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MODEL STUDIES DIRECTED TOWARDS MICROALGA POLYETHER TOXINS. A STEREOSELECTIVE ENTRY INTO C_{10} CIS AND TRANS FUSED OXANE-OXEPANE SUBUNITS

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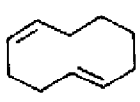
SUMMARY: A new synthetic process for the construction of cis- and trans-fused oxane-oxepane systems starting from (Z,Z)-cyclodeca-2,7-dien-1-ol is described. The Ti(O^{i}Pr)$_4$-catalysed transannular oxirane ring expansion is invoked to explain the chemoselective formation of the 11-oxobicyclo[4.4.1] undecane intermediate.

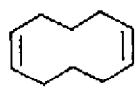
ortho-Condensed oxane-oxepane systems are important targets for chemical synthesis because they are common subunits in oxopolycyclic marine toxins.[1] Particularly significant in this area of chemical synthesis is the work of Nicolaou[2] and others,[3] who have elaborated derivatives of the ortho-condensed oxobicycles which may be readily adapted for further fusion of more ether rings.

As an extension of the work directed towards the selective construction of oxepane subunits described in the preceding article, we have attempted to develop stereocontrolled and flexible protocols for preparing fused oxane-oxepane systems with either cis or trans stereochemistry starting from inexpensive, non-carbohydrate precursors, which provide us with the option of introducing functionality as needed.

To achieve the objectives set out above and outlined in Scheme 1, a number of problems had to be solved, and in order to facilitate this all the work was carried out in the racemic series.[4] The first of these problems proved to be the preparation of the required allylic acetate **4** on the scale required. The most convenient preparation is shown below and utilizes the readily available (E,Z)-1,5-cyclodecadiene (**1**) via the monoepoxide **3** by treatment with phenyllithium in refluxing ether to give, after acetylation, compound **4** in 84% overall yield.[5] Alternatively, sodium-alumina catalysed **1** to **2** isomerization[6] followed by allylic acyloxylation[7] of **2** (t-BuOOH/AcOH/



1



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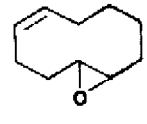

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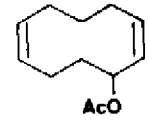
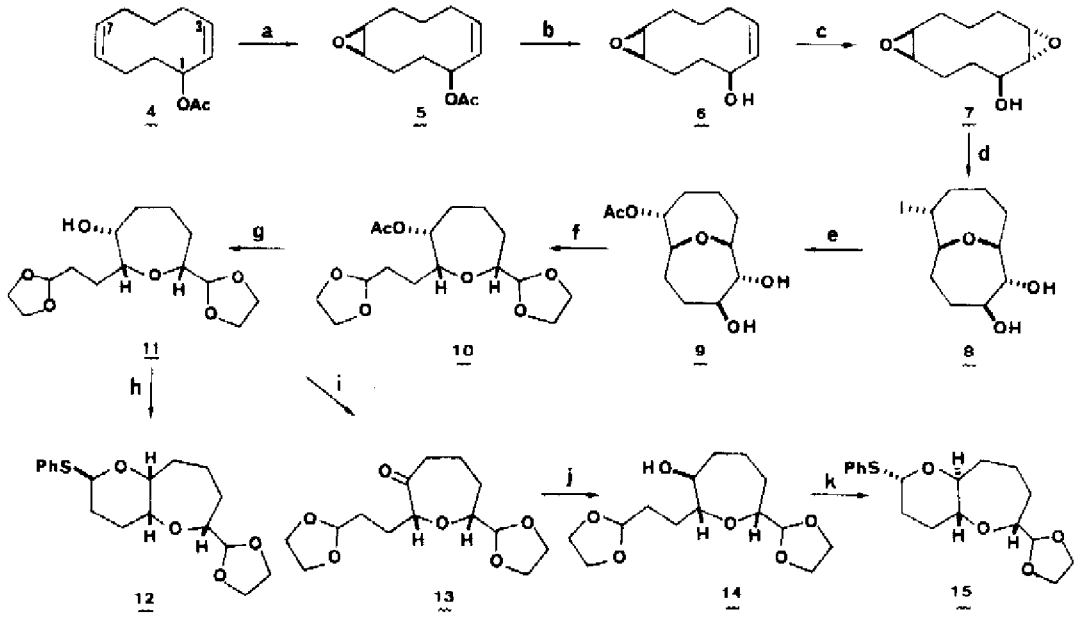


4

/Cu_2Cl_2) gave 4 in 77% overall yield.

The syn-epoxy acetate 5 (Scheme 1) was prepared upon treatment of (Z,Z)-1-acetoxy-cyclodeca-2,7-diene (7) with m-CPBA/CH_2Cl_2/0°C in 80% yield. Base hydrolysis of the epoxy-acetate 5 (K_2CO_3/MeOH/25°C/2 h) gave 6 which was treated with meta-chloroperoxybenzoic acid to give the trans-bisepoxide 7 in good yield (87%). As far as we can determine, this oxidation process gave rise to the bisepoxide 7 in high stereochemical purity, and further transformation of 7 gave no evidence of the presence of significant amounts of diastereoisomers of 7 (vide infra). Treatment of 7 with I_2/$Ti(O^iPr)_4$/



Scheme 1

Reagents and conditions: (a), m-CPBA (1.0 equiv.), CH_2Cl_2, 0°C, 2 h, 80%; (b), K_2CO_3 (2.0 equiv.), MeOH, 25°C, 1 h, 100%; (c), m-CPBA (1.5 equiv.), CH_2Cl_2, 25°C, 12 h, 87%; (d), I_2 (1.5 equiv.), $Ti(O^iPr)_4$ (0.2 equiv.), CH_2Cl_2, 25°C, 3 h, 64%; (e), AgOAc (1.5 equiv.), AcOH:$CHCl_3$ (1:4), 25°C, 5h, 83%; (f), i, $NaIO_4$ (1.5 equiv.), MeOH:H_2O (4:1), 25°C, 4 h; ii, HO⁓OH:benzene (1:1), CSA cat., reflux, 12 h, 93%; (g) K_2CO_3 (0.5 equiv.), MeOH, 25°C, 3 h, 100%; (h), PhSH (1.5 equiv.), CSA cat, CH_2Cl_2, 25°C, 48 h, 96%; (i), $(COCl)_2$(1.5 equiv.), Me_2SO (2.0 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2, -78 to 0°C, 15 min., 89%; (j), $NaBH_4$ (2.5 equiv.), MeOH, 0°C, 3 h (96% ca. 1:1 ratio); (k) PhSH (1.5 equiv.), CSA cat., CH_2Cl_2, 25°C, 12 h, 91%.

CH_2Cl_2/25°C resulted in an efficient conversion (64%) to the expanded ether 8. We propose that the effect of Ti on the observed chemoselective transannular ring expansion is attributable to the anchimerically assisted opening of the oxirane imposed on the intermediate in which the hydroxy and epoxy oxygens are both co-ordinated to the Ti catalyst.

Silver (I)-assisted iodine solvolysis of 8 (AgOAc/AcOH:$CHCl_3$/25°C) gave acetate 9 which was further submitted to fragmentation with $NaIO_4$ in MeOH : H_2O (4:1) followed by ketalization (HO^OH/PhH/CSA/reflux) to give 10 in 93% yield. Thus, cyclization/solvolysis/fragmentation of 2,7-bisepoxycyclodecan-1-ol proceeded with complete stereoselectivity to yield cis-2,7-dialkyl-3-oxygenated oxepanes and assembled in three steps the key structural elements of fused-polyether marine toxins.

Base hydrolysis of 10 (K_2CO_3/MeOH) gave 11 in quantitative yield. With intermediate 11, simple acid treatment in the presence of thiophenol led to to the cis-fused oxane-oxepane 12. Swern oxidation of the secondary alcohol group in 11 followed by sodium borohydride reduction of the resulting ketone 13 gave a 1:1 mixture of the expected alcohols 11 and 14. Acid treatment of 14 in the presence of PhSH led to the trans-fused oxane-oxepane 15. Because of the anomeric effect, the phenylthio substituent in 12 and 15 assumed an axial position as revealed by the vicinal ^1H-N.M.R. coupling constant data.[8]

In conclusion, the chemistry which is described here allows a stereocontrolled preparation of cis- and trans-fused oxane-oxepane subunits which should be useful in the total synthesis of ortho-condensed polyether toxins and related natural products.

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8. ^{1}H- and ^{13}C-N.M.R. spectra of selected compounds follow: 11: ^{1}H-N.M.R. ($CDCl_3$) δ 4.85 ($C_{10}H$, t, J=4.6 Hz), 4.84 (C_1H, d, J=3.9 Hz), 3.90 (m, 8 H), 3.71 (C_7H, br t, J=4.0 Hz), 3.62 (C_2H, ddd, J=6.5, 6.2, 3.9 Hz), 3.45 (C_6H, br dd, J=9.4, 4.0 Hz); ^{13}C-N.M.R. ($CDCl_3$) δ 18.0 (t), 27.2 (t), 29.6 (t), 30.1 (t), 36.2 (t), 64.7 (2xt), 65.1 (2xt), 71.7 (d), 79.8 (d), 81.5 d), 104.5 (d), 104.8 (d). 12: ^{1}H N.M.R. ($CDCl_3$) 7.46 (m, 2 H), 7.24 (m, 3 H), 5.58 ($C_{10}H$, dd, J=5.4, 3.4 Hz), 4.85 (C_1H, d, J=4.5 Hz), 4.40 (C_6H, br s), 3.97 (m, 4 H), 3.60 (C_7H, ddd, J=5.0, 4.4, 4.4 Hz), 3.52 (C_2H, dd, J=9.3, 4.5 Hz), 2.40 (C_9H, m); ^{13}C-N.M.R. ($CDCl_3$) δ19.6 (t), 26.2 (t), 30.6 (t), 31.7 (t), 65.2 (t), 65.4 (t), 70.8 (d), 77.9 (d), 82.7 (d), 84.8 (d), 105.1 (d), 126.6 (d), 128.7 (d), 131.0 (d), 135.9 (s). 14: ^{1}H-N.M.R. ($CDCl_3$) δ4.90 ($C_{10}H$,t, J=4.6 Hz), 4.85 (C_1H, d, J=3.5 Hz), 3.90 (m, 8 H), 3.57 (C_2H, C_7H, m), 3.22 (C_6H, ddd, J=8.0, 7.8, 2.8 Hz); ^{13}C-N.M.R. ($CDCl_3$) δ19.2 (t), 28.7 (t), 29.6 (t), 29.9 (t), 35.3 (t), 64.7 (t), 64.8 (t), 65.1 (t), 65.2 (t), 75.7 (d), 82.1 (d), 86.1 (d), 104.7 (d), 104.9 (d). 15: ^{1}H-N.M.R. ($CDCl_3$) δ 7.46 (m, 2 H), 7.27 (m, 3 H), 5.50 ($C_{10}H$, dd, J=3.6, 2.6 Hz), 4.85 (C_1H, d, J=2.2 Hz), 3.90 (m, 5 H), 3.69 (C_2H, ddd, J=10.0, 6.0, 2.2 Hz), 3.20 (C_7H, ddd, J=10.4, 10.0, 4.5 Hz); ^{13}C-N.M.R. ($CDCl_3$) δ 19.3 (t), 27.6 (t), 28.3 (t), 30.8 (t), 33.7 (t), 65.3 (2xt), 74.1 (d), 79.8 (d), 80.2 (d), 84.3 (d), 104.7 (d), 126.8 (d), 128.7 (d), 131.0 (d), 135.8 (s).

9. All new compounds exhibited satisfactory spectral and exact mass data.

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