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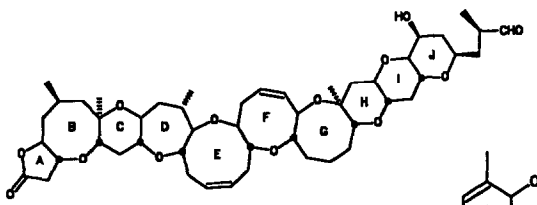
ENANTIOMERIC SYNTHESIS OF *endo*-SUBSTITUTED TETRAHYDROPYRANS

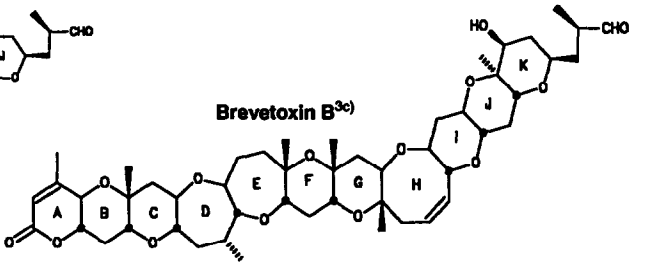
Victor S. Martín,* Maria T. Nuñez, Miguel A. Ramirez and Marcos A. Soler
Centro de Productos Naturales Orgánicos "Antonio González"
Instituto Universitario de Bio-Orgánica
Carretera La Esperanza, 2
38206 La Laguna, Tenerife, SPAIN

Summary: A general procedure for the enantiomeric synthesis of 3-hydroxy-2-alkyl-tetrahydropyran benzoates with absolute stereochemical control by using a new intramolecular diastereoselective cyclization of chiral hydroxy-α,β-chiral unsaturated esters is reported.

In our general program devoted to the total synthesis of bioactive marine natural products[1] we have directed our attention to a wide group of substances isolated from different species of *Laurencia*, as well as from *Aplysia* molluscs, which have in common the presence of polyfunctionalized cyclic ethers,[2] which are also the main structural feature of a group of very complex molecules presenting a strong toxic effect and which are produced by different microorganisms, mainly dinoflagellates, from which the **brevetoxins** have undoubtedly received more attention than any of the others, over the last decade.[3]



Brevetoxin A[3a,3b]

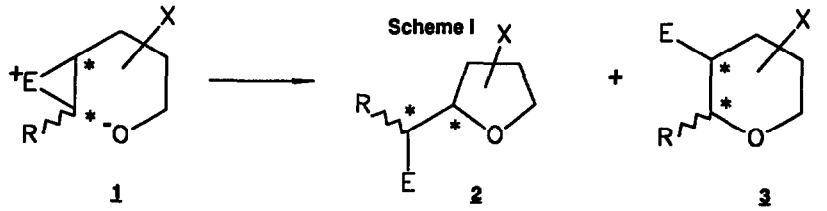


Brevetoxin B[3c]

The main problem to solve in any total synthesis of this kind of substances in their enantiomeric natural form is the proper building up of a suitable cyclic ether with sufficient functionality to join all the other rings.

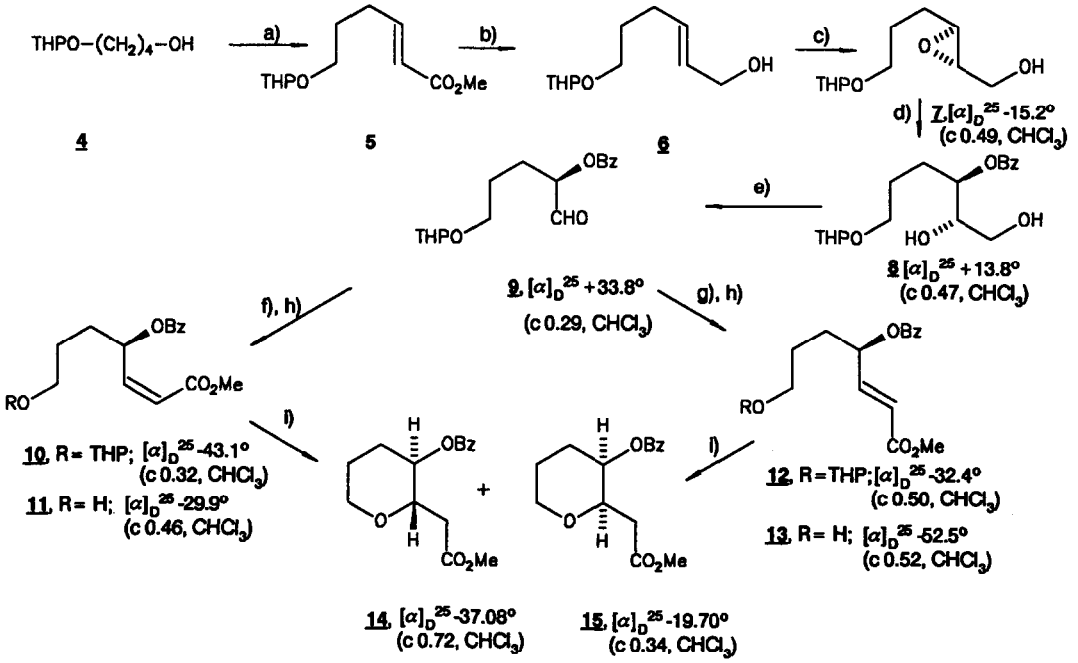
We have focussed our attention on the compounds containing the tetrahydropyran moiety, continuing our basic approach in the synthesis of polysubstituted tetrahydrofurans, of first constructing a suitable acyclic precursor which is further submitted to stereoselective cyclization.[4]

However, in the synthesis of substituted tetrahydropyrans a major difficulty arises with this approach, in the sense that at least special structural features are introduced,[5] in a cyclization of an acyclic chain 1 the smaller ring is produced when the *exo*- and *endo*-openings are competing (tetrahydrofuran 1 vs. tetrahydropyran 2), according to Baldwin's rules.[6]



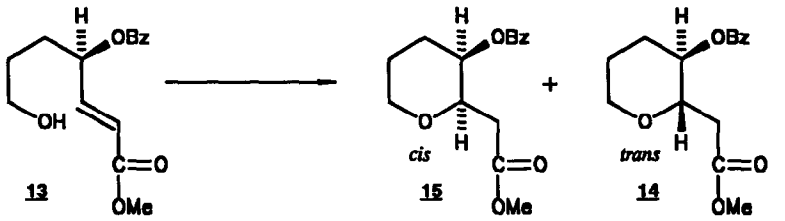
Considering the highly positive fact of the easy introduction of chirality in an acyclic chain by asymmetric epoxidation,[7] we have developed a new approach to the above-mentioned compounds, presenting our preliminary results in this communication, based on a diastereoisomeric intramolecular α,β-conjugated addition of a nucleophilic oxygen in a chiral acyclic precursor. For this study we have performed the synthesis of the unsaturated esters **11** and **13** from monoprotected 1,4-butanediol **4** (Scheme II).

Scheme II



a) i) Swern's oxidation,[8] ii) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, O°C, 83% overall; b) DIBAL, ether, O°C, 88%; c) $Ti(OPr\text{-}i)_4$, L(+) DET, TBHP, CH_2Cl_2, -20°C, >95% ee, 85%;[7] d) PhCOOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2, r.t., C-3 vs. C-2 opening (>100:1), 80%;[9] e) $NaIO_4$, MeOH, H_2O, 84%; f) $Ph_3P{=}CHCO_2Me$, MeOH, r.t., Z:E (2:1), 85%;[10] g) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, O°C, E:Z (>20:1), 93%;[10] h) MeOH, H^+, >95%; i) NaH, solvent, >95%.

Scheme III



Solvent	Temperature	*cis/trans* Ratio
THF/HMPA	0°C	4 : 1
	-78°C	10 : 1
Benzene	0°C	2 : 1
CH_2Cl_2	0°C	2.5 : 1
THF	0°C	3 : 1
CH_3CN	0°C	4 : 1
Toluene	-78°C	8 : 1

In order to study the influence of solvent and temperature in the cyclization step we have performed over the E-ester 13 the studies shown in **Scheme III**. As can be observed, only a small increase in diastereoselectivity has been detected when changing from a non-polar to a polar solvent, at the same temperature. However, the temperature has a strong influence in the course of the reaction, reaching a maximum selectivity of the *cis*-product 15[11] (10:1) a -78°C in a polar solvent.

In an attempt to reverse the diastereoselectivity, the cyclization of the Z-unsaturated ester 11was performed. We found that even at 0°C in a non-polar solvent (toluene) a diastereoselectivity of more than 20:1 in favour of the *trans*-tetrahydropyran 14[12] was reached (actually, in most run the *trans*-compound was the only product detected).

In consequence, we feel that we have in our hands a new and useful way to achieve the enantiomeric synthesis of 3-hydroxy-2-alkyl tertrahydropyrans which are the structural base of a large number of very interesting natural products, including fragments of **brevetoxins**. The synthesis of more substituted and fused chiral tetrahydropyrans using the methodology described in this communication is under way and will be published elsewhere.

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11.- ^{1}H-NMR (δ, C_6D_6): 0.87 (1H, m), 1.32 (1H, m), 1.76 (1H, m), 1.92 (1H, m), 2.56 (1H, dd, J=16 and 8.5 Hz), 2.64 (1H, dd, J= 16 and 4.9 Hz), 3.20 (1H, ddd, J= 11.7, 11.7 and <1 Hz), 3.35 (3H, s), 3.82 (1H, ddd, J= 11.7, 4.5 and 2.2 Hz), 3.96 (1H, ddd, J= 8.5, 4.9 and <1 Hz), 5.13 (1H, ddd, J= 3, <1 and <1 Hz), 7.1 (2H, m), 8.25 (1H, m). ^{13}C-NMR (δ, CCl_3D): 20.68 (t), 28.00 (t), 37.36 (t), 51.80 (q), 68.85 (t), 69.18 (d), 74.96 (d), 128.49 (d), 129.76 (d), 133.18 (d), 165.93 (s), 171.39 (s). IR ($CHCl_3$ cm^{-1}: 3000, 2940, 2830, 1720, 1270, 1090. MS m/z (relative intensity): 279 (3) (M^+ +1), 247 (1), 205 (1), 156 (72), 105 (100). HRMS calcd. for $C_{15}H_{19}O_5$: 279.1232, obsd. 279.1230.

12.- ^{1}H-NMR (δ, C_6D_6): 1.1-1.5 (2H, m), 2.14 (1H, m), 2.32 (1H, dd, J= 15 and 4.5 Hz), 2.71 (1H, dd, J= 15 and 7.9 Hz), 3.09 (1H, ddd, J= 11.6, 11.1 and 2.4 Hz), 3.31 (3H, s), 3.62 (1H, m), 4.07 (1H, ddd, J= 9.4, 7.9 and 4.5 Hz), 4.94 (1H,m), 7.1 (2H, m), 8.15 (1H, m). ^{13}C-NMR (δ, CCl_3D): 25.18 (t), 29.48 (t), 38.15 (t), 51.79 (q), 68.00 (t), 72.35 (d), 76.64 (d), 128.50 (d), 129.71 (d), 133.28 (d), 165.60 (s), 171.65 (s). IR ($CHCl_3$ cm^{-1}: 3000, 2940, 2830, 1720, 1270, 1090. MS m/z (relative intensity): 279 (1)(M^+ +1), 247 (1), 205 (2), 156 (55), 105 (100). HRMS calcd. for $C_{15}H_{19}O_5$: 279.1232, obsd. 279.1222.

13.- Satisfactory IR and NMR (^{1}H and ^{13}C) spectroscopic data and low and high resolution mass spectroscopic data for the new products were obtained.

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