Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 147–150

A short and efficient synthesis of (+)-prelactone B ☆

Luiz C. Dias,* Leonardo J. Steil and Valéria de A. Vasconcelos

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, 13084-971 Campinas, SP, Brazil

Received 19 September 2003; accepted 22 October 2003

Abstract—The asymmetric total synthesis of (+)-prelactone B, a biologically important natural β-hydroxy-δ-lactone derivative that contains a 2,3-*trans*-dialkylpyran ring system, is described. This approach involves the use of a very efficient oxazolidinone-mediated *anti*-aldol reaction, and a diastereoselective coupling between a ketene silyl acetal with an aldehyde followed by lactonization.

1. Introduction

The prelactones **1**–**4** constitute an important class of highly functionalized chiral δ-lactones isolated from various polyketide macrolide producing microorganisms (Fig. 1).[1–6] Prelactone B **2**, a β-hydroxy δ-lactone that contains a 2,3-*trans*-dialkylpyran ring system is a biologically important natural pyranone derivative, isolated from bafilomycin producing *Streptomyces griseus* (strain 2599 ana 18) by Zeek and Bindseil in 1993.[1] The discovery of these molecules supports the widely accepted hypothesis of the step by step functionalization of growing polyketide chains in the biosynthesis of macrolides.[7–11]

To date, four syntheses of prelactone B **2** have been described.[6,9,10] An efficient and flexible enantioselective synthesis of prelactone B **2** is essential for providing further material for biological studies, along with access to novel analogues. The approach herein described for (+)-prelactone B **2** may give access to the other prelactones as well as to additional derivatives with potential relevance to biological studies.[12,13]

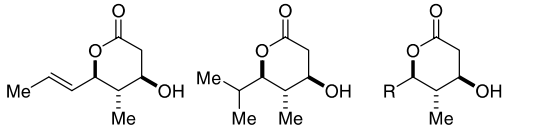
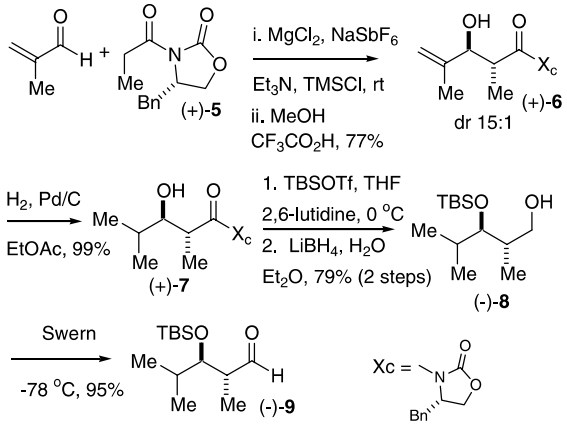


Figure 1.

2. Results and discussion

Our approach began with a highly selective *anti*-aldol reaction between oxazolidinone (+)-**5** and methacrolein to give (+)-**6** in 77% yield and 15:1 diastereoselectivity (Scheme 1).[14] The aldol adduct (+)-**6** was smoothly hydrogenated to give β-hydroxyimide (+)-**7** in 99% isolated yield after silica gel column chromatography.[14] In order to prepare the corresponding aldehyde, the attempted conversion of (+)-**7** into the corresponding Weinreb amide under standard conditions resulted in



Scheme 1.

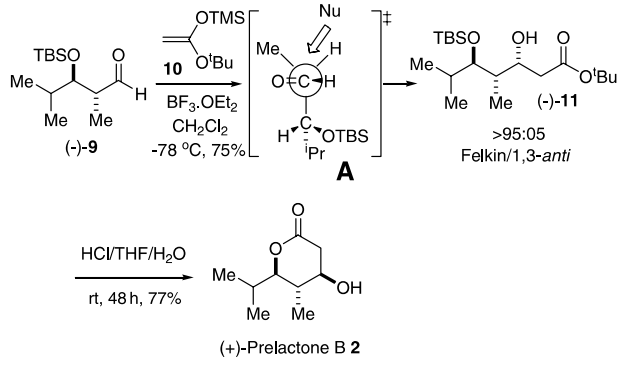
☆ This paper is dedicated to the Brazilian Chemical Society (SBQ).

* Corresponding author. Tel.: +55-019-3788-3021; fax: +55-019-3788-3023; e-mail: ldias@iqm.unicamp.br

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.10.032

significant amounts of nucleophilic attack on the oxazolidinone carbonyl.

This problem was circumvented by the protection of the –OH function as its TBS ether followed by the reductive removal of the chiral auxiliary in (+)-**7** with $LiBH_4$ and water in Et_2O (recovery of the oxazolidinone auxiliary was nearly quantitative in this reaction) to give the primary alcohol (−)-**8** in 79% yield for the two-step sequence (Scheme 1).[15] Finally, a Swern oxidation cleanly provided the *anti*-substituted aldehyde (−)-**9**.[16] This unpurified aldehyde was directly subjected to a $BF_3{\cdot}OEt_2$ promoted aldol reaction with the ketene silyl acetal **10** to give the aldol adduct (−)-**11** in 75% yield and with >95:5 diastereoselectivity (Scheme 2).[17,18] This result is readily accommodated by the merged α,β-stereoinduction model **A** (Scheme 2), which predicts the preferential formation of the Felkin/1,3-*anti* product diastereomer through an aldehyde *re*-face attack.[17] The carbonyl facial bias of *anti*-substituted aldehydes are highly predictable, since factors, which govern both 1,2- and 1,3-asymmetric induction mutually reinforce the nucleophilic addition to the Felkin aldehyde diastereoface.[17] Removal of the secondary TBS protecting group in (−)-**11** followed by lactonization was accomplished by treatment of ester (−)-**11** with HCl/THF/H_2O at rt for 48 h to give (+)-prelactone B (**2**) in 77% overall yield (Scheme 2).[6–10,19]



Scheme 2.

3. Conclusions

The spectroscopic and physical data (^1H and ^{13}C NMR, IR, $[\alpha]_D^{20}$, R_f) for **2** were identical in all respects to the published data.[6–10,19] The synthesis required seven steps from oxazolidinone (+)-**5** and produced the desired product in 33% overall yield, which compared very well with other published routes. As the *anti*-aldol reaction works with high diastereoselectivities for α,β-unsaturated aldehydes, this approach can be used also for the preparation of analogues of prelactone B containing a double bond on the side chain. As a result, the route to (+)-prelactone B **2** presented here is, in principle, readily applicable for the preparation of additional analogues with potential relevance to biological studies.[19]

4. Experimental section

4.1. (4*S*)-3-[(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpent-4-enoyl]-4-benzyl-1,3-oxazolidin-2-one 6[14b]

Oxazolidinone (+)-**5** (2.32 g, 10.0 mmol) was treated with $MgCl_2$ (96 mg, 1.0 mmol), $NaSbF_6$ (780 mg, 3.0 mmol), triethylamine (2.80 mL, 20.0 mmol), methacrolein (1.24 mL, 12.0 mmol), and chlorotrimethylsilane (1.82 mL, 15.0 mmol) in 20 mL of ethyl acetate at 25 °C for 30 h. The yellow slurry was pushed through a plug of silica gel (10 cm × 10 cm) with diethyl ether (350 mL). The ether solution was concentrated in vacuo, and 20 mL of methanol added along with 4 drops of trifluoroacetic acid. This was stirred at 25 °C for 30 min and then concentrated to a pale yellow oil. This oil was purified by flash chromatography (10 cm × 20 cm) (10–15% acetone in hexanes) to give 2.33 g of (+)-**6** as a colorless oil (77%). R_f 0.26 (25% EtOAc/hexane); $[\alpha]_D^{22}$ +57.6 (*c* 1.46, CH_2Cl_2); IR (thin film) 3500, 3069, 3029, 2978, 2936, 2881, 1778, 1698, 1650, 1604, 1498, 1461, 1454, 1386, 1351, 1291, 1251, 1211, 1109, 1014, 971, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.38–7.24 (m, 5H), 5.03 (br s, 1H), 4.98 (t, 1H, *J* 1.6 Hz), 4.71 (dddd, 1H, *J* 10.7, 6.8, 3.4, 3.4 Hz), 4.27–4.10 (m, 4H), 3.31 (dd, 1H, *J* 13.4, 3.2 Hz), 2.83 (d, 1H, *J* 5.9 Hz), 2.79 (dd, 1H, *J* 13.6, 9.7 Hz), 1.82 (s, 3H), 1.16 (d, 3H, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 176.4, 153.6, 144.6, 135.1, 129.4, 128.8, 127.2, 114.0, 79.2, 66.1, 55.6, 40.5, 37.9, 17.2, 14.9; HRMS calcd for $C_{17}H_{21}NO_4$: 303.1471, found: 303.1470.

4.2. (4*S*)-3-[(2*R*,3*R*)-2,4-Dimethyl-3-hydroxy-1-oxo-1-pentyl]-4-phenylmethyl-2-oxazolidinone 7[14c]

After two vacuum/H_2 cycles to remove air from the reaction flask, a stirred solution of 3.14 g (10.3 mmol) of the *anti*-substituted β-hydroxyimide (+)-**6** and 10% Pd/C (25 mg) in 15 mL of MeOH, was hydrogenated at 1 atm and room temperature for 2 h. The reaction mixture was filtered (Celite), and the filtrate concentrated. Purification by flash chromatography (15% EtOAc in hexane) gave 3.04 g (10.0 mmol, 97%) of (+)-**7** as a white crystalline solid. R_f 0.22 (25% EtOAc/hexane); mp 63–64 °C; $[\alpha]_D^{22}$ +61 (*c* 0.46, CH_2Cl_2); IR (thin film) 3700–3500 (br), 3015, 2895, 2890, 1785, 1690, 1455, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37–7.23 (m, 5H), 4.23–4.14 (m, 3H), 4.06 (apparent quint, 1H, *J* 7.0 Hz), 3.51 (m, 3H), 3.34 (dd, 1H, *J* 13.4, 3.3 Hz), 2.76 (dd, 1H, *J* 13.4, 9.7 Hz), 2.68 (d, 1H, *J* 8.5 Hz), 1.84 (m, 1H), 1.21 (d, 3H, *J* 6.9 Hz), 1.01 (d, 3H, *J* 6.9 Hz), 0.97 (d, 3H, *J* 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 177.4, 153.7, 135.3, 129.4, 128.9, 127.8, 79.5, 66.0, 55.6, 40.4, 37.8, 30.7, 19.9, 15.7, 14.9; HRMS calcd for $C_{17}H_{23}NO_4$: 305.1627, found: 305.1621.

4.3. (4*S*)-3-[(2*R*,3*R*)-2,4-Dimethyl-3-*tert*-butyldimethylsilyloxy-1-oxo-1-pentyl]-4-phenylmethyl-2-oxazolidinone

To a solution of 2.62 g (8.61 mmol) of the β-hydroxyimide (+)-**7** in 35 mL of THF at 0 °C was added 1.12 mL

(10.36 mmol) of 2,6-lutidine and 2.17 mL (9.45 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 15 min at 0 °C, the reaction was quenched by the addition of 7 mL of MeOH. After an additional 5 min the reaction was washed with 35 mL of aqueous $NaHSO_4$ followed by 35 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo yielding 3.33 g (92%) of the pure material, which was carried on without further purification. R_f 0.46 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.20–7.40 (m, 5H), 4.60–4.75 (m, 1H), 4.00–4.20 (m, 1H), 3.45 (dd, 1H, *J* 13.2 and 3.3 Hz), 2.64 (dd, 1H, *J* 13.2 and 10.3 Hz), 1.82 (dqq, 1H, *J* 7.0, 6.6, and 2.2 Hz), 1.18 (d, 3H, *J* 6.6 Hz), 0.98 (d, 3H, *J* 7.0 Hz), 0.96 (d, 3H, *J* 6.6 Hz), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.9, 153.5, 136.0, 129.8, 129.4, 127.7, 76.8, 66.5, 56.2, 44.4, 39.0, 31.7, 26.8, 21.3, 19.1, 17.4, 14.1, −3.2, −3.8; HRMS calcd for $C_{23}H_{37}NO_4Si$: 419.2492, found: 419.2488.

4.4. (2*S*,3*R*)-2,4-Dimethyl-3-[(*tert*-butyldimethylsilyl)-oxy]pentan-1-ol 8[6,14d]

To a solution of 2.70 g (6.43 mmol) of the *anti*-TBS protected β-hydroxyimide and 0.13 mL (7.06 mmol) of H_2O in 75 mL of Et_2O at 0 °C was slowly added 3.6 mL (7.2 mmol) of a 2.0 M solution of $LiBH_4$ in THF (gas evolution). After stirring for 1 h at 0 °C, the reaction was quenched by the addition of 45 mL of 1.0 M aqueous sodium potassium tartrate and stirred for an additional 20 min. The mixture was then diluted with 100 mL of CH_2Cl_2 and 50 mL of 1.0 M aqueous sodium potassium tartrate. The layers were separated and the aqueous layer extracted with two 50 mL portions of CH_2Cl_2. The combined organic extracts were washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to produce a residue, which was purified by silica gel column chromatography (15% EtOAc/hexane) to give 1.37 g (86%) of alcohol (−)-**8** as a colorless oil. $[\alpha]_D^{22}$ −7.8 (*c* 0.9, CH_2Cl_2); R_f 0.46 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 3.69 (ddd, 1H, *J* 10.9, 6.0, and 4.4 Hz), 3.59 (ddd, 1H, *J* 10.9, 5.8, and 5.5 Hz), 3.44 (dd, 1H, *J* 5.1 and 4.8 Hz), 2.65 (dd, 1H, *J* 6.0 and 5.5 Hz), 1.80–2.00 (m, 2H), 0.99 (d, 3H, *J* 7.0 Hz), 0.95 (d, 1H, *J* 6.6 Hz), 0.94 (s, 9H), 0.93 (d, 3H, *J* 7.0 Hz), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 82.9, 66.6, 37.5, 33.7, 26.7, 19.6, 19.1, 18.9, 17.2, −3.3; HRMS calcd for $C_{13}H_{30}O_2Si$: 246.2015, found: 246.1997.

4.5. (2*R*,3*R*)-2,4-Dimethyl-3-[(*tert*-butyldimethylsilyl)-oxy]pentanal 9[17a]

To a solution of 0.69 mL (7.74 mmol) of oxalylchloride in 30 mL of CH_2Cl_2 at −78 °C was added 1.14 mL (15.66 mmol) of DMSO (gas evolution). After 10 min, a solution of 1.24 g (5.04 mmol) of the alcohol **8** in 20 mL of CH_2Cl_2 was added. The cloudy white mixture was stirred for 15 min after which 3.9 mL (26.2 mmol) of triethylamine was added. The reaction mixture was stirred at −78 °C for 40 min and then quenched by the addition of 30 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and then diluted with 50 mL of CH_2Cl_2 and 50 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with two 30 mL portions of CH_2Cl_2. The combined organic extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. A ^{1}H NMR spectrum of the unpurified aldehyde proved to be very clean. Purification by silica gel column chromatography (50% CH_2Cl_2 in hexane) provided 1.17 g (4.79 mmol, 95%) of aldehyde (−)-**9** as a colorless liquid. $[\alpha]_D^{22}$ −35.1 (*c* 0.6, $CHCl_3$); IR (thin film) 2957, 2856, 1720, 1470, 1390, 1260, 1037, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.78 (d, 1H, *J* 2.4 Hz), 3.67 (dd, 1H, *J* 5.0 and 4.0 Hz), 2.52 (m, 1H), 1.84 (m, 1H), 1.11 (d, 3H, *J* 7.0 Hz), 0.92 (d, 3H, *J* 6.7 Hz), 0.90 (d, 3H, *J* 6.9 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.9, 79.1, 49.9, 32.8, 25.9, 18.8, 18.3, 12.1, −4.1, −4.3. This material proved to be very unstable for obtaining a high resolution mass spectral analysis.

4.6. *tert*-Butyl (3*R*,4*S*,5*R*)-5-[(*tert*-butyldimethylsilyl)-oxy]-3-hydroxy-4,6-dimethylheptanoate 11[6]

Boron trifluoride etherate (0.24 mL, 1.95 mmol) was added dropwise to a solution of 1.21 g of the enolsilane **10** (6.0 mmol) and the aldehyde (−)-**9** (0.48 g, 1.95 mmol) in 50 mL of CH_2Cl_2 at −78 °C. The reaction was stirred for 1 h, quenched at −78 °C via the addition of 50 mL of saturated aqueous $NaHCO_3$, and then warmed to ambient temperature. The mixture was diluted with 50 mL of CH_2Cl_2 and washed with 25 mL of saturated aqueous $NaHCO_3$. The aqueous washing was extracted once with 25 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by chromatography to give 0.52 g of ester (−)-**11** (1.46 mmol, 75% yield). $[\alpha]_D^{22}$ −5.1 (*c* 0.7, $CHCl_3$); R_f 0.35 (10% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) 4.50 (m, 1H), 3.50 (m, 1H), 2.49 (dd, 1H, *J* 15.4, 8.1 Hz), 2.27 (dd, 1H, *J* 15.4, 5.9 Hz), 1.95 (m, 1H), 1.70 (m, 1H), 1.46 (s, 9H), 0.99 (d, 3H, *J* 7.0 Hz), 0.95 (d, 3H, *J* 7.0 Hz), 0.93 (d, 3H, *J* 6.6 Hz), 0.92 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 171.4, 105.2, 82.7, 80.6, 67.5, 41.3, 38.3, 32.2, 28.2, 26.3, 19.9, 18.9, 18.5, 11.9, −3.5, −3.6; HRMS calcd for $C_{19}H_{40}O_4Si$: 360.2696, found: 360.2689.

4.7. (+)-Prelactone B, (3*R*,4*S*,5*R*)-3-hydroxy-4,6-dimethyl-heptanoic acid-δ-lactone 2[6–10]

To a solution of ester **11** (0.50 g, 1.38 mmol) in 10 mL of THF was added 2 mL of water. To the resulting solution was added dropwise 1 mL of concentrated HCl after which the mixture was stirred at rt for 48 h. The reaction mixture was then concentrated in vacuo, and purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to give 0.182 g (1.06 mmol, 77%) of (+)-prelactone B as a white solid. R_f 0.11 (50% EtOAc/hexane); mp 97–98 °C; $[\alpha]_D^{22}$ +39.1 (*c* 0.6, MeOH); IR (Nujol) 3466, 2360, 2341,

1722, 998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3.75 (m, 2H), 2.90 (dd, 1H, *J* 17.2, 5.8 Hz), 2.60 (br s, 1H), 2.46 (dd, 1H, *J* 17.2, 7.9 Hz), 1.97 (dsept, 1H, *J* 6.9, 2.1 Hz), 1.73 (ddq, 1H, *J* 10.4, 8.2, 6.7 Hz), 1.07 (d, 3H, *J* 6.8 Hz), 1.05 (d, 3H, *J* 6.7 Hz), 0.91 (d, 3H, *J* 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 171.2, 86.2, 69.8, 39.0, 38.9, 28.9, 20.0, 14.0, 13.6; HRMS calcd for $C_9H_{16}O_3$: 172.1099, found: 172.1107.

Acknowledgements

We are grateful to FAEP-UNICAMP, FAPESP, and CNPq (Brazil) for financial support. We also thank Prof. Carol H. Collins, from IQ-UNICAMP, for helpful suggestions about English grammar and style.

References and Notes

1. Bindseil, K. U.; Zeeck, A. *Helv. Chim. Acta* **1993**, *76*, 150.
2. Boddien, C.; GerberNolte, J.; Zeeck, A. *Liebgs Ann.* **1996**, *9*, 1381.
3. Cortes, J.; Wiesmann, K. E. H.; Roberts, G. A.; Brown, M. J. B.; Staunton, J.; Leadlay, P. F. *Science* **1995**, *268*, 1487.
4. Khosla, C.; Gokhale, R. S.; Jacobsen, J. R.; Cane, D. E. *Ann. Rev. Biochem.* **1999**, *68*, 219.
5. Esumi, T.; Fukuyama, H.; Oribe, R.; Kawazoe, K.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1997**, *38*, 4823.
6. Hanefeld, U.; Hooper, A. M.; Staunton, J. *Synthesis* **1999**, 401.
7. Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2001**, *42*, 1375.
8. Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1221.
9. (a) Fournier, L.; Gaudel-Siri, A.; Kocienski, P. J.; Pons, J. M. *Synlett* **2003**, 107; (b) Fournier, L.; Gaudel-Siri, A.; Kocienski, P. J.; Pons, J. M. *Synlett* **2003**, 584; (c) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2003**, *44*, 2541.
10. As this work was about to be submitted, a very short synthesis of (−)-prelactone B appeared: Pihko, P. M.; Erkkilä, A. *Tetrahedron Lett.* **2003**, *44*, 7607.
11. Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793.
12. (a) Dias, L. C.; de Oliveira, L. G.; de Sousa, M. A. *Org. Lett.* **2003**, *5*, 265; (b) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, *3*, 3951; (c) Dias, L. C.; de Sousa, M. A. *Tetrahedron Lett.* **2003**, *44*, 5625.
13. (a) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 185; (b) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 1593; (c) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 8883.
14. (a) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127; (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392; (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747; (d) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.
15. Treatment of aldol adduct (+)-**7** with $LiBH_4$, MeOH in THF led to epimerization of the aldol adduct, with a mixture of both *syn* and *anti* diols being obtained.
16. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
17. (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322; (b) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537; (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619; (d) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761.
18. The diastereomeric ratio for compound (−)-**11** was determined by ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic analysis of the crude product mixture.
19. After submission of this manuscript, two other syntheses of prelactone B appeared: (a) Csákÿ, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092; (b) Enders, D.; Haas, M. *Synlett* **2003**, 2182.