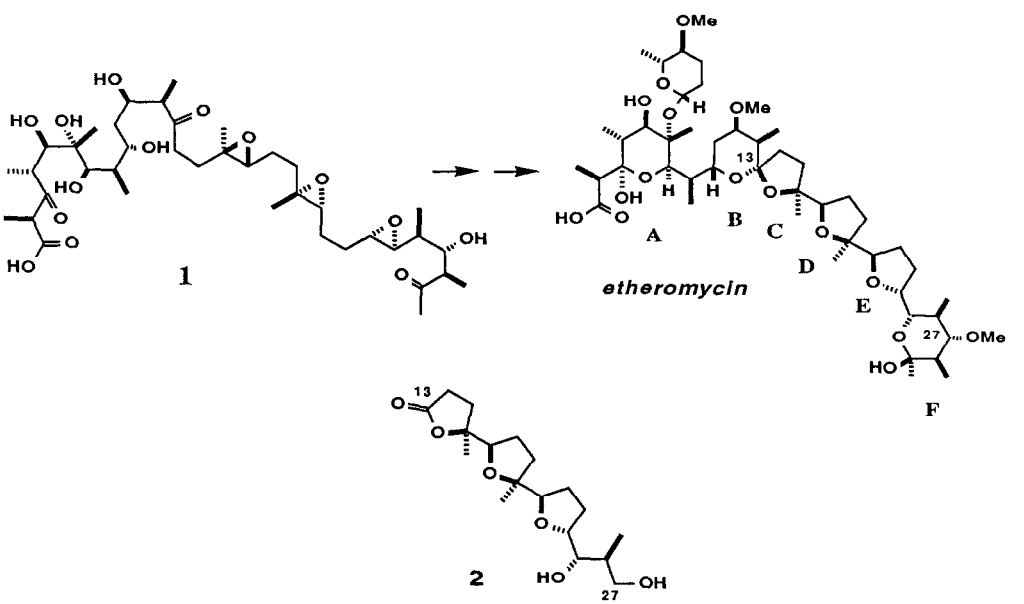
Tetrahedron Letters,Vol.28,No.43,pp 5205-5208,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STUDIES IN POLYETHER SYNTHESIS USING POLYEPOXIDE CYCLISATIONS.

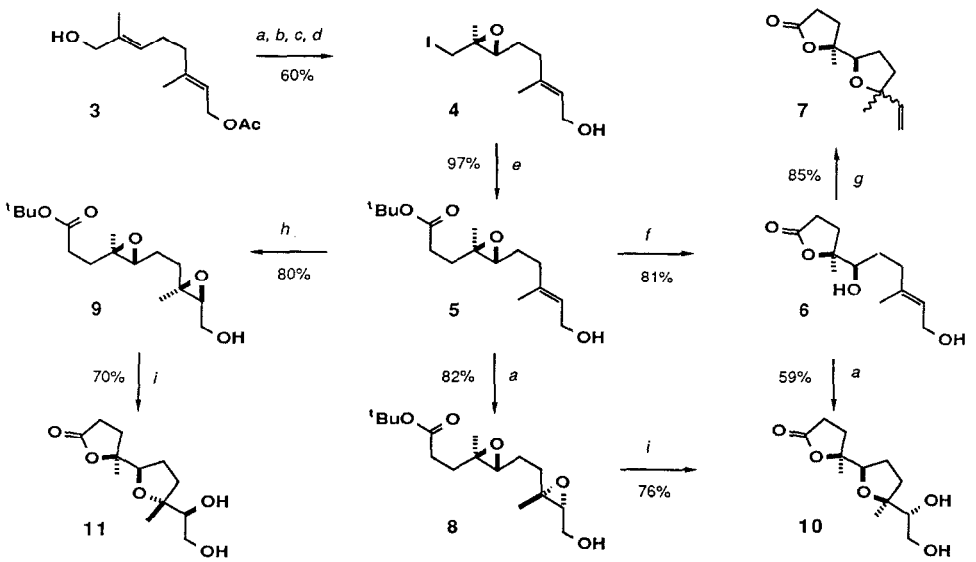
Ian Paterson*, Ian Boddy, and Ian Mason
University Chemical Laboratory, Lensfield Road,
Cambridge CB2 1EW, U.K.

Summary: The acid-catalysed directed cyclisation of mono-, di-, and triepoxy t-butyl ester derivatives is used for the asymmetric synthesis of various polyether-type fragments including a C_{13}-C_{27} fragment of etheromycin. The epoxide stereochemistry is set up by Sharpless epoxidation of allylic and homoallylic alcohols.

The polyene → polyepoxide → polyether hypothesis[1] for the formation of the characteristic cyclic ether skeleton of the polyether antibiotics is important from a synthetic as well as biosynthetic standpoint. The directed cyclisation of a suitably constructed triepoxide to give a complex multiple ring system, *c.f.* **1** → etheromycin[2], is an intriguing idea. Recent work by Still[3] and Schreiber[4] on the biomimetic synthesis of monensin B has focused on introducing the epoxide units in a single step by epoxidation of macrolide dienes and trienes followed by lactone hydrolysis and cyclisation to polyether fragments. While this work convincingly demonstrates the efficiency of the cyclisation process, the relative stereochemistry of only two of the three epoxides required was established by this macrocyclic stereocontrol approach. An alternative enantioselective approach to control of the critical epoxide stereochemistry relies on the Sharpless asymmetric epoxidation of allylic[5] and homoallylic[6] alcohols. Although the epoxides are now introduced stepwise, there is greater flexibility for controlling stereochemistry by choice of reagent chirality. We now demonstrate[7] this approach by the synthesis and cyclisation of mono-, di-, and triepoxy t-butyl ester derivatives to give various polyether-type fragments in enantiomerically pure form including tricyclic compound **2**, which contains the etheromycin CDE rings.

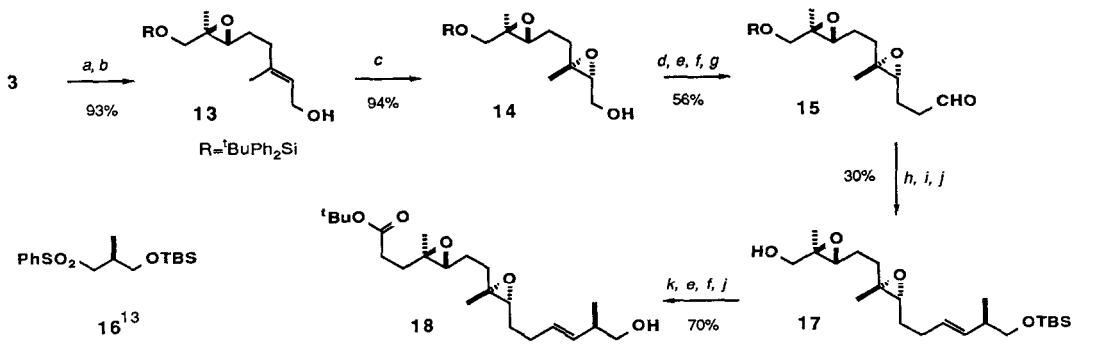


Our preliminary studies were made on mono- and diepoxy t-butyl esters (Scheme I). The unsaturated monoepoxide **5** was first prepared in 92% ee from **3**, the SeO_2 allylic oxidation[8] product of geranyl acetate. Asymmetric epoxidation of **3** by the improved catalytic[5b] Sharpless procedure was followed by conversion to the iodide **4** (60% overall). The epoxyiodide was then chain extended, **4** → **5**, by reaction[9] with the lithium enolate of t-butylacetate (THF-HMPA, -78°C, 30 min; 97%). The t-butyl ester group proved to be a good internal nucleophile for epoxide opening under a range of acidic conditions. For instance, brief exposure of **5** to HCl (1.2 eq) in MeOH (0°C, 10 min) gave lactone **6** in 81% isolated yield, which on longer contact with acid cyclised further to give **7** (3:1 diastereomeric mixture at the allylic chiral centre). By using the appropriate tartrate enantiomer, **5** could be epoxidised with 20:1 diastereoselectivity to give either **8** or **9** in enantiomerically pure form.[10] These diepoxides were then each cyclised by acid (CSA, CH_2Cl_2, 0°C, 5 min) to the corresponding 1,2-diols, **8** →**10** (76%) and **9** →**11** (70%), in which **10** represents a bicyclic portion of a large number of natural polyethers.[1,2b] Analogous cyclisation of **8** with CSA in acetone gave the corresponding acetonide derivative of **10** (70%). Product analysis (^{13}C-NMR and HPLC) indicated that these cyclisations were stereospecific with no other isomers evident.[11] When the partially cyclised compound **6** was epoxidised under stoichiometric conditions, *in situ* cyclisation by the $Ti(OPr^i)_4$ took place to give **10** directly (59% at 50% conversion).



Scheme I. Mono- and diepoxide synthesis and cyclisations: (a) (D)-DMT, $Ti(O^iPr)_4$, ^{t}BuOOH, 3A sieves, CH_2Cl_2, -23°C, 12 h; Me_2S; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 20°C, 18 h; (c) NaI, Me_2CO, 20°C, 30 h; (d) $NaHCO_3$, $MeOH/H_2O$, 20°C, 24 h; (e) $H_2C{=}C(OLi)O^tBu$, THF/HMPA, -78°C, 30 min; (f) HCl, MeOH, 0°C, 10 min; (g) HCl, MeOH, 35°C, 2 h; (h) (L)-DMT, $Ti(O^iPr)_4$, ^{t}BuOOH, 3A sieves, CH_2Cl_2, -23°C, 20 h; Me_2S; (i) CSA, CH_2Cl_2, 20°C, 5 min.

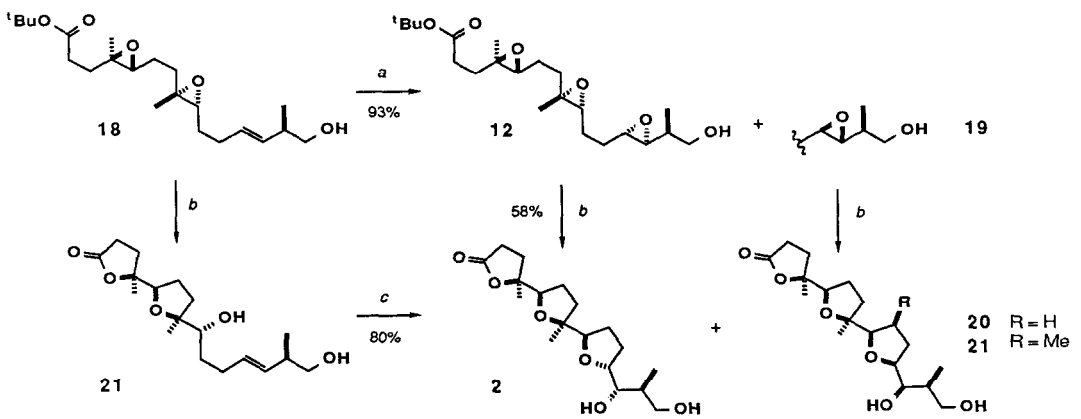
We next looked at extending this approach to the synthesis of tricyclic polyether fragments, particularly the CDE rings of etheromycin. This required the synthesis of a triepoxide such as **12** in Scheme III. The order of introduction of the three epoxides is critical, with the disubstituted epoxide clearly the most difficult to control. A successful route[12] to diepoxide **17** started from **3** and followed the order of epoxidation already used[10] (Scheme II). Chain extension of **14** through reaction of its iodide derivative with the lithium enolate of t-butylacetate was followed by DIBAL reduction (Et_2O, -98°C, 10 min) to give the aldehyde **15** (49% overall). In a Julia olefination sequence, **15** was added to the lithiated sulphone **16**[13] to give selectively the *trans*-alkene (*E*:*Z* = 3.5:1; 55%), which was desilylated (TBAF, THF) to give epoxyalcohol **17**. The t-butyl acetate 2-carbon extension was then repeated to give after deprotection homoallylalcohol **18**, which was now separated from the isomeric *cis*-alkene by HPLC.



Scheme II. Synthesis of diepoxide alkene **18**: (a) (D)-DMT, $Ti(O^iPr)_4$, ^tBuOOH, 3A sieves, CH_2Cl_2, -23°C, 12 h; Me_2S; $^tBuPh_2SiCl$, Et_3N, 20°C, 12 h; (b) K_2CO_3, $MeOH/H_2O$, 20°C, 24 h; (c) (D)-DMT, $Ti(O^iPr)_4$, ^tBuOOH, 3A sieves, CH_2Cl_2, -23°C, 18 h; Me_2S; (d) TsCl, pyr, CH_2Cl_2, 20°C, 18 h; (e) NaI, Me_2CO, 20°C, 18 h; (f) $H_2C{=}C(OLi)O^tBu$, THF/HMPA, -78°C, 5 min; (g) DIBAL, Et_2O, -98°C, 10 min; (h) **16**, ^nBuLi, THF, -78°C, 5 min; **15**, 10 min; PhCOCl, -78 to 20°C; (i) Na(Hg), THF/MeOH, -23°C, 1 h; (j) TBAF, THF, 20°C, 30 min; (k) TsCl, Et_3N, DMAP, CH_2Cl_2, 20°C, 5 h.

Two routes for conversion of **18** into **2** were examined. Epoxidation of **18** by mCPBA ($NaHCO_3$, CH_2Cl_2, 20°C, 5 h; 93%) gave an equal mixture of the isomers **12** and **19**, which were cyclised by CSA (0.5 eq, CH_2Cl_2, 0°C, 18 h; 58%) to give the separable γ-lactones **2** and **20** in a 1:1 ratio. The epoxidation stereoselectivity, however, could be improved by cyclisation of **18** to **21** by acid followed by asymmetric epoxidation and *in situ* cyclisation (80%) to give a 3:1 ratio of lactones **2** and **20**. Tricyclic compound **2** has the correct stereochemistry[11] for the C_{13}-C_{27} section of etheromycin, whereas the isomeric compound **20** is the same[14] as Still's compound **21**[3], except that it lacks a methyl group.

In summary, we have demonstrated that stepwise epoxidation using Sharpless methodology followed by biomimetic directed cyclisation can be used successfully to set up polyether fragments. Studies towards directed cyclisation to give larger fragments incorporating the spiroacetal unit of etheromycin are underway.



Scheme III. Triepoxide cyclisation: (a) mCPBA, $NaHCO_3$, CH_2Cl_2, 20°C, 5 h; (b) CSA, CH_2Cl_2, 0°C, 18 h; (c) (D)-DMT, $Ti(O^iPr)_4$, ^tBuOOH, 3A sieves, CH_2Cl_2, -23°C, 4 d.

Acknowledgements We thank the SERC and ICI Pharmaceuticals Division for support (CASE award to I.M.). We also thank Dr A. G. Brewster at ICI for his interest in this work and many helpful discussions. Professor Clark Still is thanked for providing us with a sample of compound **21** together with NMR and IR spectra.The generous gift of chemicals from ICI is gratefully acknowledged.

References and Notes

(1) D. E. Cane, W. D. Celmer, and J. W. Westley, *J. Am. Chem. Soc.* **105**, 3594 (1983).

(2) Etheromycin isolation: (a) W. D. Celmer, P. W. Cullen, M. T. Jefferson, C. E. Moppett, J. B. Routien, and F. C. Sciavolino, *Chem. Abs.* **90**, 150295X (1979) for patent; structure: (b) Polyether Antibiotics: Naturally Occurring Acid Ionophores, Vol 2, p374, Ed. J. W. Westley, Dekker, New York (1983).

(3) W. C. Still and A. G. Romero, *J. Am. Chem. Soc.* **108**, 2105 (1986).

(4) S. L. Schreiber, T. Sammakia, B. Hulin, and G. Schulte, *J. Am. Chem. Soc.* **108**, 2106 (1986).

(5) (a) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **102**, 5974 (1980); (b) R. M. Hanson and K. B. Sharpless, *J. Org. Chem.* **51**, 1922 (1986).

(6) B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.* **49**, 3707 (1984).

(7) A related approach to a diepoxy methylester and its pig liver esterase initiated cyclisation to **10** has been described by Robinson during the course of this work, see: S. T. Russell, J. A. Robinson, and D. J. Williams, *J.C.S. Chem. Comm.* 351 (1987). For other recent work on epoxide cyclisations, see: T. R. Hoye and J. C. Suhadolnik, *J. Am. Chem. Soc.* **107**, 5312 (1985); R. E. Dolle, K. C. Nicolaou, *J. Am. Chem. Soc.* **107**, 1691 (1985); P. G. M.Wuts, R. D'Costa, and W. Butler, *J. Org. Chem.* **49**, 2582 (1984).

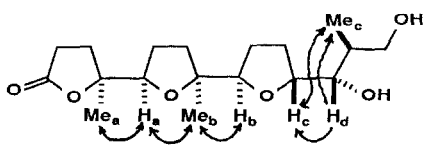
(8) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.* **99**, 5526 (1977).

(9) H. Kigoshi, M. Ojika, Y. Shizuri, N. Niwa, and K. Yamada, *Tetrahedron Lett.* **23**, 5413 (1982).

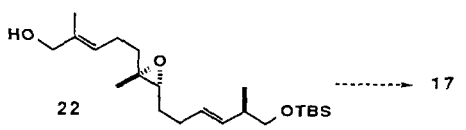
(10) The second asymmetric epoxidation resolves the major diepoxide to approaching 100% ee by selectively converting the small amount of the starting enantiomeric allylalcohol to form a separable diastereomeric diepoxide.

(11) The ring stereochemistry in cyclisation products **10**, **11**, and **2** was determined by nOe difference experiments (all new compounds gave spectroscopic data in agreement with the assigned structures). Compound **2** had ^{1}H-NMR (400 MHz, $CDCl_3$) 4.02 (1H, t, J = 8.0 Hz, H_a), 3.92 (1H, q, J = 6.3 Hz, H_c), 3.84 (1H, t, J = 7.0 Hz, H_b), 3.75 (1H, dd, J = 4.3, 5.9 Hz, H_d), 3.71 (1H, dd, J = 4.2, 10.8 Hz), 3.65 (1H, dd, J = 5.9, 10.8 Hz), 2.69 (1H, ddd, J = 7.3, 10.6, 17.0 Hz), 2.53 (1H, ddd, J = 5.8, 10.6, 17.0 Hz), 2.33 (1H, ddd, J = 5.8, 6.6, 16.3 Hz), 2.20-0.80 (12H, complex), 1.35 (3H, s, Me_a), 1.17 (3H, s, Me_b), 0.99 (3H, d, J = 7.0 Hz, Me_c); ^{13}C-NMR (100.6 MHz, $CDCl_3$) 177.3, 87.5, 85.2, 84.2, 82.4, 80.6, 75.9, 67.1, 37.3, 33.4, 29.9, 29.4, 29.3, 27.1, 26.0, 23.3, 23.2, 11.1. Results from nOe experiment:

2



(12) A more direct approach to **17** was also tried where the epoxides were introduced in the reverse order, but this has been frustrated so far by the failure of the Sharpless asymmetric epoxidation on **22** under a wide range of conditions.



(13) The sulphone **16**, $[\alpha]_D$=+8.2° (c 5.0, $CHCl_3$), was prepared in 76% yield from (***R***)-(-)-methyl-3-hydroxy-2-methylpropionate (Aldrich), by the sequence: (i) PhSSPh, Bu_3P, MeCN, 20°C, 36 h; (ii) DIBAL, CH_2Cl_2, -78°C, 1 h; (iii) mCPBA, CH_2Cl_2, 0°C, 0.5 h; (iv) TBSCl, imidazole, CH_2Cl_2, 0°C, 0.5 h.

(14) The high field NMR spectra of **20** were similar to those obtained for **21**, whose structure has been established by X-ray crystallography[3].

(Received in UK 13 August 1987)