Organocatalytic Synthesis of an Alkyltetrahydropyran

D. Díez,*[a] M. G. Núñez,[a] A. Benéitez,[a] R. F. Moro,[a] I. S. Marcos,[a] P. Basabe,[a] H. B. Broughton,[b] J. G. Urones[a]

[a] Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain
Fax +34(923)294574; E-mail: ddm@usal.es

[b] Lilly S. A., Avda de La Industria 30, 28108 Alcobendas, Madrid, Spain

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Abstract: The first synthesis of an alkyltetrahydropyran using a diarylprolinol organocatalyst is described.

Keywords: organocatalysis, tetrahydropyrans, diarylprolinol, cyclization

Tetrahydropyrans are present in many biologically active marine natural compounds[1] such as brevetoxin B[2] (Figure 1) and maitotoxin.[3] Our group has been interested for several years in the synthesis of this type of heterocycles, especially the more substituted ones.[4]

One of the most common procedures for the synthesis of tetrahydropyrans is the Michael addition of an alcohol to α,β-unsaturated esters to give *cis*-2-alkyl-3-oxy-tetrahydropyrans as described by Gung et al.[5] and Martín et al.[6] This methodology has been applied by Nicolaou et al. in the synthesis of brevetoxin B.[7]

The major drawbacks of the oxa-Michael reaction are its low reactivity, reversibility, and lack of control in stereoselectivity.[8] In order to solve this problem, several groups have made use of chiral auxiliaries.[9]

Recently, there has been a growing interest in the organocatalytic asymmetric oxa-Michael reaction.[10] The first highly enantioselective organocatalytic β-hydroxylation of α,β-unsaturated aldehydes was carried out by Jørgensen using oximes as nucleophiles.[11] Maruoka et al. have developed a biphenyldiamine-based catalyst to perform 1,4-additions of alcohols to α,β-unsaturated aldehydes.[12] In addition, the group of Falck has reported an enantioselective intramolecular oxa-Michael addition to γ/δ-hydroxy-α,β-enones using a thiourea quinine based organocatalyst.[13]

In the last years, several groups have also dedicated much effort to the organocatalytic synthesis of chiral benzopyran derivatives using trialkylsilyl-protected prolinols as catalysts. Arvidsson et al.[14] have reported a domino reaction involving an oxa-Michael attack of salicylic aldehyde derivatives onto α,β-unsaturated aldehydes, activated through iminium ion formation with the organocatalyst, followed by an intramolecular aldol reaction. The same strategy has been applied by Córdova et al.[15] and Wang et al.[16]

A pioneering application of an organocatalytic intramolecular oxa-Michael reaction was developed by Ishikawa et al. in the enantioselective synthesis of anti-HIV-1-active coumarins such as (+)-calanolide A catalyzed by quinine.[17] Recently, Scheidt et al.[18] have developed intramolecular cyclizations for the production of flavanones and chromanones using a quinine-derived thiourea catalyst to activate a β-keto ester alkylidene substrate and promote the oxa-Michael addition of the phenol. The group of Merschaert[19] has obtained chiral benzopyrans by intramolecular cyclization of phenols with α,β-unsaturated esters using cinchona alkaloids as catalysts.

However, to the best of our knowledge, there have been no reports on the organocatalytic synthesis of alkyltetrahydropyrans, so we decided to investigate an organocatalytic intramolecular oxa-Michael addition of alcohols to α,β-unsaturated aldehydes.

The first substrate chosen for our study was aldehyde **6** (Scheme 1), which was obtained from commercial δ-valerolactone (**1**) in four steps. DIBAL-H reduction[20] of the lactone **1** followed by a Wittig olefination[21] gave a mixture of hydroxy esters **3** and **4** in 65% yield and a ratio 1:10. After separating compound **4** by column chromatography, it was reduced to the allylic alcohol **5** in 87% yield. When **5** was submitted to MnO_2 allylic oxidation,[22] a mixture of the desired aldehyde **6**, and the cyclized compound **7** was obtained (Scheme 1). These compounds could not be sep-

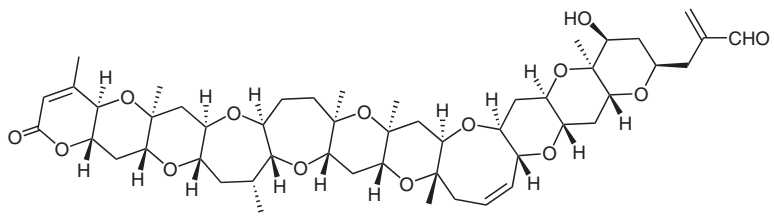

Figure 1 Brevetoxin B

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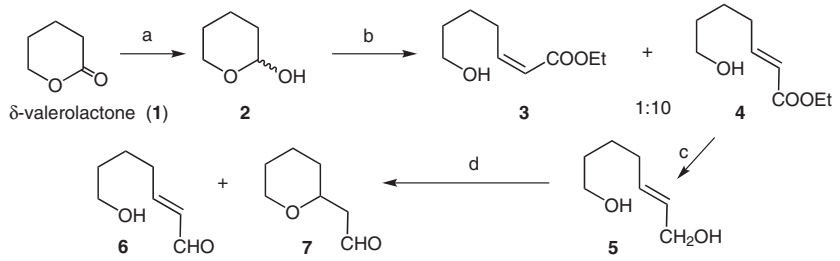
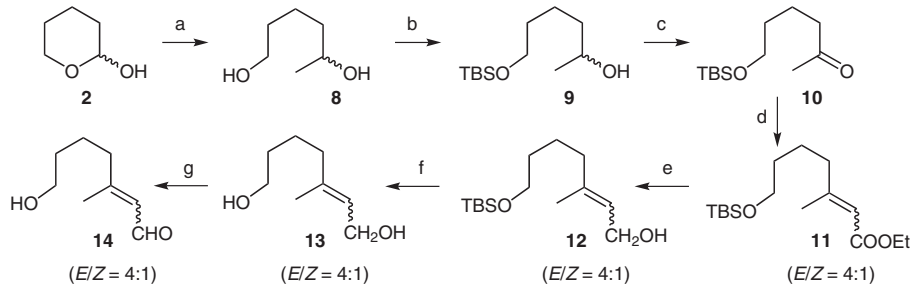


Scheme 1 *Reagents and conditions*: a) DIBAL-H, CH_2Cl_2, –78 °C; b) $Ph_3P(CH)COOEt$, C_6H_6, r.t., 12 h, 65%; c) DIBAL-H, CH_2Cl_2, –78 °C, 87%; d) MnO_2, CH_2Cl_2, r.t., 50%.



Scheme 2 *Reagents and conditions*: a) MeMgBr, THF, 0 °C, 70%; b) TBSCl, imidazole, DMF, 0 °C, 80%; c) TPAP, NMO, 3 Å MS, CH_2Cl_2, r.t., 2 h, 94%; d) $(EtO)_2Ph_3P(O)CH_2COOEt$, NaH, monoglyme, 60 °C, 96%; e) DIBAL-H, CH_2Cl_2, –78 °C, 93%; f) TBAF, THF, r.t.; g) MnO_2, CH_2Cl_2, r.t., 70% in 2 steps.

arated by column chromatography, as in the silica acidic medium aldehyde **6** underwent cyclization to give compound **7**.

We then decided to test a more hindered starting material such as aldehyde **14** (Scheme 2), starting again from δ-valerolactone (**1**).

In this case, lactol **2** was treated with methyl magnesium bromide,[23] obtaining **8** in 70% yield. This diol **8** was selectively monoprotected and oxidized with TPAP[24] to the methyl ketone **10** in 70% yield over two steps (Scheme 2). This compound was submitted to Horner–Wadsworth–Emmons reaction conditions[25] to obtain an inseparable mixture (*E*/*Z* = 4:1) of α,β-unsaturated esters **11**. This mixture was reduced with DIBAL-H to the allylic alcohol **12** in 93% yield. After deprotection and subsequent allylic oxidation with MnO_2, the required α,β-unsaturated aldehyde **14** was obtained in 70% yield over two steps.

Although compound **14** was obtained as a mixture of diastereoisomers *E*/*Z*, it was decided to use it as a substrate for organocatalytic oxa-Michael cyclizations since there are literature precedents of *E*/*Z* mixtures of olefins that lead to higher diastereomeric ratio in the final product as reported by Jørgensen in citral epoxidation[26] and of pure diastereoisomers *E* and *Z* that converge to the same enantiomer as in the hydride reduction of α,β-unsaturated aldehydes reported by MacMillan.[27]

Commercial or easily obtained pyrrolidines **C1**–**C7** and **C9**–**C10** and pyrrolidine **C8** (Figure 2), previously obtained by us,[28] were chosen to test as organocatalysts in the intramolecular oxa-Michael cyclization of substrate **14**.

Firstly, we performed the reaction at room temperature as shown in Table 1. The initial experiments showed that compound **14** did not cyclize when no catalyst was used, even when it was left reacting for a long period of time (entry 1). Pyrrolidines **C1** and **C2** catalyzed the reaction but aldehyde **15** rapidly oxidized to the carboxylic acid, so the ee could not be measured (entries 2 and 3, respectively). Catalyst **C5** gave no reaction (entry 4) and with **C6** the reaction took place, in the presence of 20 mol% of HCl (2 M), but the dimethyl acetal of **15** was obtained with no ee (entry 5).

In order to avoid the oxidation of the resulting aldehyde **15**, its in situ reduction was performed using DIBAL-H or $NaBH_4$ and a cosolvent when required.[29] The results are shown in Table 2.

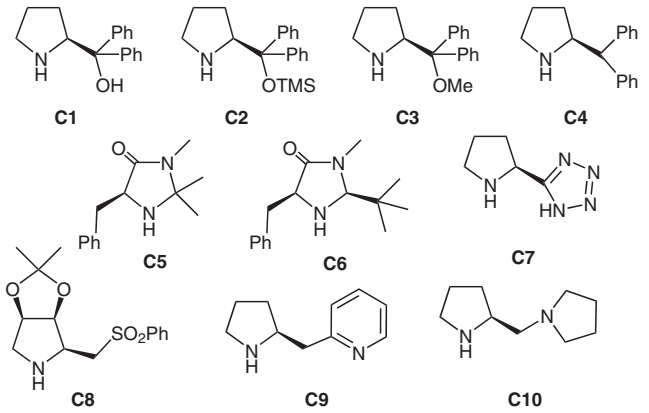
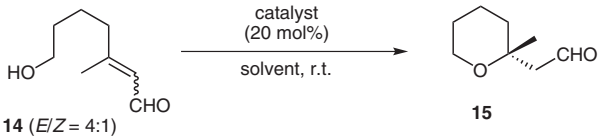


Figure 2 Organocatalysts tested in the intramolecular oxa-Michael reaction of substrate **14**

Table 1 Synthesis of Compound **15** with Various Catalysts



14 (*E*/*Z* = 4:1) **15**

Entry	Catalyst	Solvent	Time (h)	Yield (%)	ee (%)[a]
1	–	toluene	96	0	–
2	**C1**	CH_2Cl_2	112	10	n.d.
3	**C2**	toluene	2	75	n.d.
4	**C5**	MeOH	7	0	–
5	**C6**[b]	MeOH	24	53[c]	0

[a] Determined by chiral GC-MS (CHIRASIL DEX-CB).
[b] HCl (2 M; 20 mol%) was added.
[c] Dimethylacetal of **15** was obtained.

As is evident from Table 2, catalysts **C2**, **C9**, and **C10** gave the required alcohol **16** at room temperature, but the ee[30] was zero or very low (entries 1–9). So it was decided to carry out the reaction at low temperature with catalyst **C10**, since it was the one that promoted the fastest cyclization. At very low temperatures (–78 °C, –40 °C, entries 10 and 11), the reaction did not take place. However, raising the temperature to –20 °C, the cyclization took place in reasonable yield with very low ee.

In order to increase the ee, it was decided to use other catalysts such as **C3** and **C4**, which have been tested before in Michael additions,[10] and catalyst **C8**, previously synthesized by us.

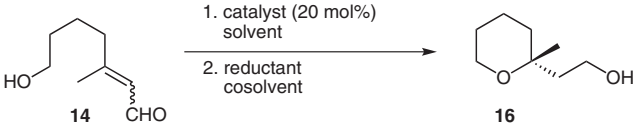
As shown in Table 2, catalyst **C8** gave compound **16** in good yield but with low ee (entry 15). Addition of benzoic acid as co-catalyst did not improve the results (entry 16). However, the use of catalyst **C3** gave better results. When the reaction was performed in toluene at –20 °C, 60% yield (in two steps) and 41% ee was obtained (entry 17), so we next investigated the effect of solvents (entries 19–21) and found that dichloromethane was the solvent of choice (entry 19).

When a temperature screening was carried out, it was found that the ee increased as temperature was lowered, while the yields remain unaffected (entries 22–25). The same effect was observed when using catalyst **C4**, bearing no methoxy group (entries 26 and 27).

Determination of the absolute configuration for tetrahydropyran **16** was carried out by obtaining the chiral compound using Sharpless asymmetric epoxidation[31] as follows (Scheme 3).

With regard to the mechanism, we assume that the reaction of the pyrrolidine-type catalyst with the α,β-unsaturated aldehyde results in an intermediary iminium ion which is then attacked by the hydroxyl moiety.[10] In order to explain the results obtained, a molecular modeling study has been carried out for the reaction of substrate **14** with catalyst **C3**. A wide variety of possible transition

Table 2 Synthesis of Compound **16** with Various Catalysts

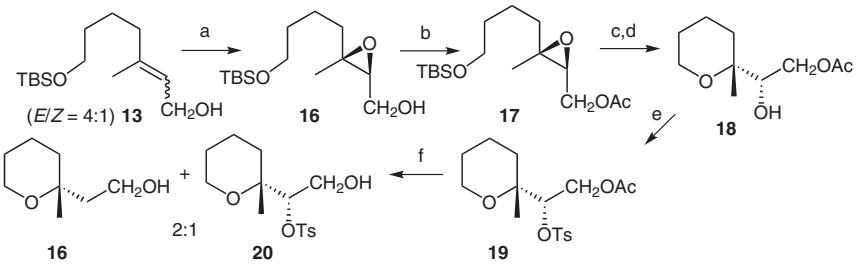


14 *E*/*Z* = 4:1 **16**

Entry	Catalyst	Solvent	Time (h)	Temp (°C)	Yield (%)[c]	ee (%)[a]	Config.[b]
1	**C2**	MeOH	7	r.t.	60	7	–
2	**C2**	toluene	1	r.t.	74	0	–
3	**C2**	CH_2Cl_2	3	r.t.	60	0	–
4	**C2**[c]	toluene	1	r.t.	68	0	–
5	**C7**	MeOH	2	r.t.	30	0	–
6	**C9**	toluene	3	r.t.	25	0	–
7	**C10**	MeOH	0.5	r.t.	30	5	–
8	**C10**	toluene	0.5	r.t.	43	0	–
9	**C10**	PhCl	0.5	r.t.	43	5	–
10	**C10**	toluene	3	–78	0	0	–
11	**C10**	toluene	3	–40	0	0	–
12	**C10**	toluene	0.5	–20	66	4	–
13	**C10**[d]	toluene	1	–20	64	5	–
14	**C10**	CH_2Cl_2	1	–20	40	4	–
15	**C8**	toluene	2	–20	80	13	*S*
16	**C8**[d]	toluene	2	–20	70	0	–
17	**C3**	toluene	2	–20	60	41	*R*
18	**C3**[d]	toluene	2	–20	63	37	*R*
19	**C3**	CH_2Cl_2	2	–20	70	44	*R*
20	**C3**	MeOH	6	–20	61	26	*R*
21	**C3**	THF	6	–20	20	33	*R*
22	**C3**	CH_2Cl_2	2	r.t.	62	0	–
23	**C3**	CH_2Cl_2	2	0	74	14	*R*
24	**C3**	CH_2Cl_2	2	–40	30	48	*R*
25	**C3**	CH_2Cl_2	12	–78	50	57	*R*
26	**C4**	toluene	1	–20	60	48	*R*

[a] Determined by chiral GC-MS (CHIRASIL DEX-CB).
[b] Determined by comparison with the chiral compound **16** obtained as described in Scheme 3.
[c] Determined after isolation of pure compound.
[d] Benzoic acid (20 mol%) was added.

states for the cyclization process has been explored according to the following protocol: RHF/AM1 has been used to perform geometry optimizations and thermochemical analysis, while for the energies of the optimized



Scheme 3 *Reagents and conditions*: a) L-(+)-DET, Ti(*i*-OPr)$_4$, TBHP, –23 °C, 12 h, 90%; b) Ac_2O, pyrdine, r.t., 92%; c) TBAF, THF, r.t., 80%; d) CSA, CH_2Cl_2, –40 °C, 60%; e) TsCl, pyridine, 0 °C to r.t., 90%; f) LAH, THF, 0 °C, 50%.

geometries, single-point calculations at the B3LYP/6-31G* level of theory were performed.[32] All these calculations were carried out with the Gaussian 03 package.[33] Our best current estimations of the two preferred transition states are shown in Figure 3. They are considered on balance the most likely to be good models for the oxa-Michael reaction. This choice is based on our analysis of the single-point B3LYP/6-31G* energy calculations, the comparison of gas-phase energies vs. solvation models, the consideration of the qualitative effect of the dipole and the calculated RHF/AM1 thermochemical parameters.[1] In the solvation model, the energy gap between transition states is 5.7 kcal/mol in favor of the *R*-isomer (ee expected >99.9%), 0.7 kcal/mol smaller than in the gas-phase calculation. Unsurprisingly, this energy difference is not fully consistent with the observed ee. At this level of theory we could not be able to make a better prediction, because the required energetic difference for the observed ee would be ca. 0.4–0.8 kcal/mol, well within the error of the method. However, the identified transition states – with minimized steric interactions and chairlike conformations for the cyclization – are consistent with our expectations, and we have been able to correctly predict the major isomer generated as *R*. We continue to work on more computationally intensive models using higher levels of theory, solvation models, and full thermochemical analysis at the same level of theory as the optimizations. Nonetheless, we believe that this preliminary result may be qualitatively useful to those wishing to use catalysts and substrates similar to those described here.

In summary, the first synthesis of a chiral alkyltetrahydropyran has been achieved using commercially available catalysts. This procedure opens the way for further research to increase the yields and ee of the tetrahydropyrans obtained.

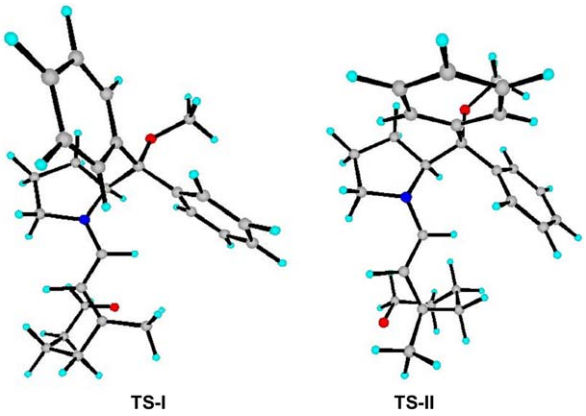


Figure 3 Chairlike transition states suggest that the methyl group is equatorial, and attack of the alcohol is from the underside of the intermediate *E*-iminium salts; favored TS-I leads to the *R* product

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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