H, s, CO*Me*); 7.20-7.36 (5H, m, *H*-Ar).

Methyl (1*S*,2*R*,5*R*)-2-amino-5-methoxy-9-oxabicyclo[3.3.1]nonane-1-carboxylate **(-)-101** (21.3 mg, 44%); $[\alpha]_D^{20}$ = -9.85 (*c* 1.02; $CHCl_3$); **IR υ_{max} (neat):** 3383 (N-H), 2951 (C-H), 1731 (C=O), 1288 (C-O), 1129, 1068 and 1041 (C-O-C) cm^{-1}. **^{1}H NMR (400 MHz; $CDCl_3$):** δ 1.65-2.21 (10H, m, H-3, H-4, H-6, H-7 and H-8); 2.38 (2H, broad singlet, NH_2); 3.20-3.25 (1H, m, H-2); 3.38 (3H, s, CO*Me*); 3.77 (3H, s, COO*Me*) . **^{13}C NMR (50 MHz; $CDCl_3$):** δ 19.8 (CH_2); 24.5 (CH_2); 29.3 (CH_2); 31.3 (CH_2); 32.8 (CH_2); 49.1 (CH_3, CO*Me*); 51.6 (CH, C-2); 52.7 (CH_3, COO*Me*); 81.2 (C, C-1); 98.0 (C, C-5); 174.2 (C, *C*OOMe). **HRMS [M+H]$^+$ *m/z* calcd. for $C_{11}H_{20}NO_4$:** 230.1387; **found** 230.1392; **Δ** = 2.2 ppm.

Entry 2:

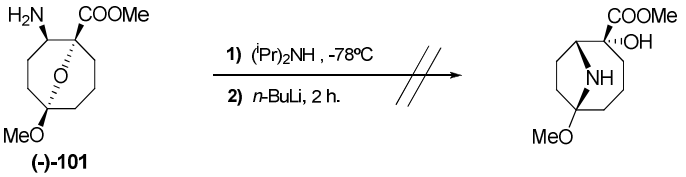
Compound **(-)-94** (72.2 mg, 0.16 mmol) was measured and dissolved in MeOH (15 mL), Pd/C (30 % Pd basis, 20.6 mg) and HCl c. (37%, 6 drops) were added into the system and connected under H_2 (4 atm.) for 70 hours. After filtration through Celite (eluent CH_3Cl/MeOH 8:2 v/v) was performed and the combined organic extracts evaporated, diluted in DCM, washed with NaOH 1M., dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) $CHCl_3$/MeOH (10:0–9:1 v/v) gave Methyl (1*S*,2*R*,5*R*)-2-amino-5-methoxy-9-oxabicyclo[3.3.1]nonane-1-carboxylate **(-)-101** (16.1 mg, 44%) and (1*R*,2*R*,5*S*)-methyl-2-hydroxy-6-(2-hydroxyethoxy)-9-azabicyclo[4.2.1]nonane-2-carboxylate **(-)-102** (8.0 mg, 19%); **IR υ_{max} (neat):** 3375 (N-H, O-H), 2947 (C-H), 1739 (C=O), 1388, 1141 and 1037 (C-O-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.75-2.15 (10H, m, H-3, H-4, H-5, H-7 and H-8); 3.68-3.72 (3H, m, H-1 and OCH_2CH_2OH); 3.78 (3H, s, COO*Me*); 3.80-3.85 (2H, m, OCH_2CH_2OH). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 20.0 (CH_2); 24.5 (CH_2 x 2); 32.1 (CH_2 x 2); 52.8 (CH_3, COO*Me*); 63.2 (CH_2, O-CH_2-CH_2-OH); 64.6 (CH_2, O-CH_2-CH_2-OH); 76.6 (CH, C-1); 92.4 (C, C-2); 98.1 (C, C-6); 174.0 (C, *C*OOMe). **HRMS [M+H]$^+$ *m/z* calcd. for $C_{12}H_{22}NO_5$:** 260.1493; **found** 260.1504; **Δ** = 4.2 ppm.

Protection reaction with Di-tert-butyl dicarbonate of compound* (-)-101*:



Under Ar atmosphere compound **(-)-101** (16.00 mg, 0.07 mmol) was dissolved in THF (0.5 mL), Boc_2O (17.50 mg, 0.08 mmol) was added previously dissolved in a minimum quantity of THF (0.5 mL) and the reaction system was stirred at r.t. for 3 hours. After, the reaction mixture was quenched with $NaHCO_3$ 5% (1 mL), extracted with EtOAc, washed with NaCl $_{(sat.)}$ and K_2CO_3 10%, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (6:4 – 4:5 v/v) gave the protected compound **(-)-103** (10 mg, 43%); **IR υ_{max} (neat):** 3368 (N-H), 2951 (C-H), 1743 (C=O), 1712 (C=O), 1249 (C-O), 1172 and 1048 (C-O-C), 998 cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.61 (9H, s, COOC(CH_3)$_3$), 1.66-2.13 (10H, m, H-3, H-4, H-6, H-7 and H-8); 3.37 (3H, s, CO*Me*); 3.73 (3H, s, COO*Me*); 4.07 (1H, ddd, *J* 8.8, 5.0 and 3.8, H-2); 4.40 (1H, d, *J* 9.6, N-H) **^{13}C NMR (50 MHz; $CDCl_3$):** δ 19.9 (CH_2); 24.9 (CH_2); 27.9 (CH_2); 28.5 (CH_3 x 3, COOC(CH_3)$_3$); 31.6 (CH_2); 32.4 (CH_2); 49.1 (CH_3, CO*Me*); 50.8 (CH, C-2); 52.9 (CH_3, COO*Me*); 77.4 (C, C-5); 79.9 (C, COO*C*(CH_3)$_3$); 97.8 (C, C-1); 155.1 (C, *C*OOC(CH_3)$_3$); 172.5 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{16}H_{27}NO_6Na$:** 352.1731; **found** 352.1748; **Δ** = 4.8 ppm.

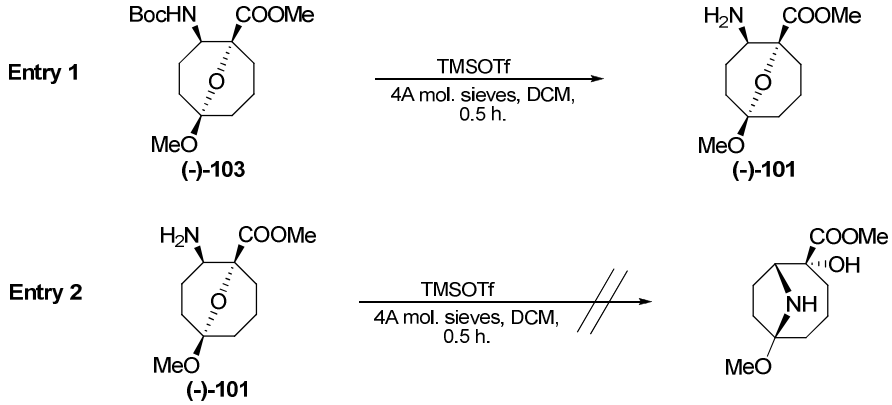
Reaction of compound* (-)-101 *with LDA:



In a dry flask and under Ar atmosphere was added the DIPA (0.01 mL, 0.06 mmol) and dissolved in THF (0.3 mL). After, the system was cooled down to -78ºC and *n*-BuLi (1.6 M, 0.03 mL, 0.05 mmol) was added and stirred for 15 min., after warming up to 0ºC for other 15 min. The system was cooled down to -78ºC again and compound **(-)-101** (10.0 mg, 0.04 mmol) was added and stirred for 2 hours. The reaction mixture was quenched with NH_4Cl $_{(sat)}$ (5 mL), extracted with EtOAc, washed with H_2O and NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. After the crude was dissolved in DCM and washed with Citric acid 10% and $NaHCO_3$, dried, filtered and

evaporated under reduce pressure. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Opening reaction of the epoxide in compound* (-)-103 *and* (-)-101*:



Procedure:

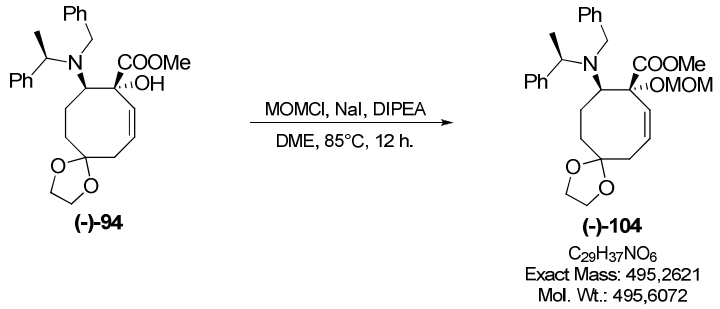
Entry 1:

Compound **(-)-103** (10.00 mg, 0.03 mmol) and 4A molecular sieves powder (9 mg) in DCM (0.3 mL) and Trimethylsilyl trifluoro-methane sulfonate (0.01 mL, 0.03 mmol) was added dropwise at r.t. After being stirred for 30 min, the mixture was quenched with $NaHCO_{3\ (sat.)}$, diluted with EtOAc, filtered through a Celite pad. After separation of the organic layer, the aqueous layer was extracted with EtOAc and washed with brine. The combined organic layers were dried and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed as the only product unprotected **(-)-101**.

Entry 2:

Compound **(-)-101** (10.00 mg, 0.04 mmol) and 4A molecular sieves powder (12 mg) in DCM (0.4 mL) and Trimethylsilyl trifluoro-methane sulfonate (0.02 mL, 0.08 mmol) was added dropwise at r.t. After being stirred for 30 min, the mixture was quenched with $NaHCO_{3\ (sat.)}$, diluted with EtOAc, filtered through a Celite pad. After separation of the organic layer, the aqueous layer was extracted with EtOAc and washed with brine. The combined organic layers were dried and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude showed the recovery of starting material.

Protection reaction with Chloro methoxymethyl of compound* (-)-94*:



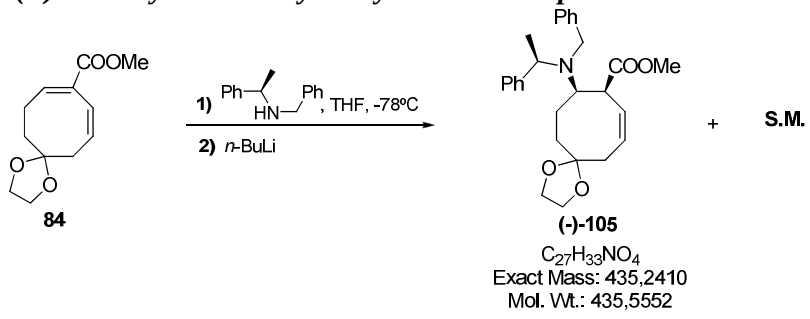
(-)-94

(-)-104

$C_{29}H_{37}NO_6$
Exact Mass: 495,2621
Mol. Wt.: 495,6072

A mixture of NaI (45.00 mg, 0.30 mmol) and MOMCl (33.00 mg, 0.41 mmol) in DME (0.5 mL) was stirred for 10 min. at r.t. Then a solution of the alcohol **(-)-94** (38.00 mg, 0.08 mmol) and DIPEA (0.08 mL, 0.44 mmol) in DME (1.0 mL) were added and the reaction system was stirred for 1 hour at r.t. and for an additional 12 hours under reflux at 85°C. The reaction mixture was quenched with $Na_2CO_{3\ (sat.)}$ (2 mL), washed with H_2O (1 mL) and extracted with DCM (4x). The combined extracts were washed with brine, dried and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (9:1 – 1:1 v/v) gave a pure fraction with the protected compound **(-)-104** (0.7 mg, 0.3%) and two fractions more with the reaction product and impurities (24 mg). It was submitted other flash column chromatography but polar impurities could not be removed. Due to the low quantity of the protected product it could not be characterized.

Addition of lithium (R)-N-benzyl-N-α-methylbenzylamide to compound 84:



84

(-)-105

$C_{27}H_{33}NO_4$
Exact Mass: 435,2410
Mol. Wt.: 435,5552

Table 22.

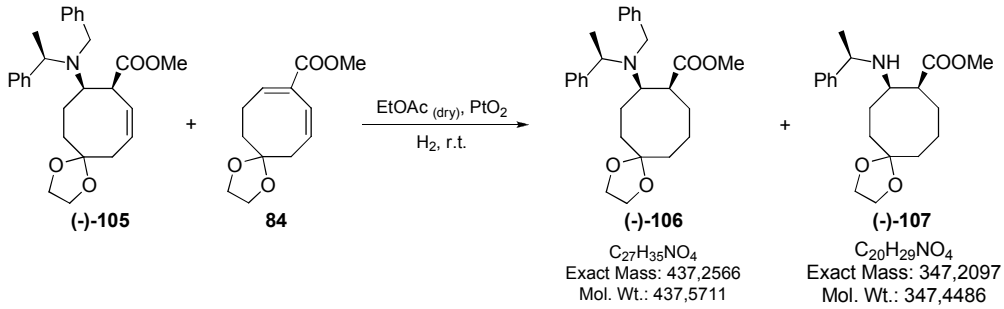
Entry	84 (mg, mmol)	(*R*)-1 (mL, mmol)	*n*-BuLi 1.6 M. (mL, mmol)	THF (mL)	t (hours)	(-)-105:S.M.	Yield (%)
1	136.00, 0.61	0.77 mL, 3.70	2.20, 3.50	1.5	2.5	2.5 : 1	43
2	184.00, 0.82	1.00 mL, 4.90	3.00, 4.80	2.0	2	3 : 1	60
3	209.00, 0.93	1.20 mL, 5.60	3.40 mL, 5.40	2.0	2	3 : 1	50

Procedure:

Entry 1-3:

Following general procedure for the Michael addition reaction, compound **84** was weight for every entry and the quantities of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine, THF and *n*-BuLi were calculated. After the addition of the unsaturated compound, the reaction was stirred at -78°C for the respectively times shown in the table. Due that the reaction product cannot be purified *via* column chromatography the yields were calculated by identification of the reaction product from the ^{1}H NMR spectrums from the crudes.

Hydrogenation reaction of the mixture of compounds* (-)-105 *and* 84*:



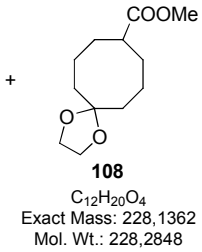


Table 23.

Entry	S.M. (crude) ≈ (mg, mmol)	EtOAc (mL)	PtO_2 (mg, mmol)	t (hours)	(-)-106 (%)	(-)-107 (%)	108 (%)
1	161.30, 0.37	15	82.00, 0.36	2.5	40	-	20
2	250.00, 0.57	15	127.00, 0.56	19	39	1	13

Procedure:

Entry 1-2:

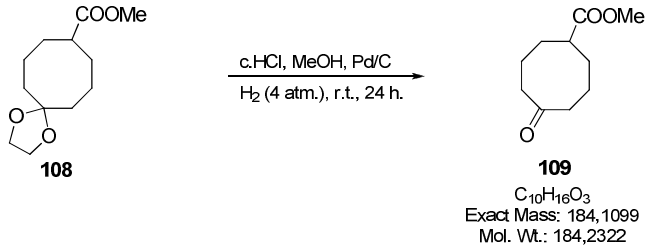
Following general procedure for a hydrogenation reaction, the crude from the previous reactions were dissolved in EtOAc, PtO_2 was added and stirred under H_2 atmosphere at r.t. for different periods of time. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 μm) Hex/EtOAc (98:2 – 0:100 v/v) gave the following compounds:

Methyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5,5-ethylenedioxycyclooctane-1-carboxylate **(-)-106**. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.30 (3H, d, *J* 6.6, C(α)*Me*); 1.40-2.04 (10H, m, H-3, H-4, H-6, H-7 and H-8); 2.52-2.65 (1H, m, H-1); 3.46 (3H, s, COO*Me*); 3.58 (1H, m, H-2); 3.68 (1H, AB, J_{AB} 9.0, NCH_ACH_BPh); 3.84 (1H, AB, J_{AB} 9.0, NCH_ACH_BPh); 3.91 (4H, m, OCH_2CH_2O); 3.99 (1H, q, *J* 5.4, C(α)*H*); 7.18-7.41 (10H, m, H-Ar).

Methyl (1*S*,2*R*,α*R*)-2-*N*-α-methylbenzylamino-5,5-ethylenedioxycyclooctane-1-carboxylate **(-)-107**. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.29 (3H, d, *J* 6.8, C(α)-*Me*); 1.39-2.05 (10H, m, H-3, H-4, H-6, H-7 and H-8); 2.63 (1H, m, H-1); 3.48 (3H, s, COO*Me*); 3.66 (1H, m, H-2); 3.84-3.93 (5H, m, N-C(α)*H* and OCH_2CH_2O); 7.18-7.36 (5H, m, *H*-Ar).

Methyl 5,5-ethylenedioxycyclooctane-1-carboxylate **108**. **IR υ_{max} (neat):** 2939 (C-H), 1731 (C=O), 1164, 1118 and 1044 (C-O-C) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.13-2.04 (12H, m, H-2-H-4 and H-6-H8); 2.51-2.57 (1H, m, H-1); 3.65 (3H, s, COO*Me*); 3.90 (4H, s, COO(CH_2)$_2$). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.5 (CH_2 x 2, C-3 and C-7); 30.6 (CH_2 x 2, C-2 and C-8); 35.1 (CH_2 x 2, C-4 and C-6); 42.5 (CH, C-1); 51.7 (CH_3, COO*Me*); 64.3 (CH_2, O*C*H_2CH_2O); 64.4 (CH_2, OCH_2*C*H_2O); 112.0 (C, C-5); 177.6 (C, *C*OOMe). **HRMS [M+Na] *m/z* calcd. for $C_{12}H_{20}O_4Na$:** 251.1254; **found** 251.1263; **Δ** = 3.6 ppm.

Deprotected reaction of compound 108:



108

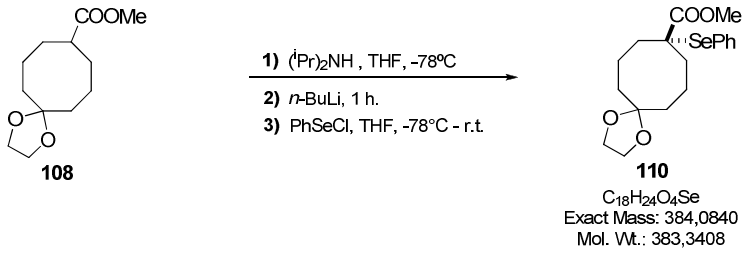
109

$C_{10}H_{16}O_3$
Exact Mass: 184,1099
Mol. Wt.: 184,2322

Compound **108** (20.00 mg, 0.09 mmol) was dissolved in MeOH (2 mL), Pd/C (30 % Pd basis, 5.0 mg) and HCl c. (37%, 2 drops) were added into the system and connected under H_2 (4 atm.) for 24 hours. After filtration through Celite (eluents DCM and MeOH) was performed and the combined organic extracts evaporated, diluted in DCM, washed with NaOH 1M., dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 – 0:100 v/v) gave recovery of starting material **108** (2 mg, 10%) and methyl 5-oxo-cyclooctane-1-carboxylate **109** (4 mg, 31%); **IR υ_{max} (neat):** 2943 and 2862 (C-H), 1735 (C=O), 1701 (C=O), 1450, 1168 (C-O) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.21-2.37 (12H, m, H-2-H-4 and H-6-H-8); 2.54-2.66 (1H, m, H-1); 3.64 (3H, COO*Me*). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.7 (CH_2 x 2, C-3 and C-7); 30.4 (CH_2 x 2, C-2 and C-8); 42.2 (CH_2 x 2, C-4 and C-6);

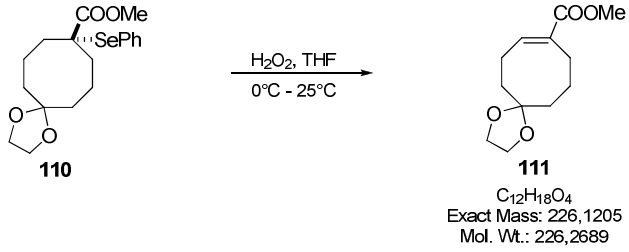
42.5 (CH, C-1); 51.9 (CH_3, COO*Me*); 176.9 (C, *C*OOMe); 178.0 (C, C-5). **HRMS (Na) *m/z* calcd. for $C_{10}H_{16}O_3Na$:** 207.0992; **found** 207.0976; **Δ** = -7.7 ppm.

Reaction of compound 108 with LDA and addition of PhSeCl in situ:



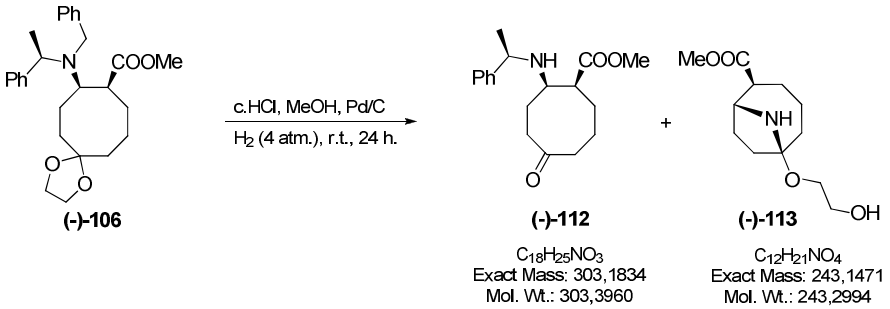
DIPA (0.01 mL, 0.10 mmol) was added and dissolved in THF (1 mL). The system was cooled down to -78ºC and *n*-BuLi (1.6 M, 0.06 mL, 0.10 mmol) was added and stirred for 15 min, after warming up to r.t. and stirred for other 15 min. The system was cooled down to -78ºC again and compound **108** (17.2 mg, 0.08 mmol) was added previously dissolved in THF (1 mL) and stirred for 1 hour. After, PhSeCl (20.00 mg, 0.10 mmol) dissolved in THF (1 mL) was added, the reaction was stirred until the system reached r.t. The reaction mixture was quenched with $NaHCO_3$ 6%, extracted with Et_2O, washed with NaCl $_{(sat)}$, dried, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (95:5–80:20 v/v) gave methyl 1-(phenylselenyl)-5,5-ethylenedioxy-cyclooctane-1-carboxylate **110** (11 mg, 29%).

Elimination reaction of the fragment –SePh:



Compound **110** (11.00 mg, 0.03 mmol) in THF (1 mL) at 0°C was added dropwise H_2O_2 (30% w/v aq., 0.02 mL, 0.12 mmol). The resulting yellow solution was stirred at 0°C for 5 min, and after at r.t. for 1 hour. Diluted with Et_2O, and washed with H_2O and NaCl $_{(sat.)}$. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 – 80:20 v/v) gave (E)-methyl 5,5-ethylenedioxycycloocta-1ene-1-carboxylate **111** (7 mg, 100%). **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.56-2.01 (8H, m, H-4, H-6, H-7 and H-8); 2.29-2.39 (2H, m, H-3); 3.73 (3H, s, COOMe); 3.89-3.92 (4H, m, O*C*H_2*C*H_2O); 7.09 (1H, t, *J* 7.5, H-2).

Hydrogenolysis and deprotected reaction of compound* (-)-106*:



Following previous procedure, compound **(-)-106** (54.00 mg, 0.12 mmol) was dissolved in MeOH (5 mL), Pd/C (30 % Pd basis, 13.0 mg) and HCl c. (37%, 4 drops) were added into the system and connected under H_2 (4 atm.) for 24 hours. After filtration through Celite (eluents DCM and MeOH) was performed and the combined organic extracts evaporated, diluted in DCM, washed with NaOH 1M., dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel for flash column chromatography (pore 60Å. 40-63 µm) Hex/EtOAc (98:2 – 0:100 v/v) – $CHCl_3$/MeOH (90:10 v/v) gave the following compounds:

Methyl (1*S*,2*R*,α*R*)-2-*N*-α-methylbenzylamino-5-oxo-cyclooctane-1-carboxylate **(-)-112** (5 mg, 14%); $[\alpha]_D^{20}$ = + 15.8 (*c* 0.33; $CHCl_3$); **IR υ_{max} (neat):** 3356 (N-H), 2951 (C-H), 1731 (C=O), 1695 (C=O), 1167 (C-O), 1095, 698 (C-H, Ph) cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.22-1.26 (3H, d, *J* 6.6, C(α)*Me*); 1.29-2.49 (10H, m); 2.61-2.74 (1H, m, H-1); 3.08-3.20 (1H, m, H-2); 3.69 (3H, s, COO*Me*); 3.80 (1H, q, *J* 6.6, C*H*(α)); 7.22-7.32 (5H, m, *H*-Ar). **^{13}C NMR (50 MHz; $CDCl_3$):** δ 24.0 (CH_2); 24.4 (CH_3, N(α)Me); 27.8 (CH_2); 29.5 (CH_2); 40.8 (CH_2); 41.3 (CH_2); 47.3 (CH, C-1); 51.8 (CH_3, COO*Me*); 56.6 (CH, CH(α)N); 57.0 (CH, C-2); 126.6, 127.1 and 128.6 (CH x 5, *o*, *m*, *p*-Ph); 146.8 (C, C_{ipso}); 175.5 (C, *C*OOMe); 194.4 (C, C-5). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{18}H_{26}NO_3$:** 304.1907; **found** 304.1912; **Δ** = -1.2 ppm.

(1*R*,2S,6S)-methyl 6-(2-hydroxyethoxy)-9-azabicyclo[4.2.1]nonane-2-carboxylate **(-)-113** (8 mg, 27%), $[\alpha]_D^{20}$ = + 14.1 (*c* 0.49, $CHCl_3$); **IR υ_{max} (neat):** 3364 (O-H, N-H), 2928 (C-H), 1728 (C=O), 1438, 1023, 1172 and 1091 (C-O-C).cm^{-1}. **^{1}H NMR (200 MHz; $CDCl_3$):** δ 1.48-2.17 (10H, m); 2.32-2.52 (1H, m, H-1); 3.20-3.50 (broad band from N-H and O-H); 3.60-3.68 (4H, m, OCH_2CH_2OH); 3.69 (3H, s, COO*Me*); 3.74-3.81 (1H, m, H-2) **^{13}C NMR (50 MHz; $CDCl_3$):** δ 21.8 (CH_2); 27.0 (CH_2); 31.3 (CH_2); 31.8 (CH_2); 41.8 (CH_2); 52.1 (CH, C-2); 52.2 (CH_3, COO*Me*); 56.2 (CH, C-1) 62.9 (CH_2, OCH_2CH$_2$OH); 64.4 (CH_2, OCH$_2$CH_2OH); 96.5 (C, C-6); 176.1 (C, *C*OOMe). **HRMS $[M+H]^+$ *m/z* calcd. for $C_{12}H_{22}NO_4$:** 244.1543; **found** 244.1555; **Δ** = 4.9 ppm.

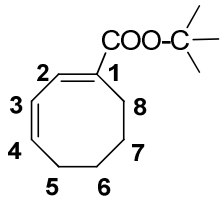


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Table 24

C	δ ^{13}C	DEPT	HMQC	HMBC
1	133.6	C		3
2	135.7	CH	6.92 (1H, s)	4, 8
3	135.4	CH	5.69 (1H, m)	1, 5
4	124.5	CH	5.69 (1H, m)	2, 6
5	29.8	CH_2	2.06 (2H, m)	3, 7
6	21.9	CH_2	1.43-1.52 (2H, m)	4, 8
7	24.1	CH_2	1.43-1.52(2H, m)	5, *C*OO
8	26.3	CH_2	2.33 (2H, m)	2, 6
COOC$(CH_3)_3$	166.0	C		2, 8
COO***C***$(CH_3)_3$	79.9	C		$(CH_3)_3$
COOC(***C***$H_3)_3$	28.2	CH_3 x 3	1.43 (9H, s)	*C*$(CH_3)_3$

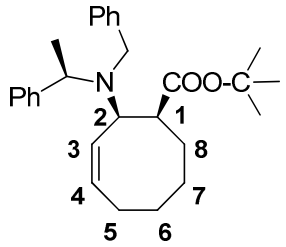

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Table 25

C	δ ^{13}C	DEPT	HMQC	HMBC
1	53.5	CH	2.50 (1H, m)	2, 3, 7
2	56.5	CH	3.85 (1H, m)	C*H*(α)N, CH_2(α)N
3	129.6	CH	6.05 (1H, t, *J* 10)	5, C*H*(α)N
4	128.0	CH	5.80 (1H, m)	5
5	27.5	CH_2	1.92 (1H_A, m) 2.08 (1H_B, m)	3, 4, 7
6	30.1	CH_2	1.20-1.65 (2H, m)	5, 8
7	25.8	CH_2	1.20-1.51 (2H, m)	5, 6, 8
8	30.6	CH_2	1.22 (1H_A, m) 1.62 (1H_B, m)	6, 7
CH_2-N	51.7	CH_2	3.85 (1H_A, AB, J_{AB} 17.1); 4.10 (1H_B, AB, J_{AB} 17.1)	2, C*H*(α)N, C_o
CH(α)N	54.7	CH	4.25 (1H, q, *J* 6.8)	2, CH_2(α)N,
CH_3(α)N	13.2	CH_3	1.45 (3H, d, *J* 6.8)	C*H*(α)N
COOC$(CH_3)_3$	174.9	C		
COO***C***$(CH_3)_3$	80.0	C		
COOC(***C***$H_3)_3$	27.9	CH_3 x 3	1.37 (9H, m)	
C *ipso*	141.9	C		C *o, m, p*, C*H*(α)N
C *ipso*	144.1	C		C *o, m, p*, C*H*(α)N
C *o, m, p*	126.5-129.9	CH x 10	7.30 (10H, m)	

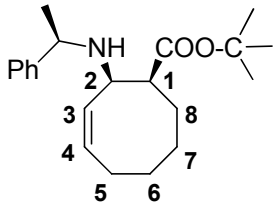

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Table 26

C	**δ ^{13}C**	**DEPT**	**HMQC**	**HMBC**
1	50.9	CH	2.81-2.85 (1H, m);	2, 8
2	52.4	CH	3.68-3.72 (1H, dd, *J* 8.8 and 5.1)	4, C*H*(α)N,
3	132.8	CH	5.51-5.55 (1H, t, *J* 10.5);	5
4	130.0	CH	5.70-5.77 (1H, dd, *J* 10.5 and 8.0)	2, 6
5	27.2	CH_2	1.85-2.10 (2H, m, H-5_A and H-5_B)	6, 7
6	25.7	CH_2	1.28-1.35 (1H, m, H-6_B); 1.55-1.85 (1H, m, H-6_A)	5, 7, 8
7	28.6	CH_2	1.10-1.28 (1H, m, H-7_B); 1.55-1.85 (1H, m, H-7_A)	5, 6, 8
8	29.8	CH_2	1.55-1.85 (2H, m, H-8)	6, 7
CH(α)	54.7	CH	3.95-4.00 (1H, q, *J* 6.5)	2, C*H* *o,* C*H*$_3$(α)N
CH_3(α)*N*	23.6	CH_3	1.31 (3H, d, *J* 6.5)	C*H*(α)N
COOC$(CH_3)_3$	173.6	C		2
COO***C***$(CH_3)_3$	80.1	C		COOC(C*H*$_3$)$_3$
COOC(***C***H_3)$_3$	28.1	CH_3 x 3	1.44 (9H, s);	
C **ipso**	145.9	C		C *o, m, p*, C*H*(α)
C ***o, m, p***	126.6-128.4	CH x 5	7.22-7.35 (5H, m, H-Ar).	C*H*(α)

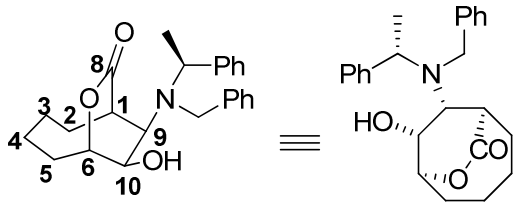

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Table 27

C	δ ^{13}C	DEPT	HMQC	HMBC
1	41.8	CH	3.05 (1H, m)	2, 8
2	33.8	CH_2	2.02 ($1H_A$, m) 2.20 ($1H_B$, m)	9
3	24.6	CH_2	1.50-1.70 (2H, m)	
4	22.7	CH_2	1.20-1.30 (2H, m)	2
5	28.9	CH_2	1.82 ($1H_A$, m) 1.91 ($1H_B$, m)	4
6	77.9	CH	4.63 (1H, td, *J* 5.6, 3.0)	5, 10
7				
8	174.8	CO		9
9	59.1	CH	3.09 (1H, dd, *J* 9.2 and 2.1)	C*H*(α)N
10	68.3	CH	3.94 (1H, dd, *J* 9.2 and 5.6)	9
CH_2-*N*	50.3	CH_2	3.79 ($1H_A$, AB, J_{AB} 14.4); 3.84 ($1H_B$, AB, J_{AB} 14.4)	C*H*(α)N
CH(α)*N*	55.7	CH	3.97 (1H, q, *J* 6.8)	CH_2(α)N, CH_3(α)N, 9, C*H* $_{o,}$
CH_3(α)*N*	13.1	CH_3	1.43 (3H, d, *J* 6.8)	
C $_{ipso}$	139.5	C		CH_2(α)N
C $_{ipso}$	143.8	C		C*H* $_{o, m, p}$, CH_3(α)N, C*H*(α)N
C $_{o, m, p}$	127.4-128.7	CH x 10	7.38 (10H, m)	

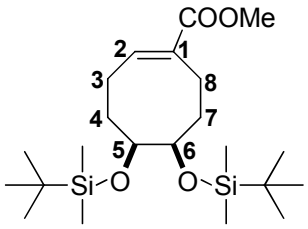

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Table 28

C	δ ^{13}C	DEPT	HMQC	HMBC
1	134.6	C		
2	141.3	CH	6.91 (1H, t, *J* 8.0)	
3	21.2	CH_2	2.63-2.75 (1H, m, H-3_A) 1.76-1.89 (1H, m, H-3_B)	
4	34.4	CH_2	1.76-1.89 (1H, m, H-4_A) 1.50-1.56 (1H, m, H-4_B)	
5	77.7	CH	3.89-3.94 (1H, m)	
Si(*C*H$_3$)$_2$	-4.6	CH_3 x 2	0.15 (6H, s)	Si(C*H$_3$*)$_2$
Si-*C*-(CH$_3$)$_3$	18.2	C x 2		Si-C-(C*H$_3$*)$_3$, Si(C*H$_3$*)$_2$
Si-C-(*C*H$_3$)$_3$	25.9	$(CH_3)_3$ x 3	1.02 (18H, s)	
6	77.7	CH	3.89-3.94 (1H, m)	
Si(*C*H$_3$)$_2$	-4.9	CH_3 x 2	0.11 (6H, s)	
7	34.2	CH_2	2.08-2.10 (1H, m, H-7_A) 1.90-1.95 (1H, m, H-7_B)	
8	22.8	CH_2	2.45-2.51 (1H, m, H-8_A) 1.76-1.89 (1H, m, H-8_B)	H-2
COO*Me*	50.7	CH_3	3.49 (3H, s, COO*Me*)	
***C*OOMe**	167.1	C		COO*Me*, H-2

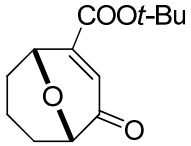

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Table 29

C	δ ^{13}C	DEPT	HMQC	HMBC
1	68.4	CH	4.87 (1H, d, *J* 5.2)	H-3, H-5
2	150.3	C		H-8
3	131.7	CH	6.87 (1H, s)	H-1
4	199.2	C		H-6
5	75.7	CH	4.23 (1H, d, *J* 4.8).	H-3, H-1
6	25.0	CH_2	1.71-2.08 (2H, m)	H-1
7	14.7	CH_2	1.68 (2H, m, H-7)	H-1, H-5
8	26.2	CH_2	1.71-2.08 (2H, m)	H-5
C$OOC(CH_3)_3$	163.4	C		H-3
COO***C***$(CH_3)_3$	82.9	C		$COOC(CH_3)_3$, $COOC(CH_3)_3$,`
$COOC($***C***$H_3)_3$	27.9	$(CH_3)_3$	1.52 (CH_3 x 3)	

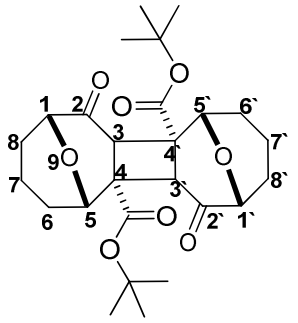

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Table 30

C	δ ^{13}C	DEPT	HMQC	HMBC
1 and **1`**	77.2	CH x 2	4.18 (2H, d, *J* 4.0)	H-5, H-5`
2 and **2`**	211.3	C x 2		H-3, H-3`
3 and **3`**	54.6	CH x 2	3.93 (2H, s)	H-5, H-5`
4 and **4`**	51.6	C x 2		H-3, H-3`
5 and **5`**	74.5	CH x 2	4.25 (2H, d, *J* 5.3).	H-3, H-3`
6 and **6`**	27.1	CH_2 x 2	1.75-1.97 (4H, m)	H-7, H-7`, H-8, H-8`
7 and **7`**	16.8	CH_2 x 2	1.48-1.65 (4H, m)	H-1, H-1`, H-5, H-5`
8 and **8`**	29.1	CH_2 x 2	1.75-1.97 (4H, m)	
C$OOC(CH_3)_3$	169.4	C x 2		H-3, H-3`
$COO\boldsymbol{C}(CH_3)_3$	83.1	C x 2		$COOC(CH_3)_3$, $COOC(CH_3)_3$,`
$COOC(\boldsymbol{C}H_3)_3$	27.9	$(CH_3)_3$ x 2	1.51 (CH_3 x 6)	

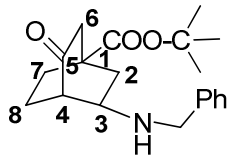

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Table 31

C	δ ^{13}C	DEPT	HMQC	HMBC
1	43.5	C		2, 6, 8
2	36.8	CH_2	1.40-1.69 ($1H_A$, m) 2.23 ($1H_B$, ddd, *J* 12.2, 9.2, 3.3)	1, 3, 6
3	54.0	CH	3.17 (1H, dt, J 9.2, 3.3)	2, 8, CH_2(α)N
4	47.0	CH	2.52 (1H, m)	7
5	213.0	C		3, 4, 6
6	45.6	CH_2	2.35 ($1H_A$, dd, *J* 18.3, 3.3) 2.55 ($1H_B$, dd, *J* 18.3, 3.3)	2, 7
7	27.2	CH_2	1.70-1.90 (2H, m)	2, 4, 6, 8
8	20.3	CH_2	1.70-1.90 (2H, m)	7
CH_2-N	50.6	CH_2	3.70 ($1H_A$, S_{AB}, *J* 13.2) 3.80 ($1H_B$, S_{AB}, *J* 13.2)	3, Ar-H
COOC$(CH_3)_3$	173.8	C		
COO***C***$(CH_3)_3$	80.8	C		$(CH_3)_3$
COOC(***C***$H_3)_3$	27.9	CH_3 x 3		*C*$(CH_3)_3$
C ipso	139.7	C		CH_2N
C orto	128.4	CH	7.21-7.32 (2H, m)	CH_2N
C meta	128.4	CH	7.21-7.32 (2H, m)	**C para**
C para	127.0	CH	7.21-7.32 (1H, m)	**C orto**

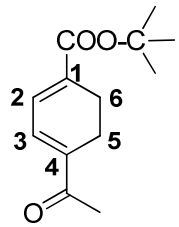

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Table 32

C	δ ^{13}C	DEPT	HMQC	HMBC
1	136.0	C		3, 5
2	130.8	CH	7.02 (1H,S_{AB}, *J* 6.0)	3, 4, 6, COO
3	138.3	CH	6.94 (1H, S_{AB}, *J* 6.0)	1, 2, 5, CO
4	140.3	C		2, 6
5	20.4	CH_2	2.46-2.48 (2H, m)	1, 3
6	21.8	CH_2	2.46 – 2.48 (2H, m)	2, 4
CO***C***H_3	25.4	CH_3	2.34 (3H, s)	CO
COOC$(CH_3)_3$	165.7	C		2
COO***C***$(CH_3)_3$	80.9	C		$(CH_3)_3$
COOC(***C***$H_3)_3$	28.0	CH_3 x 3	1.49 (3H, s)	$C(CH_3)_3$
COCH_3	196.6	C		3, CH_3

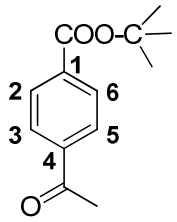

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Table 33

C	**δ ^{13}C**	**DEPT**	**HMQC**	**HMBC**
1	135.8	C		3, 5
2, 6	129.6	CH	8.07 (S_{AB}, *J* 8.6)	3, 4, COO
3, 5	128.0	CH	7.98 (S_{AB}, *J* 8.6)	1, CO
4	139.8	C		2, 6
CO***C***H_3	26.8	CH_3	2.64 (3H, s)	*C*O
CO	197.6	C		5, CH_3
COOC$(CH_3)_3$	164.8	C		2, 6
COO***C***$(CH_3)_3$	81.7	C		$(CH_3)_3$
COOC(***C***$H_3)_3$	28.1	CH_3 x 3	1.61 (9H, s)	*C*$(CH_3)_3$

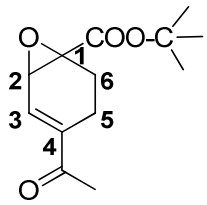

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Table 34

C	δ ^{13}C	DEPT	HMQC	HMBC
1	61.6	C		5, 6
2	52.0	CH	3.62 (1H, d, J 4.0)	3, 6
3	131.9	CH	6.89 (1H, dd, J 4.0, 2.5)	2, 5
4	143.7	C		5, 6, CH_3
5	18.4	CH_2	1.96 ($1H_A$, m) 2.72 ($1H_B$, m)	3, 6
6	21.1	CH_2	1.95 ($1H_A$, m) 2.43 ($1H_B$, m)	5
$CO\mathbf{C}H_3$	25.3	CH_3	2.32 (3H, s)	CO
CO	197.2	C		3, 5_B, $COCH_3$
C$OOC(CH_3)_3$	168.0	C		$(CH_3)_3$
$COO\mathbf{C}(CH_3)_3$	82.6	C		$(CH_3)_3$
$COOC(\mathbf{C}H_3)_3$	28.1	CH_3 x 3	1.49 (9H, s)	$C(CH_3)_3$

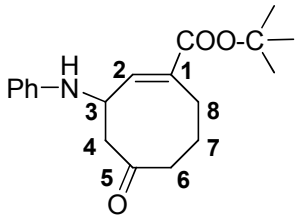

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Table 35

C	δ ^{13}C	DEPT	HMQC	HMBC
1	134.4	C		2, 8
2	144.0	CH	6.70 (1H, d, *J* 8.5)	4, 8
3	49.0	CH	4.72 (1H, ddd, *J* 12.1, 8.5,4.4)	4
4	53.4	CH_2	2.59 ($1H_A$, t, *J* 12.1) 3.08 ($1H_B$, dd, *J* 12.1, 4.4)	6_A
5	210.0	C		4_A, 6_B
6	41.2	CH_2	2.46 ($1H_A$, m) 2.64 ($1H_B$, m)	8, 4_A
7	24.9	CH_2	1.98 ($1H_A$, m) 1.60 ($1H_B$, m)	6, 8
8	27.0	CH_2	2.31 ($1H_A$, m) 2.87 ($1H_B$, m)	2, 6
C$OOC(CH_3)_3$	165.0	C		2, 8_A
COO***C***$(CH_3)_3$	81.0	C		$(CH_3)_3$
$COOC($***C***$H_3)_3$	28.0	CH_3	1.46, s	$\underline{C}(CH_3)_3$
C_{ipso}	146.0	C		C_{meta}
C_{orto}	113.3	CH	6.60 (2H, d, *J* 9.4)	C_{meta}
C_{meta}	129.4	CH	7.21 (2H, t)	C_{para}
C_{para}	118.5	CH	6.78 (1H, t)	C_{orto}

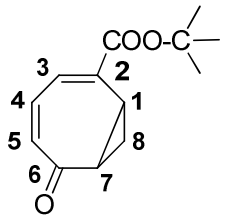

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Table 36

C	δ ^{13}C	DEPT	HMQC	HMBC
1	23.4	CH	2.72 (1H, dddd, *J* 9.0, 9.0, 9.0, 1.5)	3
2	141.0	C		3, 4
3	127.2	CH	6.86 (1H, d, *J* 7.8)	1, 5
4	131.7	CH	6.41 (1H, dd, *J* 12.5, 7.8)	3
5	131.4	CH	6.13 (1H, d, *J* 12.5)	3. 7
6	198.4	C		1, 4
7	44.4	CH	2.55 (1H, dddd, *J* 9.0, 9.0, 9.0, 1.5)	1, 8
8	14.1	CH_2	1.60 ($1H_A$, ddd, *J* 9.0, 9.0, 4.6) 1.99 ($1H_B$, ddd, *J* 9.0, 9.0, 4.6)	1
C$OOC(CH_3)_3$	165.6	C		1, 3, $(CH_3)_3$
COO***C***$(CH_3)_3$	82.0	C		$(CH_3)_3$
$COOC($***C***$H_3)_3$	28.1	CH_3 x 3	1.54 (9H, s)	*C*$(CH_3)_3$

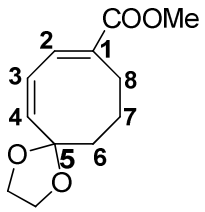

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Table 37

C	δ ^{13}C	DEPT	HMQC	HMBC
1	133.6	C		2, 3, 7, 8
2	136.6	CH	7.20 (1H, d, *J* 5.2)	4, 8
3	124.5	CH	5.89 (1H, dd, *J* 12.6 and 5.2)	
4	134.6	CH	5.59 (1H, d, *J* 12.6)	2, 3
5	108.7	C		3, 4, 7
6	31.1	CH_2	1.72 (2H, m)	4, 8
7	24.3	CH_2	1.72 (2H, m)	6, 8
8	25.3	CH_2	2.45 (2H, m);	2, 6
COO***Me***	52.2	CH_3	3.75 (3H, s)	*C*OO
O***C***H_2***C***H_2O	65.0	CH_2 x 2	3.94-4.04 (4H, m)	
COOMe	167.8	C		2, COO*Me*, 8

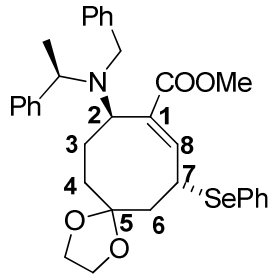

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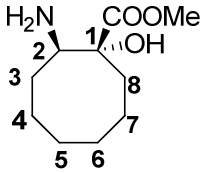
Table 38

C	δ ^{13}C	DEPT	COSY	ROESY
1	128.3	C		
2	58.3	CH	3.95-4.05 (1H, m)	C-*H*$_3$, COO*Me*
3	47.9	CH_2	1.75-1.90 (2H, m)	C-*H*$_2$
4	27.6	CH_2	1.75-1.90 (2H, m, H-4a) 2.01-2.05 (1H, dt, *J* 13.3 and 2.1, H-4b)	
5	110.2	C		
6	35.1	CH_2	1.50-1.75 (2H, m)	
7	34.5	CH	3.66-3.70 (1H, m, H-7)	C-*H*$_6$
8	138.8	CH	6.32 (1H, d, *J* 9.3)	C-*H*$_7$
COO***Me***	51.8	CH_3	3.74 (3H, s, COO*Me*);	
O***C***H_2***C***H_2O	63.7	CH_2 x 2	3.65-3.90 (4H, m)	
CH_2-N	51.1	CH_2	3.65-3.90 (2H, m)	COO*Me*
CH(α)N	57.1	CH	3.99-4.07 (1H, q, *J* 6.6)	COO*Me*
CH_3(α)N	15.9	CH_3	1.38 (3H, d, *J* 6.8);	
C *ipso*	136.9	C		
C *o, m, p*	135.3	CH x 5	7.17-7.52 (15H, m, *H*-Ar)	C-*H*$_7$
C *ipso*	143.1	C		
C *ipso*	143.4	C		
C *o, m, p*	126.4-129.3	CH x 10	7.17-7.52 (15H, m, *H*-Ar)	C-*H*$_1$, COO*Me*, C*H*$_2$-N
COOMe	168.6	C		



(-)-92

Table 39

C	δ ^{13}C	DEPT	HMQC
1	77.4	C	
2	63.8	CH	3.72 (1H, m)
3	29.3	CH_2	1.56-1.84 (2H, m)
4	25.9	CH_2	1.40-1.56 (2H, m)
5	25.9	CH_2	1.35-1.40 (2H, m)
6	25.9	CH_2	1.40-1.56 (2H, m)
7	21.7	CH_2	1.56-1.84 (2H, m)
8	29.3	CH_2	1.56-1.84 (2H, m)
COO*Me*	52.6	CH_3	3.79 (3H, s)
***C*OOMe**	176.0	C	

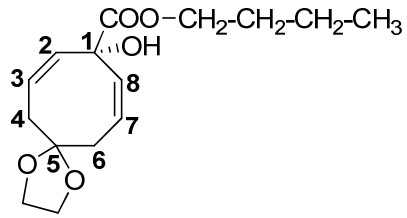


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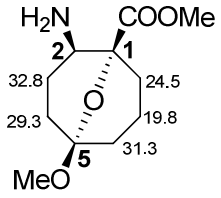
Table 40

C	δ ^{13}C	DEPT	HMQC	HMBC
1	75.4	C		
2	130.0	CH	5.73-5.81 (1H, m)	H-4
3	130.0	CH	5.73-5.81 (1H, m)	H-4
4	34.0	CH_2	2.65-2.67 (2H, dd, *J* 8.4, 6.1)	H-3, H-6
5	112.5	C		H-4, H-6
6	34.0	CH_2	2.65-2.67 (2H, dd, *J* 8.4, 6.1)	H-4, H-7, H-8
7	134.4	CH	5.73-5.81 (1H, m)	H-6
8	134.4	CH	5.73-5.81 (1H, m)	H-6
COO*C*H$_2$	66.8	CH_2	4.18-4.21 (2H, t, *J* 6.6)	COOCH$_2$-C*H$_2$*-, COO-(CH$_2$)$_2$-C*H$_2$*-
COOCH$_2$-*C*H$_2$-	30.7	CH_2	1.61-1.65 (2H, q, *J* 6.6)	COOC*H$_2$*,COO-(CH$_2$)$_2$-C*H$_2$*-, COO-(CH$_2$)$_3$-C*H$_3$*
COO-(CH$_2$)$_2$-*C*H$_2$-	19.2	CH_2	1.33-1.38 (2H, m)	COOC*H$_2$*
COO-(CH$_2$)$_3$-*CH$_3$*	13.8	CH_3	0.92 (3H, t, *J* 7.4)	
O*C*H$_2$*C*H$_2$O	64.8	CH_2 x 2	3.98 (4H, s)	
***C*OO-**	174.9	C		COOC*H$_2$*



(-)-101

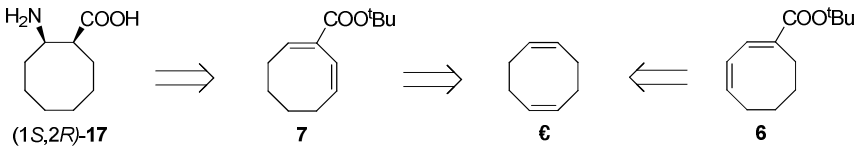
Table 41

C	δ ^{13}C	DEPT	HMBC
1	98.0	C	H-3, H-7, O*Me*
2	51.6	CH	H-4, H-8
3	32.8	CH_2	
4	29.3	CH_2	H-2
5	81.2	C	H-2, H-3, H-7
O*Me*	49.1	CH_3	
6	31.3	CH_2	
7	19.8	CH_2	
8	24.5	CH_2	H-2
COO*Me*	52.7	CH_3	
***C*OOMe**	174.2	C	H-2, H-8, COO*Me*

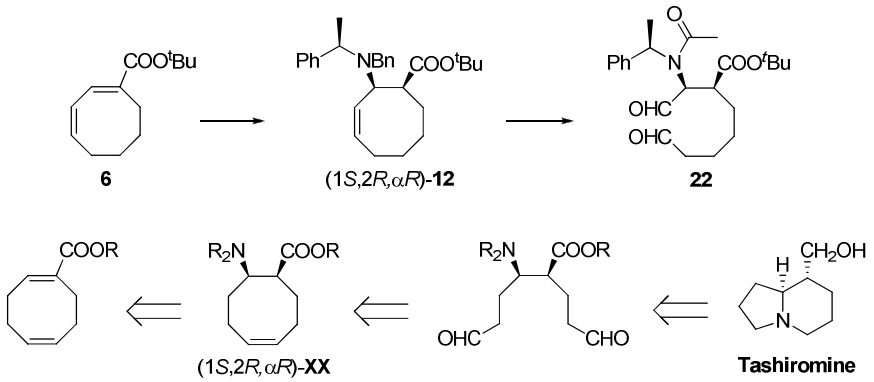
CONCLUSIONS:

1. A efficient method aimed to the synthesis of cycloocta-1,3- and 1,7-diene carboxylates has been achieved from cycloocta-1,5-diene.

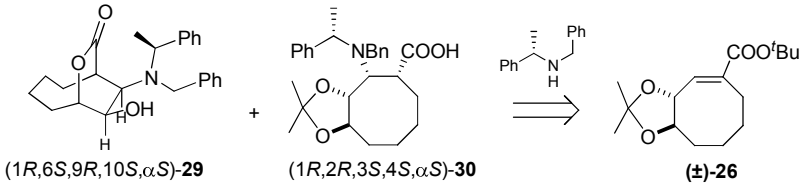
2. A highly efficient asymmetric synthesis of (1*S*,2*R*)-2-aminocyclooctanecarboxylic acid **17** has been completed using cycloocta-1,5-diene as starting material. It is achieved in 77% yield *via* a four-step sequence from *tert*-butyl cycloocta-1,7-dienecarboxylate **7** where the extra double bond adjacent to the unsaturated ester is essential to improve the yield.



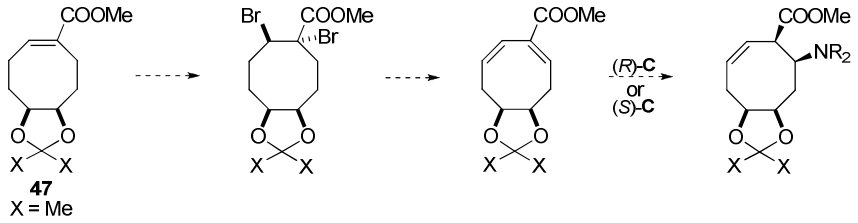
3. From the cyclooct-1,3-diene carboxylate derivative **6** has been achieved the functionalized β-amino acid **22** incorporating in its structure two aldehydes groups in 30% overall yield. This strategy will lead to the synthesis of Tashiromine by using as starting material the β-amino cycloocta-5-ene isomer **XX**.



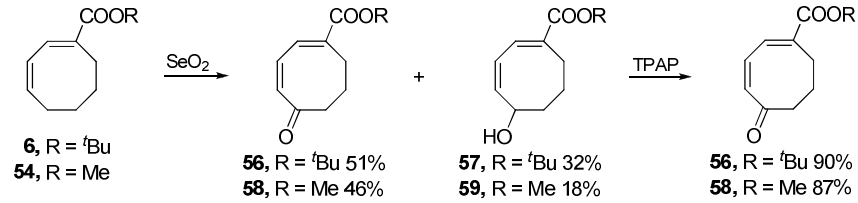
4. The highly functionalized cyclooctanic β-amino acids **29** and **30** have been obtained in 2 steps from (±)-**26** in 26% and 15%, respectively. Through a Michael addition of chiral lithium amide to the racemic mixture of isopropilidendioxi derivatives (±)-**26**, a matched pair approaches transformation accounts for the obtained results.



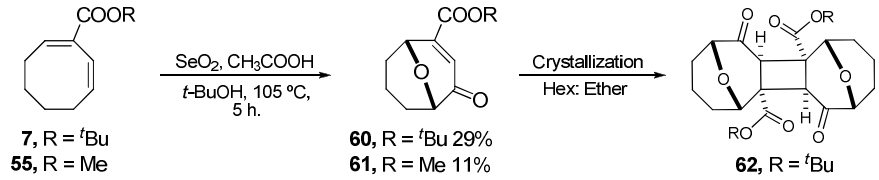
5. An oxygen functionalized C-5 and C-6 adduct **47** has been proposed to the approach of Tashiromine. As the Michael addition of chiral lithium amide did not take place, further functionalized derivatives from **47** are suggested for future research works.



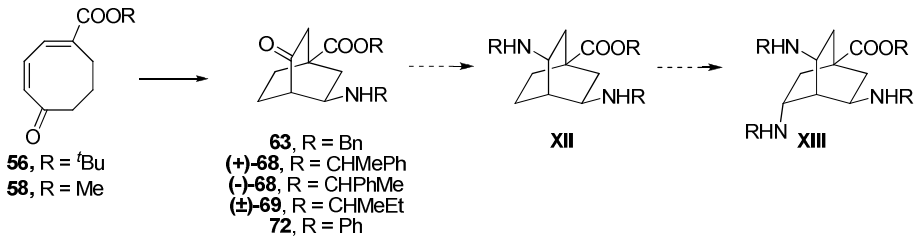
6. (1*E*,3*Z*) *tert*-butyl and methyl 5-oxo-cycloocta-1,3-diene carboxylates **56** and **58** were obtained from their respective cycloocta-1,3-diene carboxylates. The yield of the 5-oxo compounds is optimized by oxidation with TPAP of the alcohol intermediate.



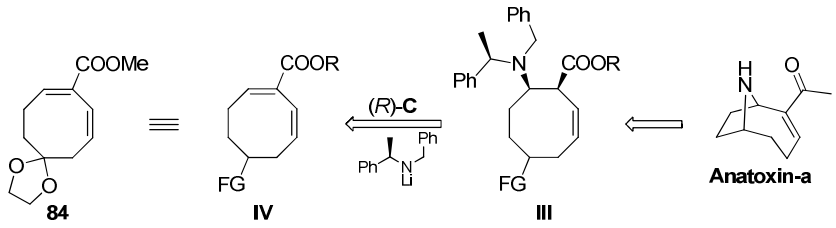
7. Through application of the same conditions used for the obtention of compounds **56** and **58** with the unsaturated esters **7** and **55**, different cyclooctanic derivatives were found such as *tert*-butyl and methyl 4-oxo-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate, **60** and **61**. When 60 is subjected to crystallization, the dimer 62 is obtained throughout a [2+2] cyclization. The structure of these compounds have been determined by X-Ray diffraction of **62**.



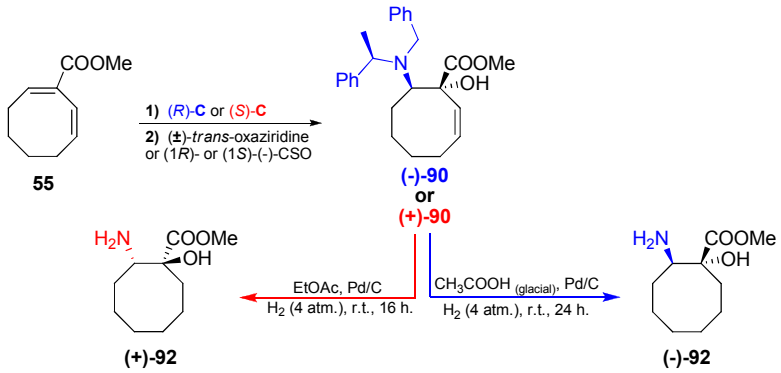
8. Through a complete study of the reactivity of **56** with amines, compounds with a bicycle[2.2.2]octane structure were obtained with primary amines. This fact opens a new and very interesting research pathway as its functionalization makes possible to obtain intermediates like **XII** or **XIII**. These type of compounds exhibit potential as organocatalysts, particularly derivative **XIII** which presents an own axis of C3 symmetry.



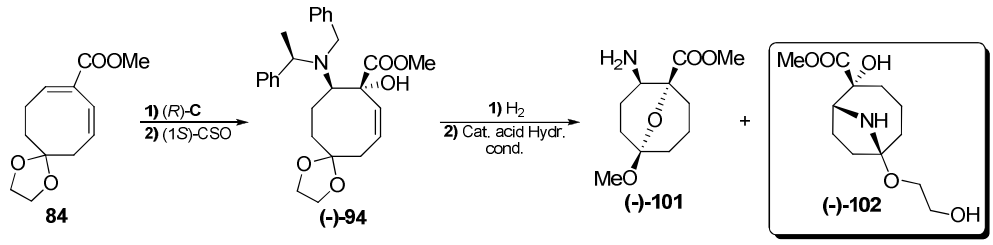
9. Methyl 5,5-ethylenedioxycycloocta-1,7-diene-1-carboxylate **84** is obtained in 6 steps from cycloocta-1,5-diene in a 75% overall yield. This compound represents a key derivative **IV** proposed in the approach to the synthesis of Anatoxin-a.



10. Methyl (1*S*,2*R*)- and (1*S*,2*S*)-1-hydroxy-2-amino-cyclooctanecarboxylates, **(-)-92** and **(+)92** are obtained in 16% and 26% overall yield from cycloocta-1,7-diene carboxylate **55**, respectively. Through a tandem reaction with chiral lithium amide followed by oxaziridine addition, which can be further converted into their respective functionalized cyclooctanic β-amino acids enriching our adducts library.



11. Using the previous tandem reaction, **(-)-94** is obtained in 32% from **84** and it has led to the synthesis of the bicycles **(-)-101** and **(-)-102**.



12. When the β-amino ester without the hydroxy group **(-)-106** is used in the previous cyclization reaction, the deprotected product from the carbonyl group and partial hydrogenolysis **(-)-112** is obtained in14% yield, together with the 9-azabicyclo[4.2.1]nonane **(-)-113** in 27% yield. The latter is a highly advanced synthon into the synthesis of Anatoxin-*a*.