An Asymmetric Synthesis of (–)-Prelactone B

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Abstract: An efficient synthesis of (–)-prelactone B has been developed using 1,2-cyclohexylidene glyceraldehyde as the chiral template. The key features of the synthesis were stereoselective crotylation of 1,2-cyclohexylidene glyceraldehyde and enantioselective reduction of a ketone, as well as operational simplicity and use of inexpensive reagents/chemicals.

Key words: chiral template, enantioselective synthesis, prelactone B

It has been proposed that the so called prelactones exist for some macrolides and their production can be stimulated under certain conditions.[1a] The prelactone B **1a** and prelactone C **1b** (Scheme 1) are two such microbial δ-lactones isolated[1b] from the culture-filtrate extract of *Streptomyces griseus* (strain Tü 2599 and 18) and the mycelium extract of *Streptomyces sp.* (strain GÖ 22/15).

These are the first wild-strain derived metabolites representing the early steps of the polyketide pathway.[2a] Availability of all possible stereomers would assist the mechanistic studies of the polyketide synthesis (PKS) of avermectins and help their bioevaluation.[2b] In particular, the stereomers would be useful standards to decipher the selectivities of the PKS enzymes, ketoreductase and dehydratase. Given that similar δ-lactones are known[3a,b] to possess impressive cytotoxicity, compound **1a** also appears promising. Furthermore, these types of functionalized chiral δ-lactones serve as important structural motifs in the asymmetric syntheses of a large number of bioactive natural products such as mevinolin and compactin,[4a] phomalactone,[4b] asperlin,[4c] massoialactone[4d] etc.

Several asymmetric syntheses of **1a** have been reported.[5a–j] Of these, the proline-catalyzed crossed-aldol strategy[5d] is by far the best in terms of brevity and efficiency. Many of the other methods suffer from the limitations of using expensive reagents, formation of side products, low yields and/or poor selectivity requiring HPLC separation of the desired enantiomer from a mixture of stereomers. In light of the above, we developed an expeditious synthesis of (–)-**1a** from easily accessible and inexpensive reagents. It is worth noting that amongst the earlier syntheses, only one synthesis of (–)-**1a** has been reported so far.[5d]

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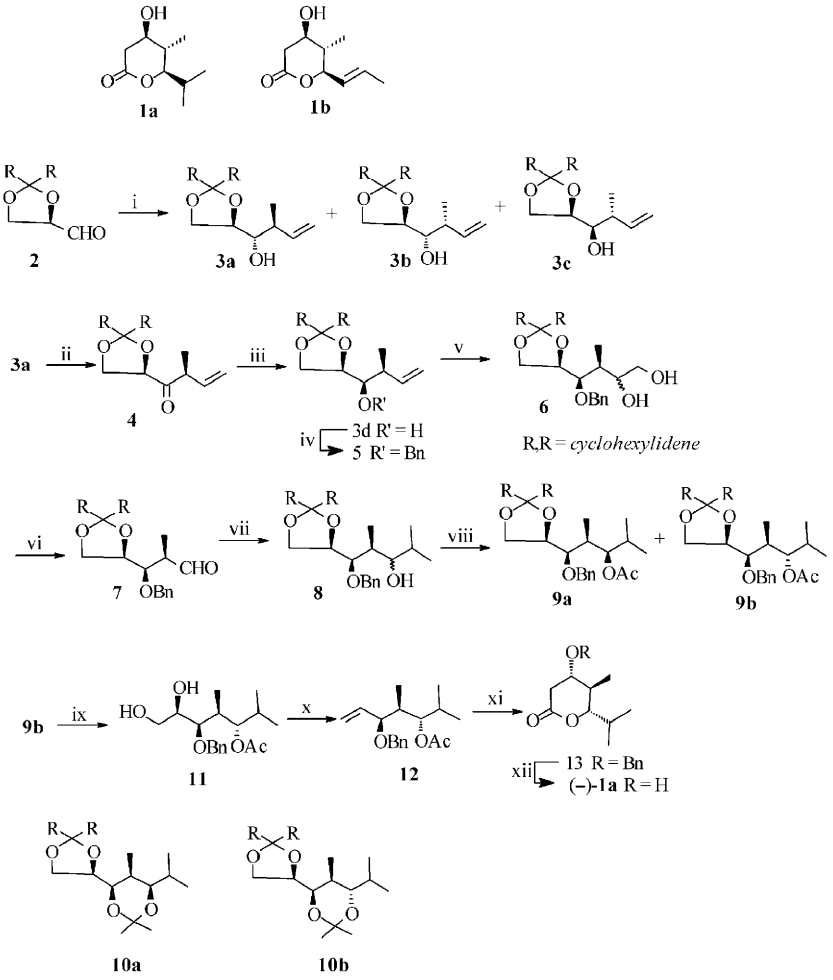
Earlier, we have shown[6a–c] that the addition of Grignard reagents to glyceraldehyde derivative **2** provides easy access to the C-3 epimers of alkanetriol derivatives which are useful chirons for the synthesis of various classes of bioactive compounds. Extending this work, a Barbier-type reaction of allylic halides with **2** was also developed.[6d] It was envisaged that the homoallylic alcohol **3a** obtained via crotylation of **2**, would be suitable for a brief synthesis of (–)-**1a** (Scheme 1).

The Zn-mediated crotylation of **1** afforded a mixture of diastereomers **3a** and **3b** as the major products in a 64:34 ratio along with a trace amount of **3c**. All the stereomers could be separated easily by normal column chromatography and were characterized from their ^{1}H NMR spectra.[6d] According to our synthetic plan, for (–)-**1a**, we required the (2*R*,3*R*,4*S*)-stereomer **3d** of the crotylated product, while the major product **3a** obtained by the above reaction was the (2*R*,3*S*,4*S*)-stereomer. However, the stereoreversal of the carbinol centre could be easily accomplished following our own method.[7] Compound **3a** was oxidized with PCC[8] to give the ketone **4**, which on reduction with K-selectride furnished **3d** as the sole product. The three ^{1}H NMR multiplets (1:1:2) at 3.25–4.10 ppm were in conformity with those reported earlier for the corresponding isopropylidene derivative.[9a,b] Benzylation of **3d** to **5** followed by OsO_4-mediated dihydroxylation gave **6** as an epimeric mixture, which on $NaIO_4$ cleavage gave the aldehyde **7**. This on reaction with isopropylmagnesium bromide furnished **8** as a mixture of inseparable C-5 epimers. Fortunately, the epimers could be easily separated by column chromatography after acetylation to furnish **9a** and **9b** in a ratio of 3:7. Based on our previous experience the more polar isomer **9b** (major product) was assigned the 3,5-*anti* configuration. The stereochemical outcome of the reaction was in accordance with earlier reports.[9c] Confirmation of the *syn* and *anti* configurations of **9a** and **9b** could not be unambiguously assigned from their ^{13}C NMR resonances. Consequently, this was accomplished by their derivatization to the corresponding 3,5-acetonides and analyzing their ^{13}C NMR signals. For this, **9a** and **9b** were converted to the respective acetonides **10a** and **10b** by debenzylation, deacetylation, and acetalization. The ^{13}C NMR spectrum of **10a** showed the methyl resonances 19.8 and 31.1 ppm along with a resonance at 98.6 ppm (acetal carbon) of the six-membered acetonide moiety confirming its 3,5-*syn* relationship.[10a–c] Likewise, the acetonide methyl resonances at 23.8 and 24.1 ppm and the ac-



Scheme 1 i) Crotyl bromide, Zn, aq NH_4Cl; ii) PCC, NaOAc, CH_2Cl_2; iii) K-selectride, THF, –78 °C; iv) NaH, BnBr, THF, Δ; v) OsO_4, NMO, acetone–H_2O; vi) $NaIO_4$, CH_3CN–H_2O; vii) *i*-PrMgBr, THF; viii) Ac_2O, pyridine, column chromatography; ix) aq TFA; x) MsCl, pyridine; Zn, NaI, DMF, Δ; xi) BMS, THF; Na_2CrO_4, H_2SO_4, Δ; xii) H_2, 10% Pd/C, EtOH.

etal carbon resonance at 100.3 ppm in the ^{13}C NMR spectrum of **10b** established its 3,5-*anti* configuration.

The required isomer **9b** was subsequently deacetalized to **11** by treatment with aqueous trifluoroacetic acid (TFA). This was converted to olefin **12** by mesylation of the diol followed by heating with NaI in the presence of Zn dust in DMF. This on hydroboration with borane dimethyl sulfide (BMS) followed by in situ oxidation[11] with Na_2CrO_4 directly afforded the δ-lactone **13**. Finally catalytic hydrogenolysis of **13** afforded the title compound (–)-**1a**, which was characterized by comparing the chiroptical and spectral data with those reported.[5d]

Thus, a simple synthesis of (–)-**1a** has been developed using the easily accessible aldehyde **2** as the chiral template. The bulky cyclohexylidenedioxy group in **2** ensured generation of the stereogenic centers with good stereocontrol and also provided the δ-lactone moiety of the target compound. Furthermore, the cyclohexylidene protection was also stubborn to even mild acidic work-up and improved the solubilities of the intermediates involved in the synthesis. It is worth noting that the synthetic protocol described herein, can also be used for the syntheses of all the stereomers of prelactone B. For example, the homoallylic alcohol **3b** produced during the synthesis can be elaborated to (+)-**1a** using the above sequence of reactions. Likewise, the other stereomers of **1a** could be synthesized from **9a** or its other diastereomers that can be synthesized from **3b**. Furthermore, following this method, (+)-**1a** can also be prepared using the aldehyde (*S*)-**2**[12] as the starting material. Finally, our synthesis is very simple, requires inexpensive reagents, and the stereomers produced at some of the stages can be separated by normal column chromatography.

The IR spectra were scanned as thin films with a Jasco FT-IR spectrometer. The ^1H NMR were recorded with a Bruker AC-200 (200 MHz for ^1H NMR and 50 Hz for ^{13}C NMR) instrument. Optical rotations were measured with a Jasco DIP 360 polarimeter. All anhydrous reactions were carried out under an Ar atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-ol (3a)

To a cooled and well stirred mixture of **2** (5.0 g, 0.029 mol), Zn dust (5.7 g, 0.088 mol), and crotyl bromide (7.9 g, 0.059 mol) in THF (50 mL), was added dropwise aq sat. NH_4Cl. After stirring the mixture for 4 h at ambient temperature, the mixture was filtered and the residue thoroughly washed with Et_2O (25 mL). The filtrate was washed with H_2O (2 × 10 mL), brine (1 mL), and dried. The solvent was removed in vacuo and column chromatography of the residue afforded pure alcohols **3a–c** (85% overall yield).

3a

Yield: 3.62 g (54.4%); colorless oil; $[\alpha]_D^{22}$ +2.4 (*c* 1.21, $CHCl_3$).

IR (film): 3408, 1657, 990 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (d, *J* = 6.6 Hz, 3 H), 1.40–1.59 (m, 10 H), 2.07 (br s, D_2O exchange, 1 H), 2.20–2.43 (m, 1 H), 3.53–3.58 (m, 1 H), 3.82–4.06 (m, 3 H), 5.0–5.12 (m, 2 H), 5.71–5.91 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.7, 16.4, 23.9, 25.1, 34.8, 36.2, 40.7, 65.1, 71.7, 74.8, 109.1, 115.9, 139.8.

(2*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-one (4)

To a cooled (0 °C) and stirred suspension of PCC (1.9 g, 8.85 mmol) and NaOAc (0.1 g, 1.2 mmol) in CH_2Cl_2 (80 mL) was added **3a** (0.8 g, 3.54 mmol) in one portion. After stirring for 8 h, the reaction was quenched with Et_2O (80 mL) and the supernatant passed through a pad of silica gel. Removal of the solvent afforded pure **4**.

Yield: 0.658 g (83%); colorless oil; $[\alpha]_D^{22}$ +5.7 (*c* 1.12, $CHCl_3$).

IR (film): 1730 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.17 (d, *J* = 6.8 Hz, 3 H), 1.41–1.65 (m, 10 H), 2.43–2.51 (m, 1 H), 3.98–4.19 (m, 2 H), 4.56 (d, *J* = 7.4 Hz, 1 H), 5.13–5.24 (m, 2 H), 5.76–5.94 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.7, 16.4, 23.8, 25.0, 34.9, 36.1, 43.6, 65.1, 71.7, 108.9, 116.8, 139.8, 177.1.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.77; H, 9.12.

(2*R*,3*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-ol (3d)

To a cooled (–78 °C) and stirred suspension of **4** (0.62 g, 2.77 mmol) in THF (30 mL) was injected K-selectride (3.3 mL, 1.0 M in THF). After stirring for 3 h at the same temperature, the reaction mixture was allowed to warm to r.t., quenched with H_2O (5 mL), and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (1 mL), dried, and concentrated in vacuo. Column chromatography (silica gel, 0–15% EtOAc–hexane) of the residue afforded pure **3d**.

Yield: 0.470 g (75%); colorless oil; $[\alpha]_D^{22}$ +12.1 (*c* 1.16, $CHCl_3$).

IR (film): 3408, 1648, 990 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (d, *J* = 6.8 Hz, 3 H), 1.33–1.58 (m, 10 H), 1.96 (br s, D_2O exchange, 1 H), 2.17–2.37 (m, 1 H), 3.25–3.36 (m, 1 H), 3.64–3.71 (m, 1 H), 3.92–4.10 (m, 2 H), 4.96–5.09 (m, 2 H), 5.76–5.94 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.4, 16.9, 23.9, 25.1, 35.0, 36.2, 41.3, 65.7, 74.6, 75.4, 109.6, 112.8, 139.6.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.68.

(2*R*,3*R*,4*S*)-3-Benzyloxy-1,2-cyclohexylidenedioxy-4-methylhex-5-ene (5)

To a stirred suspension of NaH (0.253 g, 5.28 mmol, 50% suspension in oil) in THF (20 mL) was added **3d** (1.0 g, 4.4 mmol) in THF (10 mL). After the brisk evolution of H_2 was over, the mixture was refluxed for 0.5 h, warmed to r.t., and BnBr (0.907 g, 5.3 mmol) in THF (10 mL) was added. The mixture was subsequently refluxed until the reaction was complete (ca. 4 h, monitored by TLC). The reaction was cooled to r.t., poured into ice–water (25 mL), the organic layer separated, and the aqueous portion extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 5 mL), brine (1 mL), dried, and the solvent was removed. Column chromatography (silica gel, 0–10% EtOAc–hexane) afforded pure **5**.

Yield: 1.14 g (82%); colorless oil; $[\alpha]_D^{22}$ –7.4 (*c* 2.51, $CHCl_3$).

IR (film): 3060, 1694, 990, 910 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.10 (d, *J* = 6.8 Hz, 3 H), 1.40–1.62 (m, 10 H), 2.01–2.05 (m, 1 H), 3.48–3.57 (m, 1 H), 3.78–3.98 (m, 2 H), 4.10–4.14 (m, 1 H), 4.52–4.75 (m, 2 H), 4.88–5.10 (m, 2 H), 5.70–5.97 (m, 1 H), 7.33 (s, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.7, 14.6, 25.7, 32.7, 37.5, 64.4, 65.7, 73.0, 83.1, 109.8, 114.2, 127.6, 128.1, 129.3, 130.4, 139.8.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.09; H, 9.15.

(2*R*,3*R*,4*S*,5*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxy-4-methylhexane-5,6-diol (6)

To a stirred solution of **5** (1.0 g, 3.2 mmol) and NMO (0.773 g, 6.4 mmol) in acetone–H_2O (8:1, 10 mL) was added OsO_4 (0.04 g, 0.16 mmol) in *t*-BuOH (1 mL). After stirring for 12 h, when the reaction was complete (TLC), aq $NaHSO_3$ (4 mL) was added to the mixture, and the aqueous extracts were extracted with $CHCl_3$ (2 × 15 mL). The organic extracts were washed with H_2O (2 × 10 mL), brine (1 mL), dried, and the solvent was removed. Column chromatography of the residue (silica gel, 0–5% MeOH–$CHCl_3$) afforded pure **6**.

Yield: 0.946 g (86%); colorless oil; $[\alpha]_D^{22}$ +16.0 (*c* 1.98, $CHCl_3$).

IR (film): 3431, 3060, 1060 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (two overlapping d, *J* = 6.4 Hz, 3 H), 1.29–1.59 (m, 10 H), 2.00–2.08 (m, 1 H), 3.18 (br s, D_2O exchangeable, 2 H), 3.42–3.78 (m, 5 H), 3.87–4.09 (m, 1 H), 4.24–4.38 (m, 1 H), 4.62–4.89 (m, 2 H), 7.32 (s, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.8, 14.1, 14.6, 25.2, 25.6, 35.3, 36.2, 36.8, 46.4, 64.6, 65.9, 73.0, 73.5, 73.6, 79.6, 81.2, 110.1, 128.3, 127.8, 138.5, 138.6.

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.71; H 8.67.

(2*R*,3*R*,4*R*)-3-Benzyloxy-4,5-cyclohexylidenedioxy-2-methylpentanal (7)

To a cooled (0 °C) and stirred solution of **6** (0.9 g, 2.6 mmol) in CH_3CN (30 mL) and H_2O (20 mL) was added $NaIO_4$ (1.1 g, 5.2 mmol) in portions. After stirring for 1 h at the same temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was taken in Et_2O (25 mL) and the organic extract washed successively with H_2O (5 mL), aq $NaHSO_3$ (2 mL), H_2O (5 mL) , aq $Na_2S_2O_3$ (2 mL), H_2O (5 mL), and brine (2 mL). The ethereal phase was concentrated in vacuo to afford pure **7**, which was used as such in the next step.

Yield: 0.754 g (92%); colorless oil; $[\alpha]_D^{22}$ –1.6 (*c* 1.34, $CHCl_3$).

IR (film): 3070, 2733, 1714 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.98 (d, *J* = 7.0 Hz, 3 H), 1.26–1.55 (m, 10 H), 2.72–2.78 (m, 1 H), 3.81–3.86 (m, 2 H), 4.08–4.16 (m, 2 H), 4.49–4.65 (m, 2 H), 7.33 (s, 5 H), 9.67 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.5, 14.2, 25.2, 25.6, 36.8, 46.4, 66.5, 68.2, 73.9, 81.0, 109.8, 126.3, 126.7, 129.4, 138.0, 175.1.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.79; H, 8.08.

(2*R*,3*R*,4*S*,5*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxy-4,6-dimethylheptan-5-ol (8)

To a cooled (0 °C) and stirred solution of isopropylmagnesium bromide [prepared from 2-bromopropane (0.812 g, 6.6 mmol) and Mg (0.193 g, 8.0 mmol)] in THF (20 mL) was added **7** (0.7 g, 2.2 mmol). After stirring the mixture for 2 h at 0 °C and 2 h at r.t., the reaction was quenched by the addition of aq sat. NH_4Cl (5 mL). The organic layer was separated, the aqueous phase extracted with Et_2O (2 × 20 mL), the combined organic extracts were washed with brine (1 mL), and dried. Removal of the solvent followed by column chromatography of the residue (silica gel, 0–15% EtOAc–hexane) afforded pure **8** as an epimeric mixture.

Yield: 0.555 g (70%); colorless oil; $[\alpha]_D^{22}$ +2.8 (*c* 2.20, $CHCl_3$).

IR (film): 3476, 1649, 1450, 1359, 1090 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (d, *J* = 7.2 Hz, 3 H), 0.99 (two overlapping d, *J* = 6.2, 7.2 Hz, 6 H), 1.41–1.62 (m, 12 H), 2.70 (br s, D_2O exchange, 1 H), 3.36–3.46 (m, 2 H), 3.50–3.54 (m, 1 H), 3.94–4.01 (m, 1 H), 4.38–4.42 (m, 1 H), 4.57 (d, *J* = 9.0 Hz, 1 H), 5.00 (d, *J* = 9.0 Hz, 1 H), 7.32 (s, 5 H).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.72; H, 9.27.

(2*R*,3*R*,4*S*,5*S*)-3-Benzyloxy-1,2-cyclohexylidenedioxy-4,6-dimethylheptyl-5-acetate (9b)

A mixture of **8** (0.5 g, 1.4 mmol), Ac_2O (2 mL), and pyridine (2 mL) was stirred overnight. The mixture was treated with ice–cold water, stirred for 1 h, and extracted with Et_2O (2 × 10 mL). The ethereal layer was washed with 10% aq NH_4Cl (5 mL), H_2O (2 × 10 mL), 10% aq Na_2CO_3 (5 mL), H_2O (2 × 10 mL), brine (2 mL), and dried. Removal of the solvent followed by column chromatography of the residue (silica gel, 0–10% EtOAc–hexane) afforded **9a** (0.156 g) and **9b** (0.364 g, total yield 92%).

9a

Colorless oil; $[\alpha]_D^{22}$ +4.1 (*c* 1.41, $CHCl_3$); R_f 0.42 (15% EtOAc–hexane).

IR (film): 1730 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.85 (d, *J* = 7.8 Hz, 6 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 1.25–1.80 (m, 11 H), 1.96–2.06 (m containing a s at 1.99, 4 H), 3.44 (t, *J* = 6.4 Hz, 1 H), 3.85 (t, *J* = 7.6 Hz, 1 H), 4.01–4.11 (m, 1 H), 4.20–4.26 (m, 1 H), 4.46–4.62 (m, 2 H), 5.10–5.15 (m, 1 H), 7.25–7.32 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 10.8, 17.5, 19.4, 21.0, 23.9, 24.0, 25.2, 29.5, 34.8, 36.2, 36.6, 66.1, 73.8, 75.7, 80.5, 109.4, 127.5, 127.7, 128.3, 138.6, 170.9.

9b

Colorless oil; $[\alpha]_D^{22}$ +6.9 (*c* 1.70, $CHCl_3$); R_f 0.35 (15% EtOAc–hexane).

IR (film): 3070, 1729, 1242 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (d, *J* = 7.0 Hz, 6 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.27–1.48 (m, 3 H), 1.52–1.70 (m, 8 H), 1.97–2.12 (m containing a s at 1.99, 4 H), 3.37–3.43 (m, 1 H), 3.48–3.59 (m, 1 H), 3.94–4.03 (m, 1 H), 4.28–4.36 (m, 1 H), 4.57–4.63 (m, 1 H), 4.87–4.94 (m, 2 H), 7.28–7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.2, 16.1, 16.2, 19.6, 19.8, 23.9, 25.1, 28.8, 35.1, 36.5, 65.7, 72.7, 75.7, 78.6, 109.9, 127.3, 127.7, 128.1, 138.8, 170.8.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.17; H, 9.17.

(2*R*,3*R*,4*S*,5*S*)-3-Benzyloxy-1,2-dihydroxy-4,6-dimethylheptyl-5-acetate (11)

A mixture of **9b** (0.246 g, 0.61 mmol) and 80% aq TFA (15 mL) in CH_2Cl_2 (15 mL) was stirred at –20 °C for 24 h. The mixture was concentrated in vacuo, the residue taken in $CHCl_3$ (20 mL), the organic extract washed with H_2O (2 × 5 mL), brine (1 mL), and dried. Removal of the solvent followed by column chromatography of the crude product (silica gel, 0–5% MeOH–$CHCl_3$) afforded pure **11**.

Yield: 0.158 g (80%); colorless thick syrup; $[\alpha]_D^{22}$ –17.6 (*c* 1.78, $CHCl_3$).

IR (film): 3431, 3090, 1729 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (d, *J* = 6.6 Hz, 6 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 1.15–1.22 (m, 1 H), 1.27–1.48 (m, 1 H), 2.03 (s, 3 H), 2.84 (br s, D_2O exchange, 2 H), 3.32–3.42 (m, 1 H), 3.48–3.65 (m, 2 H), 3.99–4.22 (m, 1 H), 4.38–4.68 (m, 2 H), 4.86–4.92 (m, 1 H), 7.33 (s, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.7, 17.6, 19.1, 29.5, 30.9, 65.8, 67.4, 74.1, 74.3, 80.1, 127.6, 127.9, 137.4, 137.8, 170.7.

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.84; H 8.86.

(3*R*,4*S*,5*S*)-3-Benzyloxy-4,6-dimethylhept-1-enyl-5-acetate (12)

To a cooled (0 °C) and stirred solution of **11** (0.36 g, 1.11 mmol) in pyridine (5.0 mL) was injected MsCl (0.216 mL, 2.79 mmol) and the mixture stirred for 12 h at r.t. The mixture was poured into ice-cold H_2O (15 mL), the organic layer separated, washed with H_2O (2 × 5 mL), brine (1 mL), and dried. Removal of the solvent afforded the mesylate, which was used as such for the next step.

Yellowish oil.

IR (film): 1739, 1362, 1172 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (d, *J* = 6.6 Hz, 6 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.15–1.18 (m, 1 H), 1.93–2.12 (m containing a s at 2.06, 4 H), 3.06 (s, 6 H), 3.63–3.77 (m, 1 H), 4.01–4.26 (m, 2 H), 4.48–4.62 (m, 3 H), 5.06–5.12 (m, 1 H), 7.34 (s, 5 H).

A mixture of the above mesylate, NaI (607.5 mg, 4.05 mmol) and Zn dust (2.63 g, 4.05 mmol) in DMF (25 mL) was heated at 90 °C for 8 h. The reaction mixture was cooled to r.t., diluted with Et_2O (25 mL), and the supernatant was passed through a pad (5 cm) of silica gel. The eluent was concentrated in vacuo, diluted with H_2O (15 mL), and extracted with Et_2O (2 × 15 mL). The ethereal layer was washed with H_2O (2 × 10 mL), brine (1 mL), and dried. The solvent was removed in vacuo followed and column chromatography of the residue (silica gel, 0–15% EtOAc–hexane) afforded pure **12**.

Yield: 0.210 g (65%); colorless oil; $[\alpha]_D^{22}$ –27.1 (*c* 2.5, $CHCl_3$).

IR (film): 1740, 1230, 990, 910 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (merged d, *J* = 6.4 Hz, 6 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 1.22–1.32 (m, 1 H), 1.81–1.97 (m, 1 H), 2.16 (s, 3 H), 4.24–4.30 (m, 1 H), 4.54–4.62 (m, 1 H), 4.75–4.88 (m, 1 H), 4.99–5.15 (m, 1 H), 5.19–5.36 (m, 2 H), 5.57–5.86 (m, 1 H), 7.29–7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.8, 17.3, 19.2, 29.5, 30.8, 73.9, 80.1, 81.4, 116.2, 127.7, 128.6, 130.7, 135.1, 139.8, 170.7.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.63; H 9.17.

(3*S*,4*R*,5*S*)-3-Benzyloxy-4-methyl-5-isopropyl-(5)-hexanolide (13)

To a cooled (–78 °C) and stirred solution of **12** (0.12 g, 0.41 mmol) in THF (10 mL) was injected BMS (0.7 mL). After stirring for 2 h, a solution of Na_2CrO_4 (0.2 g, 1.23 mmol) and H_2SO_4 (0.2 mL) in H_2O (2.0 mL) was added to the mixture at 0 °C, and the mixture refluxed for 1 h. The mixture was poured in iced-water (15 mL), ex-

tracted with Et_2O (2 × 15 mL), the organic extract was washed with H_2O (2 × 5 mL), brine (1 mL), and dried. The solvent was removed in vacuo and preparative TLC (silica gel, 10% EtOAc–hexane) afforded pure **13**.

Yield: 51.6 mg (48%); colorless oil; $[\alpha]_D^{22}$ –45.2 (*c* 0.72, $CHCl_3$).

IR: 2880, 1727 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (d, *J* = 6.8 Hz, 3 H), 1.06 (merged d, *J* = 6.1, 6.8 Hz, 6 H), 1.68–1.75 (m, 1 H), 1.98–2.06 (m, 1 H), 2.20–2.27 (m, 1 H), 2.94–2.99 (m, 1 H), 3.49–3.75 (m, 2 H), 4.46–4.59 (m, 2 H), 7.33 (s, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.5, 14.0, 19.9, 28.6, 38.9, 39.1, 68.8, 81.4, 86.2, 126.8, 127.2, 136.1, 139.2, 170.9.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45, Found: C, 73.37; H, 8.61.

(3*S*,4*R*,5*S*)-Prelactone B (1a)

A mixture of **13** (0.1 g, 0.38 mmol) and 10% Pd/C (30 mg) in EtOH (15 mL) was shaken under a positive pressure of H_2; after the required uptake of H_2, the mixture was passed through a pad of silica gel (5 cm) and the pad was eluted with Et_2O (20 mL). The combined eluents were concentrated to furnish pure **1a**.

Yield: 59.0 mg (90%); colorless oil; $[\alpha]_D^{22}$ –41.7 (*c* 0.57, MeOH), {lit.[4d] $[\alpha]_D^{22}$ –46 (*c* 0.42, MeOH)}.

IR (film): 3370, 1728, 1063 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.93 (d, *J* = 7.0 Hz, 3 H), 1.05 (merged d, *J* = 6.3, 6.6 Hz, 6 H), 1.70–1.78 (m, 1 H), 1.88 (br s, D_2O exchange, 1 H), 1.97–2.04 (m, 1 H), 2.42–2.48 (m, 1 H), 2.89–2.96 (m, 1 H), 3.63–3.77 (m, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.5, 13.9, 19.9, 28.7, 38.9, 39.1, 69.6, 86.3, 170.9.

(2*R*,3*R*,4*S*,5*R*)-1,2-Cyclohexylidenedioxy-3,5-isopropylidinedioxy-4,6-dimethylheptane (10a)

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.4, 13.9, 19.8, 23.6, 23.8, 24.6, 29.7, 31.1, 34.7, 36.3, 64.8, 66.8, 67.3, 67.9, 98.6, 109.9.

(2*R*,3*R*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-3,5-isopropylidinedioxy-4,6-dimethylheptane (10b)

^{13}C NMR: δ = 13.5, 14.2, 23.8, 24.1, 24.8, 25.0, 25.1, 31.7, 34.8, 36.4, 66.2, 66.7, 66.9, 68.2, 100.3, 109.8.

References

(1) (a) Boddien, C.; Gerber-Nolte, J.; Zeeck, A. *Leibigs Ann.* **1996**, 1381. (b) Bindseil, K. U.; Zeeck, A. *Helv. Chim. Acta* **1993**, *76*, 150.

(2) (a) Khosla, C.; Gokhale, R. S.; Jacobson, J. R.; Cane, D. E. *Ann. Rev. Biochem.* **1999**, *68*, 219. (b) O'Hagen, D. In *The Polyketide Metabolites*; O'Hagen, D., Ed.; Ellis Horwood: New York, **1991**, 116–137.

(3) (a) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539. (b) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737.

(4) (a) Endo, J. A. *J. Med. Chem.* **1985**, *28*, 401. (b) Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1733. (c) Schlessinger, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257. (d) Cavil, G. W. K.; Clark, D. V.; Whitefield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819.

(5) (a) Hanefeld, U.; Hooper, A. M.; Staunton, J. *Synthesis* **1999**, 401. (b) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2003**, *44*, 2541. (c) Fournier, L.; Gaudel-Siri, A.; Kocienski, P. J.; Pons, J. M. *Synlett* **2003**, 107. (d) Pihko, P.; Erkkila, A. *Tetrahedron Lett.* **2003**, *44*, 7607. (e) Csaky, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092. (f) Aggarwal, V. K.; Bae, I.; Lee, H. Y. *Tetrahedron* **2004**, *60*, 9725. (g) Yadav, J. S.; Reddy, K. B.; Sabitha, G. *Tetrahedron Lett.* **2004**, *45*, 6475. (h) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185. (i) Dias, L. C.; Steil, L. J.; Vasconcelos, V. D. *Tetrahedron: Asymmetry* **2004**, *15*, 147. (j) Enders, D.; Haas, M. *Synlett* **2003**, 2182.

(6) (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585. (b) Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1999**, *10*, 883. (c) Sharma, A.; Chattopadhyay, S. *Enantiomer* **2000**, *5*, 175. (d) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104.

(7) Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571.

(8) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(9) (a) Mulzer, J.; De Lasalle, P.; Freissler, A. *Leibigs Ann. Chem.* **1986**, 1152. (b) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (c) Baker, D. C.; Hawkins, L. D. *J. Org. Chem.* **1982**, *47*, 2179; and references cited therein.

(10) (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (c) Rychnovsky, S. D.; Rogers, B. M.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

(11) Mandal, A. K.; Mahajan, S. W. *Synthesis* **1991**, 311.

(12) Benagila, M.; Caporale, M.; Puglisi, A. *Enantiomer* **2002**, *7*, 383.