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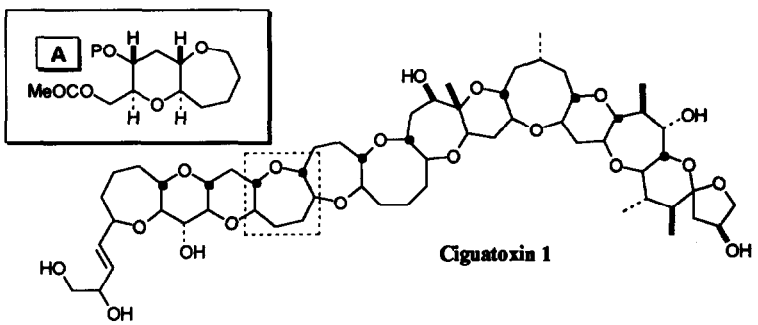
Stereocontrolled Synthesis of Cyclic Ethers by Intramolecular Hetero-Michael Addition. 4. Enantiomeric Synthesis of Substituted and Fused Oxepanes

Marcos A. Soler, José M. Palazón and Victor S. Martín*

Centro de Productos Naturales Orgánicos "Antonio González"
Instituto Universitario de Bio-Orgánica, Universidad de La Laguna
Carretera de La Esperanza, 2, 38206 La Laguna, Tenerife, Spain

Abstract: The use of an intramolecular hetero-Michael addition of enantiomerically enriched 7-alkoxy-4-benzoyloxy-2,3-unsaturated esters for the synthesis of *endo*-substituted oxepanes is described. The stereochemistry in the cyclization step is governed by the geometry of the double bond in the unsaturated ester and the presence of a *Z*-double bond in the linear chain is required in order to achieve good yields. The synthesis of the fused oxepane-tetrahydropyran nucleus of marine polyether toxins with absolute control of all the stereocentres is described.

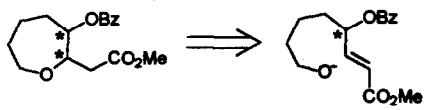
The oxepane ring is frequently encountered in polyether toxins such as brevetoxins,[1] ciguatoxin 1,[2] yessotoxin,[3] gambierol,[4] gambieric acids[5] and maitotoxin,[6] *trans*-fused to other cyclic ethers whose size oscillates from 6 to 9 members, with two *cis*-substituents near to the oxygen atom. The stereoselective synthesis of such a ring is currently receiving a great deal of attention.[7]



Ciguatoxin 1

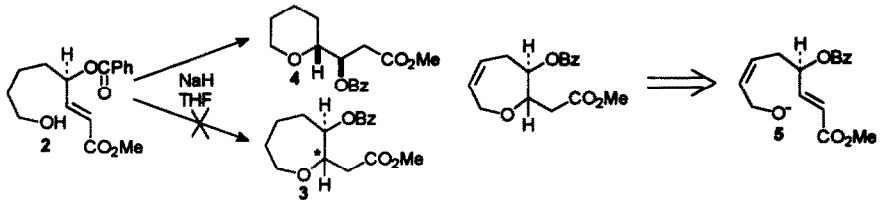
Figure I

Recently, we have reported an approach to the stereocontrolled synthesis of *endo*-substituted tetrahydropyrans by an intramolecular hetero-Michael addition of a γ-substituted-α,β-unsaturated ester in which the stereochemistry in the ring closure is controlled by the geometry of the double bond.[8] We wondered if such methodology could be applicable to the synthesis of oxepanes. The idea, in principle, is very attractive since the precursors are similar to those used in the oxane synthesis.

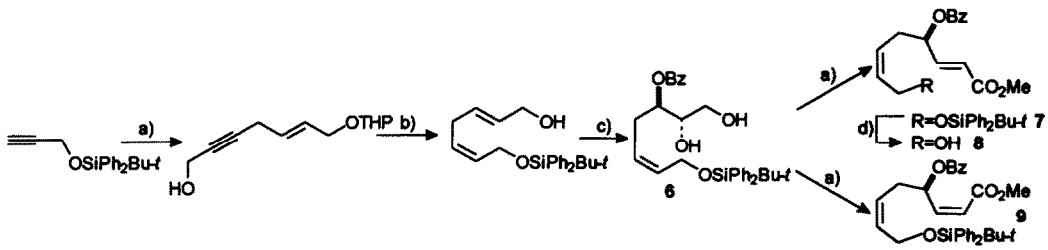


We realized, however, that the hetero-Michael reaction leading to the seven-membered ring should be thermodynamically disfavoured. This proved to be the case when we treated the α,β-unsaturated ester **2**[9] under basic conditions, because instead of the desired oxepane **3**, the *exo*-tetrahydropyran **4** was obtained, probably by a benzoate participation. It is well known, however, that the introduction of a *Z*-double bond in a linear chain

introduces thermodynamic and entropic factors which may favour the cyclization reaction. In our case a tentative approach could be the intramolecular cyclization of **5**.



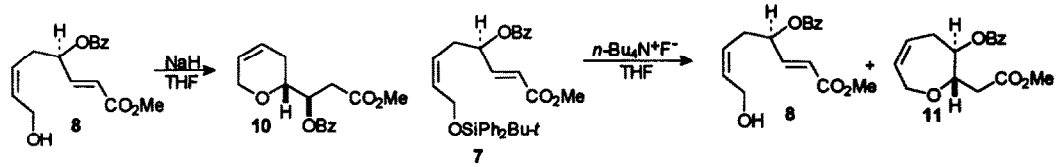
In order to prove our idea the double unsaturated ester **7** was synthesized from propargylic alcohol according to **Scheme I**.



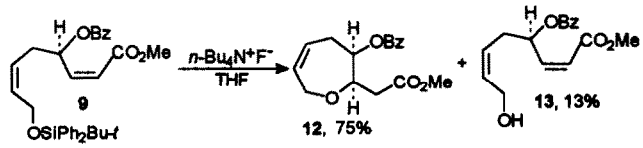
a) Ref. 8; b) i) Lindlar's catalyst, quinoline (cat), MeOH, 90%; ii) *n*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt, 1 h; 92%; iii) MeOH, HCl (cat.), 1 h, 87%; c) i) $Ti(OPr\text{-}i)_4$, (R,R)-(+)-DET, TBHP, CH_2Cl_2, 3Å MS, -20 °C, 80%; ii) PhCOOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2, rt, 84%; d) HF, CH_3CN, rt, 18 h, 91%.

Scheme I

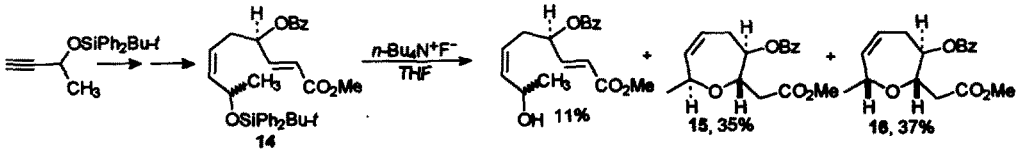
However, when **8** was submitted to basic conditions (NaH, THF, -78°C) again the *exo*-oxane **10** was obtained. Surprisingly, when we tried to remove the silyl protection under standard conditions using *n*-$Bu_4N^+F^-$ the *trans*-oxepene **11**, $[\alpha]_D^{25}$ -25.7° (c 0.30, $CHCl_3$), was obtained as the only sterereoisomer in 75% isolated yield with a small amount of the free alcohol **8** (≈15%).



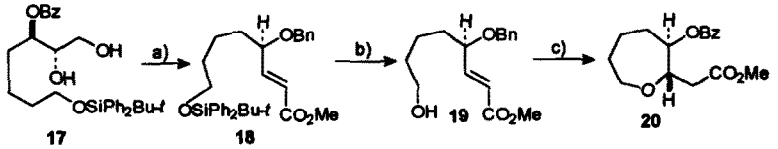
The most striking features of the procedure are that the stereochemistry can be controlled by the geometry of the double bond and the only observed byproduct is the free alcohol which, obviously, can be recycled. Thus when the *Z*-isomer **9** was treated with *n*-$Bu_4N^+F^-$, in THF solution, the *cis*-oxepene **12**, $[\alpha]_D^{25}$ -19.7° (c 0.27, $CHCl_3$) was obtained as the only stereoisomer with a small amount of **13**.



In an attempt to find a more similar model to that found in the polyether toxins we studied the cyclization of the diastereoisomeric mixture **14** in which the nucleophilic oxygen is located in a secondary alcohol. Again in this case the stereochemistry in the cyclization is completely controlled by the double bond geometry of the α,β-unsaturated ester, the *trans*-substituted oxepenes **15**, $[\alpha]_D^{25}$ -27.6° (c 0.29, $CHCl_3$), and **16**, $[\alpha]_D^{25}$ -28.4° (c 0.32, $CHCl_3$) being obtained in equimolecular amounts.



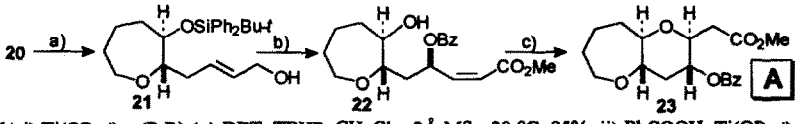
In order to explain the role of the fluoride, we studied the cyclization reaction over the more simple compound, changing the protecting group of the precursor. Thus, when the benzyl protected diol **18** obtained from **17**[9] (**Scheme II**), was treated with *n*-$Bu_4N^+F^-$, in THF solution, only the free alcohol **19** was obtained. The role of the F^- seems to be simply to generate sufficient alkoxide to perform the cyclization. On the other hand, when **19** was treated under our standard basic conditions the only stereoisomer *trans*-oxepane **20**, $[\alpha]_D^{25}$ -35.6° (c 2.02, $CHCl_3$), was obtained although with only 15% isolated yield.



a) i) $PhCH(OMe)_2$, CSA (cat), CH_2Cl_2, rt, 5 min; ii) NaOMe, CH_2Cl_2, rt, 10 min; iii) BnBr, NaH, *n*-$Bu_4N^+I^-$ (cat.), THF, 18 h; iv) MeOH, CSA (cat.), rt, 74% overall; v) $NaIO_4$, THF:H_2O (5:1), rt; vi) $(MeO)_2P(O)CH^-CO_2Me$, benzene, 0 °C, *E* : *Z* (>20 : 1), 86% overall; b) *n*-$Bu_4N^+F^-$, THF, rt, 92%; c) NaH, THF, -78°C, 1 h, 12%.

Scheme II

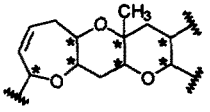
The synthesis of the oxepane-tetrahydropyran nucleus **A** (**Figure I**) present in ciguatoxin and related polycyclic toxins has been performed in a straightforward manner with the conjunction of the methodology described above and the previously reported synthesis of fused tetrahydropyrans.[8] Thus, the *trans*-oxepane **20** was homologated to the allylic alcohol **21** necessary to introduce the additional stereocentre by a new asymmetric epoxidation with the proper choice of the chiral auxiliary. The control of the stereochemistry of the newly created ring was obtained by performing the new hetero-Michael cyclization over the *Z*-isomer **22** of the α,β-unsaturated ester, yielding the *trans-trans*-oxepane-oxane **23** as the sole stereoisomer (**Scheme III**).[10]



a) Ref. 8; b) i) $Ti(OPr\text{-}i)_4$, (R,R)-(+)-DET, TBHP, CH_2Cl_2, 3Å MS, -20 °C, 85%; ii) PhCOOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2, rt, 89%; iii) $NaIO_4$, THF:H_2O (5:1), rt; iv) $Ph_3P{=}CHCO_2Me$, MeOH, rt, 12 h, *Z* : *E* (2 : 1),[11] 78% overall; v) HF, CH_3CN, rt, 18 h, 92%; c) NaH, THF, -78°C, 1h, 91%.

Scheme III

In summary, we have described a general methodology to the enantiomeric synthesis of fused polycyclic ethers with absolute control in all the stereocentres.



The application of such methodology to fragments occurring in polyether toxins is under study and will be published in due course.

Acknowledgement: This research was supported by a grant from the DGICYT (MEC of Spain) PB89-0402. M. A. S. thanks the M.E.C. for a F.P.I. fellowship.

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8. See the preceding paper in this issue. See also: a) Martín, V.S.; Nuñez, M.T.; Ramírez, M.A.; Soler, M.A. *Tetrahedron Lett.*, **1990**, *31*, 763; b) Martín, V.S.; Palazón, J.M. *Tetrahedron Lett.*, **1992**, *33*, 2399.
9. **2** and **17** have been obtained using the same procedure reported in ref. 8a.
10. **23**, $[\alpha]_D^{25}$ -7.8° (c 0.69, $CHCl_3$), ^{1}H-NMR (400 MHz, C_6D_6) δ: 1.36 (m, 5 H), 1.74 (dddd, J=11.5, 11.5, 5.6, 5.6 Hz, 1 H), 2.06 (dd, J=5.3, 5.3 Hz, 1H), 2.61 (m, 3H), 2.93 (dddd, J=13.8, 9.2 Hz, 4.6, 4.6 Hz, 1H), 3.18 (dd, J=9.0, 4.0 Hz, 1 H), 3.30 (s, 3H); 3.34 (dd, J=11.4, 6.0 Hz, 1H), 3.59 (ddd, J=7.8, 1.3, 1.3 Hz, 1H), 4.15 (dddd, J=12.3, 8.0, 4.3, 4.3 Hz, 1H), 5.05 (dddd, J=14.5, 9.8, 4.7, 4.7 Hz, 1H), 7.08 (t, J=7.4 Hz, 2H), 7.16 (t, J=7.4 Hz, 1H), 8.12 (dd, J=7.4, 1.44 Hz, 2H); ^{13}C-RMN ($CDCl_3$) δ: 20.31 (t), 29.54 (t), 34.64 (t), 37.44 (t), 38.18 (t), 52.10 (q), 69.57 (t), 71.56 (d), 76.09 (d), 76.78 (d), 77.19 (d), 82.64 (d), 128.64 (d), 130.11 (d), 133.69 (d), 165.87 (s), 171.82 (s); HRMS calculated for $C_{19}H_{25}O_6$ (M^+ + 1): 349.1651, found: 349.1657.
11. We are currently performing the generation of the *Z*-unsaturated esters using $(TFEO)_2P(O)CH_2CO_2Me$ and $KN(TMS)_2$/18-crown-6 in THF, achieving *Z*:*E* ratios >10:1. See: Still, W.C.; Gennari, C. *Tetrahedron Lett.*, **1983**, *24*, 4405.
12. Satisfactory spectroscopic data were obtained for the new compounds. The absolute configuration in all chiral products has been determined by ROESY and NOEDIFF experiments (BRUKER AMX400) assuming the expected sterochemical course of the asymmetric epoxidation: a) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1980**, *102*, 5976; b) Martín, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M; Sharpless, K.B. *J. Am. Chem. Soc.*, **1981**, *103*, 6237; c) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1987**, *109*, 5763.

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