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STUDIES IN POLYETHER SYNTHESIS:

CONTROLLED BISEPOXIDE CYCLISATION USING A β-DIKETONE GROUP.

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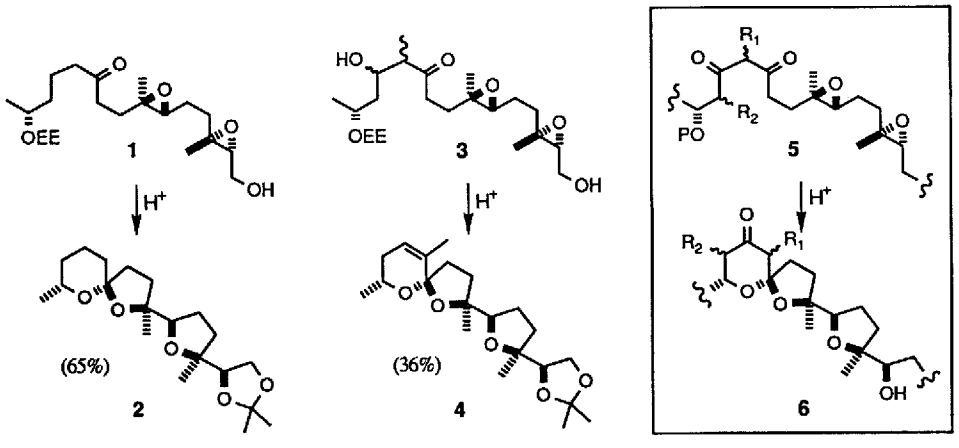
Summary: Ketospiroacetals of general structure **6** can be prepared by bisepoxide cyclisation using a suitable β-diketone participating group, *e.g.* **14** cyclises to give the tricyclic systems **15** and **16**.

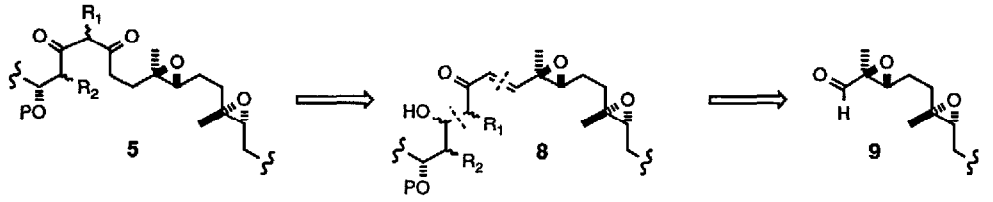
The biomimetic cyclisation of polyepoxides[1] is potentially a powerful and versatile strategy for the synthesis of polyether ionophores.[2,3] The rapid assembly of the complete cyclic ether ring system by the cyclisation cascade of an acyclic polyepoxide substrate, with the minimum introduction of protecting groups and surplus functionality, makes this approach especially attractive. We[4] and others[5] have shown that various di- and triepoxides, internally equipped with suitable participating nucleophilic groups (*e.g.* a *t*-butyl ester[4a] or a carboxylic acid[5a-c]), can be cyclised stereospecifically to give substantial polyether segments. However, attempts to apply these polyepoxide → polyether cascades to the synthesis of more elaborate segments containing spiroacetal and tetrahydrofuran units have, so far, only met with limited success.[4b] Under acidic conditions (CSA, Me_2CO), the spirocyclisation reaction **1** → **2** occurred efficiently, whereas the β-hydroxy ketone **3** cyclised in poor yield with concomitant dehydration to give **4** (**Scheme 1**). Since most of the natural polyethers containing a spiroacetal unit carry an oxygen atom at this ring position (monensin, etheromycin, *etc.*), which participates in ligating metal ions, this necessitated the search for a better cyclisation substrate.



Scheme 1

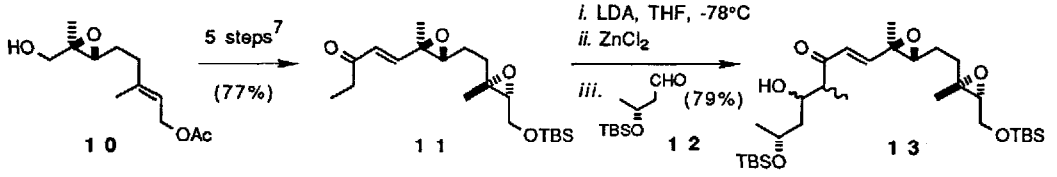
We now report that bisepoxides, equipped with a suitable β-diketone participating group, as in **5**, can be cyclised to give ketospiroacetal tetrahydrofuran systems of general structure **6**.[6] Hence, the synthesis of this class of polyethers[1,2] with the required oxygenation pattern is now possible directly from appropriately substituted polyepoxides.

Our strategy for the synthesis of polyepoxide cyclisation substrates like **5**, as summarised in **Scheme 2**, initially employs Sharpless asymmetric epoxidation to set up the epoxide stereochemistry in the aldehyde fragment **9**. While **5** is being assembled, the nucleophilic ketone carbonyl group in **8** is constrained by a *trans* double bond from premature internal opening of the neighbouring epoxide. When required, however, reduction of this double bond should allow a controlled cyclisation cascade.



Scheme 2

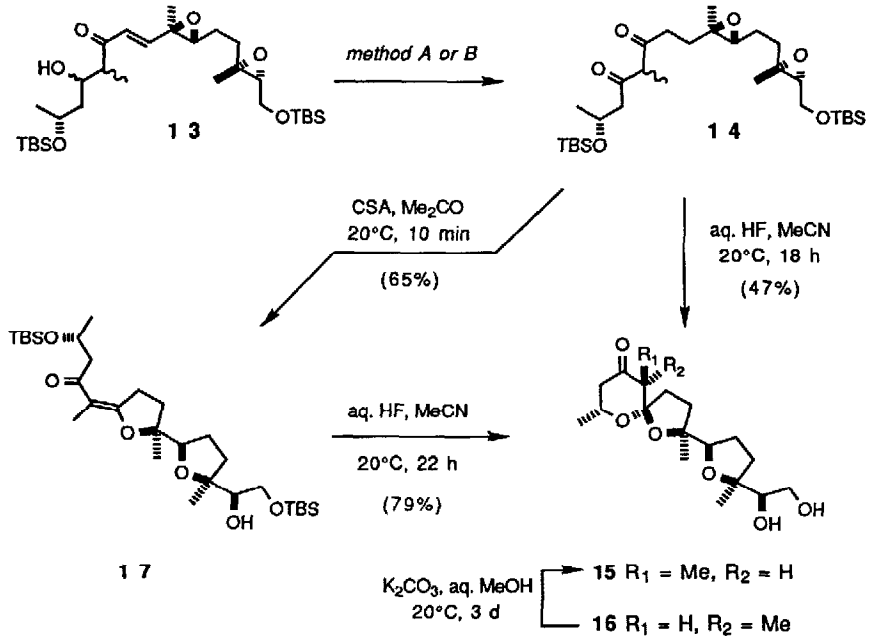
In our previous work (see **Scheme 1**),[4b] the cyclisation substrate **3** was set up by an aldol reaction between an enone (H for TBS in **11**) and an ethoxyethyl protected β-hydroxy aldehyde, followed by catalytic hydrogenation of the enone double bond using Rh/Al_2O_3. By varying the protecting groups in the two components and optimising the aldol conditions, this route has now been improved, as shown in **Scheme 3**. The aldol reaction to give **13** employs the zinc enolate of **11**[7,8], prepared by use of LDA (1.7 equiv., THF, -78°C, 30 min) and then addition of $ZnCl_2$ (2 equiv.; 10 min) in THF solution, and the TBS protected aldehyde **12**[4b,9] (1.5 equiv.; -78°C, 20 min). Under these new conditions, the mixture of aldol isomers **13** can be isolated in 79% yield (93% based on recovered starting enone **11**).



Scheme 3

Conversion of **13** into the saturated β-diketone **14** was initially performed (**Scheme 4**) by catalytic hydrogenation (5% Rh/Al_2O_3) followed immediately by Swern oxidation (*method A*, 41% from **13**). Both **14** and its precursor β-hydroxy ketone were unstable and showed signs of epoxide opening both on silica gel chromatography and storage at -23°C. Cyclisation reactions on the β-diketone **14** were carried out on freshly prepared material without purification. Swern oxidation on **13** itself was found to give the corresponding unsaturated β-diketone as a 1:1 mixture of epimers in high yield (96%). In this route (*method B*), catalytic hydrogenation proved unsuccessful and reduction of the double bond employed the method of Keinan[10] using $^{n}Bu_3SnH$ and catalytic $Pd(PPh_3)_4$ in THF. After the reduction was complete, the reaction was worked up and the tin residues were removed by rapid chromatography to give **14** (60%).

When the β-diketone **14** was treated with aq. HF (40%) in acetonitrile (20°C, 18 h), the ketospiroacetal tetrahydrofuran cyclisation product **15**[11] was isolated in 39% yield together with 8% of an isomer. The minor isomer was deduced to be epimeric at the α-carbon to the ketone, *i.e.* **16**[11], as base treatment (K_2CO_3, aq. MeOH) converted it into **15**, which is the more stable isomer having both methyl groups equatorial. A two stage cyclisation could also be performed. Brief exposure of **14** to CSA in acetone (20°C, 10 min) gave the bistetrahydrofuran **17**. Here the acid catalysed opening of the epoxides is presumably internally intercepted by the enol of the β-diketone. Desilylation of **17** by exposure to HF in acetonitrile (20°C, 22 h) then gave a 79% yield of the tricyclic systems **15** and **16** in a 2.2:1 ratio.



Scheme 4. *Method A*: (i) H_2, 5% Rh/Al_2O_3, THF, 20°C, 40 min; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1 h; Et_3N, -78 → 20°C. *Method B*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1.5 h; Et_3N, -78 → 0°C, 15 min; (ii) $^nBu_3SnH$ (2.2 equiv.), $Pd(PPh_3)_4$ (*ca* 1 mol %), THF, 20°C, 100 min.

Since **16** can be epimerised by base to give **15**, the polyepoxide → polyether cascade is now reasonably efficient, although further optimisation is desirable. Application of this chemistry to the synthesis of etheromycin is being pursued.

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References and Notes

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6. For recent syntheses of a ketospiroacetal system for monensin, see: (a) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046; (b) Chai, D.; Still, W. C. *J. Org. Chem.* **1988**, *53*, 4641.
7. The homochiral bisepoxide **11** can now be obtained in 8 steps from geraniol in 38% overall yield.[4] The sequence **10** → **11** was carried out in an improved[4b] yield (77%) by: (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 40 min; Et_3N; (ii) K_2CO_3, MeOH-H_2O, 20°C, 2.5 h; (iii) $EtCOCH_2PO(OMe)_2$, LiCl, Et_3N, MeCN, 3A sieves, 20°C, 3 h; (iv) (*D*)-DMT, $Ti(O^iPr)_4$, ^{t}BuOOH, 3A sieves, CH_2Cl_2, -23°C, 5 h; Me_2S; (v) TBSCl, imidazole, CH_2Cl_2, 0°C, 35 min.
8. All new compounds gave spectroscopic data in agreement with the assigned structures.
9. The aldehyde **12** was prepared from (3*R*)-(-)-methyl 3-hydroxybutyrate (97% yield) by: (i) TBSCl, imidazole, CH_2Cl_2, 0 → 20°C, 16 h; (ii) DIBAL, CH_2Cl_2, -78°C, 1 h.
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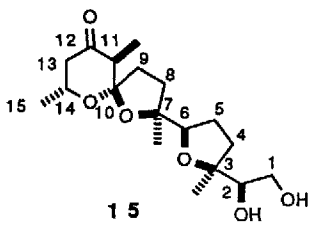
11. The stereostructure of the pyranone ring in **15** and **16** was assigned by ^{1}H NMR from *J* values and NOE studies on the bisacetate derivative of **15**. Spiroacetal **15** had $[\alpha]_D^{21}$ = -20.2° (*c* 0.80, $CHCl_3$); ν_{max} ($CHCl_3$) 3684, 3550, 3504, 1718 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 4.15 (dqd, *J* = 11.4, 6.2, 2.8 Hz, H_{14ax}), 3.82 (dd, *J* = 7.3, 7.3 Hz, H_6), 3.68 (dd, *J* = 11.0, 3.1 Hz, H_{1A}), 3.59 (dd, *J* = 7.2, 3.1 Hz, H_2), 3.51 (dd, *J* = 11.0, 7.2 Hz, H_{1B}), 2.60-2.76 (m, 2 OH), 2.68 (qd, *J* = 6.7, 0.9 Hz, H_{11ax}), 2.38 (dd, *J* = 13.6, 2.8 Hz, H_{13eq}), 2.23 (ddd, *J* = 13.5, 11.4, 0.9 Hz, H_{13ax}), 2.01-2.14 (m, 4H), 1.70-1.92 (m, 3H), 1.48-1.56 (m, 1H), 1.30 (s, 3-CH_3), 1.23 (d, *J* = 6.2 Hz, 15-CH_3), 1.13 (s, 7-CH_3), 1.04 (d, *J* = 6.7 Hz, 11-CH_3); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 207.1 (C_{12}), 111.2 (C_{10}), 86.9 (C_7), 84.8 (C_3), 83.0 (C_6), 76.5 (C_{14}), 65.6 (C_2), 63.1 (C_1), 51.0 (C_{11}), 48.6 (C_{13}), 35.8, 32.7 (2), 26.5 (C_4, C_5, C_8, C_9), 25.1 (7-CH_3), 22.5 (3-CH_3), 21.6 (15-CH_3), 8.5 (11-CH_3); HRMS (CI, NH_3) calcd for $C_{18}H_{31}O_6$+H: 343.2120, found 343.2126 (M+H).



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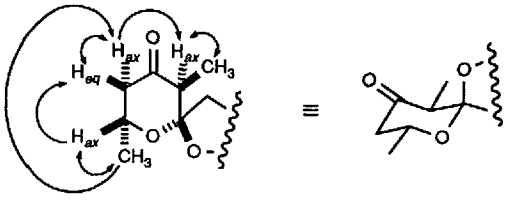

NOE study on *bis*acetate of **15**

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