Tetrahedron Letters, Vol. 34, No. 27, pp. 4389-4392, 1993
Printed in Great Britain

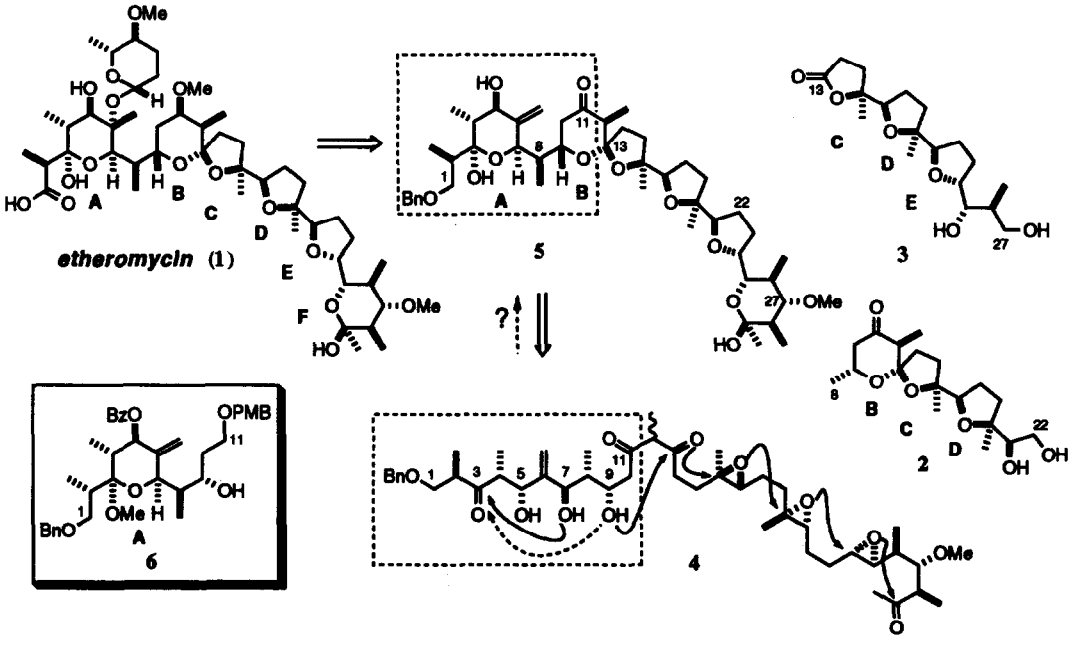
0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Studies in Biomimetic Polyether Synthesis: Synthesis of an A–Ring Subunit of Etheromycin.

Ian Paterson,* Richard D. Tillyer, and Glen R. Ryan
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract: The β-hydroxyketones **7**, **20**, and **22** were prepared by stereocontrolled aldol reactions of (*S*)- and (*R*)-**18** with the enal **8**. Acetonide hydrolysis gave the bicyclic acetals **23–25**, while the benzoate **26** gave the tetrahydropyran **6**, corresponding to an A-ring subunit for 2-*epi*-etheromycin.

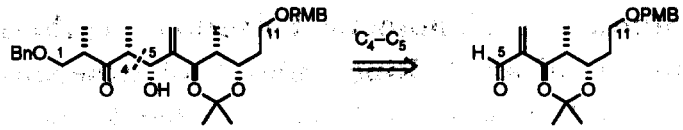
Etheromycin (**1**), an ionophore antibiotic isolated from *S. Hygroscopicus*, is characterised structurally by a complex array of six ether rings (A–F) with a multitude of stereocentres.[1] In studies towards a biomimetic[2] synthesis of etheromycin, we have demonstrated[3] that the BCD/CDE ring systems in **2** and **3** (**Scheme 1**) can be assembled using appropriate polyepoxide → polyether cyclisation cascades.[4] More elaborate cyclisations such as **4** → **5**, directed towards the complete polyether skeleton, require access to a suitable C_1–C_{11} subunit to act as a precursor for the AB rings. We have now examined the acid-promoted cyclisation behaviour of a series of potential C_1–C_{11} segments, and have found that formation of the A–ring derivative **6** can be efficiently accomplished.



Scheme 1

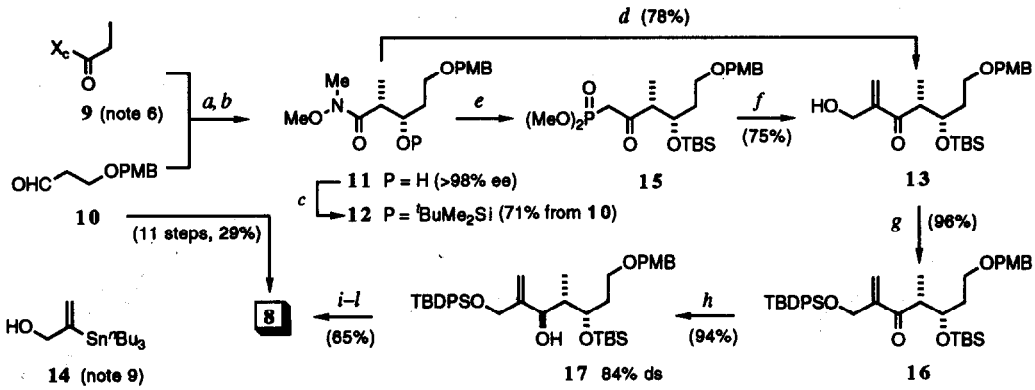
The proposed cyclisation cascade for etheromycin, **4** → **5**, requires the 7–OH to form the A–ring hemiacetal as the 9–OH triggers the triepoxide opening (*solid arrows* in **4**). For this to be synthetically viable, an alternative cyclisation mode for **4** (*dashed arrow*), involving bicyclic acetal formation at the C_3 ketone by the 7– and 9–OH groups, must be less favourable. It was therefore desirable to first examine the cyclisation

preferences of an appropriate C_1–C_{11} segment alone. For this study, we targeted the ketone **7**, corresponding to 2-*epi*-etheromycin, together with other readily accessible aldol isomers derived from the α-methylene-β-alkoxy aldehyde **8**.



7 **8**

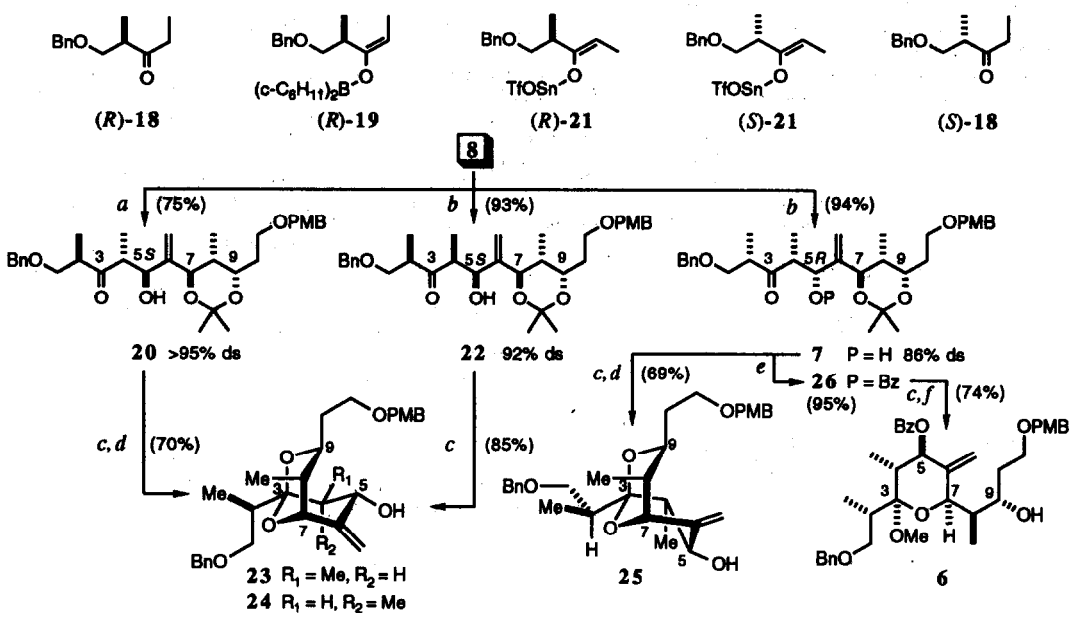
An efficient, multi-gram synthesis of the pivotal aldehyde **8** is outlined in **Scheme 2**. An Evans aldol reaction[5] between the chiral imide[6] **9** and the aldehyde **10** was followed by formation of the Weinreb amide[7,8] **11**. After protection as its *tert*-butyldimethylsilyl ether **12**, this was directly converted into the allylic alcohol **13**, $[\alpha]_D^{20} = -15.9°$ (*c* 0.66, $CHCl_3$), using the vinyl lithium reagent derived from the stannane **14**.[9] On a large scale (≥100 mmol), a better procedure involved the initial formation of the β-ketophosphonate **15**. Reaction of **15** with formaldehyde, promoted by K_2CO_3, then gave **13** in 75% overall yield. After *O*-silylation, the reduction[10] **16** → **17** proceeded with 84% ds using $LiAlH_4$, as expected[11] from Felkin-Anh control. Finally, a series of protecting group manipulations on **17**, followed by a Dess-Martin[12] oxidation, then gave the enantiomerically pure enal **8**, $[\alpha]_D^{20} = +12.2°$ (*c* 0.26, $CHCl_3$), in 65% overall yield (29% from **10**).



Scheme 2 (*a*) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 30 min; **10**, –78 °C, 2 h; H_2O_2; (*b*) HN(Me)OMe.HCl, Me_3Al, THF, 0 °C, 2 h; (*c*) $^tBuMe_2SiCl$, imidazole, cat. DMAP, DMF, 25 °C, 15 h; (*d*) **14**, ^nBuLi, THF, –78 → 0 °C; **12**, –78 → 0 °C, 15 min; (*e*) $(MeO)_2P(O)CH_2Li$, THF, –78 °C, 2 h; (*f*) *aq.* HCHO, K_2CO_3, THF/H_2O, 25 °C, 3 h; (*g*) $^tBuPh_2SiCl$, imidazole, CH_2Cl_2, 25 °C, 1 h; (*h*) $LiAlH_4$, Et_2O, –78 °C, 10 min; (*i*) AcOH, THF/H_2O, 40 °C, 12 h; (*j*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 25 °C, 4 h; (*k*) TBAF, THF, 25 °C, 2 h; (*l*) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 25 min.

Using the dipropionate reagents[13] (*R*)- and (*S*)-**18** (**Scheme 3**), several highly stereocontrolled aldol couplings were next performed. The α-methylene-β-alkoxy aldehyde **8** exhibited a low π-facial selectivity,[14] yet contributed to the observed stereoselectivities for these aldol reactions by double asymmetric induction. Addition of the *E* dicyclohexylenol borinate[13c] (*R*)-**19** to **8** in Et_2O smoothly gave the anti-anti aldol adduct **20** in >95% ds. In contrast, however, various *Z* enol borinates derived from (*R*)-**18** proved to be insufficiently reactive and failed to add cleanly to **8**. This necessitated the use of more reactive metal enolate derivatives to achieve syn selective aldol additions. Using the *Z* tin(II) enolate[13b] (*R*)-**21** in CH_2Cl_2, the syn isomer **22** was now easily prepared in 92% ds. In these two cases, the chiral enolate contributes a high level of diastereofacial selectivity for preferred *si*-face attack on the aldehyde **8**, giving the (5*S*) adducts **20** or **22**. In a similar manner, reaction with the enantiomeric tin(II) enolate (*S*)-**21** gave the syn isomer **7** (*via* mismatched *re*-face attack on **8**) in 86% ds. The two syn aldol isomers **7** and **22** could also be selectively prepared using the corresponding titanium enolates from (*S*)- and (*R*)-**18**, respectively.[14]

The cyclisation behaviour of these three keto acetonides was next investigated. To minimise dehydration to the enone, the acetonide hydrolysis was best accomplished using 0.5 *M* HCl in THF (1:2 by volume) at room temperature for 6–10 h. Under these conditions, the aldol adduct **22**, having the (5*S*) configuration, cleanly gave the bicyclic acetal **23**, $[\alpha]_D^{20} = -33°$ (*c* 2.1, $CHCl_3$), in 85% yield. For the ketone **20**, however, this led to a mixture of open-chain keto triol, hemiacetal, and the bicylic acetal **24**. Further treatment of this mixture with Dowex® acid resin (50X12-400) in MeOH/$(MeO)_3CH$ (10 : 1) gave **24** in 70% overall yield. Appropriate ^1H NMR decoupling and NOE difference experiments[8] confirmed the stereochemistry and indicated that these two bicyclic acetals adopted a chair-chair conformation. Using a similar procedure for the ketone **7**, which has the (5*R*) configuration, gave a 69% yield of the bicyclic acetal **25**, $[\alpha]_D^{20} = -48.6°$ (*c* 1.1; $CHCl_3$) — now having the less stable, chair-boat conformation.



Scheme 3 (*a*) (*R*)-**18**, $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2.5 h; **8**, –78 → –20 °C, 16 h; (*b*) (*R*)- or (*S*)-**18**, $Sn(OTf)_2$, Et_3N, CH_2Cl_2, –78 °C, 2 h; **8**, –78 → –50 °C, 3 h; (*c*) *aq.* 0.5 *M* HCl, THF, 25 °C, 6–10 h; (*d*) Dowex® 50X H^+ resin, MeOH, $(MeO)_3CH$, 25 °C, 10 min; (*e*) $(PhCO)_2O$, Et_3N, DMAP, CH_2Cl_2, 25 °C, 15 h; (*f*) PPTS, MeOH, $(MeO)_3CH$, 25 °C, 8 h.

In the (5*R*) series, simply protecting the 5–OH as its benzoate prevented the undesired formation of the bicyclic acetal (presumably due to further destabilisation of the chair-boat conformation in the 5–benzoate of **25**). Thus acid hydrolysis of the acetonide in **26**, followed by treatment with MeOH/$(MeO)_3CH$, gave only **6**, $[\alpha]_D^{20} = +59.8°$ (*c* 1.1, $CHCl_3$), in 74% yield. This has the A–ring tetrahydropyran as its methyl acetal between the 7–OH and the C_3 ketone, with the 9–OH available to form the etheromycin B–ring.

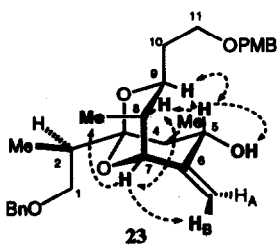
In conclusion, we have found that control of extended cyclisation cascades, such as **4** → **5** in **Scheme 1**, appears to be feasible provided the 5–OH is carried through as its benzoate. Further studies directed towards the biomimetic synthesis of etheromycin are underway.

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

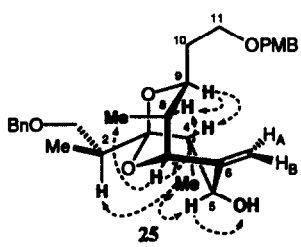
References and Notes

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.; Craw, P. A. *Tetrahedron Lett.* **1989**, *30*, 5799; (b) Paterson, I.; Boddy, I. *Tetrahedron Lett.* **1988**, *29*, 5301; (c) Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett.* **1987**, *28*, 5205.
4. For a recent review of polyepoxide cyclisation chemistry, see: 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).
5. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
6. We initially made **11** in >98% ee using the *N*-propionyl oxazolidinone derived from *D*-valine. This same amide, prepared from the cheaper (1*S*,2*R*)-norephedrine-derived auxiliary, was subsequently reported by Evans *et al.* as an intermediate in the synthesis of cytovaricin. We now follow the Evans route to **11** on a large scale. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.A.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
7. (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Comm.* **1982**, *12*, 989; (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
8. All new compounds gave spectroscopic data in agreement with the assigned structures. **24** had ^{1}H NMR δ (400 MHz, C_6D_6) 1.05 (3H, d, *J* = 6.8 Hz, C8-Me), 1.17 (1H, m, C8-H), 1.20 (3H, d, *J* = 6.8 Hz, C4-Me), 1.36 (3H, d, *J* = 6.9 Hz, C2-Me), 1.41 (1H, m, OH), 1.45–1.72 (2H, m, C10-H), 2.16 (1H, m, C4-H), 2.36 (1H, m, C2-H), 3.29 (3H, s, OMe), 3.33 (1H, dd, *J* = 9.8, 6.6 Hz, C1-H_a), 3.38–3.57 (2H, m, C11-H), 3.75 (1H, dd, *J* = 9.8, 5.8 Hz, C1-H_b), 4.13 (1H, ddd, *J* = 9.2, 3.1, 3.1 Hz, C9-H), 4.19 (1H, br s, C7-H), 4.25-4.38 (4H, m, OCH_2Ar, OCH_2Ph), 4.40 (1H, m, C5-H), 4.79 (1H, bs, H_B), 5.22 (1H, dd, *J* = 1.9, 1.9 Hz, H_A), 6.80 (2H, m, aromatic), 7.05-7.29 (7H, m, aromatic); ^{13}C NMR δ (100 MHz, C_6D_6) 12.4, 12.7, 13.6, 34.5, 36.4, 41.3, 46.6, 54.7, 66.2, 68.0, 72.3, 72.97, 73.9, 80.8, 101.4, 110.4, 114.0, 127.5, 127.7, 128.5, 129.5, 131.1, 139.3, 149.5. **25** had ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* = 7.0 Hz, C8-Me), 1.11 (3H, d, *J* = 6.6 Hz, C2-Me), 1.26 (3H, d, *J* = 7.1 Hz, C4-Me), 1.43 (1H, m, C8-H), 1.50-1.58 (2H, m, C10-H_a and OH), 1.68 (1H, m, C10-H_b), 1.88 (1H, dq, *J* = 10, 7.1 Hz, C4-H), 2.19 (1H, m, C2-H), 3.23 (1H, dd, *J* = 9.1, 9.1 Hz, C1-H_a), 3.39 (2H, m, C11-H), 3.70 (1H, dd, *J* = 9.1, 2.5 Hz, C1-H_b), 3.79 (3H, s, OMe), 3.93 (1H, m, C5-H), 4.19 (1H, ddd, *J* = 8.9, 3.3, 3.3 Hz, C9-H), 4.31–4.46 (5H, m, OCH_2Ph, OCH_2Ar and C7-H), 4.45 (2H, m, OCH_2Ar or OCH_2Ph), 4.84 (1H, dd, *J* = 2.1, 2.1 Hz, $H_{A/B}$), 5.25 (1H, dd, *J* = 2.4, 2.4 Hz, $H_{B/A}$), 6.86 (2H, m, aromatic), 7.20-7.33 (7H, m, aromatic); ^{13}C NMR δ (100 MHz) 11.3, 13.3, 15.0, 33.1, 38.4, 40.6, 55.2, 63.6, 66.1, 72.6, 73.0, 73.2, 73.3, 77.4, 101.2, 105.0, 113.8, 127.4, 127.6, 128.3, 129.3, 130.6, 138.8, 151.3, 159.2. **6** had ^{1}H NMR δ (400 MHz, C_6D_6) 1.03 (3H, d, *J* = 6.9 Hz, C4-Me), 1.14 (3H, d, *J* = 7.0 Hz, C9-Me), 1.23 (3H, d, *J* = 6.9 Hz, C2-Me), 1.35 (1H, m, OH), 1.67 (1H, m, C10-H_a), 2.04 (1H, m, C8-H), 2.08 (1H, m, C10-H_b), 2.44 (2H, m, C4-H and C2-H), 3.12 (3H, s, OMe), 3.17 (1H, dd, *J* = 8.5, 8.5 Hz, C1-H_a), 3.34 (3H, s, OMe), 3.56 (1H, dd, *J* = 8.5, 2.7 Hz, C1-H_b), 3.65 (2H, t, *J* = 6.0 Hz, C11-H), 4.16 (1H, d, *J* = 3.9 Hz, C7-H), 4.29-4.38 (4H, m, OCH_2Ph and OCH_2Ar), 4.70 (1H, m, C9-H), 4.91 (s, 1H, H_A), 5.23 (1H, s, H_B), 6.00 (1H, d, *J* = 8.2 Hz, C5-H), 6.84 (2H, d, aromatic), 7.15-7.33 (11H, m, aromatic), 8.38 (2H, m, aromatic); ^{13}C NMR δ (100 MHz) 11.1, 12.6, 14.2, 35.6, 39.2, 40.2, 47.9, 54.5, 68.2, 68.3, 72.1, 72.7, 73.0, 75.1, 75.9, 102.8, 108.9, 113.8, 128.4, 128.5, 129.2, 130.0, 130.6, 131.0, 132.95, 138.96, 143.0, 159.5, 165.6.

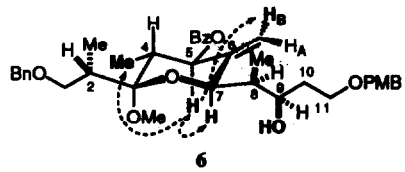
   Summary of NOE results (the conformations shown were supported by molecular modelling):



23



25



6

9. The vinylstannane **14** was prepared in 75% yield from methyl propiolate in a one-pot procedure: ^{n}Bu_3SnH, $(Ph_3P)_2PdCl_2$ (5 mol %), THF, 25 °C, 15 min; DIBAL, –95 → 0 °C, 1 h. For this hydrostannation protocol, see: Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
10. The use of $Me_4NBH(OAc)_3$ on the free β-hydroxyketone **13** (H for TBS) led to non-selective reduction giving a 1 : 1 mixture of *syn* and *anti* 1,3-diols. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
11. Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021.
12. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
13. (a) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821; (b) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233; (c) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121; (d) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585.
14. Paterson, I.; Bower, S.; Tillyer, R. D. *Tetrahedron Lett.* **1993**, *34*, 0000 (following paper in this issue).

(Received in UK 30 April 1993)