The Total Synthesis of Both Enantiomers of the Macrocyclic Lactone Zearalane

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Keywords: Macrocycles / Lactones / Hydroboration / Cross-coupling / Zearalane

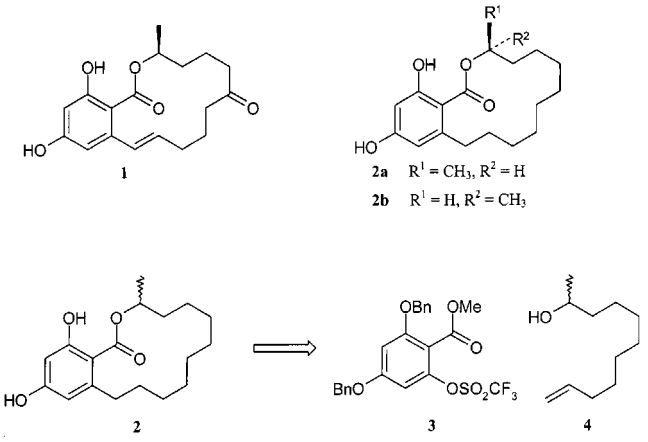
A straightforward approach to both enantiomers of zearalane is described from the enantiomerically pure alkenol (*S*)-**4**, prepared by a kinetic enzymatic resolution of the racemate. The key step is a Pd-catalyzed cross-coupling of an arene trifluoromethanesulfonate with a 9-alkyl-9-borabicyclo-[3.3.1]nonane derivative. The two enantiomers **2a** and **2b** have been obtained in an enantiodivergent manner by macrolactonization of the hydroxy acid (*S*)-**7** with either Gerlach's modification of the Corey lactonization or a Mitsunobu lactonization.

Introduction

In 1962 Stob et al. isolated the 14-membered macrocyclic lactone zearalenone (**1**) from the fungus *Gibberella zeae* (syn.: *Fusarium graminearum*).[1] This compound showed interesting estrogenic and anabolic activities. Starting from this natural product Urry and Wehrmeister[2] prepared a number of derivatives, which show higher anabolic and estrogenic activities. The macrocyclic lactone (*S*)-zearalane (**2a**) was prepared from **1** by hydrogenation of the double bond and reduction of the ketone to a methylene group. Compound **2a** also showed estrogenic and anabolic activities, but it also has anthelminthic and immunomodulating properties.[3]

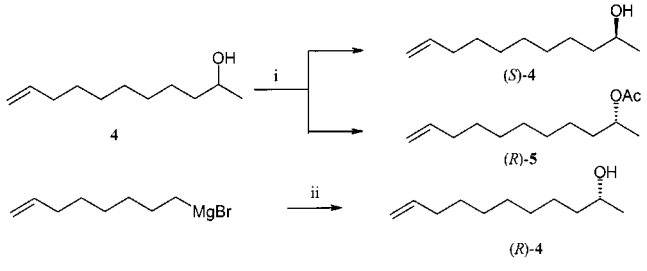
Results and Discussion

In continuation of our work on polyketide-derived natural products [4–7] we describe here the total synthesis of both enantiomers of **2**. These lactones were prepared from two building blocks: the enantiopure carbinols (*R*)- or (*S*)-**4** and the known arene triflate **3**,[8] as shown in the retrosynthetic scheme (Scheme 1).



Scheme 1

The chiral carbinols (*S*)-**4** and (*R*)-**4** were synthesized in two different ways (Scheme 2). The (*S*)- enantiomer is available starting from dec-9-en-1-ol. This alcohol was oxidized under Swern conditions to the known dec-9-enal,[9] which was reacted with methylmagnesium iodide to give (±)-undec-10-en-2-ol (**4**). Racemate **4** was submitted to a kinetic enzymatic resolution with a lipase from *Pseudomonas* species in the presence of vinyl acetate leading to the acetate (*R*)-**5** (*ee* = 60%) and unchanged alcohol (*S*)-**4** (*ee* > 98%). The enantiomeric excess of (*S*)-**4** and (*R*)-**5** was determined by GLC after derivatization with (*R*)-phenylethyl isocyanate. The enzyme could be recovered from the reaction mixture by simple filtration and could be used again for the same reaction without significant loss of activity. (*R*)-**4** is also a natural product, which can be isolated from the fresh bark of *Litsea ellipti*ca.[10] Since (*R*)-**4** could be obtained from (*R*)-**5** by alkaline ester hydrolysis only with low enantiomeric excess, we developed another synthesis of (*R*)-**4** by reaction of (*R*)-propylene oxide with 7-octenylmagnesium bromide. The product was obtained with high enantiomeric excess (> 96%), but only in poor yield.



Scheme 2. i. lipase PS, vinyl acetate; ii. (*R*)-propylene oxide

Therefore it appeared reasonable to use readily available (*S*)-**4** for the preparation of both enantiomers of zearalane (**2**) in an enantiodivergent synthesis.

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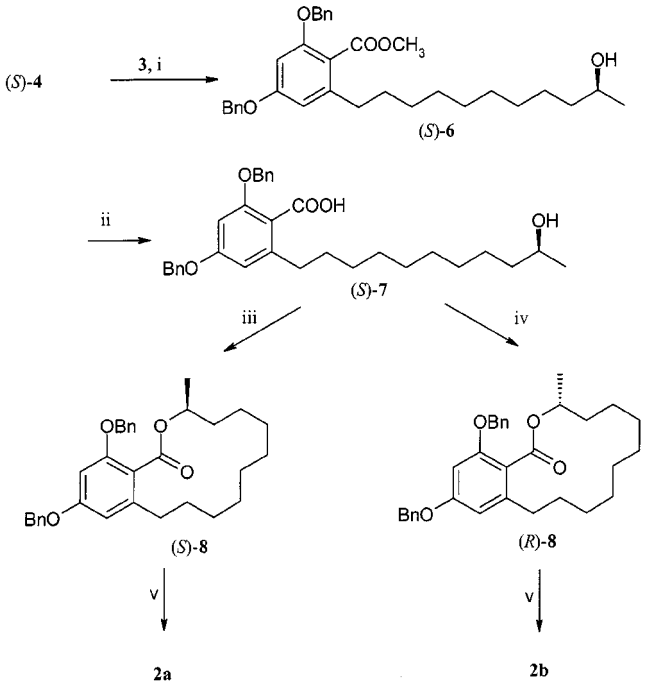
Thus, the enantiopure hydroxy olefin (*S*)-**4** was reacted with two equivalents of 9-BBN to give an organoborane (Scheme 3). In this reaction one equivalent of 9-BBN added to the double bond to give a terminal B-alkyl-9-BBN derivative, whereas the second equivalent was consumed by reaction with the carbinol group.[4] The crude organoborane was employed for a Pd-catalyzed cross-coupling reaction[11] with the arene triflate **3** to give, after aqueous workup, the alkylated arene (*S*)-**6**. Alkaline ester hydrolysis of (*S*)-**6** gave the hydroxy acid (*S*)-**7**, which was converted into (*R*)-*O,O*-dibenzylzearalane [(*R*)-**8**] by lactonization under Mitsunobu conditions.[12] This reaction occurs with clean inversion at the chiral centre. Enantiomerically pure (*S*)-**8** was obtained by lactonization of (*S*)-**7** using Gerlach's modification of the Corey conditions[4,13] with complete retention at the chiral centre. Debenzylation of (*R*)-**8** and (*S*)-**8** by catalytic hydrogenation gave pure (*R*)-zearalane (**2b**) and (*S*)-zearalane (**2a**).



Scheme 3. i. 2 equiv. 9-BBN, $Pd(PPh_3)_4$, K_3PO_4; ii. 4 M KOH; iii. $(PyS)_2$, PPh_3, $AgClO_4$; iv. PPh_3, DEAD; v. H_2/Pd (C)

Experimental Section

General: Elemental analyses were performed on a Carlo Erba CHNO Elemental Analyser. FTIR spectra were recorded on a Pye-Unicam PU-9800 spectrometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard on a Bruker AM-400 (^{1}H: 400.1 MHz; ^{13}C: 100.5 Hz) spectrometer. *J* values are given in Hz. Mass spectra were recorded on a Finnigan MAT-8430 spectrometer. Optical rotations were recorded on a Perkin−Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was carried out on Merck Kieselgel 60 (230−400 mesh). Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. The organic extracts were dried over anhydrous sodium sulfate which was later removed by filtration. The solvent used was concentrated using a rotary evaporator under reduced pressure. GLC was performed on a phenylmethylsilicone stationary phase (AT-50, Alltech) on a Shimadzu GC-14 A gas chromatograph equipped with FID.

(±)-Undec-10-en-2-ol (4): A solution of methylmagnesium iodide (5.0 mmol) in diethyl ether (4 mL) was added during 30 min to a stirred solution of dec-9-enal[9] (0.46 g, 3.0 mmol) in 2 mL diethyl ether. The mixture was stirred for 30 min and then poured into 10 mL of a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and after evaporation of the organic layer the residue was purified by flash column chromatography (hexane/ethyl acetate, 5:1) to give 430 mg (80%) of **4** as a colourless oil. $C_{11}H_{22}O$ (170.29): calcd. C 77.59, H 13.01; found C 77.03, H 13.54. ^{1}H NMR (CD_3COCD_3): δ = 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.18−1.58 (m, 12 H, 6 CH_2), 1.96 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2), 4.83 (tq, *J* = 6.4, *J* = 7.0, 1 H, CH), 4.91 (m, 1 H, HC=), 4.98 (ddt, *J* = 1.7, *J* = 17.2, *J* = 2.1, 1 H, H_2C=), 5.80 (ddt, *J* = 6.7, *J* = 10.1 Hz, *J* = 17.2 Hz, 1 H, -CH=). ^{13}C NMR (CD_3COCD_3): δ = 20.2 (CH_3), 21.1 (CH_3), 26.1 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 30.4 (CH_2), 36.6 (CH_2), 71.0 (C-2), 114.6 (CH_2=), 139.8 (−CH=), 170.5 (COO). IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2929, 2858, 1735, 1462, 1373, 1272, 1248, 1125, 1072, 743. MS (70 eV): *m/z* (%) = 197 (0.8) [M^+ − 15], 152 (10), 124 (19), 110 (22), 82 (38), 43 (100).

Kinetic Enzymatic Resolution of Racemate 4: (±)-Undec-10-en-2-ol (**4**; 0.20 g, 1.2 mmol) was dissolved in *tert*-butyl methyl ether (3 mL), and lipase PS (Amano; 100 mg) and vinyl acetate (0.50 g, 6.0 mmol) were added. The suspension was stirred for 2 days at room temperature. It was then filtered and the organic solvent was evaporated. The residue was purified by flash column chromatography (ethyl acetate/hexane, 1:5) to give 89 mg (35%) of (*R*)-**5** and 80 mg (40%) of (*S*)-**4** as colourless liquids.

(*R*)-Undec-10-en-2-yl Acetate [(*R*)-5]: $C_{13}H_{24}O_2$ (212.33): calcd. C 73.54, H 11.39; found C 73.55, H 11.40. ^{1}H NMR ([D_6]acetone): δ = 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.18−1.58 (m, 12 H, 6 CH_2), 1.96 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2), 4.83 (tq, *J* = 6.4, *J* = 7.0, 1 H, CH), 4.91 (m, 1 H, -CH=), 4.98 (ddt, *J* = 1.7, *J* = 17.2, *J* = 2.1, 1 H, H_2C=), 5.80 (ddt, *J* = 6.7, *J* = 10.1 Hz, *J* = 17.2 Hz, 1 H, -CH=). ^{13}C NMR ([D_6]acetone): δ = 20.2 (CH_3), 21.1 (CH_3), 26.1 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.4 (CH_2), 36.6 (CH_2), 71.0 (C-2), 114.6 (CH_2=), 139.8 (−CH=), 170.5 (CO). IR (film): $\tilde{\nu}$ =2958 cm^{-1}, 2929, 2858, 1735, 1462, 1373, 1272, 1248, 1125, 1072, 743. MS (70 eV): *m/z* (%) = 197 (0.8) [M^+ − 15], 152 (10), 124 (22), 82 (38), 43 (100). $[\alpha]_D^{25}$ = −0.975 (*c* = 5.129, $CHCl_3$). *ee* = 60% (GLC after alkaline hydrolysis and derivatization with (*R*)-phenylethyl isocyanate).

(*S*)-Undec-10-en-2-ol [(*S*)-4]: The spectroscopic data of (*S*)-**4** were in full agreement with those of **4**; $[\alpha]_D^{25}$ = + 6.62 (*c* = 0.455, $CHCl_3$). *ee* > 98% (GLC after derivatization with (*R*)-phenylethyl isocyanate).

(*R*)-Undec-10-en-2-ol [(*R*)-4]: A solution of oct-7-enylmagnesium bromide (8.0 mmol) in THF (3 mL) was added at −70 °C to a stirred suspension of $CuBr{\cdot}S(CH_3)_2$ (1.6 g, 7.4 mmol) in 5 mL THF and the mixture was allowed to warm to −10 °C. After cooling to −70 °C a solution of (*R*)-propylene oxide (0.46 g, 3.0 mmol) in THF (2 mL) was added. After 12 h the reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The organic layer was purified as described above.

The spectroscopic data of (*R*)-**4** were in full agreement with those of **4**; $[\alpha]_D^{25}$ = −6.85 (*c* = 0.16, $CHCl_3$). *ee* > 96% (GLC after derivatization with (*R*)-phenylethyl isocyanate).

(*S*)-Methyl 2,4-Dibenzyloxy-6-(10-hydroxyundecyl)benzoate [(*S*)-6]: An oven-dried flask equipped with a reflux condenser and a septum inlet was flushed with N_2, charged with a solution of 9-BBN (0.5 M in THF; 4.8 mL, 2.4 mmol) and then the alkenol (*S*)-**4** (0.20 g, 1.2 mmol) was added at 0 °C. The mixture was warmed slowly to room temperature and stirred for 4−6 h to give a solution of the alkyl-9-BBN derivative. Dioxane (4 mL), water (5 mL), powdered K_3PO_4 (0.37 g, 1.7 mmol), $Pd(PPh_3)_4$ (134 mg, 0.11 mol) and arene triflate **3** (595 mg, 1.2 mmol) were then added to this solution. The mixture was heated at 95 °C for 16 h, then extracted with diethyl ether and the organic layer was evaporated. The residue was separated by flash column chromatography (hexane/ethyl acetate 5:1) to give 330 mg (53%) of (*S*)-**6** as a colourless oil. $C_{33}H_{42}O_5 \cdot 1/2H_2O$ (527.70): calcd. C 75.16, H 8.15; found C 75.05, H 8.54. ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.25−1.63 (m, 16 H, 8 CH_2), 2.55 (dd, *J* = 7.7, *J* = 8.0, 2 H, CH_2), 3.77 (m, 1 H, CH), 3.85 (s, 3 H, OCH_3), 5.02 (s, 2 H, OCH_2), 5.04 (s, 2 H, OCH_2), 6.43 (s, 2 H, aromat. CH), 7.30−7.39 (m, 10 H, aromat. CH). ^{13}C NMR ($CDCl_3$): δ = 23.5 (CH_3), 25.8 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 33.9 (CH_2), 39.4 (CH_2), 52.0 (OCH_3), 68.2 (CHOH), 70.1 (OCH_2), 70.4 (OCH_2), 98.4 (aromat. CH), 107.3 (aromat. CH), 117.0 (quat. C), 126.9−128.6 (m, aromat. CH), 136.6 (quat. C), 136.8 (quat. C), 143.17 (quat. C), 157.1 (quat. C), 160.4 (quat. C), 168.8 (COOH). IR (film): $\tilde{\nu}$ = 2926 cm^{-1}, 2854, 1727, 1603, 1585, 1432, 1326, 1267, 1160, 736; 697. MS (70 eV): *m*/*z* (%) = 518 (12) [M^+]; 395 (12), 272 (10), 181 (14), 91 (100). $[\alpha]_D^{25}$ = 2.60 (*c* = 0.96, $CHCl_3$).

(*S*)-2,4-Dibenzyloxy-6-(10-hydroxyundecyl)benzoic Acid [(*S*)-7]: Methyl ester (*S*)-**6** (0.3 g, 0.6 mmol) was dissolved in ethanol (5 mL) and 4 M KOH (5 mL). The solution was refluxed for 30 h, extracted with 10 mL diethyl ether and the aqueous layer was acidified with 4 M HCl (10 mL). The solution was then extracted with diethyl ether (3 × 10 mL). The organic layer was evaporated to give 120 mg (49%) of (*S*)-**7** as a yellow oil. $C_{32}H_{40}O_5 \cdot 2H_2O$ (540.70): calcd. C 71.08 H 8.20; found C 69.43 H 8.37. ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, *J* = 6.2 Hz, 3 H, CH_3,), 1.21−1.38 (m, 12 H, 6 CH_2), 1.59 (m, 2 H, CH_2), 2.79 (m, 2 H, CH_2), 3.82 (m, 1 H, CH), 5.03 (s, 2 H, CH_2), 5.09 (s, 2 H, CH_2), 6.46 (d, *J* = 2.2 Hz, 1 H, aromat. CH), 6.47 (d, *J* = 2.2 Hz, 1 H, aromat. CH), 7.25−7.40 (m, 10 H, aromat.CH). ^{13}C NMR ($CDCl_3$): δ = 23.4 (CH_3), 25.5 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.2 (CH_2), 34.7 (CH_2), 68.4 (CHOH), 70.1 (CH_2O), 71.3 (CH_2O), 98.6 (aromat. CH), 108.8 (aromat. CH), 127.2 (aromat. CH), 127.6 (aromat. CH), 128.1 (aromat. CH), 128.2 (aromat. CH), 128.6 (aromat. CH), 128.7 (aromat. CH), 135.8 (quat. C), 136.3 (quat. C), 146.7 (quat. C), 161.0 (quat. C), 158.0 (quat. C), 168.9 (COOH). IR (film): $\tilde{\nu}$ = 2927 cm^{-1}, 2854, 2360, 1706, 1602, 1286, 1163. MS (70 eV): *m*/*z* (%) = 504 (0.6) [M^+], 460 (3), 214 (6), 91 (100). $[\alpha]_D^{25}$ = 2.45 (*c* = 1.13, $CHCl_3$).

(*R*)-*O,O*-Dibenzylzearalane [(*R*)-8]: PPh_3 (0.70 g, 2.5 mmol) was dissolved under N_2 in 290 mL toluene. DEAD (0.4 mL, 2.6 mmol) was added to the solution and stirred for 20 min. Over a period of 6 h half of a solution of the hydroxy acid (*S*)-**7** (240 mg, 0.5 mmol) in THF (1.5 mL) and toluene (3.7 mL) was added very slowly with a syringe pump. After stirring for 10 h more PPh_3 (0.35 g, 1.3 mmol) and DEAD (0.2 mL, 1.3 mmol) were added and the rest of the solution of the hydroxy acid was then added over 6 h. After stirring for 10 h the organic solvent was evaporated and the residue was separated by flash column chromatography (hexane/ethyl acetate, 20:1) to give 120 mg (49%) of (*R*)-**8** as a white solid, m.p.: 96 °C. $C_{32}H_{38}O_4$ (486.65): calcd. C 78.98, H 7.86; found C 77.95, H 8.35. ^{1}H NMR ($CDCl_3$): δ = 1.11 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.28−1.75 (m, 16 H, 8 CH_2), 2.30−2.77 (m, 2 H, CH_2), 4.99 (d, *J* = 6.2 Hz, 2 H, CH_2O), 5.03 (s, 2 H, CH_2O), 5.22 (tq, *J* = 6.2, *J* = 6.0, 1 H, CH), 6.44 (d, *J* = 2.1 Hz, 1 H, aromat. CH), 6.47 (d, *J* = 2.1 Hz, 1 H, aromat. CH), 7.28−7.42 (m, 10 H, aromat.CH). ^{13}C NMR ($CDCl_3$): δ = 20.0 (CH_3), 21.9 (CH_2), 24.2 (CH_2), 25.1 (CH_2), 25.6 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 29.8 (CH_2), 32.4 (CH_2), 35.0 (CH_2), 70.1 (CH_2O), 70.5 (CH_2O), 70.7 (HCOH), 98.1 (aromat. CH), 106.8 (aromat. CH), 117.8 (quat. C), 126.9 (quat. C), 127.5 (aromat. CH), 127.6 (aromat. CH), 127.9 (aromat. CH), 128.1 (aromat. CH), 128.4 (aromat. CH), 128.6 (aromat. CH), 136.7 (quat. C), 142.8 (quat. C), 156.9 (quat. C), 160.2 (quat. C), 168.5 (COO). IR (film): $\tilde{\nu}$ = 2928 cm^{-1}, 2859, 1717, 1606, 1579, 1498, 1380, 1322, 1164, 758, 701, 661. MS (70 eV): *m*/*z* (%) = 486 (6) [M^+], 279 (19), 167 (46), 149 (100), 91 (68). $[\alpha]_D^{25}$ = −54.25 (*c* = 0.153, $CHCl_3$).

(*S*)-*O,O*-Dibenzylzearalane [(*S*)-8]: Hydroxy acid (*S*)-**7** (100 mg, 0.20 mmol), di(2-pyridyl)disulfide (60 mg, 0.26 mmol) and PPh_3 (68 mg, 0.26 mmol) were dissolved in anhydrous acetonitrile (10 mL). This solution was stirred at room temperature for 1 h and then added dropwise over 2 h to a refluxing solution of anhydrous silver perchlorate (188 mg, 0.9 mmol) in anhydrous acetonitrile (100 mL). After complete addition the mixture was refluxed for a further 30 min and then cooled to room temperature and the solvents evaporated. The residue was partitioned between a solution of sodium cyanide (1 g) in water (30 mL) and ethyl acetate (3 × 30 mL) followed by flash column chromatography (hexane/ethyl acetate, 20:1) to give 29 mg (30%) of (*S*)-**8** as a viscous yellow oil.

The spectroscopic data for (*S*)-**8** were in full accordance with those of (*R*)-**8**; $[\alpha]_D^{25}$ = 50.96 (*c* = 5.0, $CHCl_3$).

(*R*)-Zearalane (2b): (*R*)-*O,O*-dibenylzearalane [(*R*)-**8**] (0.10 g, 0.20 mmol) was dissolved under N_2 in 1 mL ethyl acetate and 10 mL methanol, Pd /C (10%; 20 mg) was then added and the mixture was hydrogenated for 4 h. After filtration the organic solvents were evaporated and the residue separated by flash column chromatography (hexane/ethyl acetate, 40:3) to give 50 mg (79%) of **2b** as white crystals, m.p.: 157 °C. $C_{18}H_{26}O_4$ (486.65): calcd. C 70.57, H 8.55; found C 70.25, H 8.41. ^{1}H NMR ($CDCl_3$): δ = 1.23−1.65 (m, 10 H, 5 CH_2), 1.36 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.70−1.92 (m, 2 H, CH_2), 2.42 (dt, *J* = 4.4, *J* = 12.5 Hz, 1 H, CH_2), 3.26 (dt, *J* = 4.4, *J* = 12.3 Hz, 1 H, CH), 5.19 (dtq, *J* = 1.1, *J* = 4.4, *J* = 6.1 Hz, 1 H, CH), 5.74 (s, 1 H, OH), 6.24 (d, *J* = 2.7 Hz, 1 H, aromat. CH), 6.29 (d, *J* = 2.7 Hz, 1 H, aromat. CH), 12.23 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 22.5 (CH_2), 22.5 (CH_2), 22.7 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 31.3 (CH_2), 34.8 (CH_2), 37.2 (CH_2), 73.7 (CH), 101.5 (aromat. CH), 105.4 (quat. C), 110.6 (aromat. CH), 149.2 (quat. C), 160.3 (quat. C), 165.6 (quat. C), 171.8 (COO). IR (KBr): $\tilde{\nu}$ = 3391 cm^{-1}, 2946, 2922, 2870, 2853, 1639, 1585, 1257, 1177, 1098, 1020, 839. MS (70 eV): *m*/*z* (%) = 306 (40) [M^+], 288 (20), 168 (100). $[\alpha]_D^{25}$ = −30.84 (*c* = 0.32, $CHCl_3$).

(*S*)-Zearalane (2a): This compound was prepared from (*S*)-**8** under the conditions described for **2b**. The spectroscopic data for **2a** were in full agreement with those of **2b**; $[\alpha]_D^{25}$ = 36.8 (*c* = 1.0, $CHCl_3$). White crystals, m.p.: 154 °C (ref.:[3] 154 −156 °C).

Acknowledgments

We thank the Fonds der Chemischen Industrie for financial support and Amano for a gift of *Pseudomonas* lipase.

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Received January 30, 2001
[O01041]