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Synthesis of (+)-prelactone B

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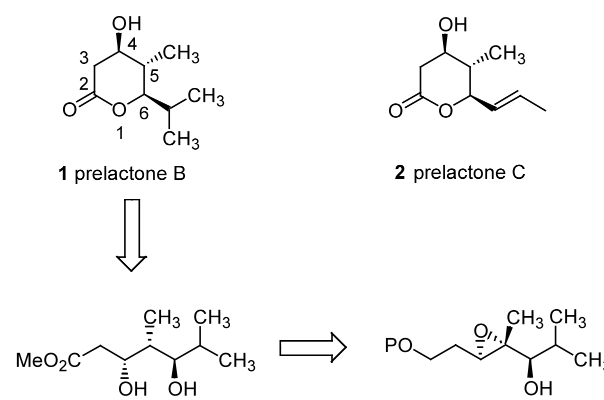
Abstract—Radical-mediated opening of a trisubstituted epoxy alcohol using cp_2TiCl was followed by diastereoselective reduction of the resulting product with a centrally located methylene group, flanked on both sides by two chiral hydroxyl-bearing carbons, to build all the three chiral centers of (+)-prelactone B **1** in their desired stereochemistries leading to the total synthesis of the molecule.

The prelactone B **1** and prelactone C **2**, isolated from the culture-filtrate extract (0.2 mg/l) of *Streptomyces griseus* (strain Tü 2599 and 18) and the mycelium extract of *Streptomyces* sp. (strain Gö 22/15), are highly functionalized chiral δ-lactones which are of interest as starting materials or as building blocks for the synthesis of biologically active natural products.[1] They are the first wild-strain-derived metabolites representing the early steps of the polyketide pathway.[2] An expeditious route to these molecules will help to prepare them in large quantities for use as standards during the mechanistic studies of the polyketide synthases and related biological studies.[3]

In this paper, we describe the total synthesis of (+)-prelactone B.[4] Retrosynthetically, lactone **1** can be obtained from its linear precursor **3**, a '2-methyl-1,3-diol' containing molecule. It was envisaged the '2-methyl-1,3-diol' moiety of **3** having all the stereocenters of the final product could be built by a radical mediated opening of the trisubstituted epoxide **4** using cp_2TiCl, a method developed by us earlier[5,6] and used in the synthesis of many polyketide natural products.[7] The chiral epoxide **4** could be easily prepared by kinetic resolution of the corresponding allylic alcohol using the Sharpless asymmetric epoxidation method.[8] The actual synthesis is outlined in Scheme 1.

Starting with the monoprotected propane-1,3-diol **5**, synthesized from the diol using NaH, BnBr and a catalytic amount of TBAI, the α,β-unsaturated ester **6**



1 prelactone B

2 prelactone C

3

4

was prepared in two steps—Swern oxidation of **5** to an aldehyde and then a three carbon stabilized Wittig olefination to give exclusively the *E*-isomer of the unsaturated ester **6**[9] in 70% overall yield. Reduction of **6** with LAH furnished an allylic alcohol, which on Swern oxidation followed by isopropyl Grignard addition gave compound **7** in 65% yield from **6**. Sharpless kinetic resolution[8] of **7** with titanium(IV) isopropoxide and unnatural diethyl D-(−)-tartrate gave the chiral epoxy alcohol **8** in 30% yield. While the enantiomeric outcome of the reaction is yet to be determined, the diastereoisomeric purity of product **8** was ascertained on the basis of ^1H NMR studies and verified after subsequent steps by studying the ^1H and ^{13}C NMR spectra of the acetonide of the final '2-methyl-1,3-diol' moiety.

With the trisubstituted chiral epoxide **8** in hand, the stage was now set to carry out the radical-mediated ring opening reaction. However, treatment of **8** with cp_2TiCl, generated in situ according to the procedure

Keywords: prelactone B; Sharpless kinetic resolution; epoxide opening; 2-methyl-1,3-diol.

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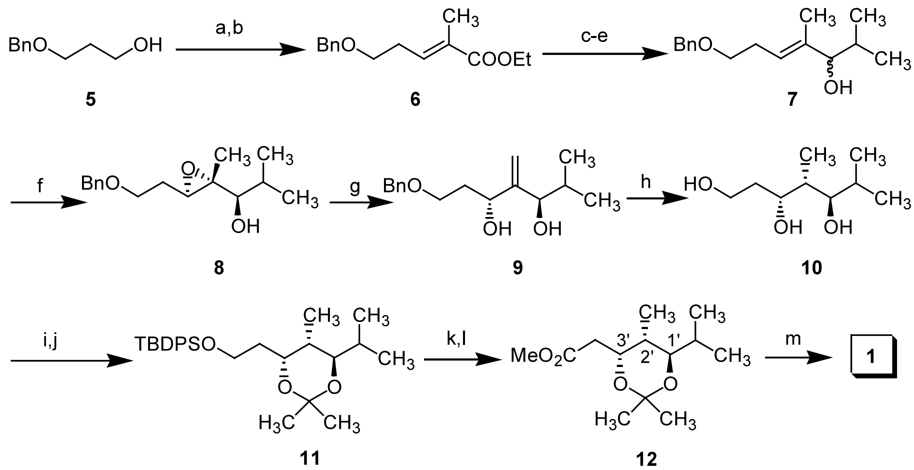

Scheme 1. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to rt, 1.5 h. (b) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 0°C to rt, 2 h, yield 70% from **5**. (c) LAH, Et_2O, 0°C, 10 min. (d) Same as in step a. (e) $(CH_3)_2CHMgBr$, Et_2O, 0°C, 10 min, yield 65% from **6**. (f) $Ti(O^iPr)_4$, (−)-DET, TBHP (3.32 M in CH_2Cl_2), 4 Å MS, CH_2Cl_2, −23°C, 30 min, yield 30%. (g) Cp_2TiCl_2, Zn dust, cyclohexa-1,4-diene, THF, −23°C to rt, 6 h, yield 50%. (h) H_2, 10% Pd/C, CH_3OH, rt, 30 min, yield 20%. (i) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0°C to rt, 2 h. (j) 2,2-Dimethoxypropane, CSA, CH_2Cl_2, 0°C to rt, 2 h, yield 91% from **10**. (k) TBAF, THF, 0°C to rt, 2 h. (l) (i) $RuCl_3·3H_2O$, $NaIO_4$, $CH_3CN:CCl_4:H_2O$ (2:2:3), rt to 0°C, 1 h; (ii) CH_2N_2, Et_2O, 0°C, 5 min, yield 40% from **11**. (m) $AcOH:H_2O$ (4:1), 0°C to rt, 2 h, yield 80%.

reported by us earlier,[5,6] and cyclohexa-1,4-diene did not give the desired '2-methyl-1,3-diol' moiety. Instead, it gave a β-hydride eliminated product **9** in 50% yield. The formation of such olefins during the Ti(III)-mediated epoxide opening reaction has been observed earlier by us in certain sterically hindered substrates[10,11] and also by others.[12] Next, the olefin **9** was subjected to hydrogenation and debenzylation with H_2, 10% Pd/C to furnish the triol **10** with the desired stereochemistry at the C-5 methyl group. Although excellent diastereoselectivity (9:1, determined by ^{1}H NMR method) was achieved in this step, the yield was poor due to the formation of some side products that include a 3,6-dihydro-2*H*-pyran moiety, a major side-product, formed by an intramolecular cycloetherification process involving the debenzylated free hydroxyl group and the C-5 methylene unit. Further study of this step to improve the yield has not yet been carried out. Protection of the primary hydroxyl group of **10** was followed by acetonide protection of the secondary hydroxyls to give the intermediate **11** in 91% yield in two steps. Deprotection of the silyl group of **11** and subsequent oxidation of the primary hydroxyl group using $RuCl_3·3H_2O$ and $NaIO_4$ to the acid, followed by *O*-methylation with CH_2N_2 furnished the methyl ester **12** in 40% yield from **11**. In this step the major and minor diastereoisomers were separated by standard silica gel column chromatography. The ^{13}C NMR spectrum of the major isomer **12** shows that the *gem* dimethyls of the acetonide unit resonate at 23.9 and 25.1 ppm and that of the ketal carbon at 100.5 ppm, proving the *anti* relationship between $C_{1'}$-OH and $C_{3'}$-OH with a twist-boat conformation.[13] Coupling constant measurements, $J_{1',2'} = 7.5$ Hz and $J_{2',3'} = 5.2$ Hz certainly suggested the *anti* relationship between $C_{1'}$-OH and $C_{2'}$-Me and *syn* relationship between $C_{2'}$-Me and $C_{3'}$-OH.[14] The major isomer **12** was then subjected to acetonide deprotection and concomitant cyclization using the $AcOH/H_2O$ system to give the final product **1** in 80% yield.

Our synthetic prelactone B showed rotation $[\alpha]_D^{20}$ +37.2 (*c* 0.22, MeOH), matching with the lit.[1] value: $[\alpha]_D^{20}$ +38.3 (*c* 0.6, MeOH). Furthermore, the spectroscopic data, namely, IR, NMR and mass spectra of our synthetic product[15] were in conformity with those of the naturally occurring prelactone B.

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15. Selected physical data of **1**. $R_f = 0.4$ (silica, 70% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +37.2 (c 0.22, MeOH); mp 90–92°C; IR (KBr): ν_{max} 3473, 2966, 2923, 1714, 1276, 1231, 1005 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.77 (m, 2H, C4-*H*, C6-*H*), 2.95 (dd, $J = 17$, 6 Hz, 1H, C3-*H*), 2.48 (dd, $J = 17$, 8 Hz, 1H, C3-*H′*), 1.99 (m, 1H, C1′-*H*), 1.78 (ddq, $J = 10$, 7, 6 Hz, 1H, C5-*H*), 1.11 (d, $J = 6.5$ Hz, 3H, C1′-CH_3), 1.08 (d, $J = 6$ Hz, 3H, C5-CH_3), 0.94 (d, $J = 6.5$ Hz, 3H, C1′-CH_3); ^{13}C MR (75 MHz, $CDCl_3$): δ 170.78, 86.19, 69.86, 39.04, 38.96, 28.91, 19.99, 14.02, 13.54; MS (EI): m/z (%): 129 (26) $[M^{+}-C_3H_7]$, 111 (31), 87 (50), 58 (94).