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STUDIES DIRECTED TOWARD THE SYNTHESIS OF LYSOCELLIN CLASS POLYETHER ANTIBIOTICS. THE ASYMMETRIC SYNTHESIS OF THE C_1-C_9 FERENSIMYCIN SYNTHON

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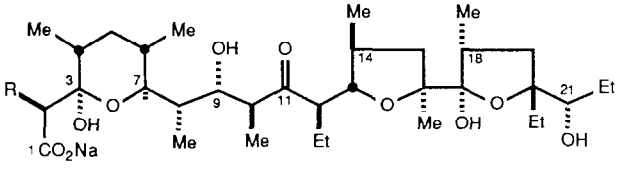
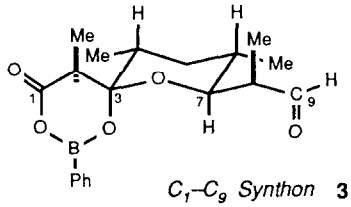
Abstract: The asymmetric synthesis of the C_1-C_9 ferensimycin synthon **3** is described. The absolute stereochemical relationships in this target structure were established through chiral enolate methodology.

As part of an ongoing effort to develop asymmetric carbon-carbon bond-forming reactions in the context of acyclic stereocontrol,[2] we have undertaken the asymmetric synthesis of ferensimycin B (**1**),[3] one of the more challenging members of the lysocellin (**2**) family of polyether antibiotics.[4] Inspection of the structures of **1** and **2** reveals a close homology in both gross structures and stereochemical relationships; however, the ferensimycin structure contains an additional C_2 methyl-bearing stereocenter not found in lysocellin which is flanked by two acidifying functional groups, the C_1 carboxyl and latent C_3 ketone moieties. At the outset of this project, it was not obvious how this labile stereochemical issue might be approached. For this reason, ferensimycin B was chosen as the primary objective for total synthesis. The purpose of this Letter is to decribe the stereoselective synthesis of the C_1-C_9 ferensimycin synthon **3**.

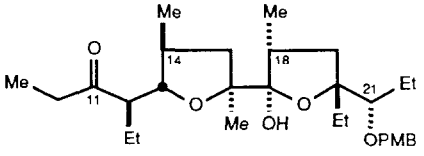
R = Me, Ferensimycin B, **1**
R = H, Lysocellin, **2**





C_1–C_9 Synthon **3**

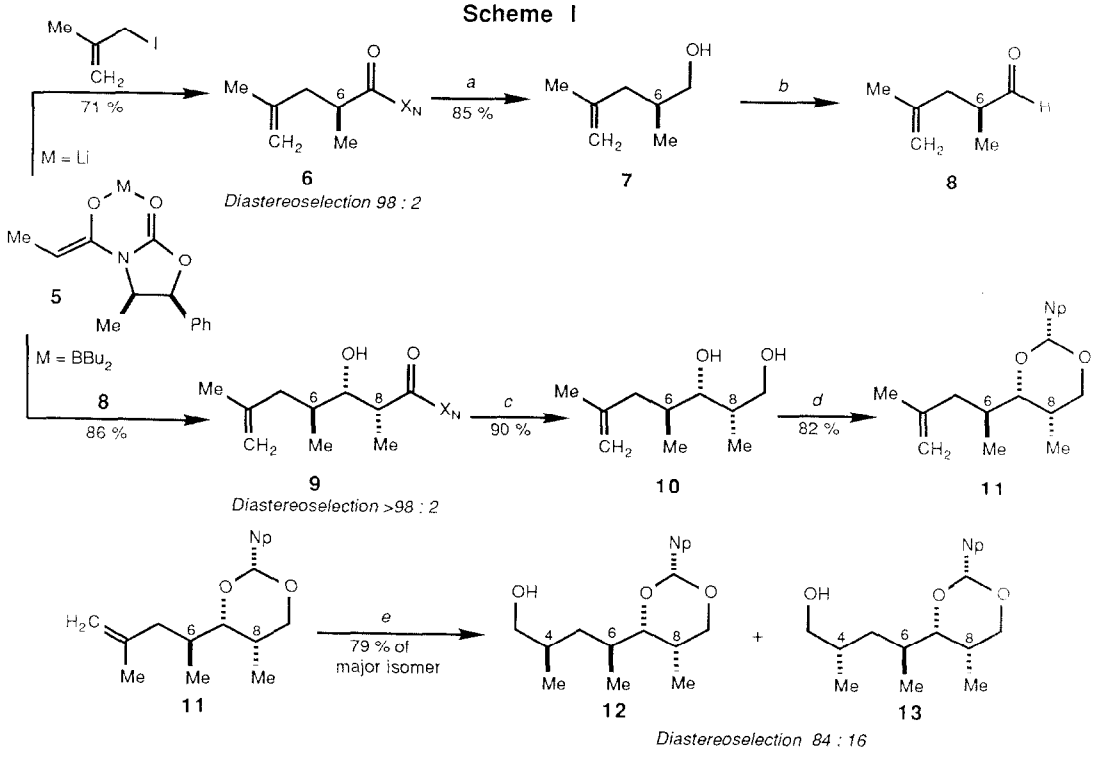
C_9–C_{10}



C_{10}–C_{23} Synthon **4**

The initial phases of the synthesis are illustrated below (Scheme I). All absolute stereochemical control in this series of reactions is ultimately derived from the chiral propionate enolate **5** (M=Li, BBu_2). The utilization of **5** in the illustrated alkylation[5] and aldol[6] reaction sequence to give the aldol adduct **9**, mp 110-111 °C has been described in a previous communication.[7] The further elaboration of **9** was accomplished via the illustrated series of reactions. Reduction of **9** to the diol **10**, $[\alpha]_D$ -3.82 °C (c 2.5, CH_2Cl_2), was accomplished with lithium borohydride (1.1 mol equiv, THF, -30 to 0 °C, 4 h) in 90% yield. Protection of this diol as the derived α-naphthylidene acetal was effected by stirring a benzene solution of **10** with 1-naphthaldehyde (2 equiv) and a catalytic amount of trichloroacetic acid in the presence of 4A or 5A molecular sieves.[8] Based upon prior precedent from our laboratory,[9] we were cautiously optimistic that the hydroboration of olefin-acetal **11** might proceed in a stereoselective manner to give the resultant alcohol **12** through 1,3-asymmetric induction.[12] The experiment confirmed this projection. Hydroboration of **11** with thexylborane (2 equiv, 0.5 M in THF, -15 ° to -5 °C, 5 h) followed by a bicarbonate peroxide oxidation afforded an 84:16 ratio of the diastereomeric alcohols **12** and **13** from which the desired isomer **12** could be isolated in 79% yield after flash chromatography. The stereochemical assignment for the major product diastereomer **12** was confirmed at a later point in the synthesis (vide infra).

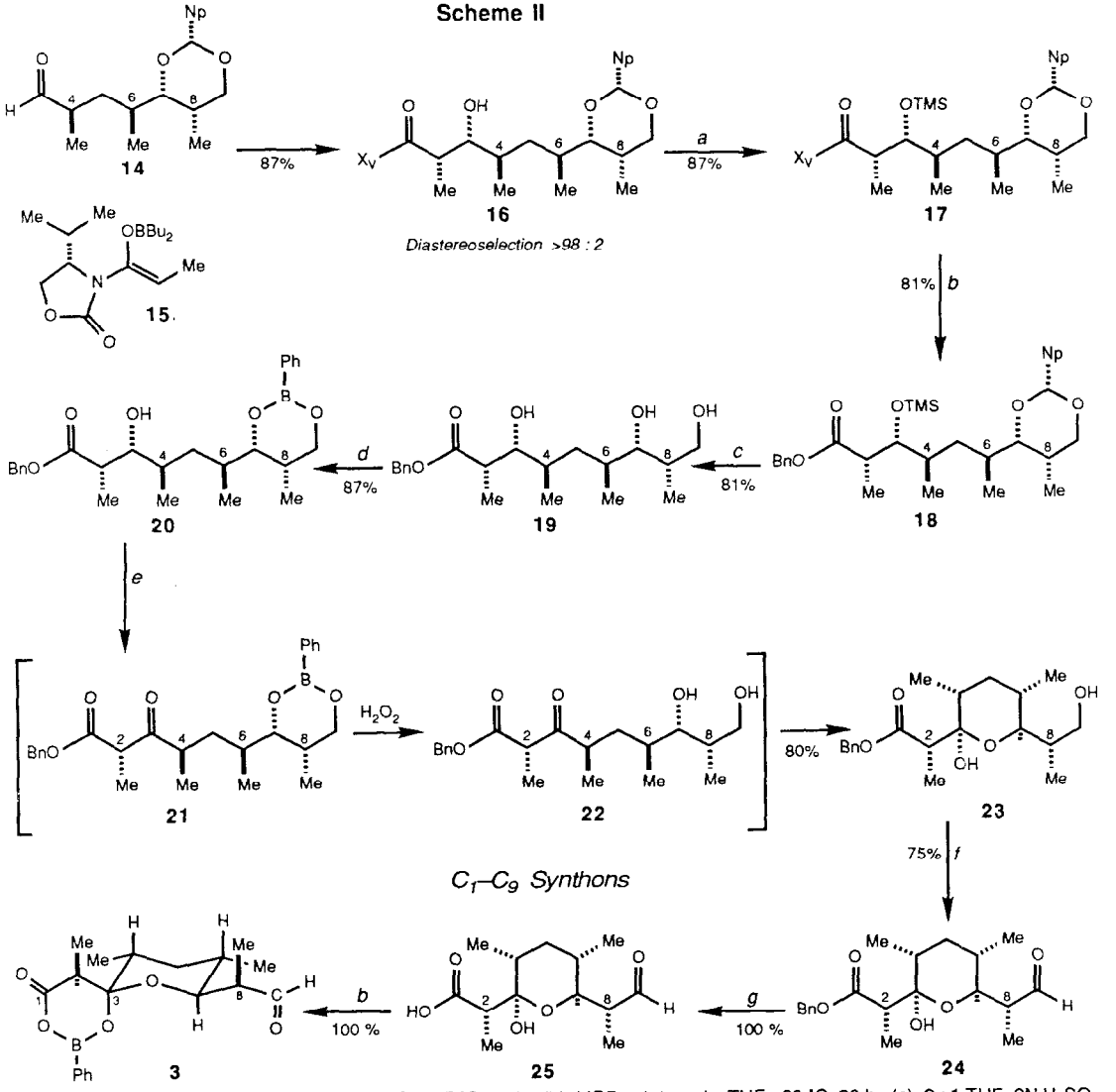
Scheme I



(a) $LiAlH_4$, 0.7 equiv, Et_2O, -15 to +25 °C, 3.5 h. (b) DMSO, $(ClCO)_2$, Et_3N, CH_2Cl_2. (c) $LiBH_4$, 1.1 mol equiv, THF, -30 to 0 °C, 4 h. (d) 1-naphthaldehyde, 2 equiv, CCl_3COOH, benzene, 25 °C, 12 h. (e) Thexylborane, 2 equiv, THF, -15 to -5 °C, 5 h.

The final C-C bond construction and subsequent refunctionalization reactions are illustrated in Scheme II. After a Swern oxidation of **12** to give the aldehyde **14** (95%), the aldol bond construction between **14** and the chiral propionate enolate **15**[6] was effected in 87% yield to give the adduct **16.** No other aldol diastereomers were detected in this reaction. In effect, the oxidation of the C_3 and C_9 hydroxyl functions in **16** would constitute the minimal number of chemical operations required for the completion of a C_1-C_9 *ferensimycin* synthon. The remaining sequence of reactions illustrated in Scheme II constitutes the realization of this set of refunctionalization operations. The sequential silylation[11] and

Scheme II



(a) TMS-imidazole,1.6 equiv, DMAP, CH_2Cl_2, 25 °C, 20 h. (b) LiOBn, 1.1 equiv, THF, -20 °C, 20 h. (c) 2 : 1 THF–2N H_2SO_4, 45 °C, 31h. (d) $PhB(OH)_2$, benzene, 25 °C, 12 h. (e) DMSO, $(ClCO)_2$, $EtN(i\text{-}Prop)_2$,CH_2Cl_2, -78 to 0 °C. (f) Pyr-SO_3, DMSO, Et_3N, 0 °C, 3 h. (g) 10% Pd-C, 15 psi H_2, EtOAc, 0 °C, 30 min.

transesterification[5] of **16** provided the benzyl ester **18** in a 70% yield for the two steps. At this point, prior to the delicate oxidation of alcohol **20**, a more labile diol protecting group was incorporated into the synthesis. Accordingly, the α-naphthylidene acetal was hydrolyzed (2:1 THF-2N H_2SO_4, 45 °C, 31 h) to give the triol ester **19** which was cleanly transformed to the phenylboronate ester **20** by treatment with phenylboronic acid (benzene, 25 °C, 12 h)[12]. At this point hydroxy ester **20** was oxidized to **21** under modified Swern oxidation conditions[13] in which the obligatory triethylamine base was replaced with the more hindered amine, diisopropylethylamine. In conjunction with the workup of this reaction, the cold (0 °C) solution was cannulated into ice water, and the keto ester **21** was isolated by methylene chloride extraction. Without purification the phenylboronate protecting group was removed by treating a solution of **21** in ethyl acetate with 30% aqueous hydrogen peroxide to give the lactol ester **23** in 80% yield as a clear oil $[\alpha]_D$ +42.4° (c 0.76 CH_2Cl_2). A careful inspection of the reaction revealed no other discernable product diastereomers. It thus appears that C_2 epimerization of either β-keto esters **21** or **22** is not a problem during either the oxidation or hydrolysis steps!

We have found that lactol **23** is a convenient precursor to the ferensimycin synthons **3**, **25** and **24**. For example, oxidation of **23** via the method of Parikh and Doering[14] afforded the lactol aldehyde **24**, $[\alpha]_D$ -18° (c -0.56, CH_2Cl_2) with no accompanying C_2 epimerization. The lactol acid **25** was also prepared in high yield by benzyl ester hydrogenolysis (10% Pd-C, EtOAc, 15 psi H_2, 0 °C, 30 min). Finally, the conveniently protected phenylboronate ester **3** was prepared as a crystalline solid, mp 167-167.5 °C, in quantitative yield by treatment of **25** with phenylboronic acid (C_6H_6, 25 °C, 12 h). We consider **3** to be ideally protected for the subsequent elaboration to ferensimycin B.

While the successful synthesis of **3** is of obvious relevance to the projected synthesis of ferensimycin, the precedents established in this study are also relevant to the synthesis of polyethers such as lonomycin-A and mutalomycin.[15]

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References and Notes

1. National Institutes of Health Postdoctoral Fellow, 1983-1986. Present address: Duke University, Department of Chemistry, Durham, NC 27706.
2. Evans, D.A. Proceedings of the Robert A. Welch Foundation **1983**, 27, 13.
3. Kusakabe, Y., Mizuno, T., Kawabata, S., Tanji, S., Seino, A., Seto, H., Otake, N. J. Antibiotics **1982**, 35, 1119.
4. Ebata, E., Kasahara, H., Sekine, K., Inoue Y. J. Antibiotics **1975**, 28, 118.
5. Evans, D.A., Ennis, M.D., Mathre, D.J. J. Am. Chem. Soc. **1982**, 104, 1737.
6. Evans, D.A., Bartroli, J., Shih, T.L. J. Am. Chem. Soc. **1981**, 103, 2127.
7. Evans, D.A.; Bartroli, J. Tetrahedron Lett. **1982**, 23, 807-810.
8. Meskins, F.A.J. Synthesis **1981**, 501.
9. Evans, D.A., Bartroli, J., Godel, T. Tetrahedron Lett. **1982**, 807.
10. See Ref. 9 for a rationalization for the sense of 1,3-asymmetric induction in this hydroboration reaction. A subsequent more quantitative analysis of this reaction has been published: Houk, K.N.; Rondan, N.G.; Wu, Y-D.; Metz, J.T.; Paddon-Row, M.N. Tetrahedron **1984**, 40, 2257-2274.
11. Torkelson, S. Ainsworth, C. Synthesis **1976**, 622.
12. Ferrier, R.J. Meth. Carbohyd. Chem. **1972**, 6, 419.
13. Swern, D.A. Omura, K. Tetrahedron **1978**, 34, 1651.
14. Parikh, J.R., Doering, W.v.E. J. Am. Chem. Soc. **1967**, 89, 5505.
15. For a useful pictorial survey of polyether structures see: Cane, D.E., Celmer, W.D.; Westley, J.W. J. Am. Chem. Soc. **1983**, 105, 3594-3600.

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