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Studies in Biomimetic Polyether Synthesis: Construction of an ABCD-Ring Subunit of Etheromycin Using Polyepoxide Cascade Cyclisations.

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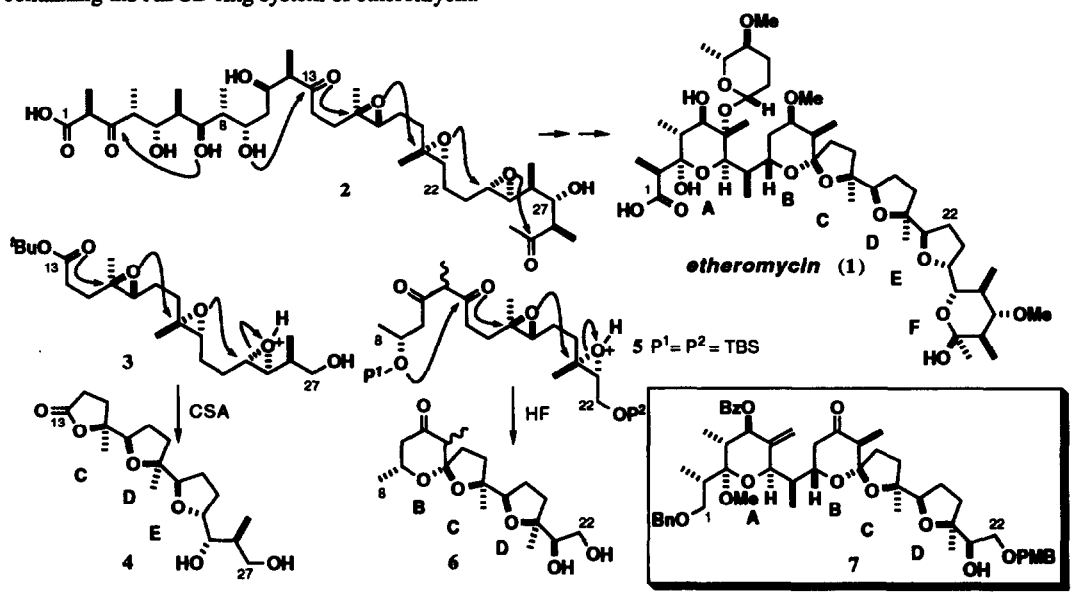
Abstract: The diepoxides **8** and **9** were prepared by Horner-Emmons and aldol coupling reactions from **21** and **13**, respectively. The derived β-diketones **22** and **24** were cyclised under acidic conditions to generate the C_1–C_{22} segment **7**, which contains the ABCD rings of etheromycin.

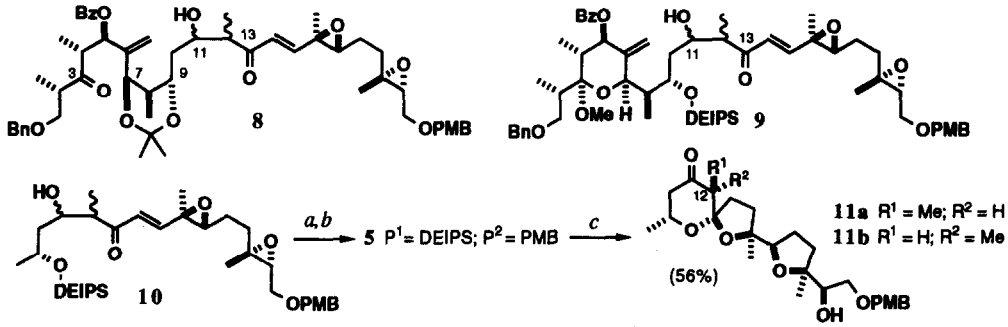
The polyether antibiotic etheromycin (**1**) is characterised structurally by a complex array of six ether rings (A–F) with a multitude of associated stereocentres.[1] The Cane-Celmer-Westley hypothesis[2] suggests that it might arise biosynthetically from cyclisation of the polyepoxide **2**, as shown in **Scheme 1**. We have been mimicking this biogenetic model in the chemical synthesis[3] of etheromycin and related partial structures. Previous studies[3-5] to this end have concentrated on the preparation and acid-mediated cascade cyclisations of polyepoxide precursors to the CDE[3a] and BCD[3b] rings, as in **3** → **4** and **5** → **6**. We now report our results for the formation and cyclisation of more highly functionalised diepoxides, which leads to the C_1–C_{22} segment **7** containing the ABCD ring system of etheromycin.



Scheme 1

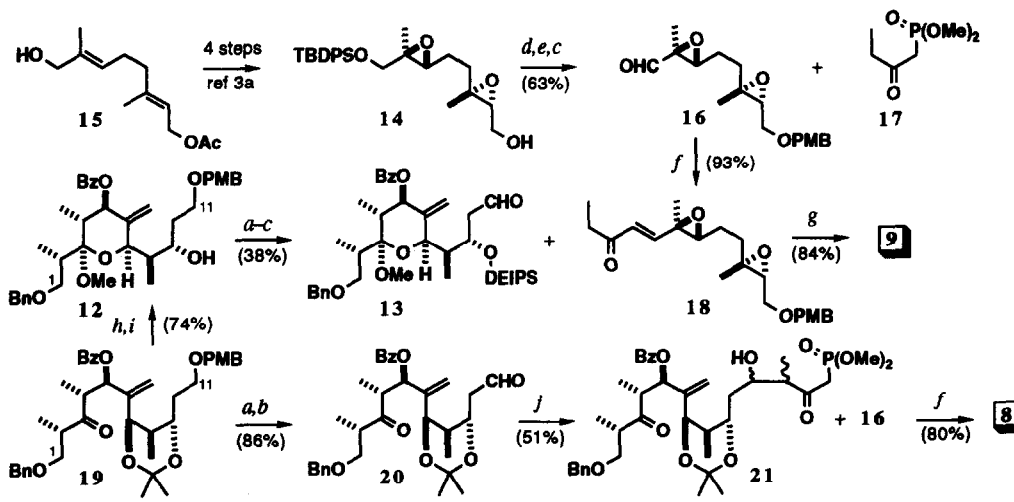
By analogy with our earlier work,[3b] the enones **8** and **9** (**Scheme 2**) were chosen as potential acyclic precursors for the ABCD rings of etheromycin, where the C_{13} ketone group is constrained by the *trans* double bond from premature internal opening of the neighbouring epoxide. When required, however, the reductive removal of this double bond and oxidation at C_{11} should give a β-diketone[6] to trigger the cyclisation cascade.

Two alternative procedures for this transformation emerged from studies on simpler systems, *viz.* (*i*) enone reduction[3c] using H_2 and Rh/Al_2O_3 followed immediately by Dess-Martin[7] oxidation, or (*ii*) Swern oxidation to the unsaturated β-diketone followed by 1,4-reduction using $^nBu_3SnH$ and catalytic $(Ph_3P)_4Pd$.[8] Using the former conditions on the model[9] enone **10**, with a subsequent acid-promoted cyclisation step, the tricyclic ketones[10] **11a** and **11b** (= 60 : 40 mixture of C_{12}-epimers) were obtained *via* **5** (P^1 = DEIPS, P^2 = PMB) in 56% overall yield.



Scheme 2 (*a*) H_2, Rh/Al_2O_3, CH_2Cl_2, 25 °C, 2 h; (*b*) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 0.5 h; (*c*) 0.5 *M* HCl, THF, 25 °C, 15 min.

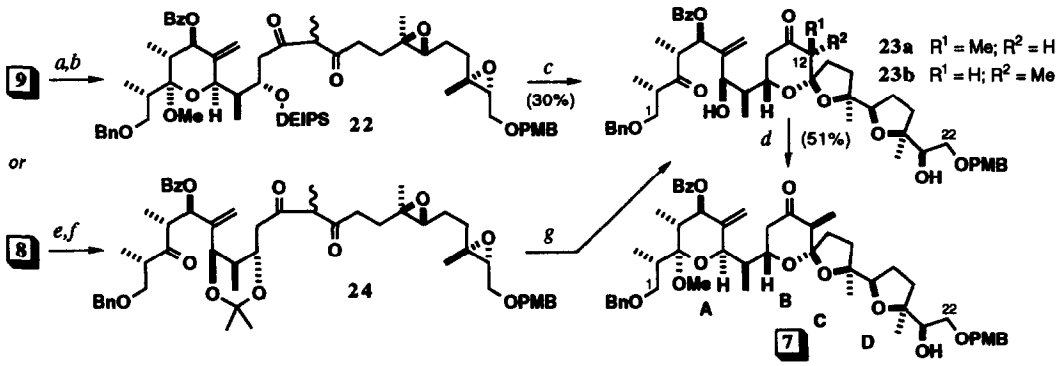
The synthesis of the more complex enones **8** and **9** is shown in **Scheme 3**. In the latter case, the etheromycin A-ring is already in place as its methyl acetal. Here, the previously reported[3d] acetal **12** was first converted into the aldehyde **13**, $[\alpha]_D^{20}$ = +45.1° (*c* 1.4, $CHCl_3$), in three steps by protecting group adjustment and Dess-Martin oxidation. The synthesis of the diepoxide **14** from **15** relies on sequential Sharpless asymmetric epoxidation, as described previously,[3a] for control of the epoxide stereochemistry. Subsequent conversion into the aldehyde **16** was followed, in turn, by a $Ba(OH)_2$-mediated[11] Horner-Emmons reaction with **17** to give the enone **18**, $[\alpha]_D^{20}$ = +6.0° (*c* 1.7, $CHCl_3$), in 59% overall yield. Using the Zn enolate[3b] derived from **18**, the aldol coupling with the aldehyde **13** gave an 84% yield of the enone adducts **9**.



Scheme 3 (*a*) $Et_2{}^iPrSiCl$, imidazole, DMAP, DMF, 25 °C, 16 h; (*b*) DDQ, H_2O, CH_2Cl_2, 25 °C, 3 min; (*c*) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 0.5 h; (*d*) $PMBOC(CCl_3)$=NH, cat TfOH, Et_2O, 25 °C, 40 min; (*e*) TBAF, THF, 25 °C, 0.5 h; (*f*) $Ba(OH)_2.8H_2O$ (0.7 equiv), *aq.* THF, 25 °C, 40 min; (*g*) LDA, THF, -78 °C; $ZnCl_2$; **13**, 1 h; (*h*) 0.5 *M* HCl, THF, 25 °C, 10 h; (*i*) PPTS, MeOH, $(MeO)_3CH$, 25 °C, 10 h; (*j*) **17**, ^{n}BuLi, THF, 0 °C; **20**, -78 °C, 1 min.

The alternative cyclisation precursor **8** has C_3 as the free ketone, while the 7-OH is protected together with the 9-OH as the acetonide. As shown in **Scheme 3**, this was prepared from **19** (the precursor of **12**)[3d] beginning with the DDQ deprotection of the PMB ether and oxidation to give the aldehyde **20**, $[\alpha]_D^{20} = -2.5°$ (*c* 1.6, $CHCl_3$), in 86% yield. Addition[3b] of a β-ketophosphonate dianion (**17**, ^{n}BuLi) to **19** then gave the adducts **21**. A Horner-Emmons coupling of **21** with the aldehyde **16**, again mediated by $Ba(OH)_2$,[11] finally gave the required enone **8** as a mixture of epimers at C_{11} and C_{12}.

Most of our effort was directed towards achieving a polyepoxide cyclisation from **9**, since we anticipated that the diethylisopropylsilyl (DEIPS) protecting group[12] should come off more rapidly than the acetonide hydrolysis in **8**, allowing the free 9-OH to participate in the cyclisation cascade (cf. **Scheme 2**). Thus, **9** was primed for cyclisation by careful reduction of the enone double bond by H_2 and Rh/Al_2O_3 in THF (**Scheme 4**), followed by oxidation using the Dess-Martin periodinane. The resulting β-diketone **22** was not isolated, but was treated directly with 0.5 *M* HCl in THF to generate the polyether sequence in **23a** and the 12-*epi* compound[13] **23b** in 30% overall yield (70 : 30 ratio). The major ketone **23a** was then subjected to acetal formation (PPTS, $(MeO)_3CH$, MeOH), leading to the isolation of the fully cyclised compound **7**, $[\alpha]_D^{20} = +40.0°$ (*c* 0.7, $CHCl_3$), where the ABCD rings are now all in place.[14] At this stage, the ^1H and ^{13}C NMR data[10] for **7** matched as expected with those obtained for the simpler systems **11a** and **12**. The stereochemistry in **7** was determined by the assignment of the ^1H and ^{13}C NMR spectra (COSY, HETCOR) followed by extensive NOE experiments (supported by molecular modelling of the conformational preferences).[10]



Scheme 4 (*a*) H_2, Rh/Al_2O_3, THF, 25 °C, 0.5 h; (*b*) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 0.5 h; (*c*) 0.5 *M* HCl, THF, 25 °C, 2.5 h; (*d*) PPTS, $(MeO)_3CH$, MeOH, 25 °C, 8 h; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 45 min; Et_3N, -78 → -20°C; (*f*) $^n Bu_3SnH$, $(Ph_3P)_4Pd$ (5 mol%), THF, 25 °C, 45 min; (*g*) 0.5 *M* HCl, THF, 25 °C, 16 h.

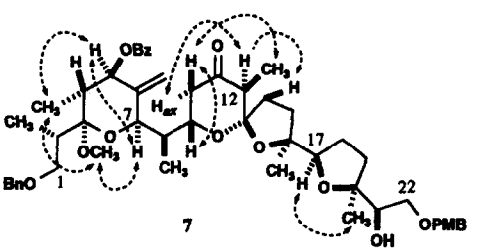
Less satisfactory results were obtained by starting from the acetonide-containing enone **8**. In this system, the β-diketone cyclisation substrate **24** was generated from **8** by Swern oxidation, followed by Pd(0)-catalysed 1,4-reduction with $^n Bu_3SnH$.[3b] Treatment of the intermediate β-diketone **24** with 0.5 *M* HCl in THF again induced a cyclisation cascade leading to the isolation of **23a** and **23b** after HPLC purification, which were again converted into the ABCD ring system in **7**. A lower overall yield was now obtained, presumably due to the inefficiency of acetonide removal relative to cleavage of the DEIPS ether in **22**.

Altogether this work underlines the power and utility of directed polyepoxide → polyether cascade cyclisations in rapidly constructing the tetrahydrofuran and tetrahydropyran rings of etheromycin.[13,14] Future work in this area will address the biomimetic synthesis of the complete ABCDEF ring system.

Acknowledgement: We thank the SERC (GR/F43505) and Pfizer Central Research for support and Dr J. M. Goodman (Cambridge) for assistance with molecular modelling.

References and Notes

1. (a) Celmer, W. D.; Cullen, P. W.; Jefferson, M. T.; Moppett, C. E.; Routien, J. B.; Sciavolino, F. C. *Chem. Abs.* **1979**, *90*, 150295X. Structure: (b) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*, Vol 2, p 374, Ed. Westley, J. W., Dekker, New York (1983).
2. Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
3. (a) Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett.* **1987**, *28*, 5205; (b) Paterson, I.; Craw, P. A. *Tetrahedron Lett.* **1989**, *30*, 5799; (c) Paterson, I.; Boddy, I. *Tetrahedron Lett.* **1988**, *29*, 5301; (d) Paterson, I.; Tillyer, R. D.; Ryan, G. R. *Tetrahedron Lett.* **1993**, *34*, 4389.
4. For biomimetic polyepoxide cyclisations directed towards the synthesis of monensin, see: (a) Russell, S. T.; Robinson, J. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 351; (b) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105 (c) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106.
5. Review: Altenbach, H.-J. In *Organic Synthesis Highlights*; Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. Ed., pp 145-150, VCH, Weinheim (1991).
6. The use of the β-diketone is necessary, since the precursor β-hydroxyketone undergoes competitive dehydration under the cyclisation conditions employed (see ref 3c).
7. The Dess-Martin procedure proved to be superior to that of our earlier protocol (ref 3b) using Swern oxidation. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
8. Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.
9. Compound **10** was prepared by an analogous route to the enone precursor of **5** (P^1 = P^2 = TBS), see ref 3b.
10. All new compounds gave spectroscopic data in agreement with the assigned structures. **23a** had ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, *J* = 7.0 Hz, C8-Me), 0.99 (3H, d, *J* = 6.7 Hz, C12-Me), 1.04 (3H, d, *J* = 7.0 Hz, C2-Me), 1.10 (3H, s, C20-Me), 1.21 (3H, s, C16-Me), 1.28 (3H, d, *J* = 7.1 Hz, C4-Me), 1.58–2.11 (9H, m, C8-H, C14-$H_{a,b}$, C15-$H_{a,b}$, C18-$H_{a,b}$, C19-$H_{a,b}$), 2.29 (1H, dd, *J* = 3.1, 13.8 Hz, C10-H_{eq}), 2.42 (1H, dd, *J* = 12.1, 13.8 Hz, C10-H_{ax}), 2.54 (1H, br s, OH), 2.59 (1H, q, *J* = 6.7Hz, C12-H), 3.15 (1H, m, C2-H), 3.25 (1H, m, C4-H), 3.34 (1H, dd, *J* = 5.2, 8.7Hz, C1-H_a), 3.40 (1H, dd, *J* = 7.9, 9.7 Hz, C22-H_a), 3.58 (2H, m, C1-H_b, C22-H_b), 3.66 (1H, dd, *J* = 2.8, 7.9 Hz, C21-H), 3.79 (1H, m, C17-H), 3.79 (3H, s, OMe), 4.06 (1H, d, *J* = 8.5 Hz, C7-H), 4.33–4.47 (5H, m, C9-H, OCH_2Ph, OCH_2Ar), 5.31 (2H, bs, $C=CH_2$), 5.87 (1H, d, *J* = 5.1 Hz, C5-H), 6.87 (2H, m, arom), 7.18-7.56 (10H, m, arom), 8.00 (2H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5, 11.4, 11.6, 14.1, 21.8, 23.8, 27.3, 32.5, 33.7, 36.3, 41.2, 43.3, 45.1, 49.1, 51.4, 55.3, 69.6, 70.8, 72.3, 73.1, 73.2, 73.8, 75.5, 75.9, 82.4, 84.0, 87.6, 111.4, 113.9(x2), 116.0, 127.6(x3), 128.4(x2), 128.4(x2), 129.4(x2), 129.6(x2), 130.1(x2), 133.1, 137.8, 147.7, 159.3, 165.4, 207.0, 213.2; HRMS (FAB, NaI) m/z calcd for $C_{51}H_{66}NaO_{12}$ $(M+Na)^+$ 893.448, found 893.445. **7** had ^{1}H NMR (500 MHz, C_6D_6) δ 1.00 (3H, d, *J* = 6.8 Hz, C4-Me), 1.10 (3H, d, *J* = 7.0 Hz, C8-Me), 1.10 (3H, s, C20-Me), 1.18 (3H, d, *J* = 6.7 Hz, C12-Me), 1.23 (3H, d, *J* = 6.9 Hz, C2-Me), 1.31 (3H, s, C16-Me), 1.36–2.04 (8H, m, C14-$H_{a,b}$, C15-$H_{a,b}$, C18-$H_{a,b}$, C19-$H_{a,b}$), 2.17 (1H, ddq, *J* = 6.1, 6.1, 6.4 Hz, C8-H), 2.27 (1H, dd, *J* = 13.7, 13.7 Hz, C10-H_{ax}), 2.34 (1H, q, *J* = 6.7 Hz, C12-H), 2.44 (1H, dq, *J* = 6.8, 7.8 Hz, C4-H), 2.51 (2H, m, C2-H, OH), 2.69 (1H, dd, *J* = 2.7, 13.7 Hz, C10-H_{eq}), 3.10 (3H, s, OMe), 3.16 (1H, dd, *J* = 8.9, 8.9 Hz, C1-H_a), 3.30 (3H, s, ArOMe), 3.43 (1H, dd, *J* = 8.0, 9.4 Hz, C22-H_a), 3.59 (1H, dd, *J* = 2.9, 8.9 Hz, C1-H_b), 3.64 (1H, dd, *J* = 3.0, 9.4 Hz, C22-H_b), 3.73 (2H, m, C17-H, C21-H), 4.12 (1H, d, *J* = 6.4 Hz, C7-H), 4.29 (2H, s, OCH_2Ph), 4.31 (1H, d, *J* = 11.3 Hz, OCH_aAr), 4.35 (1H, d, *J* = 11.3 Hz, OCH_bAr), 4.58 (1H, ddd, *J* = 2.7, 6.1, 13.7 Hz, C9-H), 4.96 (1H, s, $C=CH_a$), 5.28 (1H, s, $C=CH_b$), 5.87 (1H, d, *J* = 7.8 Hz, C5-H), 6.79 (2H, d, *J* = 8.5 Hz, arom), 7.07-7.29 (10H, m, arom), 8.23 (2H, m, arom); ^{13}C NMR (100 MHz, C_6D_6) δ 9.0 (C12-Me), 13.5 (x2, C4-Me, C8-Me), 14.3 (C2-Me), 21.8 (C20-Me), 24.2 (C16-Me), 27.5 (C18), 32.8, 34.7, 36.6 (C14, C15, C19 interchangeable), 40.5 (C2), 41.1 (C4), 41.8 (C8), 47.0 (C10), 48.3 (OCH_3), 51.4 (C12), 54.7 ($ArOCH_3$), 69.9 (C9), 71.3 (C22), 72.3 (C1), 73.2 (x2, OCH_2Ph, OCH_2Ar), 74.6 (C7), 75.9 (C21), 76.3 (C5), 83.1 (C17), 84.3 (C20), 87.5 (C16), 103.0 (C3), 111.4 (C13), 112.3 ($C=CH_2$), 114.1 (x2, arom), 128.5-128.7 (x6, arom), 129.5 (x3, arom), 130.0 (x2, arom), 130.8 (arom), 130.9 (arom), 133.1 (arom), 139.3 (arom), 142.6 (C6), 159.8 (arom), 165.8 ($OCOPh$), 205.4 (C11); HRMS (FAB, NaI) m/z calcd for $C_{52}H_{68}NaO_{12}$ $(M+Na)^+$ 907.461, found 907.464.
Summary of results from NOE difference experiments on **7** (supported by molecular modelling):



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11. Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 0000.
12. Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369.
13. We have previously shown (ref 3b) that the methyl-bearing stereocentre at C_{12} can be epimerised to the natural (12*R*) configuration. To assist structural elucidation, the 12-*epi* compound **23b** was also subjected to acetal formation, giving a compound with an analogous ^{1}H NMR spectrum to that of the fully cyclised compound **7**.
14. At present, the C_2 stereocentre in **7** corresponds to 2-*epi*-etheromycin, but it should be possible to epimerise this after oxidation to the carboxylic acid at C_1.

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