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NEW SYNTHETIC STRATEGY FOR THE CONSTRUCTION OF TRANS-FUSED MEDIUM-SIZED CYCLIC ETHERS: SYNTHESIS OF THE IJK FRAMEWORK OF THE POLYETHER CIGUATOXIN

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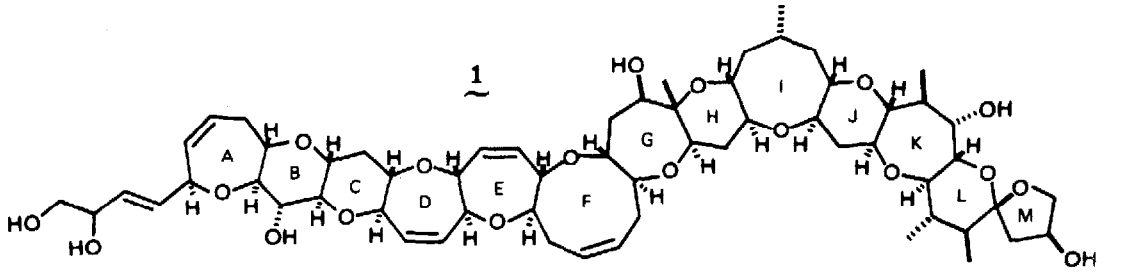
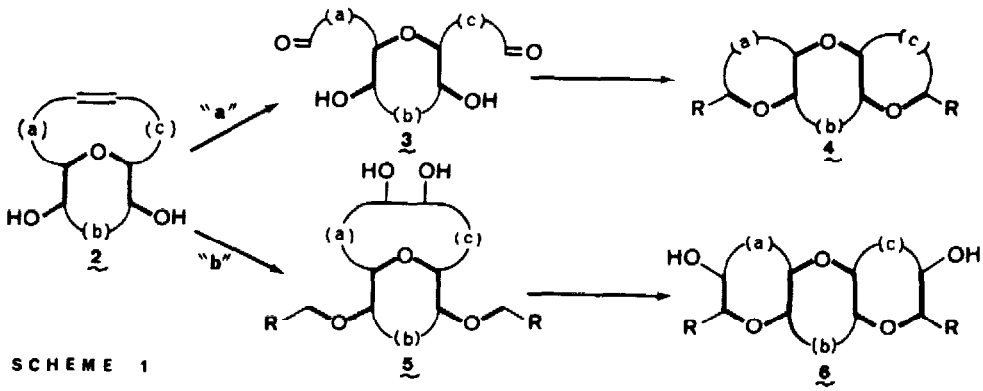
Key Words: β-Alkoxy-substituted cyclic ethers, trans-fused polyether toxins.

Abstract: The synthesis of a conveniently functionalised oxocene-oxane-oxepane framework was achieved by two simultaneous one-carbon homologations followed by a one-pot double carbon-carbon bond-forming strategy.



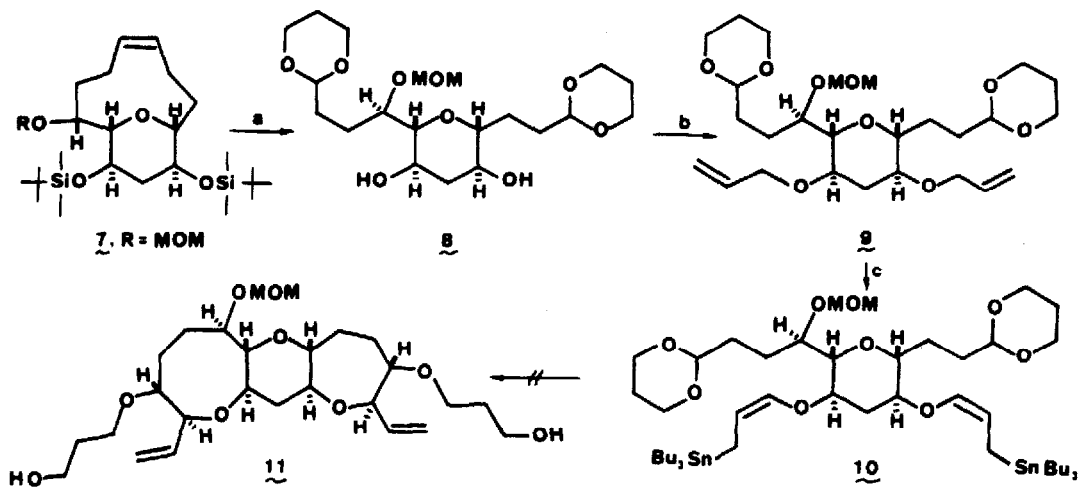
Ciguatoxin (1)[1] is the toxic principle of ciguatera, which is the agent responsible for the most widespread food poisoning of nonbacterial origin. The toxin is also a potent activator of voltage-dependent Na^+ channels[2] and thus is of particular interest to the biomedical research community. Yet the total world supply of pure toxin has never exceeded 1.3 mg, which has made structural elucidation a challenging task.[3] This molecular structure presents a formidable synthetic objective, particularly with regard to the construction of its fused medium-sized rings. Considerable synthetic progress has been made on this problem over the years and much fascinating chemistry has recently been reported[4] that utilizes both carbon-carbon and carbon-oxygen bond-forming processes to effect cyclization.

In connection with the total synthesis of ciguatoxin (1) and related trans-fused polyethers, currently in progress in these laboratories,[5] we have sought a "symmetrical" approach to the construction of trans-fused oxatricyclic subunits in which two identical groups were simultaneously created and allowed to close by two simultaneous carbon-oxygen bond formations based on the general synthetic sequence depicted in Scheme 1 (pathway "a", 2 → 4).[5c] As an extension of this methodology, we describe here the synthesis of the conveniently functionalised oxocene-oxane-oxepane subunit 17 by two simultaneous one-carbon homologations concluding in the generation of both external rings of the tricyclic system by a one-pot double carbon-carbon bond-forming strategy (Scheme 1, pathway "b", 2 → 6).



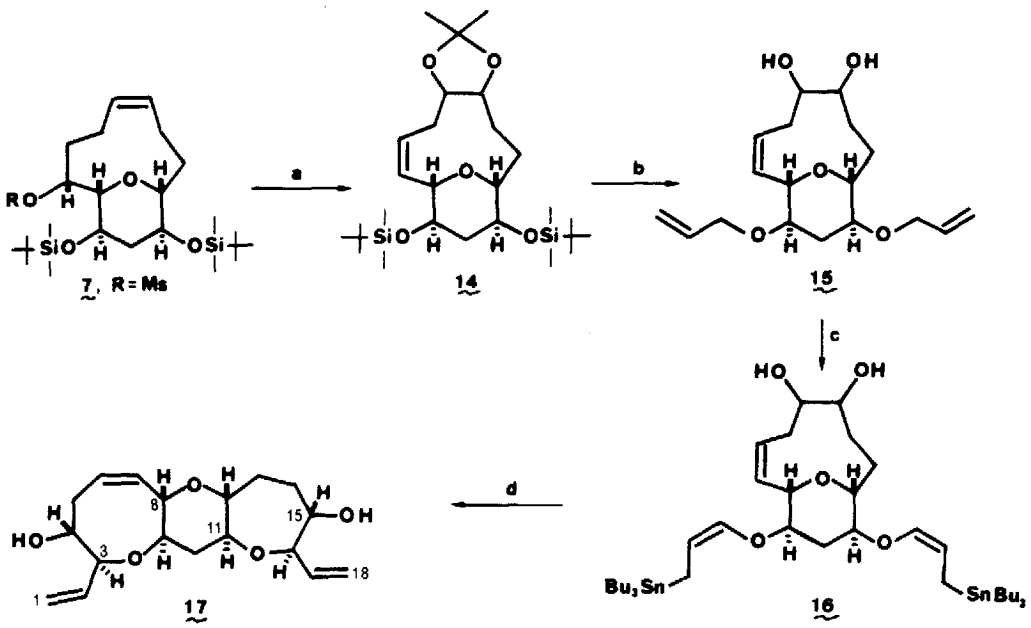
SCHEME 1

Starting from the oxabicyclic system 7[5c] our initial studies were conducted on the already published Lewis acid-mediated intramolecular cyclization of ω-trialkylstannyl ether acetals[4a] which, however, proved unsuccessful in yielding the projected oxatricyclic framework 11.[6] More recently, the same group have reported[7] that the use of the corresponding aldehydes gives the desired cyclization product in better yield with higher diastereoselectivity compared to the reaction of the acetals, which entirely agrees with the results obtained by us in the one-pot process which includes vic-diol fragmentation and cyclization of the resulting aldehyde-allylic tin system. The six- and seven- membered β-hydroxy cyclic ethers 13, n=1, 2 were thus obtained in high yields with exclusive trans stereoselectivity.[8]



SCHEME 2. Reagents and conditions: (a), i, NMO (4.0 equiv.), OsO_4 (0.2 equiv.), acetone:H_2O (4:1), 25°C, 10 h; ii, $NaIO_4$ (1.5 equiv.), MeOH:H_2O (4:1), 25°C, 5 h; iii, HO⁓OH (5.0 equiv.), CSA cat., reflux, 12 h; iv, n-Bu_4NF (2.5 equiv.), THF, 0°C, 3 h, 78% from 7; (b) allyl bromide (4.4 equiv.), NaH (2.6 equiv.), DMF, 0-25°C, 3 h, 96%; (c) sec-BuLi (2.4 equiv.), n-Bu_3SnCl (2.1 equiv.), HMPA, THF, -78°, 30 min, 83%.

Based upon these findings and starting from the bridged oxabicycle **7**, R= Ms, we undertook the construction of the trans-fused oxocene-oxane-oxepane system **17**, following the sequence outlined in Scheme 3. The one-pot double alkylation to give **17** was accomplished by reaction of **16** with $n\text{-Bu}_4NIO_4$ (0-25°C for 4 h) followed by treatment with $BF_3.Et_2O$ (-78°C, 5 min) to afford **17** in 63% yield.[9]



SCHEME 3. Reagents and conditions: (a), i, NMO (3.1 equiv.), OsO_4 (0.05 equiv.), $THF:H_2O$ (1:1), 25°C, 6 h, 96%; ii, DBU (10.0 equiv.), toluene, reflux, 12 h, 79%; iii, 2-methoxypropene (1.5 equiv.), PPTS (0.5 equiv.), CH_2Cl_2, 0°C, 3 h, 100%; (b), i, n-Bu_4NF (2.5 equiv.), THF, 0°C, 4 h, 98%; ii, allyl bromide (4.5 equiv.), NaH (2.5 equiv.), DMF, 0-25°C, 30 min, 99%; iii, MeOH, CSA cat., 25°C, 2 h, 100%; (c) sec-BuLi (4.4 equiv.), n-Bu_3SnCl (2.2 equiv.), THF, -78°C, 15 min, 79%; (d) n-Bu_4NIO_4 (1.2 equiv.), CH_2Cl_2, 0-25°C, 4 h, then add $BF_3.OEt_2$ (2.0 equiv.) at -78°C, 5 min, 63%.

The chemistry described above sets the stage for the construction of the IJK ring system of ciguatoxin (1). The synthesis follows a highly economical strategy designed by recognizing the subtle symmetry present in the tricyclic system.

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6. Unexpectedly, when **10** was induced to react by the presence of $TiCl_3(O^iPr)$ or other Lewis acids, such us $BF_3.OEt_2$, $TiCl_4$, $MgBr_2.OEt_2$ failed to give desired cyclic ethers.
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8. The synthesis of **12** from n=0 to n=3, will be published in a full account of this work. The cyclization to **13**, n=1 is a representative. To a stirring solution of **12**, n=1 (840 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added $n\text{-}Bu_4NIO_4$ (1.1 mmol), and the mixture was maintained at 0°C for 5 min and at 25°C for 10 min. The reaction mixture was cooled at -78°C and a CH_2Cl_2 solution (2 mL) of $BF_3.OEt_2$ (2.0 mmol) was slowly added. Stirring at -78°C was continued for 15 min. The reaction then was quenched by the addition of 2% NaOH followed by extraction with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. To this solution at 0°C was added an excess of p-bromobenzoyl chloride (2.0 mmol) and Et_3N (2.5 mmol). The reaction was stirred at 25°C for 6 h, diluted with CH_2Cl_2, and washed sequentially with 10% HCl, H_2O, and brine.The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to yield the p-bromobenzoate of **13**, n=1 (389 mg, 63%) as a colourless oil; 400-MHz ^1H NMR ($CDCl_3$) δ 5.85 (C_2H, ddd, J= 17.2, 12.5, 6.6 Hz), 5.34 (C_1H, dd, J=17.2, 1.1 Hz), 5.19 (C_1H, dd, J= 12.5, 1.1 Hz), 4.84 (C_4H, ddd, J=9.5, 9.4, 4.6 Hz), 4.03 (C_7H, dddd, J= 11.5, 4.4, 2.0, 2.0 Hz), 3.85 (C_3H, dd, J=9.4, 6.6 Hz), 3.49 (C_7H, ddd, J=11.5, 11.5, 2.8 Hz), 2.31 (C_5H, m), 1.80 (C_6H_2, m), 1.65 (C_5H, m).
9. The relative stereochemistry and proton connectivities of **17** were determined by detailed analyses of $^1H\text{-}^1H$ and $^{13}C\text{-}^1H$ COSY experiments. The transfusing manner of the ether rings was suggested by the coupling constants of angular protons and fully confirmed by NOE's on a ROESY experiment. **17** [bis-(p-bromobenzoate)] 400-MHz ^1H-NMR ($CDCl_3$)δ 5.89 ($C_{17}H$, ddd, J=17.2, 10.6, 5.3 Hz), 5.84 (C_7H, br dd, J=11.6, 11.6 Hz), 5.80 (C_2H, ddd, J=16.8, 10.4, 5.0 Hz), 5.71 (C_6H, br dd, J=11.6, 9.4 Hz), 5.36 ($C_{18}H$, br d, J=17.2 Hz), 5.28 (C_1H, br d, J=16.8 Hz), 5.23 ($C_{15}H$, m), 5.17 ($C_{18}H$, br d, J=10.6 Hz), 5.12 (C_4H, ddd, J=10.0, 4.0, 3.5 Hz), 5.10 (C_1H, br d, J=10.4 Hz), 4.21 ($C_{16}H$, dd, J=5.0, 5.0 Hz), 4.14 (C_3H, dd, J=10.0, 5.3 Hz), 4.02 (C_8H, br dd, J=11.6, 9.2 Hz), 3.41 ($C_{11}H$, ddd, J=13.5, 9.2, 44 Hz), 3.32 (C_9H, ddd, J=13.2, 9.2, 4.6 Hz), 3.19 ($C_{12}H$, ddd, J=9.6, 9.2, 4.4 Hz), 2.85 (C_5H, ddd, J=13.6, 9.4, 3.5 Hz), 2.53($C_{10}H$, ddd, J=12.0, 4.6, 4.4 Hz), 2.50 (C_5H, br d, J=13.6 Hz), 2.00 ($C_{14}H_2$, m), 1.90 ($C_{13}H$, m), 1.88 ($C_{13}H$, m), 1.73 ($C_{10}H$, ddd, J=13.5, 13.2, 12.0 Hz). 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 136.6, 136.4 (C-2, C-17), 135.5, 125.7 (C-6, C-7), 116.5, 116.4 (C-1, C-18), 83.5 (C-16), 81.4 (C-12), 80.5 (C-9), 80.1 (C-3), 79.7 (C-8), 79.3 (C-11), 77.6, 76.8 (C-4, C-15), 39.5 (C-10), 30.3 (C-14), 27.4 (C-13), 24.8 (C-5).

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