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MODEL STUDIES DIRECTED TOWARD MICROALGA POLYETHER MACROLIDES: A ROUTE TO 12-CARBON TETRAHYDROFURAN AND TETRAHYDROPYRAN SUBUNITS

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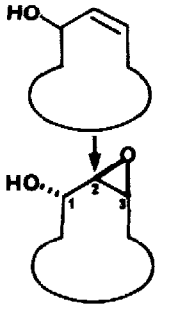
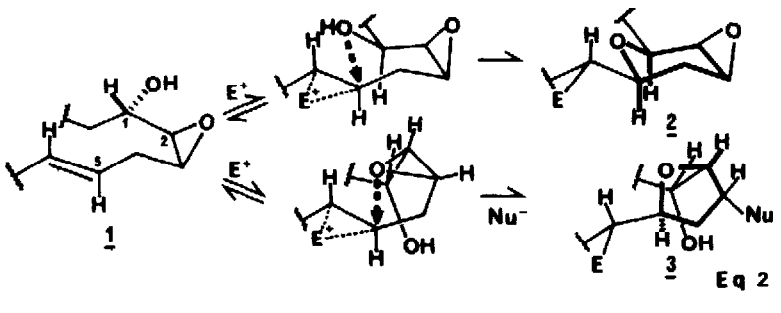
SUMMARY: A new synthetic strategy for the regio- and stereo-specific synthesis of heterosubstituted tetrahydrofuran and tetrahydropyran systems involving intramolecular iodoetherification of 2,3-epoxy-cycloalkenols were studied. Unambiguous stereochemical assignments are available from X-ray studies.

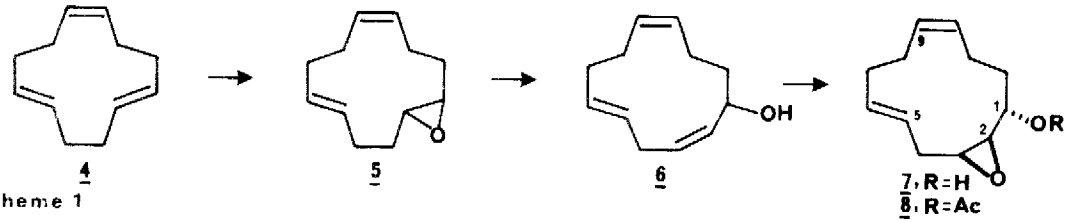
The realization of convergent total syntheses of the recently found cytotoxic marine polyether macrolides, prorocentrolide[2] or fijianolides[3] (laulimalides[4]) requires coordinated solutions to the functionalized tetrahydrofuran and -pyran systems. Our present strategy for these polyether building blocks has emerged from a combination of studies on the conformational preferences and stereoselective reactions of macrocycles[5] and current chiral epoxidation methodology using adjacent hydroxyl groups.[6] We have recently reported[7] that Sharpless asymmetric epoxidation of medium-size allylic Z-cycloalkenols provided a single epoxide with the stereochemistry indicated in eq 1. To address the problem of marine macrolide polyether syntheses, we reasoned that a related macrocycle extended with an E-double bond at C5 could adopt the local conformation 1 that is free of torsional strain. Theoretically, exo-ring closure induced by peripheral electrophilic attack at the double bond, would occur by internal nucleophilic participation of the hydroxyl group to give cis-α,α'-dialkylated tetrahydropyrans 2, or by the epoxide oxygen participation to yield trans-α,α'-dialkylated tetrahydrofuran units 3 (eq 2). Herein we report on applications of these principles that



Eq 1



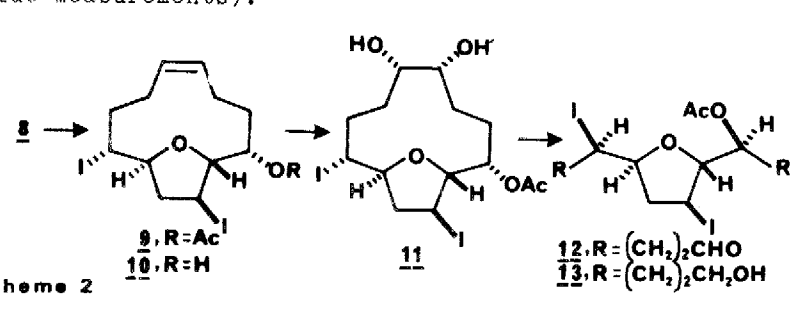
Eq 2



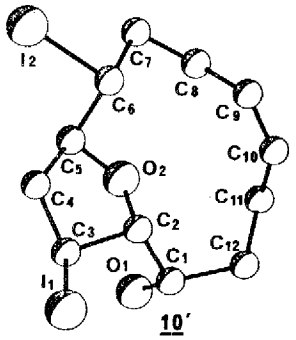
4 5 6

Scheme 1

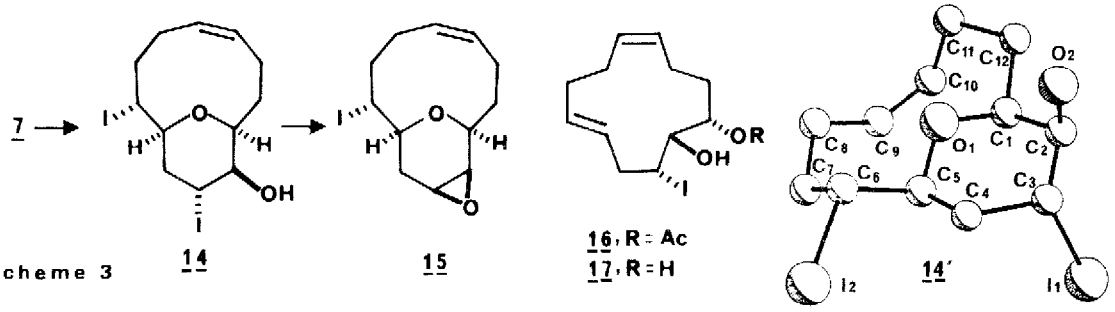
employ cyclododecatrienes as templates and have resulted in the preparation of 12-carbon subunits contained in prorocentrolide,[2] fijianolide-A[3,4] and in other marine polyether toxins.[8] As a model substrate for our study, we have chosen (Z,E,Z)-1-hydroxy-cyclododeca-2,5,9-triene (6), available on a large scale as a crystalline solid (mp 75 °C) from (E,E,Z)-cyclododeca-1,5,9-triene (4) via epoxide 5 by treatment with phenyllithium in refluxing ether (86% overall yield) (Scheme 1). The asymmetric epoxidation of 6 led to the epoxide 7 as a single product (98% yield). The stereochemistry of 7 (mp 54 °C) was suggested by NMR experiments and confirmed by X-ray crystallographic analysis.[9] The use of this 12-membered macrocyclic template to prepare the substituted tetrahydrofuranyl system 13 is outlined in Scheme 2. Addition of iodine to the epoxy-acetate 8 in methylene chloride and a catalytic amount of $Ti(Pr^iO)_4$ gave 2,11-diiodo-9-acetoxy-13-oxabicyclo[8.2.1]tridec-5-ene (9) as the less polar component of the mixture in 66% yield, which was hydrolized with base to give the crystalline alcohol 10 (mp 119 °C). The structure of 10 was deduced from ^{1}H- and ^{13}C-NMR spectra, particularly from ^{1}H-^{1}H COSY NMR data (regular and long range) and the regular and long range ^{1}H-^{13}C COSY NMR which allowed the connections shown in 10 for all the carbons. The sugested stereochemistry for 10 was confirmed by X-ray crystallographic analysis (10').[10] The cis-dihydroxylation of 9 (OsO_4/NMMO) proceeded stereoselectively to afford, as the only product, the diol 11 that would arise from peripheral dihydroxylation of the conformation observed in the crystal structure (10'). Treatment of 11 with 1 equiv of $NaIO_4$ in dioxane provided dialdehyde 12 in 82% yield, which was further reduced quantitatively to the diol 13 ($NaBH_4$, MeOH). Stereochemical assignments could be made at this stage through a combination of ^{13}C NMR and high-field ^{1}H NMR experiments (NOE difference and J value measurements).



Scheme 2



10'



Scheme 3

The reaction of 7 with $I_2/Ti(Pr^iO)_4$ cat/0-25°C, proceeded stereoselectively to afford, as the major product, 2,11-diiodo-10-hydroxy-13-oxabicyclo [7.3.1]tridec-5-ene (14) (54% yield), which was converted quantitatively to the epoxide 15 (Scheme 3). The stereochemistry of 14 (mp 136°C) was determined by X-ray crystallographic analysis (14').[11]

The more polar components in both iodine-assisted cyclization reactions on 7 and 8, correspond respectively with the iodohydrins 16 and 17 (30 and 33% yields, respectively), which are quantitatively converted into the starting epoxy-alcohol 7 upon base treatment (K_2CO_3, aq acetone). No cyclization products were obtained from the iodohydrin 17 after $I_2/Ti(Pr^iO)_4$ long treatment. The stereochemistry of 17 was determined by X-ray crystallographic analysis.[9] All new compounds gave spectroscopic[12] and analytical data entirely in accord with the structures shown. Extension of this strategy to higher ring homologues and the total synthesis of fijianolide-A[3,4] are continuing.

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108, 514 (1986).
9. Unpublished results.
10. Crystal data for 10: $C_{12}H_{18}I_2O_2$, orthorhombic, space group Fdd2, a= 43.570 (34), b=32.361 (14), c=8.584 (3) Å; V=12104 Å^3, Z=32. Data were collected on a Siemens AED four circle computer-controlled diffractometer, with CuKα graphite monochromated radiation. Of 2354 measured independent reflections, 2027 with I>2σ (I) were considered as observed. The structure was solved by Patterson method (SHELXS-86) and sucessive Fourier synthesis (XRAY-80). An empirical absorption correction was performed (DIFABS). Hydrogen for carbon atoms placed in calculated positions. Full matrix l.s. refinement, with anisotropic iodine atoms, isotropic carbon and oxygen atoms and fixed isotropic contribution for hydrogens. Final R=0.077.
11. Crystal data for 14: $C_{12}H_{18}I_2O_2$, orthorhombic, space group P $2_1/n$, a= 8.428 (16), b=24.299 (76), c=14.052 (60) Å; V=2877 Å^3, Z=8. Of 3247 measured independent reflections, 2665 with I>2σ(I) were considered as observed. The structure was solved and refined as above. Final R=0.076. The details for both crystal structures will be given in a full paper.
12. ^{1}H- and ^{13}C NMR spectra of selected compounds follow. 6: ^{1}H NMR ($CDCl_3$) δ5.82(1H, ddd, J=10.5, 8.0, 8.0 Hz), 5.36(5H, m), 4.33(1H, m), 2.88(1H, ddd, J=15.5, 7.4, 7.0 Hz), 2.60(1H, dd, J=15.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ135.1(d), 131.7(d), 130.1(d), 130.0(d), 129.5(d), 128.0(d), 65.1(d), 37.1(t), 30.7(t), 29.6(t), 28.0(t), 22.5(t). 7: ^{1}H NMR ($CDCl_3$) δ 5.32(4H, m), 3.42(C_1H, ddd, J=14.0, 8.2, 1.2 Hz), 3.30(C_3H, ddd, J=9.8, 4.5, 4.5 Hz), 2.87(C_2H, dd, J=8.2, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 131.7(d), 130.9(d), 128.9(d), 124.5(d), 66.3(d), 61.1(d), 58.0(d), 35.1(t), 32.1(t), 28.0(t), 22.1(t). 10: ^{1}H NMR ($CDCl_3$)δ4.03(C_1H,br s), 3.67(C_2H,br d, J=10.6 Hz), 3.79(C_3H, ddd, J=10.6, 7.5, 7.3 Hz), 2.06(C_4Ha, ddd, J=13.6, 7.5, 7.4 Hz) 2.91(C_4Hb, ddd, J=13.6, 7.4, 7.3 Hz), 4.27(C_5H, ddd, J=12.0, 7.4, 7.4 Hz) 3.95(C_6H, ddd, J=12.0, 12.0, 4.0 Hz), 2.34(C_7Ha, dddd, J=13.5, 12.0, 3.0, 3.0 Hz), 2.48(C_7Hb, m), 2.97(C_8Ha, m), 1.72(C_8Hb, m), 5.20(C_9H, ddd, J= 11.4, 11.0, 2.6 Hz), 5.40(C_{10}H, ddd, J=11.0, 10.8, 2.4 Hz), 1.72(C_{11}Ha, m) 2.48(C_{11}Hb, m), 1.55(C_{12}Ha, dddd, J=14.4, 10.8, 3.4, 0.5 Hz), 2.08(C_{12}Hb, m); ^{13}C NMR ($CDCl_3$) δ65.8(C1), 85.9(C2), 19.6(C3), 47.3(C4), 84.2(C5), 36.9 (C6), 42.1(C7), 29.2(C8), 127.6(C9), 132.7(C10), 20.3(C11), 35.7(C12). 11: ^{1}H NMR ($CDCl_3$) δ 5.23(C_1H, br d, J=5.6 Hz), 3.74(C_2H, d, J=11.8 Hz), 3.66 (C_3H, ddd, J=11.8, 10.6, 7.0 Hz), 2.16 (C_4Ha, ddd, J=14.0, 10.6, 7.0 Hz), 2.95 (C_4Hb, ddd, J=14.0, 7.0, 7.0 Hz), 4.31 (C_5H, ddd, J=11.0, 7.0, 7.0 Hz), 4.10(C_6H, ddd, J=11.0, 11.0, 4.7 Hz), 3.70(C_9H, m), 3.70(C_{10}H, m); ^{13}C NMR ($CDCl_3$)δ78.0(C1), 83.2(C2), 17.6(C3), 48.2(C4), 88.3(C5), 34.8(C6) 39.3(C7), 25.0(C8), 68.4(C9), 68.4(C10), 28.15(C11), 31.5(C12). 12: ^{1}H NMR ($CDCl_3$)δ5.06(C_1H, ddd, J=6.6, 6.6, 2.8 Hz), 4.20(C_2H, dd, J=8.8, 2.8 Hz), 3.80 (C_3H, ddd, J=10.3, 8.8, 6.4 Hz), 2.14 (C_4Ha), ddd, J=12.8, 10.3, 6.4 Hz), 2.86(C_4Hb, ddd, J=12.8, 6.4, 6.4 Hz), 3.87(C_5H, ddd, J=8.4, 6.4, 6.4 Hz), 4.08(C_6H, ddd, J=8.4, 8.4, 1.4 Hz), 9.73(C_9H, s), 9.77(C_{10}H, s); ^{13}C NMR ($CDCl_3$) δ 70.3(C1), 82.2(C2), 15.0(C3), 45.8(C4), 88.3(C5), 39.3(C6), 43.7(C7), 24.3(C8), 200.5(C9), 200.9(C10), 28.8(C11), 40.1(C12). 13: ^{1}H NMR ($CDCl_3$) δ 5.12(C_1H, ddd, J=7.0, 7.0, 2.7 Hz), 4.24(C_2H, dd, J=9.0, 2.7 Hz) 3.92(C_3H, ddd, J=9.0, 8.6, 6.0 Hz), 2.26(C_4Ha, ddd, J=12.8, 8.6, 6.0 Hz), 2.89(C_4Hb, ddd, J=12.8, 6.0, 6.0 Hz), 3.86(C_5H, ddd, J=8.0, 6.0, 6.0 Hz), 4.12(C_6H, ddd, J=8.0, 8.0, 4.0 Hz), 3.67(C_9HaHb, m), 3.67(C_{10}HaHb, m). 14: ^{1}H NMR ($CDCl_3$) δ 4.0(C_1H, m), 3.53(C_2H, d, J=2.0 Hz), 4.48(C_3H, ddd, J=4.0 2.4, 2.0 Hz), 3.55(C_5H, ddd, J=9.6, 9.6, 1.3 Hz), 4.0(C_6H, m), 5.4(C_9H, m), 5.4(C_{10}H, m); ^{13}C NMR ($CDCl_3$)δ 74.0(C1), 70.0(C2), 31.9(C3), 38.5(C4), 80.1(C5), 33.1(C6), 43.1(C7), 29.7(C8), 126.8(C9), 132.4(C10), 22.4(C11), 27.4(C12). 15: ^{1}H NMR ($CDCl_3$) δ 3.2(C_1H, m), 2.8(C_2H, m), 3.50(C_3H, dd, J= 10.5, 1.7 Hz), 3.2(C_5H, m), 3.78(C_6H, ddd, J=13.2, 10.3, 3.0 Hz). 17: ^{1}H NMR ($CDCl_3$) δ 3.80(C_1H, C_2H, m), 4.58(C_3H, ddd, J=9.9, 3.5, 3.5 Hz), 2.59 (C_4Ha, ddd, J=15.1, 8.9, 3.5 Hz), 2.78(C_4Hb, dd, J=15.1, 2.6 Hz), 5.35 (C_5H, C_6H, m), 5.56 (C_9H, C_{10}H, m).

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