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MODEL STUDIES DIRECTED TOWARD MICROALGA POLYETHER MACROLIDES: A ROUTE TO OXYGENATED 2,5-CIS TETRAHYDROFURAN SUBUNITS

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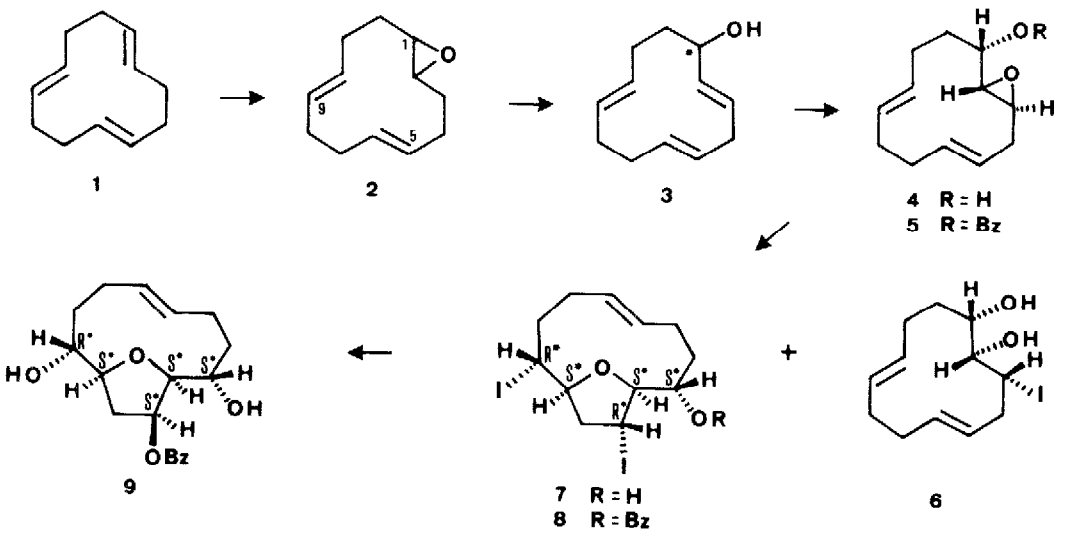
SUMMARY: The regio- and stereochemistry of iodine-promoted transannular ring expansion of a cyclic trans-1,2-epoxy-4(E)-ene system is used to synthesize a cis-α,α'-dialkylated tetrahydrofuran subunit.

The stereochemical complexity of the polyether toxins from marine microalga have made their synthesis a proving ground for methods for cyclic ether formation.[2] Our interest in these targets[3] has focussed on the development of strategies for the regio- and stereocontrolled construction of α,α'-substituted tetrahydrofurans and -pyrans, utilizing intramolecular iodoetherification reaction on cyclo epoxyalkenes to introduce stereocentres with asymmetric induction. In the preceding communication[4], we established that iodine induced cyclization of cis-2,3-epoxy-cyclododeca-5(E),9(Z)-dien-1-ol occurs with neighbouring group participation of the epoxide oxygen in the opening of iodonium ions to give a trans-α,α'-dialkylated tetrahydrofuran derivative. Now we describe that this sequence of transformations with trans-2,3-epoxy-cyclododeca-5(E),9(E)-dien-1-ol (**4**) gave a cis-α,α'-dialkylated tetrahydrofuran homologue **7** containing, after iodine-hydroxyl conversion, an oxygenation pattern **9** similar to that found in several marine polyether macrolides.[5]

As a model template for our study, we have chosen (E,E,E)-1-hydroxy-2,5,9-cyclododecatriene (**3**), available on a large scale from (E,E,E)-cyclododeca-1,5,9-triene (**1**) via the monoepoxide **2** by treatment with phenyllithium in refluxing ether (90% overall yield) (Scheme 1). In the ^{1}H NMR spectrum of **3**, a coupling constant for 15.6 Hz indicated that the newly created Δ^2 double bond is trans. The asymmetric epoxidation of **3** afforded a 98% yield of a 3:2 mixture of α-epoxy alcohols. The major product was the erythro-isomer **4**. The minor product, not shown, was the threo system. The trans epoxide ring at C2/3 in **4** was identified by the characteristic ^{13}C/^{1}H NMR ($CDCl_3$) shifts at δ68.9/3.1 dd=2.2, 1.8 Hz (C/H-2) and δ60.5/3.2 ddd=6.4, 4.2, 2.2 Hz (C/H-3) which correlated with methine and methylene carbons signals at 54.6 (C1) and 34.9 ppm (C4), respectively. The suggested stereochemistry of **4** was confirmed by X-ray crystallographic analysis of the crystalline benzoate **5**.[6]

The iodine induced ring-expansion of 4 was run under kinetic[7] conditions, namely 3 equiv of I_2, cat $Ti(Pr^iO)_4$, in CH_2Cl_2 solvent at room temperature, with efficient stirring. After workup, a mixture of two products was obtained in nearly quantitative yield, and the ^1H NMR spectrum suggested a 2:3 ratio of 7 and 6. The major component of the reaction mixture it corresponds with the non-cyclized iodohydrin 6 which remaining unchanged after treatment with $I_2/Ti(Pr^iO)_4$ for 2 days at room temp. The compound 6 was quantitatively converted to the starting epoxy-alcohol 4 by base treatment (K_2CO_3, acetone). The minor compound was the diiodo ether 7. The ^1H-^1H and ^1H-^{13}C COSY NMR spectra ($CDCl_3$) revealed that the furan oxygenated carbons at positions 2 (δ 95.2/4.3 d = 9.8 Hz) and 5 (δ 83.5/4.68 dd = 11.1, 6.1 Hz) were joined to the carbons at position 1 (δ 74.1/3.18 ddd = 9.8, 4.2, 2.3 Hz) and 6 (δ 35.0/3.7 ddd = 11.1, 3.9, 3.9 Hz), respectively. The relative stereochemistry between the C3-I and C1-C2 bonds was found to be trans, on the basis of the

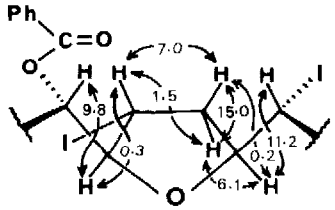


Scheme 1

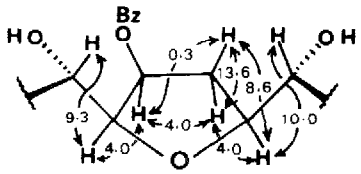
relative strong enhancement observed at H1 when H3 is irradiated, and vice versa. The weakness of the H2-H3 and H1-H2, mutual enhancements, as well as the presence of an H2-H5 enhancement strengthened these conclusions. The next issue to be addressed was that of the stereochemistry of the C-I bond at position 6. In the cis-2,3-epoxy-4(E)-ene iodine-induced expansion reaction,[4] we have determined the stereochemistry at C6 on the basis of an X-ray diffraction analysis, and we have found that the reaction proceeds with overall trans addition across the olefin, in a stereospecific manner with respect to the olefin geometry. There are no obvious reasons why a similar mechanism should not be operative in the trans-2,3-epoxy-4(E)-ene series, and therefore, we shall consider a proof of stereoselectivity as a strong

support for a similar trans-addition mechanism, from which we can deduce the relative stereochemistry of the five stereocentres as 1S*, 2S*, 3R*, 5S* and 6R* as is shown in 7. A significant NOE between H1 and H6 further support the stereochemistry proposed.

Silver (I)-assisted iodine solvolysis of the diiodobenzoate 8 with $AgClO_4$ in aqueous 1,2-dimethoxyethane underwent instant reaction at room temperature to give 9. The reaction is anchimerically assisted by the benzoate group with inversion at C3 and by the ether oxygen antiperiplanarly oriented to the C6-I bond, allowing the iodine-hydroxyl substitution with retention of the configuration at C6.[8] Stereochemical assignments could be made at this stage by high-field ^1H NMR experiments (J value measurements, partial structures 8′ and 9′).



8′



9′

In this strategy, the stereogenic atom marked with an asterisk in compound 3 (Scheme 1) is responsible for controlling stereochemistry of the oxygenated stereocentres at C2, C3, C5 and C6 in 9 in five steps from 1 via remote internal asymmetric induction. All new compounds gave spectroscopic[9] and analytical data entirely in accord with the structures shown.

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REFERENCES AND NOTES

1. Authors to whom correspondence related with the X-ray analysis should be adressed.

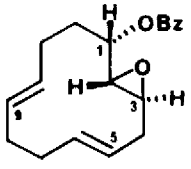
2. (a) C.P. Holmes, P.A. Bartlett, J.Org.Chem., 54, 98 (1989). (b) Y. Tamaru, M. Hojo, S. Kawamura, S. Sawada, Z. Yoshida, J.Org.Chem., 52, 4062 (1987). (c) K.C. Nicolaou, M.E. Duggan, C.-K. Hawang, P.K. Somers, J.Chem.Soc.Chem.Commun., 1359 (1985). (d) L.E. Overman, T.A. Blumenkopf, A. Castañeda, A.S. Thompson, J.Am.Chem.Soc., 108, 3516 (1986). (e) G.S. Cockerill, P. Kocienski, J.Chem.Soc.Chem.Commun., 705 (1983). (f) S.L. Schreiber, S.E. Kelly, Tetrahedron Lett., 25, 1757 (1984).

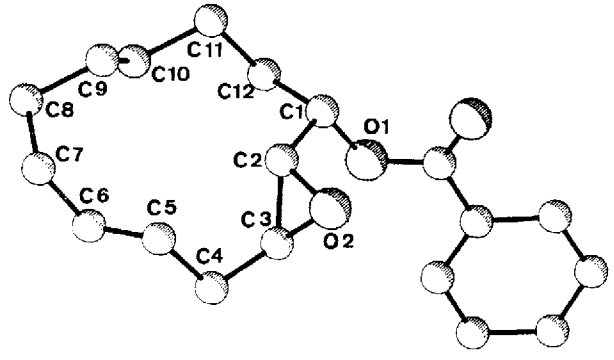
3. (a) E. Alvarez, E. Manta, J.D. Martín, M.L. Rodríguez, C. Ruiz-Pérez, Tetrahedron Lett., 29, 2093 (1988). (b) E. Alvarez, E. Manta, J.D. Martín, M.L. Rodríguez, C. Ruiz-Pérez, D. Zurita, Tetrahedron Lett., 29, 2097 (1988).

4. M. Zárraga, M.L. Rodríguez, C. Ruiz-Pérez, J.D. Martín, preceding paper in this issue.

5. For examples of tetrahydrofuranyl substructures comparable to 9 being ascribed to marine microorganisms see: D. Uemura; Abstract of Papers, Japan-U.S. Seminar on Bio-organic Marine Chemistry; June 30-July 5, Okinawa, Japan, III-3, 11 (1986).

6. Suitable crystals formed from hexane, $C_{19}H_{22}O_3$, triclinic with space group symmetry of P1 and cell constants of a=9.701(1), b=13.201(2), c=13.719(2) Å, α=74.88(6), β=89.85(8), γ=78.08(13)° ; V=1657Å^3 ; Z=4; F(0,0,0)=644. Data were collected on a Siemens AED four circle computer-controlled difractometer equipped with Cu radiation. The structure was solved with a direct methods approach (MULTAN 80) and difference Fourier analysis and refined using full matrix least square techniques. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. Final R=0.0115. No significative residual electron density in final difference synthesis map. Further refinement seems difficult because the two molecules in the asymmetric units are related by a pseudomonoclinic symmetry (P2/c; x+1/2, y, $\bar{z}$), which is broken by the z coordinate. The details of the crystal structure will be given in a full paper.





7. P.A. Bartlett, D. Richardson, J. Myerson, Tetrahedron, 40, 2317 (1984).

8. P. Kocovsky, J.Org.Chem., 53, 5816 (1988).

9. ^{1}H- and ^{13}C NMR spectra of selected compounds follow. 3: ^{1}H NMR ($CDCl_3$) δ4.18(C_1H, ddd, J=7.8, 5.9, 5.6 Hz), 5.86(C_2H, ddd, J=15.6, 5.9, 0.2 Hz), 5.74(C_3H, ddd, J=15.6, 4.2, 4.2 Hz), 2.60(C_4Ha,b, dd, J=7.0, 4.2 Hz), 5.42(C_5H, ddd, J=15.4, 7.0, 7.0 Hz), 5.30(C_6H, C_9H, C_{10}H, m); ^{13}C NMR ($CDCl_3$) δ135.2(d), 135.1(d), 133.9(d), 130.5(d), 129.7(d), 129.4(d), 73.7(d), 36.8(t), 34.0(t), 33.1(t), 31.6(t), 27.8(t). 4: ^{1}H NMR ($CDCl_3$) δ4.00(C_1H, ddd, J=10.0, 3.2, 1.8 Hz), 3.10(C_2H, dd, J=2.2, 1.8 Hz), 3.20 (C_3H, ddd, J=6.4, 4.2, 2.2 Hz), 2.66(C_4Ha, ddd, J=14.2, 4.2, 4.2 Hz), 5.31(C_5H, C_6H, C_9H, C_{10}H, m); ^{13}C NMR ($CDCl_3$) δ134.1(d), 134.0(d), 130.5 (d), 126.5(d), 68.9(d), 60.5(d), 54.6(d), 34.9(t), 34.8(t), 31.8(t), 31.6 (t), 27.3(t). 6: ^{1}H NMR ($CDCl_3$) δ 4.44(C_1H, ddd, J=8.7, 8.0, 2.5 Hz), 4.04 (C_2H, ddd, J=8.0, 8.0, 2.5 Hz), 3.63(C_3H, m), 2.77(C_4H_2, m), 5.30(C_5H, C_6H, C_9H, C_{10}H, m). 7: ^{1}H NMR ($CDCl_3$) δ 3.18(C_1H, ddd, J=9.8, 4.2, 2.3 Hz), 4.30(C_2H, d, J=9.8 Hz), 4.70(C_3H, dd, J=7.0, 1.5 Hz), 2.00(C_4Ha, m), 2.75 (C_4Hb, ddd, J=15.0, 6.1, 1.5 Hz), 4.68(C_5H, dd, J=11.1, 6.1 Hz), 3.70 (C_6H , ddd, J=11.1, 3.9, 3.9 Hz), 5.50(C_9H, C_{10}H, m); ^{13}C NMR ($CDCl_3$) δ74.1(C1), 95.2(C2), 23.7(C3), 45.9(C4), 83.9(C5), 35.0(C6), 33.2(C7), 30.4(C8), 131.2(C9), 133.3(C10), 27.4(C11), 39.2(C12). 9: ^{1}H NMR ($CDCl_3$) δ3.57(C_1H, ddd, J=10.0, 9.3, 3.9 Hz), 3.99(C_2H, dd, J=9.3, 4.0 Hz), 5.67 (C_3H, ddd, J=4.0, 4.0, 0.3 Hz), 2.43(C_4Ha, ddd, J=13.6, 8.6, 4.0 Hz), 4.16((C_5H, ddd, J=10.0, 8.6, 4.0 Hz), 4.70(C_6H, ddd, J=10.0, 3.2, 3.2 Hz) 5.45(C_9H, C_{10}H, m).

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