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APPROACHES TO THE SYNTHESIS OF THE TETRAHYDROPYRAN SUBUNITS OF MARINE TRANS-FUSED POLYETHER TOXINS

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SUMMARY: Cyclization/solvolysis of 2,3-epoxy cycloalk-5-en-1-ols proceed with complete regio- and stereoselectivity to yield cis-2,6-dialkyl-3,5-oxygenated tetrahydropyrans and thus assemble in two steps the key structural unit present in marine syn-trans-fused polyether toxins.

Since the molecular structure of the polyether brevetoxin-B was discovered in 1981,[1a] the number of novel trans-fused polyethers isolated from marine microorganisms has increased considerably.[1] These substances possess a novel polycyclic structure in which each ring corresponds to an oxygenated heterocycle, all of the rings being coupled to one another by trans fusion (Figure 1). The structural complexity of these molecules,[1] the bioactivity they present,[2] the novelty of their polyether systems and, finally, the difficulty and paucity with which they are isolated from their natural medium make them most attractive from the synthetic point of view, and considerable effort is presently being devoted to the search for a synthetic methodology that will lead to the preparation of simplified models of these substances.[3] These new structures indeed require the development of new methods of synthesis and careful design of the strategy to be adopted, before undertaking their total syntheses with any expectations of success.

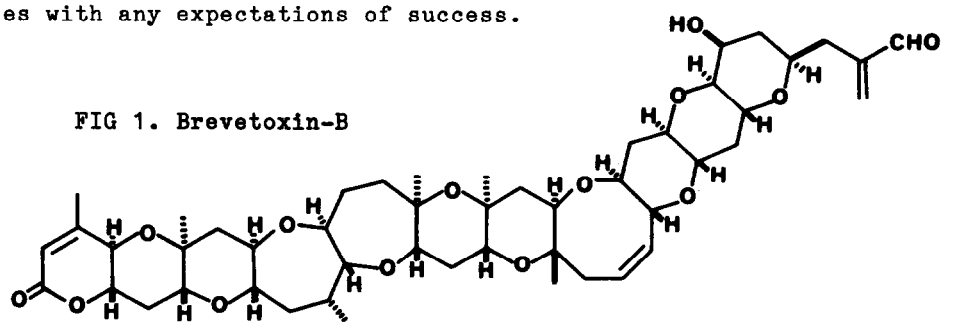
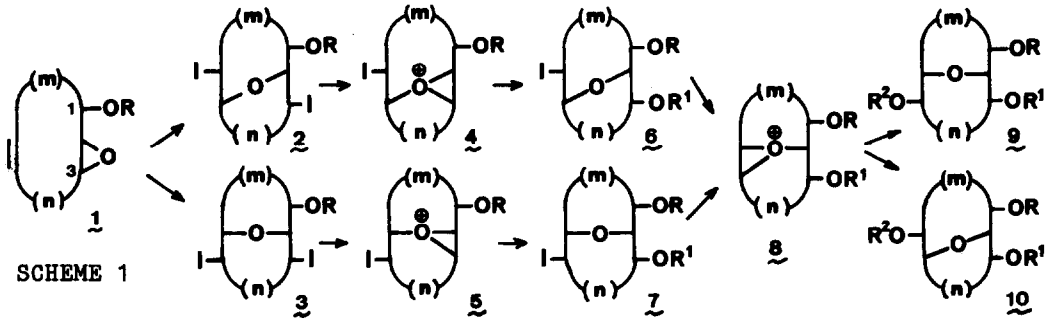


FIG 1. Brevetoxin-B

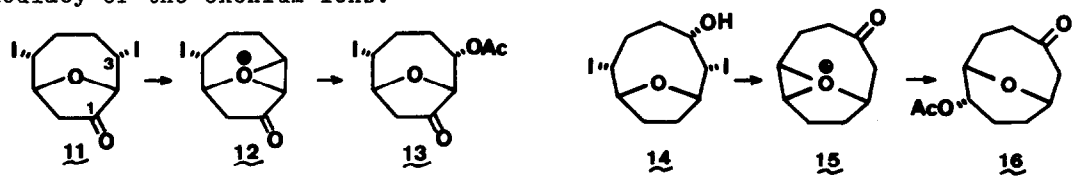
Recent work in our laboratory[4] has focused on the use of iodine-induced transannular ring expansion of 2,3-epoxy cycloalken-1-ols (1) to give the iodine-containing oxacycles 2 and/or 3 which are obvious precursors to valuable α,α'-dialkyl β,β'-oxygenated oxocycles (9 and/or 10), provided the

iodine functions can be further manipulated in a regio- and stereocontrolled fashion (Scheme 1). We reasoned that two structural aspects of the oxonium ion intermediates would be crucial in controlling the ring size of the silver (I) induced solvolysis products: the C1-oxygen substituent which exerts chemo- and regioselective C3 substitution to give 6 and/or 7, and torsional



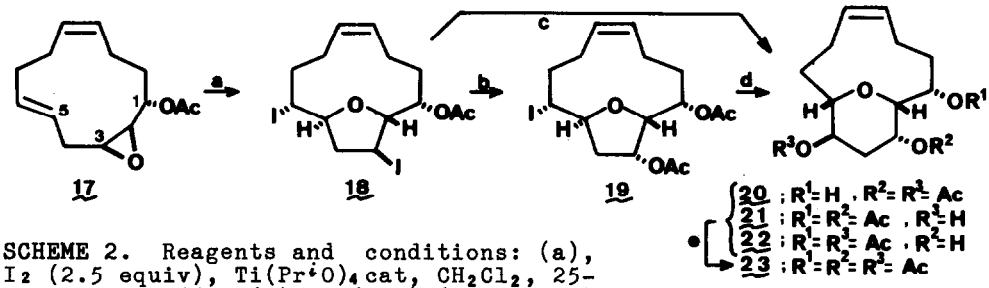
SCHEME 1

and geometric constraints that favour formation of one over the other ring system (9 and/or 10). To independently explore these two effects we chose the previously synthesized iodine-containing oxacycles 11[4a] and 14[4b] as model substrates. Treatment of 11 with 1 equiv AgOAc/HOAc:CH_2Cl_2(1:10)/r t/ 24 h, followed by aqueous work up leads to the acetyl derivative 13 in 75% yield. This isomer is the expected product from solvolysis through the oxonium ion intermediate 12 by regioselective substitution at the C3 site. Solvolysis of 14 under the above described conditions leads to the ring expanded acetate 16 in 85% yield. It is interesting to note that the opening of the oxonium ion intermediate, in the absence of vicinal oxygenated carbons , is directed towards the thermodynamically favoured product isomer. The regioselectivity of the solvolytic process would then depend on the relative importance of these two effects. The fact that the iodide in 11 and 14 is replaced with retention of configuration, i.e, double inversion, is evidence for the intermediacy of the oxonium ions.



Iodocyclization of the readily available[4d] epoxy-acetate 17 followed by silver ion-induced solvolysis of the resulting iodo-ether gave, after acetylation of the resulting mixture, the triacetate 23 in 45% overall yield (Scheme 2). Compound 23 possesses an oxygenated oxane pattern similar to that found in trans-fused polyether toxins. Iodine-induced cyclization affords the iodide 18 in 66% yield; however, solvolysis leads to a mixture of diacetates: 20, 21 and 22, and triacetate 23, in a combined yield of 77%. A

stepwise solvolysis of 18 can be achieved by chemoselective extrusion of iodine to give 19 by treatment of the former with $Cu(OAc)_2$/HOAc/reflux/ 12 h (78% yield). The relative stereochemistry in 19 was determined by X-ray



SCHEME 2. Reagents and conditions: (a), I_2 (2.5 equiv), $Ti(Pr^iO)_4$ cat, CH_2Cl_2, 25-30°C, 10 h, 66%; (b), $Cu(OAc)_2$(1.2 equiv) AcOH, reflux, 12 h, 78%; (c), AgOAc (2 equiv), AcOH:$CHCl_3$(1:10), 25 30°C, 24 h, 77%; (d), AgOAc (1.0 equiv), AcOH:$CHCl_3$(1:10), 25-30°C, 12 h, 82%; (e), Ac_2O, pyridine, 25°C, 100%.

crystallographic analysis (Figure 2).[5] These findings clearly show that the pulling effect of the silver ion and the pushing ability of the antiperiplanar carbonyl C1-acetate and ether oxygens work together. Cyclization/solvolysis of 2,3-epoxy cycloalken-1-ols of this latter type, moreover, proceed with complete stereoselectivity to yield cis-2,6-dialkyl-3,5-oxygenated tetrahydropyrans and, thus, assemble in two steps the key structural elements of fused-polyether marine toxins. We believe that the presently developed regio- and stereochemically well-defined transformations will have considerable synthetic utility.

All new compounds gave spectroscopic[6] and analytical data entirely in accord with the structures shown.

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5. Crystal data for compound 19: $C_{16}H_{25}IO_5$, monoclinic, a=5.268(4), b=15.802 (8), c=20.810(15) Å, β=91.3(1)°, V=1731.8 Å^3, space group $P2_1/n$, z=4.

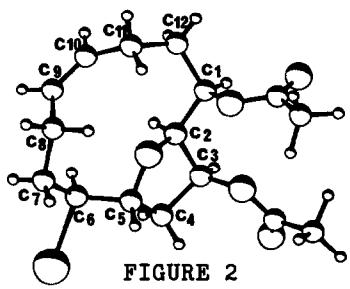

FIGURE 2

The structure was solved by Patterson and successive Fourier syntheses.An empirical absorption correction was performed at the isotropic level. Anisotropic temperature factors were used for the refinement of the non-H atoms. The hydrogen atoms were located on a difference electron synthesis map and added in the final stages of the refinement as fixed isotropic contribution. Final R=0.037 for 2079 independent reflections [$I>2\sigma(I)$, $3°<2\theta<120°$] Full details of the crystal structure will be given in a full paper.

6. ^{1}H- and ^{13}C-NMR spectra of selected compounds follow: 13:^{1}H NMR (C_6D_6) δ5.01 (C_3H, dd, J=9.7, 6.5 Hz), 4.44 (C_7H, dd, J=8.8, 4.3 Hz), 4.01 (C_2H, d, J=1.0 Hz), 3.75 (C_6H, ddd, J=12.3, 4.3, 3.8 Hz), 2.43 (C_8H, ddd, J=18.6, 1.0, 1.0 Hz), 2.04(C_8H, dd, J=18.6, 8.8 Hz), 1.65 (C_5H, m), 1.54 (C_4H, m), 1.24 (C_4H, m), 1.07 (C_5H, m); ^{13}C NMR ($CDCl_3$) δ 212.0 (C1), 83.7 (C2), 80.6 (C7), 75.9 (C3), 39.6 (C8), 31.9 (C6), 31.2 (C4), 30.5 (C5). 16:^{1}H NMR (C_6D_6) δ 4.98 (C_6H, ddd, J=10.0, 6.0, 6.0 Hz), 4.00 (C_7H, ddd, J=10.5, 7.5, 6.0 Hz), 3.78 (C_3H, m), 2.42 (C_2H, dd, J=12.3, 9.7 Hz), 2.30 (C_9H, ddd, J=14.0, 13.5, 3.5 Hz), 2.16 (C_9H, m), 1.93 (C_2H, dd, J=12.3, 8.0 Hz), 1.62 (C_8H, m), 1.53 (C_5H_2, C_4H, m), 1.14 (C_8H, m), 0.76 (C_4H, m); ^{13}C NMR ($CDCl_3$)δ175.4(s), 70.5(d), 70.3(d), 66.7(d), 45.0(t), 38.1(t), 28.2(t), 23.8(t), 21.2(q), 19.4(t). 19: ^{1}H NMR ($CDCl_3$) δ 5.40 (C_9H, C_{10}H, m), 5.30 (C_3H, br s), 5.17 (C_1H, ddd, J=5.0, 5.0, 2.5 Hz), 4.52 (C_5H, ddd, J=11.1, 7.0, 7.0 Hz), 3.95 (C_6H, ddd, J=11.5, 11.1, 3.7 Hz), 3.75 (C_2H, d, J=2.5 Hz). 20: ^{1}H NMR ($CDCl_3$) δ 5.42 (C_{10}H, ddd, J=11.0, 11.0, 2.5 Hz), 5.34 (C_9H, ddd, J=11.5, 11.0, 2.5 Hz), 5.22 (C_3H, br s), 4.92 (C_5H, ddd, J=10.5, 10.5, 5.0 Hz), 3.89 (C_1H, ddd, J=7.3, 3.3, 3.3 Hz), 3.23 (C_6H, ddd, J=10.5, 10.5, 5.0 Hz), 3.14 (C_2H, br s), 2.27 (C_4H, ddd, J=13.9, 5.0, 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 69.5 (C1), 80.9 (C2), 71.4 (C3), 36.5 (C4), 69.1 (C5), 79.0 (C6), 35.6 (C7), 22.0 (C8), 126.7 (C9), 133.3 (C10), 20.8 (C11), 29.0 (C12). 21: ^{1}H NMR ($CDCl_3$) δ 5.40 (C_9H, C_{10}H, m), 5.02 (C H, dd, J=3.2, 3.2 Hz), 4.80 (C H, dd, J=2.3, 1.2 Hz), 4.10 (C_5H, ddd, J=12.3, 10.5, 4.5 Hz), 3.39 (C_2H, d, J=1.2 Hz), 3.34 (C_6H, ddd, J=10.5, 10.5, 4.5 Hz). 22: ^{1}H NMR ($CDCl_3$) δ 5.45 (C_9H, C_{10}H, m), 5.13 (C_1H, dd, J=3.2, 3.2 Hz), 4.99 (C_5H, ddd, J=10.5, 10.1, 5.2 Hz), 3.96 (C_3H, br s), 3.19 (C_2H, s), 3.17 (C_6H, ddd, J=10.5, 10.5, 4.6 Hz). 23: ^{1}H NMR ($CDCl_3$) δ 5.45 (C_3H, C_9H, C_{10}H, m), 5.07 (C_1H, dd, J=3.2, 3.2 Hz), 4.93 (C_5H, ddd, J=10.6, 10.6, 5.0 Hz), 3.24 (C_2H, s), 3.16 (C_6H, ddd, J=10.6, 10.6, 4.5 Hz), 2.28 (C_4H, ddd, J=14.0, 5.0, 2.8 Hz).

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