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Stereocontrolled Synthesis of Cyclic Ethers by Intramolecular Hetero-Michael Addition. 3. Enantiomeric Synthesis of Highly Functionalized and Fused Tetrahydropyrans

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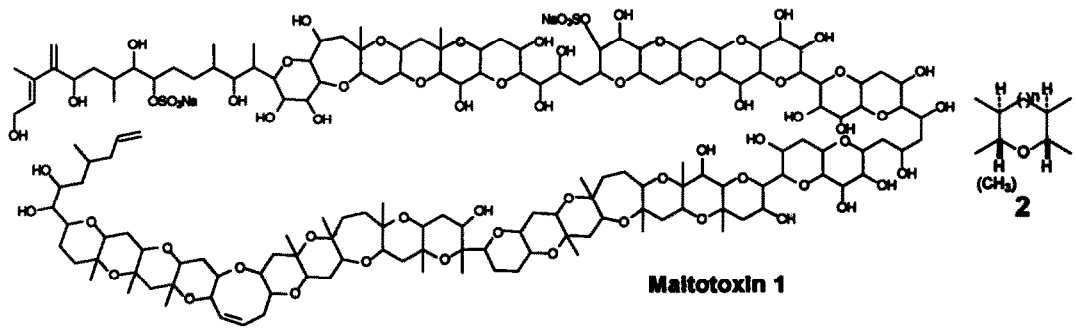
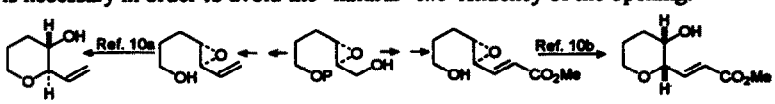
Abstract: A methodology based on intramolecular hetero-Michael addition of properly functionalized alkoxy-γ-benzoyloxy-α,β-unsaturated esters for the synthesis of highly substituted and fused poly-tetrahydropyran nuclei of marine polyether toxins with absolute control of all the stereocentres is described.

Maitotoxin 1, with a molecular weight of 3422 DA, is one of the largest natural products known.[1] It exceeds palytoxin in size and lethality (LD_{50} 50 ng/kg, ip) and it has been implicated in ciguatera food poisoning by a Ca^{+2} channel-dependent mechanism.[1] Other structurally related toxins such as brevetoxins,[2] ciguatoxin,[3] yessotoxin,[4] gambierol[5] and gambieric acids[6] have also been described as substances interacting with the cation channels of cellular membranes.[7] These highly complex molecules are characterized by having fused cyclic ether units whose size oscillates from 5 to 9 members and with a well-defined stereochemistry, usually with a *trans*-relationship between the two substituents (H or CH_3) in the fusion of rings and a *cis*-stereochemistry in the substituents (H or CH_3) close to the oxygen atom of the cyclic ether 2 (n = 0→4). The synthesis of such fused systems is currently receiving a great deal of attention since they are the key step in any possible total synthesis of such molecules.[8]



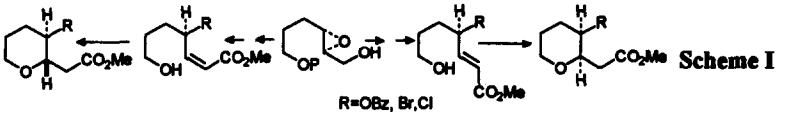
Maitotoxin 1

The tetrahydropyran ring 2 (n=1) is the most frequently encountered cyclic unit in this class of compounds. The enantiomeric synthesis of such rings has been performed by the intramolecular opening of chiral epoxyalcohols, available by the use of the Sharpless asymmetric epoxidation,[9] although the presence of a π-directing group is necessary in order to avoid the "natural" *exo*-tendency of the opening.[10]



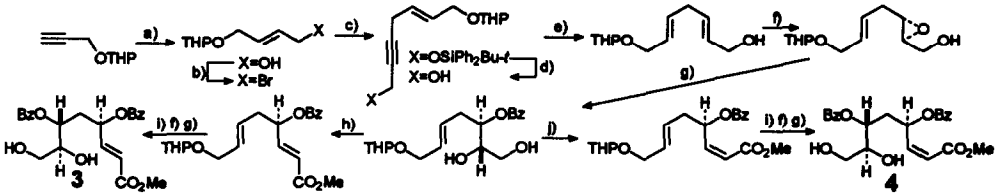
Recently, we have described a procedure to synthesize *endo*-substituted tetrahydropyrans based on an intramolecular hetero-Michael addition on chiral alkoxy-γ-benzoyloxy-α,β-unsaturated esters, in which the

cyclization stereochemistry is controlled by the geometry of the double bond (**Scheme I**).[11] Because in this methodology the unsaturated precursors were also obtained from chiral epoxides a formal *endo*-opening of such epoxides was achieved.



Scheme I

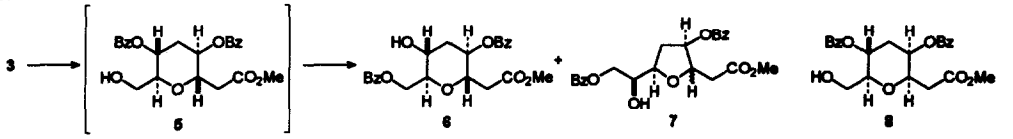
With this synthetic tool in our hands we expected that such a procedure could be applied to the synthesis of the highly substituted system **2** (n=1) by the proper choice of the geometry of the double bond in the unsaturated linear compound. Thus the necessary *E*- and *Z*-unsaturated esters **3** and **4** were synthesized according to **Scheme II**.



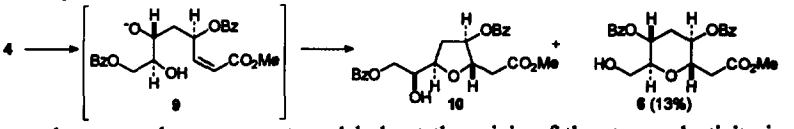
a) i) *n*-BuLi, THF, -78 °C, 15 min, then $(CH_2O)_n$, -78 °C → rt, 95%; ii) $LiAlH_4$, THF, rt, 4 h, then NaOMe, 15 min, 85 %; b) i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min; ii) LiBr, DMF, rt, 16 h, 87%; c) *t*-$BuPh_2SiOCH_2C{\equiv}CMgBr$, Cu_2Cl_2, THF, rt →70 °C, 1 h, 79%; d) $(n\text{-}Bu)_4N^+F^-$, THF, 1 h, 92%; e) $LiAlH_4$, THF, 5h, 91%; f) $Ti(OPr\text{-}i)_4$, (R,R)-(+)-DET, TBHP, CH_2Cl_2, 3Å MS, -20 °C, 80%; g) PhCOOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2,rt, 84%; h) i) $NaIO_4$, MeOH, rt; ii) $(MeO)_2P(O)CH^-CO_2Me$, benzene, 0 °C, *E*:*Z* (>20:1), 88% overall; i) MeOH, HCl conc. (cat.), 95%; j) $Ph_3P{=}CHCO_2Me$, MeOH, rt, 12 h, *Z* : *E* (2 : 1), 85% overall.

Scheme II

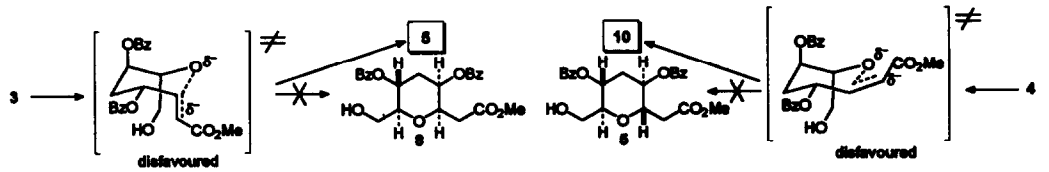
However when **3** was submitted to basic conditions [NaH (>2 equiv), THF, -78 °C, 1h][11] the all *trans*-substituted tetrahydropyran **6**, $[\alpha]_D^{25}$ +4.98° (c 0.7, $CHCl_3$), was obtained in 75% isolated yield together with a small amount of the diastereoisomeric mixture of tetrahydrofurans **7**, instead of the expected *cis*-compound **8**.[11] Although the stereochemical course of the simple model (**Scheme I**) was not followed, the cyclization was produced with excellent diastereoselection. It should be pointed out that **5** has been isolated when less than 1 equiv of NaH was used in the cyclization step, although conversion to the cyclic products was incomplete in this case.



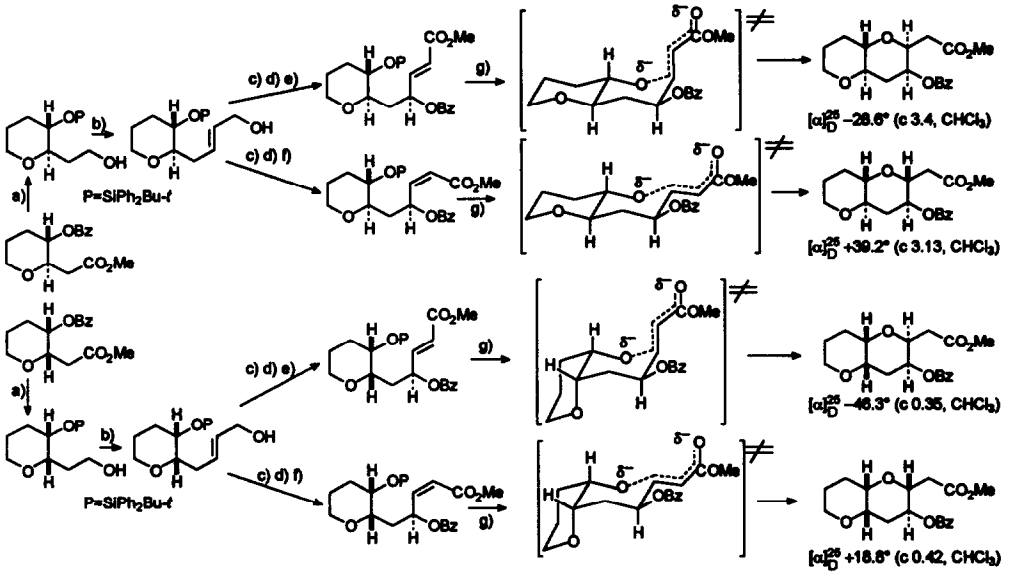
The basic cyclization of the *Z*-isomer yielded a small amount of the expected **6**. However, the main obtained product was the tetrahydrofuran **10**, $[\alpha]_D^{25}$ -6.1° (c 0.34, $CHCl_3$), (80% isolated yield) as the sole stereoisomer, probably via the trans-esterified alkoxy intermediate **9**.



Although we do not yet have an exact model about the origin of the stereoselectivity in the cyclization step, we conjecture that a possible cause of the unexpected results in the former cases compared with the models (**Scheme I**)[11] could be the presence of the additional groups located in disfavoured conformational positions (*trans*-diaxial mode) making it difficult to reach a proposed chair-like transition state.[12]



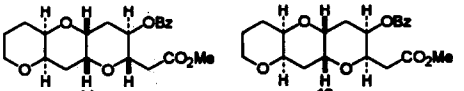
Obviously, if such an assumption were correct in systems in which such a transition state could be reached, the cyclization step should follow the expected reaction stereochemistry. Fortunately, this was the case when a cyclic ether[10] was already present. The cyclization of any γ-benzoyloxy-α,β-unsaturated ester obtained from either a *cis*- or a *trans*-tetrahydropyran according to **Scheme III** yielded the expected stereochemistry in all the fused tetrahydropyran-tetrahydropyrans by choosing the stereochemistry of the benzoyloxy group (controlled by the second asymmetric epoxidation step) and the double bond geometry.



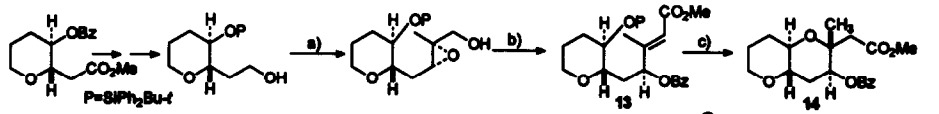
a) i) $LiAlH_4$, THF, 0°C, 10 min; ii) BzCl (1.1 equiv), CH_2Cl_2, Et_3N; 0°C, 30 min, iii) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt, 2 h; iv) NaOMe, CH_2Cl_2, rt, 15 min, 73% overall; b) i) SO_3-Py, DMSO, rt, 1h; ii) $(MeO)_2P(O)CH^-CO_2Me$, benzene, 0 °C, *E* : *Z* (>20:1), iii) DIBAL®, ether, 0°C, 10 min, 78% overall; c) $Ti(OPr\text{-}i)_4$, (S,S)-(−)-DET, TBHP, CH_2Cl_2, 3Å MS, -20 °C, 88%; d) PhCOOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2, rt, 84%; e) i) $NaIO_4$, THF: H_2O (5:1), rt; ii) $(MeO)_2P(O)CH^-CO_2Me$, benzene, 0 °C, 88% overall; f) i) $NaIO_4$, THF: H_2O (5:1), rt; ii) $Ph_3P{=}CHCO_2Me$, MeOH, rt, 12 h, *Z*:*E* (2 : 1), 81% overall; g) i) HF, CH_3CN, 16 h, 92%; ii) NaH, THF, -35 °C, 1h, >90%.

Scheme III

The iterative procedure has been extended to the synthesis of the tri-tetrahydropyran systems **11**, $[\alpha]_D^{25}$ +9.1° (c 0.46, $CHCl_3$), and **12**, $[\alpha]_D^{25}$ +47.8° (c 1.33, $CHCl_3$), in a straightforward manner.



At this point we considered that the methodology could be extended to the synthesis of methyl substituted oxanes with the proper choice of the α,β-unsaturated ester. This was really the case when the *E*-methyl derivative **13** was submitted to our basic standard conditions because the methyl substituted di-tetrahydropyran **14**, $[\alpha]_D^{25}$ +45.8° (c 2.5, $CHCl_3$), was obtained as the only stereoisomer (**Scheme IV**). It should be pointed out that in this case both **13** and its *Z*-geometrical isomer yielded the same stereochemical course affording the *trans*-functionalized (CH_3 and H) oxane. Although only one case has been shown in **Scheme IV**, the cyclization mode has been observed to be general in other related systems.



a) i) SO_3-Py, DMSO, rt, 1h, ii) $Ph_3P{=}C(CH_3)CO_2Me$, benzene, rt, 6h; iii) DIBAL®, ether, 0°C, 10 min, 83% overall; iv) Ti(OPr-*i*)$_4$, (S,S)-(−)-DET, TBHP, CH_2Cl_2, 3Å MS, -20 °C, 90%; b) i) PhCOOH, Ti(OPr-*i*)$_4$, CH_2Cl_2, rt, 84%; ii) $NaIO_4$, THF: H_2O (5:1), rt; ii) $(MeO)_2P(O)CH^-CO_2Me$, benzene, 0 °C, 85% overall; c) i) HF, CH_3CN, 16 h, 89%; ii) NaH, THF, -78°C, 1h, 94%.

Scheme IV

The application of the described methodology to the synthesis of the poly-tetrahydropyran nucleus of some marine polyether toxins is underway and will be reported in due course.

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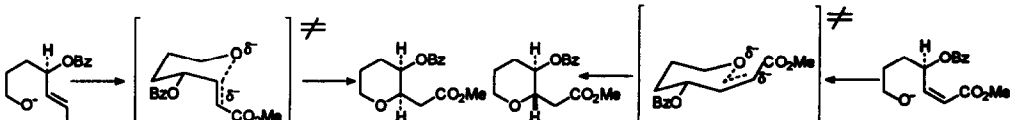
12. By the use of extensive semiempirical calculations we have found that the transition states for the cyclization of both *E*- and Z-alkoxy-γ-benzoyloxy-α,β-unsaturated esters shown below explain the observed stereochemical results. These studies will be published elsewhere.



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 stereochemical course of the asymmetric epoxidation (see ref. 9).

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