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TOTAL SYNTHESIS OF THE IONOPHORE ANTIBIOTIC IONOMYCIN. ASYMMETRIC SYNTHESIS OF THE C_1-C_{10} AND C_{11}-C_{16} SYNTHONS.

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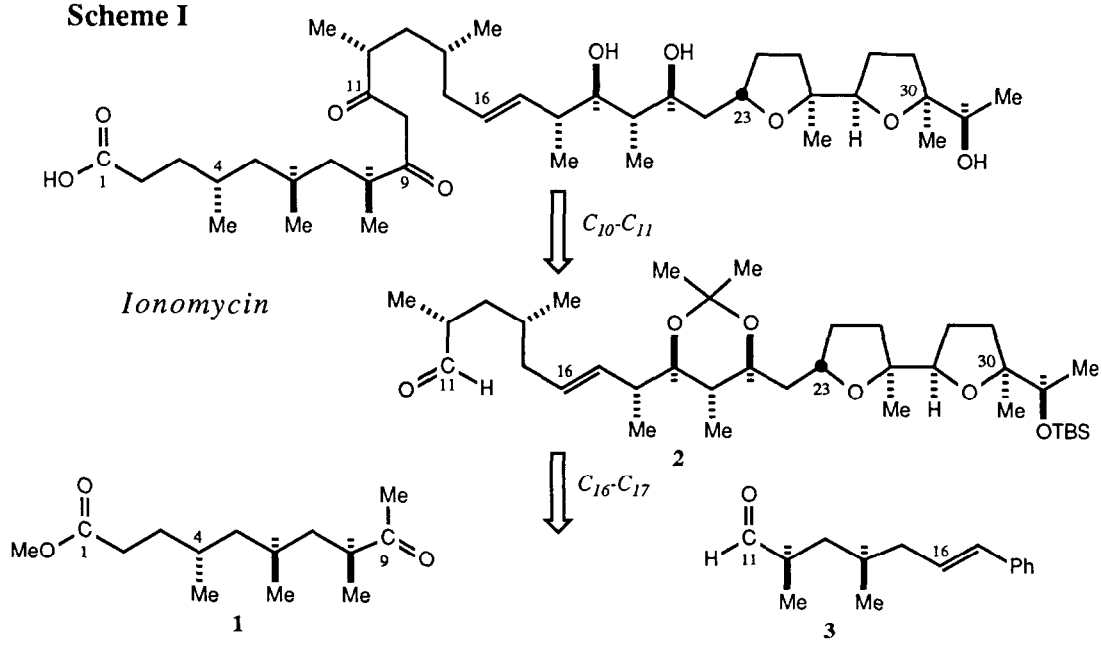
Abstract Asymmetric synthesis of the synthons **1** and **3** are described. Absolute stereochemical relationships in these intermediates have been established via chiral enolate and directed hydrogenation processes.

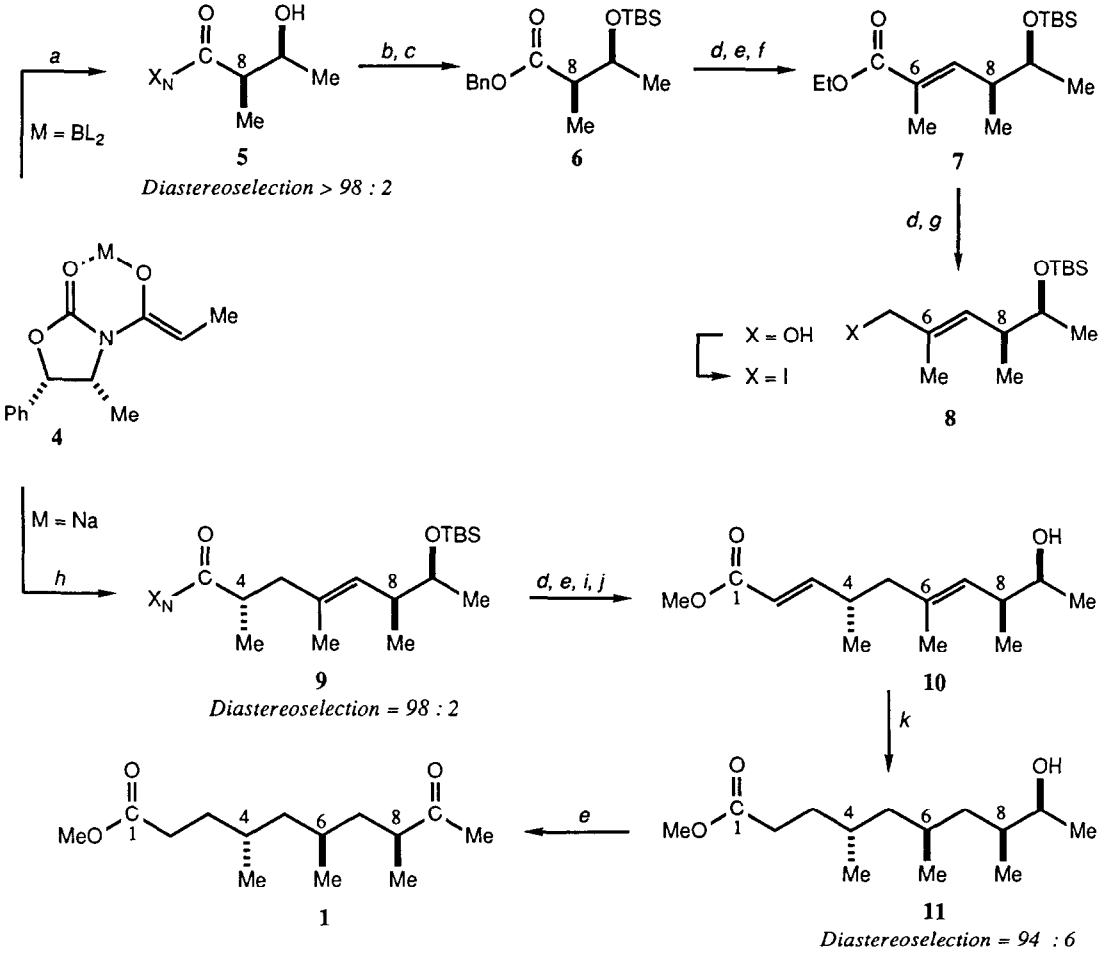
From the standpoint of chemical synthesis, the polyether antibiotics present a formidable challenge.[1] In particular, the acyclic stereochemical issues which are manifest in any projected synthesis of even simple members of this class of natural products have stimulated the development of a host of new stereoselective reactions.[2] In conjunction with our general interest in developing reaction methodology relevant to the synthesis of such target structures, we have been concerned with the asymmetric synthesis of the calcium-selective ionophore ionomycin.[3]

Scheme I



The purpose of this Letter is to describe a successful strategy for the construction of 1,3-dimethyl relationships, a stereochemical issue of considerable relevance to the construction of the C_1-C_{10} and C_{11}-C_{16} ionomycin synthons. The synthesis of the keto ester **1** serves to illustrate how such problems might be successfully addressed (Scheme II).

Scheme II



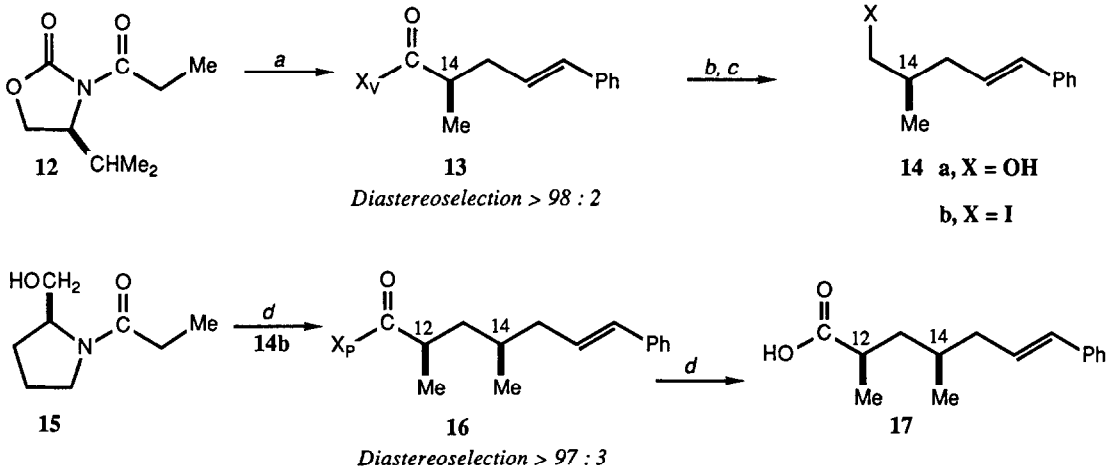
(a) Bu_2BOTf, Et_3N, CH_2Cl_2, MeCHO, -78°C ; (b) t-BuSiMe_2Cl, imidazole, DMF ; (c) LiOBn, THF, 0°C ; (d) DIBAL, CH_2Cl_2, -78 to 0°C ; (e) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2 ; (f) $EtO_2CC(Me)=PPh_3$, toluene, 70°C ; (g) $(PhO)_3$P-MeI, DMF, 0°C ; (h) THF, -50°C, 10 h ; (i) $MeO_2CCH=PPh_3$, CH_2Cl_2 25°C ; (j) HF (aq), MeCN ; (k) [Rh(NBD)DIPHOS]BF_4, CH_2Cl_2, H_2 at 15 psi.

The stereoselective synthesis of **1** was initiated with the aldol reaction of the boron enolated **4** (M = BBu_2) with acetaldehyde (diastereoselection 98:2) to give the crystalline syn addition product **5** (R = H), mp 116-117°C, in 93% yield.[4] Although the hydroxyl group in this intermediate will eventually be trans-

formed into the C_{10} carbonyl function in ionomycin, the utilization of this functionality in the construction of the C_6 methyl-bearing stereocenter was anticipated (vide infra). Hydroxyl protection and subsequent transesterification with lithium benzyloxide (2 equiv ROLi, THF, 0°C, 3 h)[5] afforded an 83% yield of the benzyl ester **6** which was uneventfully transformed to the unsaturated ester **7** ((E):(Z) = 98:2) in 74% overall yield. Subsequent reduction of this ester with diisobutylalum num hydride afforded allylic alcohol **8** in 98% yield. In preparation for utilizing this intermediate in the illustrated alkylation reaction with the chiral enolate **4** (M=Na), **8** (X=OH) was transformed into the corresponding (E) allylic iodide with methyltriphenoxyphosphonium iodide (DMF, 25°C, 15 min).[6] This reagent was particularly successful in this delicate transformation, and the desired allylic iodide was contaminated by no more that 5% of what was presumed to be the isomeric (Z) allylic isomer. Due to the sensitivity of **8** (X=I) towards olefin isomerization, it was employed in the subsequent reaction without purification. The illustrated alkylation of the sodium enolate **4** (3 equiv) with allylic iodide **8** (THF, -50°C, 10 h)[5] proceeded with excellent diastereoselection (4S:4R = 98:2) and the diastereomerically pure norephedrine-derived carboximide **9**, mp 80.5-81.5°C, was obtained in 73% yield after flash chromatography. The routine homologation of **9** via the illustrated transformations afforded the unsaturated ester **10** (81% overall), a precursor to the C_1-C_{10} synthon **1**, which lacked only the C_6 methyl-bearing stereocenter and an oxidation state adjustment. The completion of the synthesis of keto ester **1** was predicated on the successful hydroxyl-directed hydrogenation of hydroxy olefin **10** to give the desired (6S) stereocenter. Hydrogenation of hydroxy diene **10** in the presence of 5 mol% of the cationic rhodium catalyst, Rh(NBD)DIPHOS-4 BF_4,[7] (CH_2Cl_2, 15 psi H_2, 25°C, 12 h) afforded a 93% yield of a 94:6-mixture of (4S) and (4R) diastereomers from which the desired (4S) isomer **11** was isolated by medium pressure chromatography. The synthesis of **1** was completed by oxidation of **11** to the desired C_1-C_{10} synthon **1**.[8] The relative and absolute stereochemical relationships established during the course of the synthesis of **1** were established via an independent, unambiguous route.[9]

It is evident that the precedents established in the synthesis of keto ester **1** might also be applied to the synthesis of the C_{11}-C_{16} synthon **3** however, at the time that this synthesis exercise was undertaken, the relevant directed hydrogenation reactions[7] utilized in the synthesis of **1** had not yet been developed. As a consequence, the chiral enolate based methodology illustrated in Scheme III was utilized. Transformation of the carboximide **12** to its derived lithium enolate (LDA, THF, -78°C) and subsequent alkylation with (E)-cinnamyl bromide (1.5 equiv, -20°C for 1 h, 0°C for 2 h)[5] afforded **13** in 84% (14R:14S = 80).[10] The synthesis of the iodide **14b** which was required for the next alkylation, was accomplished via the illustrated reactions in good yield. Due to the modest nucleophilicity exhibited by enolates derived from **12**,[5] the more reactive enolate derived from the prolinol propionamide **15** was employed in the construction of **16**.[11] The enolate derived from **15** was prepared by the successive addition of KH (2 equiv) and LDA (1.2 equiv of a 0.6 M solution in THF) to a 0.35 M solution of **15** in THF. After 30 min at 25°C the solution was cooled (-78°C), HMPA (2 equiv) was added along with alkyl iodide **14b**. After 7 h at -78°C and an additional 1 h at -35°C, the desired product **16** was isolated in 83% yield after flash chromatography. Analysis of the unpurified reaction products revealed the reaction diastereoselection to be 97.3:2.7.[10] Amide hydrolysis to the olefinic acid **17** was effected by acid catalyzed N-O acyl transfer (1.0 N HCl-H_2O, 0°C, 10 min) to the olefinic acid **17**.

Scheme III



(a) LDA, THF, -40 to 0°C ; (b) $LiAlH_4$, THF, 0°C ; (c) $MeSO_2Cl$, Et_3N, CH_2CL_2, 0°C; NaI, Me_2CO, 55°C; (d) See text.

Both of the synthons whose syntheses have been described in the preceeding discussion have been successfully incorporated into a total synthesis of ionomycin.[12] These studies will be reported shortly.

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