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Diastereoselective opening of trisubstituted epoxy alcohols: application in the synthesis of (+)-prelactone C

Tushar K. Chakraborty* and Subhasish Tapadar

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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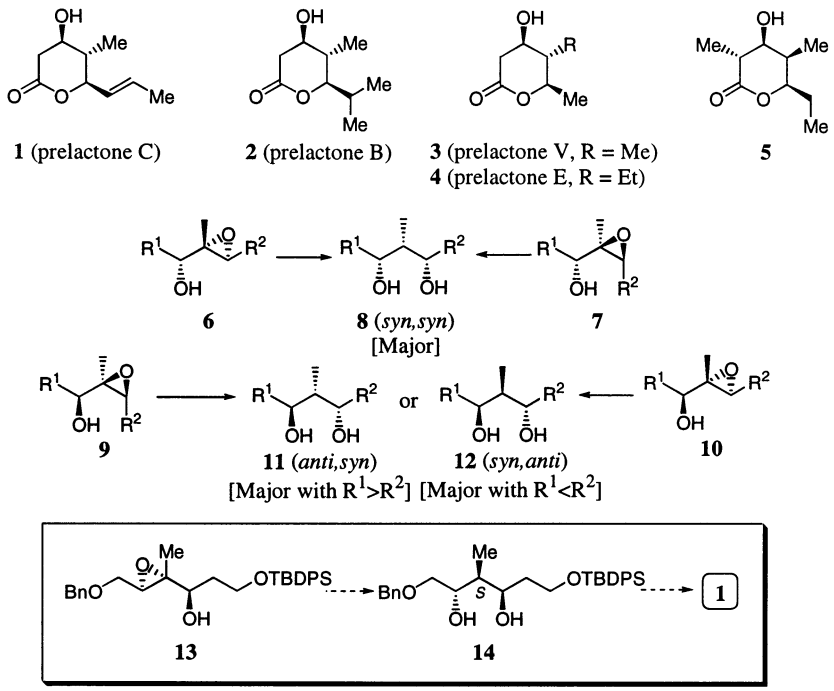
Abstract—A novel method developed by us for the synthesis of chiral 2-methyl-1,3-diols by radical-mediated diastereoselective opening of trisubstituted epoxy alcohols at the more substituted carbon was the key step in the synthesis of (+)-prelactone C (**1**).

Small and medium ring lactones, essential structural components of a large number of organic natural products, are attracting a lot of attention as organic chemists develop new methodologies for their synthesis.[1–3] Prelactones **1**–**5** constitute an important class of highly functionalized chiral δ-lactones isolated from various polyketide macrolide producing microorganisms.[4–7] They seem to be the wild-strain-derived compounds representing early steps of the polyketide biosynthesis pathway.[8] Their production can actually be stimulated under certain conditions.[9] The discovery of these molecules supports the widely accepted hypothesis of step by step functionalization of growing polyketide chains in the biosynthesis of macrolides.[10] A general strategy for the synthesis of these prelactones will prepare material for use as standards during the mechanistic studies of the polyketide synthases.



Scheme 1. Radical-mediated opening of trisubstituted epoxy alcohols.

* Corresponding author.

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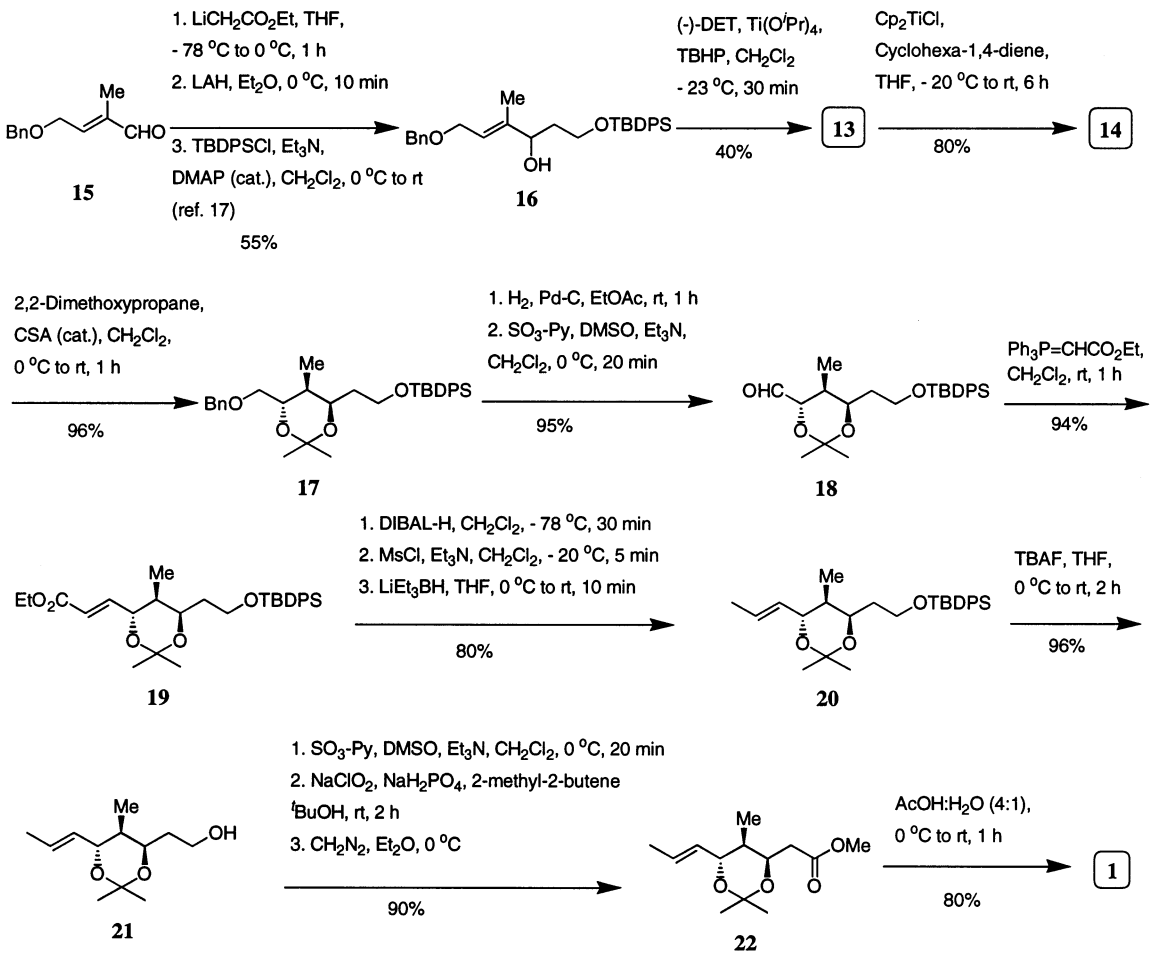
In this paper, we describe the total synthesis of (+)-prelactone C (**1**).[6,11–13] The key feature in our synthesis is the application of an excellent method developed by us recently[14] for the synthesis of chiral 2-methyl-1,3-diols by radical-mediated anti-Markovnikov opening of trisubstituted epoxy alcohols at the more substituted carbon, using cp_2TiCl in the presence of cyclohexa-1,4-diene (which acts as a donor of hydrogen atoms) to construct the three stereocentres of **1**.[15–18] According to our study, as shown in Scheme 1, both *syn* and *anti* epoxy alcohols, **6** and **7**, respectively, on epoxide ring opening with cp_2TiCl-cyclohexa-1,4-diene should give *syn*,*syn*-diol **8** as the major product, whereas the products from epoxy alcohols **9** and **10** depend on the relative sizes of R^1 and R^2. When R^1 is bigger than R^2, the major product is the *anti*,*syn* diol **11**. With smaller R^1, the *syn*,*anti* product **12** predominates. Based on this scheme, we decided to use the *anti* epoxy alcohol **13** as the precursor for the stereoselective synthesis of the crucial '2-methyl-1,3-diol' moiety of the C_3–C_5 segment **14** of the molecule. As the $BnOCH_2$ substituent is bigger than $CH_2CH_2OTBDPS$, the epoxy alcohol **13** was expected to deliver the *anti*,*syn* stereoisomer **14** on ring opening.

The actual synthesis is outlined in Scheme 2. The allylic alcohol **16** was prepared from the aldehyde **15** in 55% overall yield in three steps following the procedure reported by us earlier[17]—addition of the Li-enolate of ethyl acetate to the aldehyde **15**, LAH reduction to obtain the diol, and finally selective protection of the primary hydroxyl as a *tert*-butyldiphenylsilyl (TBDPS) ether. Sharpless kinetic resolution[19] of **16** with unnatural diethyl D-(−)-tartrate gave the chiral epoxy alcohol **13** in 40% yield. While the enantiomeric outcome of the reaction is yet to be determined, the diastereoisomeric purity of the product **13** was ascertained on the basis of ^1H NMR studies and subsequently verified after two steps: opening up of the epoxide ring and making an acetonide from the resulting diol.

To carry out the crucial epoxide ring opening reaction, the epoxy alcohol **13** was subjected to cp_2TiCl, generated in situ according to the procedure reported by us earlier, and cyclohexa-1,4-diene.[14] The diastereoisomer **14** was formed as the major product in a 6:1 ratio, as determined by ^1H NMR spectroscopy of the mixture, in 80% yield. The mixture of diols was next converted to the acetonides in 96% yield. The major isomer **17** was separated from the mixture by standard silica gel column chromatography.[20] The ^{13}C NMR spectrum of **17** showed acetonide methyl signals at δ 25.1 and 24.0 and that of ketal carbon at 100.6 ppm, proving a 3,5-*anti* relationship.[21,22] Debenzylation of **17** was fol-



Scheme 2. Stereoselective synthesis of (+)-prelactone C (**1**).

lowed by oxidation using the SO_3–pyridine complex giving the aldehyde **18** in 95% yield. Olefination of the aldehyde **18** with stabilized ylide $Ph_3P{=}CHCO_2Et$ gave the (*E*)-α,β-unsaturated ester **19** in 94% yield. The ester function was transformed into a methyl group to furnish **20** in three steps in 80% overall yield—DIBAL-H reduction to an allylic alcohol, mesylation, followed by reduction of the mesylate with lithium triethyl borohydride. Next, desilylation of **20** gave the primary alcohol **21** in 96% yield. The hydroxyl group in **21** was oxidized to the methyl ester **22** in three steps in 90% yield—oxidation using the SO_3–pyridine complex to the aldehyde, subsequent oxidation of the aldehyde using sodium chlorite, followed by esterification with CH_2N_2. Acid treatment of the ester **22** deprotected the acetonide ring with concomitant cyclization furnishing the targeted prelactone **1** in 80% yield.

Our synthetic prelactone C showed rotation $[\alpha]_D^{20}$ +37.8 (*c* 0.7, MeOH); lit.[6] value: $[\alpha]_D^{20}$ +57.6 (*c* 0.5, MeOH). The lower specific rotation of the final product reflects the moderate enantiomeric excess obtained in the Sharpless kinetic resolution step (**16→13**), a phenomenon often encountered with trisubstituted epoxy alcohols.[23] Efforts are now underway to standardize the reaction conditions of the resolution step to improve the enantioselectivity of the product. The spectroscopic data of our synthetic product[24,25] were identical with those of the naturally occurring prelactone C.[6]

In conclusion, the synthesis demonstrates the practical utility of the radical-mediated opening of trisubstituted epoxy alcohols to construct an important structural moiety consisting of 2-methyl-1,3-diol framework that appears in various propionate-derived polyketides. The methodology can be successfully employed in the synthesis of many natural products.

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25. Selected physical data of **1**. R_f=0.5 (silica, 70% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +37.8 (*c* 0.7, MeOH); IR (neat): ν_{max} 3400, 2925, 1730, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddq, J=15.2, 6.6, 1 Hz, 1H, C7-*H*), 5.43 (ddq, J=15.2, 8.2, 2 Hz, 1H, C6-*H*), 4.17 (dd, J=10.4, 8.2 Hz, 1H, C5-*H*), 3.74 (ddd, J=8, 7, 5.8 Hz, 1H, C3-*H*), 3.07 (br s, 1H, O*H*), 2.87 (dd, J=17, 5.8 Hz, 1H, C2-*H*), 2.46 (dd, J=17, 8 Hz, 1H, C2-*H'*), 1.77 (dd, J=6.6, 2 Hz, 3H, C8-H_3), 1.64 (ddq, J=10.4, 7, 6.8 Hz, 1H, C4-*H*), 1.02 (d, J=6.8 Hz, 3H, C4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.34, 132.41, 127.61, 84.11, 69.53, 41.49, 39.08, 17.62, 13.66; MS (EI): m/z 153 [M^++H–H_2O].