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Tetrahedron Letters 45 (2004) 6475–6476
Tetrahedron Letters

An efficient synthesis of (+)-prelactone B☆

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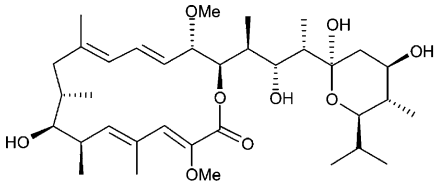
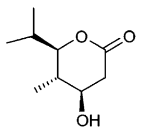
Received 6 May 2004; revised 16 June 2004; accepted 25 June 2004
Available online 19 July 2004

Abstract—An enantioselective synthesis of (+)-prelactone B **1** has been achieved on a multigram scale starting from a known bicyclic precursor **2**. The key feature of the strategy is the generation of 3-stereogenic centres from a single bicyclic precursor, which has been utilized as a chiral building block for the synthesis of various natural products.

The prelactones are highly functionalized chiral δ-lactones isolated from various polyketide macrolide producing microorganisms.[1] They represent essential structural motifs in a large number of bioactive natural products, such as mevinolin and compactin, inhibitors of cholesterol biosynthesis;[2] phomalactone[3] and asperlin,[4] antibiotics; massoialactone[5] and tetrahydro-6-(1-hydroxyundecyl)-*2H*-pyran-2-one;[6] attractant or defence substances for animals and insects. (+)-Prelactone B **1** was isolated from bafilomycin producing microorganisms, *Streptomyces griseus* (strain Tü 2599 ana 18) by Zeeck and Bindseil in 1993.[7] It is believed to be the product of polyketide synthase (PKS), and is used as a standard for investigations concerning the mechanism of PKS. To the best of our knowledge, to date, only three asymmetric syntheses[8] of prelactone B and one leading to the racemate[9] have been reported. In connection with our ongoing research into the total synthesis of the macrolide antibiotic, bafilomycin A_1,[10] which is a specific vacular-type H^+-ATPase inhibitor, possessing interesting activities, such as antibacterial, antifungal and immunosuppressive activities, we needed a new method for the preparation of a large amount of (+)-prelactone B. We report herein a concise method for the multigram scale preparation of (+)-prelactone B **1** by a convergent route.



Bafilomycin A_1



1
(+)-prelactone B

Our synthetic approach towards the target molecule was based on the utilization of the bicyclic precursor **2** and the key feature of our strategy is that all the three stereogenic centres of the molecule at C-4, C-5 and C-6 are generated from this precursor. This bicyclic precursor was earlier used by our group towards the synthesis of rifamycin S[11] and discodermolide.[12]

Asymmetric hydroboration of the olefin **2** using (−)-diisopinocampheylborane gave **3** in high optical purity. The alcohol **3** was converted to the lactone **4** by a two step sequence, PCC oxidation followed by Baeyer–Villiger oxidation of the resulting ketone. The key reaction is opening of the appropriately functionalized bicyclic lactone. The reduction of lactone **4** with LAH furnished the triol **5** in 85% yield. The 1,3-diol moiety was converted to the acetonide and the primary hydroxyl group was tosylated with TsCl in the presence of NEt_3 in DCM to afford the tosylate **6** in 95% yield. The $-CH_2OTs$ group of **6** was transformed into a methyl group by LAH in refluxing THF, followed by acetonide deprotection to give the diol **7** in 88% yield. Selective oxidation of the primary hydroxyl group using IBX afforded the

Keywords: Prelactone B; Bicyclic precursor; *Streptomyces griseus*; Bafilomycin.
☆ IICT Communication No: 040426.
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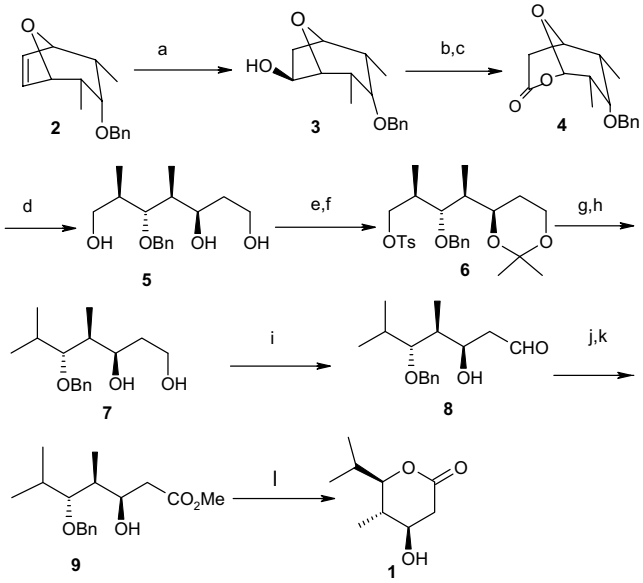
doi:10.1016/j.tetlet.2004.06.121



Scheme 1. Reagents and conditions: (a) (−)-Ipc$_2$BH, −23 °C, THF, 24 h, then 3 N NaOH, 30% H_2O_2, rt, 6 h, 95%. (b) PCC, DCM, rt, 3 h, 94%. (c) *m*-CPBA, $NaHCO_3$, DCM, rt, 10 h, 88%. (d) LAH, THF, 0 °C–rt, 4 h, 85%. (e) 2,2-DMP, CSA, acetone, 3 h, 73%. (f) TsCl, NEt_3, DMAP, DCM, 95%. (g) LAH, THF, reflux, 3 h, 92%. (h) CSA, MeOH, 2 h, rt, 88%. (i) IBX, DMSO, DCM, 0 °C–rt, 3 h, 83%. (j) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, DMSO, H_2O, 30 min. (k) CH_2N_2, Et_2O, 30 min, yield 85% from **8**. (l) H_2/$Pd(OH)_2$, EtOH, rt, 1 h, 93%.

aldehyde **8**, which was characterized by the presence of an aldehyde proton at δ 9.80 in the ^{1}H NMR spectrum. The aldehyde was converted into its methyl ester **10** by oxidation using $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$ in DMSO followed by in situ esterification of the resulting acid using diazomethane. Finally, hydrogenation using H_2 on $Pd(OH)_2$ in EtOH at rt resulted in smooth removal of the Bn protecting group and concomitant lactonization afforded (+)-prelactone B **1** as a crystalline solid (mp 97–98 °C, lit.[8c] mp 97–98 °C). The synthetic substance exhibited spectral properties[13] (^{1}H, ^{13}C NMR, IR, mass) and specific rotation, $[\alpha]_D^{25}$ +38.7 (c = 0.75, MeOH) {lit.[8c] $[\alpha]_D^{25}$ +39.1 (c 0.6, MeOH)}, in accord with those reported (Scheme 1).

In conclusion, we have achieved a short and highly efficient asymmetric synthesis of (+)-prelactone B in 24% overall yield. Efforts towards the total synthesis of bafilomycin A_1 are in progress and the results will be published in due course.

Acknowledgements

K.B.R. thanks UGC, New Delhi for the award of a fellowship.

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13. Selected physical data for **1**. R_f = 0.45 (silica, 60% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +38.7 (c = 0.75, MeOH); mp 97–98 °C; IR (KBr) ν_{max} 3475, 2969, 2925, 1718, 1465, 1274, 1004 cm^{-1} ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (m, 2H), 2.89 (dd, J = 17.6, 5.9 Hz, 1H), 2.52 (br s, OH), 2.48 (dd, J = 17.8, 8.0 Hz, 1H), 1.98 (m, 1H), 1.76 (ddq, J = 10.0, 7.0, 6.1 Hz, 1H), 1.12 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.33, 86.38, 69.65, 38.96, 38.89, 28.89, 19.94, 14.04, 13.60; MS (EI): *m*/*z* 173 (M + H).