Enantioselective Chemoenzymatic Synthesis of the *S*-Enantiomer of the Systemic Fungicide Fenpropimorph

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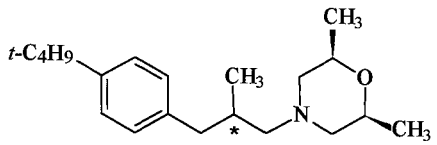
Chemoenzymatic synthesis of the *S*-(−)-enantiomer of fenpropimorph (*S*)-**1** in high optical and chemical purity is described. One feature of this process entails the enantioselective acetylation of prochiral 1,3-propanediol **4** by *Pseudomonas sp.* lipases, and subsequent transformation of the monoacetate (*R*)-**5** into the final product by the selected order of transformations that comprise; chlorination or tosylation under non-racemizing conditions, hydrogenolysis of the resulting chloromethyl or tosyl group in (+)-**6** and (+)-**8**, second chlorination of (−)-**9**, and alkylation of *cis*-3,5-dimethylmorpholine by 1-chloropropane derivative (+)-**10**. This sequence of reactions affords (*S*)-**1**, the more active enantiomer in the commercialized racemic mixture with systemic fungicidal activity.

The biological activity of systemic fungicides derived from 3-phenylpropylamines is substantially governed by their configurational and conformational properties.[1-3] Their most important representative fenpropimorph (*rac*-**1**) was selected from the large number of *p*-alkyl substituted 3-phenylpropylamines, in particular 3-phenylpropylmorpholines, for use in crop protection of cereals. Extensive biological testing showed that the *S*-enantiomer **1** is superior, and *R*-enantiomer inferior, to the racemate against mildew and brown rust wheat.[4] In spite of these results, and except for an early claimed separation of enantiomers by crystallization of diastereomeric salts of (−)-camphorsulphonic acid,[5] until recently no preparation of enantiomerically pure (*S*)-fenpropimorph was described.[6] Ever growing importance of the enantiomerically pure compounds (EPC) for crop protection[3] indicated fenpropimorph (**1**) as an important target for a "racemic switch", i.e. for replacing the racemate with the more active *S*-enantiomer for commercial use. Generally, this trend of replacing racemates for the optically pure, more active or less toxic enantiomers, is nowadays no longer limited to biologically active compounds used in human therapy, but also extended to veterinary applications and fragrance and agrochemical industries.[7-9]



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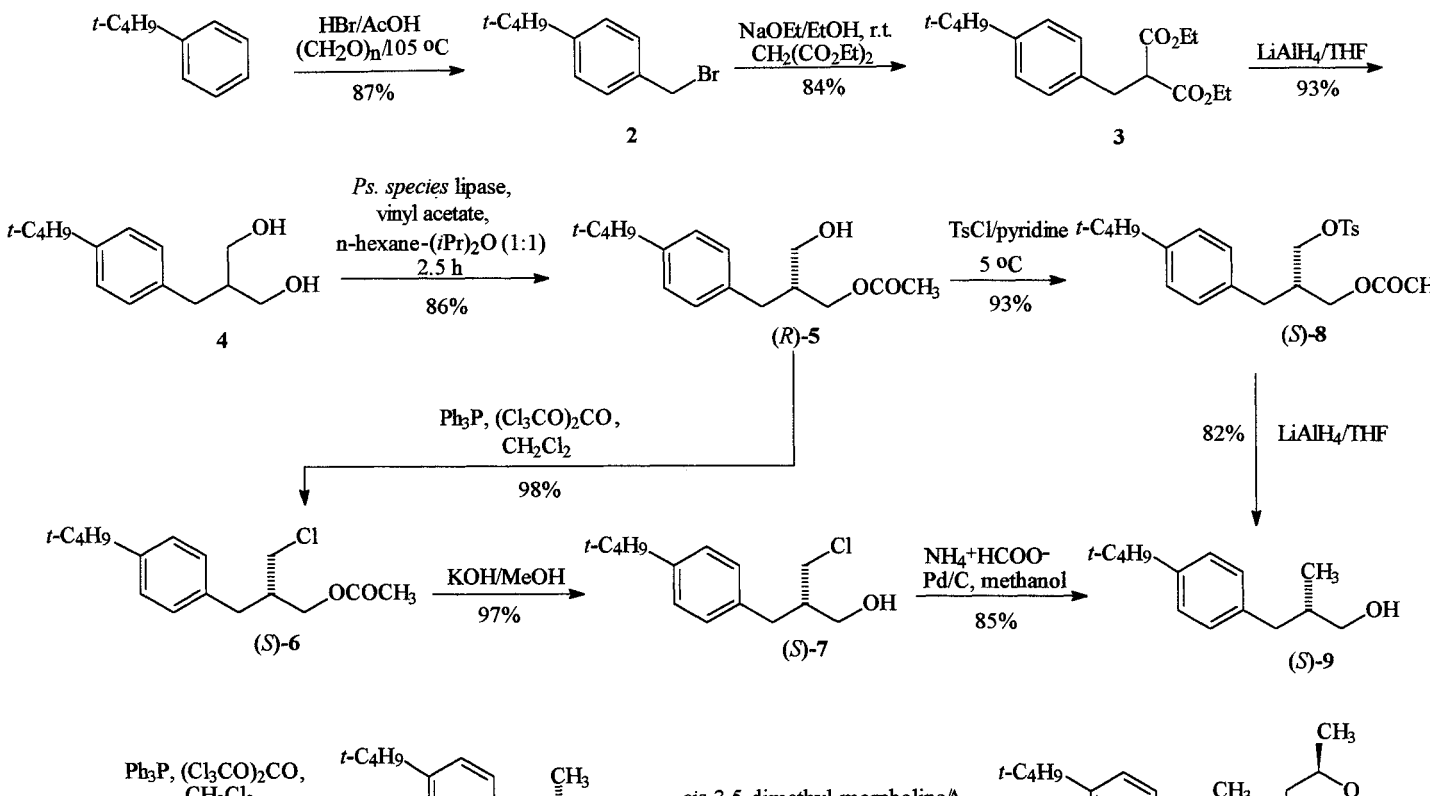
Although our recently reported method[6] has some amenability for scale-up, a relatively narrow range of optimized conditions for kinetic resolution by enzymatic hydrolysis and the need for recycling 50% of the starting material as "wrong" enantiomer, make it a poor candidate for an economically feasible process. We therefore designed a completely enantioselective synthesis of (*S*)-(−)-fenpropimorph, as outlined in Scheme 1.

The synthesis starts from inexpensive materials, diethyl malonate and *tert*-butylbenzene. Selective monobromomethylation of the former, as described recently,[6] benzylation of diethyl malonate and reduction afford the prochiral 1,3-diol **4** in ca. 80% overall yield. Acylation of the prochiral 2-substituted 1,3-diols have been already studied by Schneider et al,[10] and Ramos Tombo et al.[11]; some related studies are reviewed.[12] The origin of enantioselectivity of lipases has been recently analyzed by Klibanov.[13]

Guided by these results, we examined in detail the enantioselective monoacetylation of **4**. The results of the screening experiments are collected in Table 1. They reveal diverse efficasy of microbial lipases towards prochiral substrate **4**, that ranges from low reactivity, over high selectivity in monoacylation, to the fast and complete conversion to diacetate. *Pseudomonas sp.* lipase turned out to be the best candidate for ulterior optimization of this step. Proper selection of the solvent assures control

Table 1. Acetylation of **4** by Microbial Lipases

Lipase	Time (h)	Diol (%)	Mono-acetate (%)	Diacetate (%)
Rhizopus oryzae	3	100	0	0
	24	90.54	9.46	0
Geotrichum candidum	3	90.32	9.68	0
	4	86.93	13.07	0
	6	77.50	22.50	0
	24	31.20	68.80	0
Aspergilus niger	3	94.17	5.83	0
	4	92.92	7.08	0
	6	86.26	13.74	0
	24	57.19	42.81	0
Candida lipolitica	3	100	0	0
	24	100	0	0
Penicillium camembertii	1	15.26	63.57	21.17
	3	0	52.49	47.51
	4	0	44.13	55.87
	6	0	33.47	66.53
	24	0	16.05	83.95
Humicola lanuginosa	1	36.56	63.44	0
	2	6.11	90.29	3.60
	3	0	92.19	7.81
	4	0	87.34	12.66
	6	0	82.25	17.75
	24	0	48.12	51.88
Pseudomonas species	1	2.31	97.69	0
	3	0	95.82	4.18
	6	0	91.77	8.83
	24	0	63.95	36.05
Candida cylindracea	3	0	0	100
	6	0	0	100
	24	0	0	100



Scheme 1

of the rate of monoacetylation and complete suppression of diacetylation (Figure).

Monoacetylation by *Pseudomonas sp.* on the gram-scale was monitored by HPLC, and stopped at over 90% conversion and ca. 99% optical purity (e.e.) of (+)-**5**. This chiral intermediate was chlorinated to **6** by the bistrichloromethylcarbonate (BTC)/Ph_3P reagent. Interestingly, the rotation of **6** was essentially zero in the solvents we usually used for this series of compounds. Referring to the recently proposed mechanism of the BTC/Ph_3P chlorination,[14] we assumed that racemization via 1,3-acyl shift could take place, according to the well known acyl migration in sugar chemistry[15] (Scheme 2).

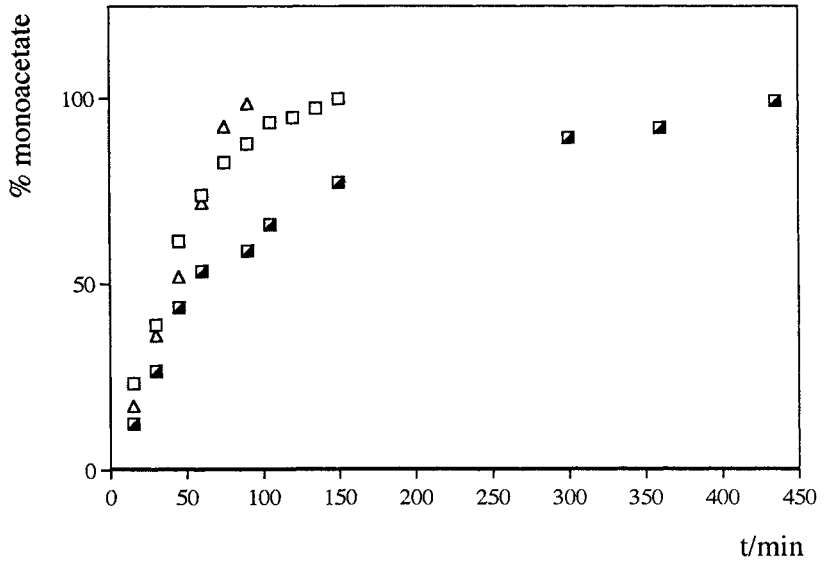
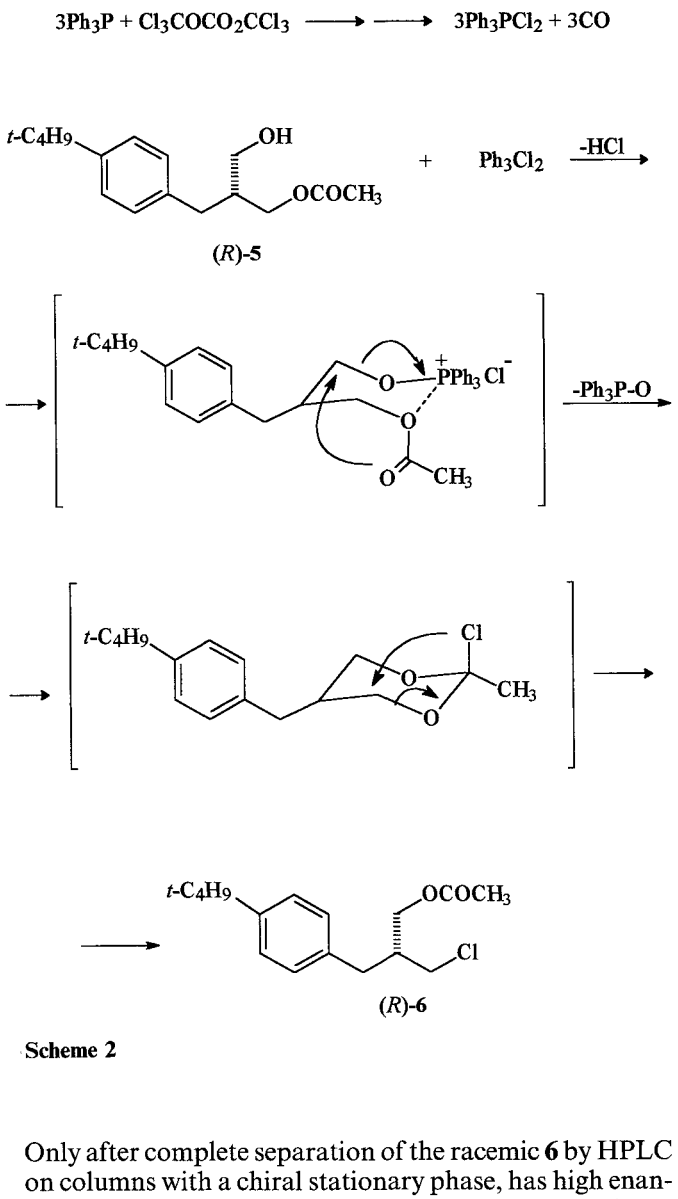


Figure. Progress curves for monoacetylation of **4** into (−)-**5** by *Pseudomonas sp.* lipase: (Δ–Δ–Δ) in hexane, (◪-◪-◪) in hexane/light petroleum (1:1), (□-□-□) in hexane/CH_2Cl_2 (1:1)



Scheme 2

Only after complete separation of the racemic **6** by HPLC on columns with a chiral stationary phase, has high enantiomeric purity of (+)-**6** been established. Chemical correlation of configuration of (+)-**6** with known *S*-configuration of (−)-fenpropimorph has excluded the mechanism that entails acyl migration, and confirmed that chlorination in (+)-**6** proceeds under retention of configuration. Palladium catalyzed hydrogenolysis of chlorine in (+)-**6** or (−)-**7**, according to the recently described protocol,[16] afforded (−)-**9** with somewhat lower optical purity than the starting compounds, indicating racemization via elimination (of hydrogen chloride)-addition (of hydrogen). Interestingly, this stereochemical aspect of catalytic hydrogenolysis was not discussed in the original paper.[12] To enhance the enantiomeric purity and to examine an alternative, we performed the reduction of the tosylate (+)-**8** into (−)-**9** by complex hydride.[17] Intermediate (+)-**8** was obtained in high optical purity (98.4%), and the final (−)-**1** in 92.2% e.e., which on one crystallization affords optically pure product. The final steps in Scheme 1 were optimized concerning only solvent and temperature; (*S*)-(−)-**1** was obtained in 40–45% overall yield.

The synthetic Scheme 1 is characterized by an interesting feature: if the most effective lipase would have produced (*S*)-(−) **5**, final (*S*)-(−)-**1** could have been obtained by the reversal of the final steps; first alkylation of *cis*-3,5-dimethylmorpholine by the chloroacetoxy derivative (−)-**6**, then reductive removal of the acetoxy group would again afford (*S*)-(−)-**1**.

It is important to notice that the final steps **6** (or **7**) → **8** → **9** → **1** do not invert the absolute configuration at the chiral center. The spatial relationship of the three C–C and one C–H bond remains, only the priority order of the ligands on the chiral center changes following the Cahn-Ingold-Prelog sequence rules.

In conclusion, we have accomplished a five-step chemoenzymatic synthesis of the *S*-(−)-enantiomer of fenpropimorph **(1)** starting from prochiral diol **4**. Complete control of the enantioselectivity, easy recycling of the microbial lipase in an organic solvent, and the possibility to obtain (*S*)-**1** from either enantiomer of monoacetate **5**, make this synthesis an attractive alternative to the previously disclosed procedures.[5,6]

Melting points were determined on Buchi mp apparatus, and are not corrected. IR spectra were obtained on a Perkin Elmer M 137 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, on Varian XL-GEM 300 spectrometer; shifts are given in ppm downfield from TMS as an internal standard. TLC was performed on Merck DC-Alufolien with Kieselgel 60_{254}, and flash chromatography on silica gel Merck. Organic extracts after usual workup were dried over Na_2SO_4 and evaporated in vacuo. GC was performed on a Hewlett Packard 5890 II instrument, using HP-17 (crosslinked 50% Ph–Me silicone) column. HPLC was performed on the HP 3396 instrument, with UV detector at 225 nm and HP 396A integrator, using chiral columns as indicated in Table 2. It reports separation conditions, retention times and optical purities of the prevailing enantiomer of **1** and **5–9**.

Screening of microbial lipases for transesterification was performed on a thermostated shaker (Techtnica) at 200 rpm and 30 ± 0.5 °C.

Table 2. Determination of Optical Purity of **1**, **5–9**

Compound	Column	Eluent	Flow/Pressure (mL/min/bar)	Ret. Time (min)		e.e. (%)
1	Chiral-AGP	0.01 M NH_4OAc/AcOH (pH 4.5)/2.5% *i*-PrOH	0.5/50	5.45	8.49	92.2
5	Chiralcel OJ	hexane/*i*-PrOH (97 : 3)	0.8/20	34.2	42.0	98.6
6	Chiralcel OD	hexane/*i*-PrOH (99.7 : 0.3)	0.3/30	34.9	34.7	98.6
7	Chiralcel OD	hexane/*i*-PrOH (98 : 2)	0.5/17	34.6	36.9	92.1
8	Chiralcel OD	hexane/*i*-PrOH (96 : 4)	0.5/9	42.5	44.3	98.4
9	Chiralcel OD	hexane/*i*-PrOH (98 : 2)	0.4/9	33.7	36.0	92.4

Progress of acetylation was followed using reverse phase column Econsphere C_8 (250 × 4.6 mm, Altech), with MeOH/water (4:1) as eluent at the flow rate 0.7 mL/min, and pressure 180 bar.

tert-Butylbenzene and diethyl malonate were purchased from Fluka, and BTC was from RI.C.E. S.c.p.A. (Torviscosa, Italy) (> 98% purity). Microbial lipases were non-commercial samples obtained from Amano Co. Light petroleum used refers to bp 60–80 °C.

For all new compounds satisfactory microanalysis were obtained: C ± 0.3, H ± 0.2.

2-(4-*tert*-Butylbenzyl)diethylmalonate (3):
Starting from 4-*tert*-butylbenzyl bromide (18.4 g, 81 mmol) and diethyl malonate (11.7 mL, 77 mmol) benzylation was performed in EtOH in the presence of NaOEt (4.15 g, 61 mmol). Crude product was purified by distillation; bp 109–112 °C/Torr; yield: 19.7 g (84%).

IR (film): ν = 2950, 1750, 1510, 1430 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.22 (t, J = 7.0 Hz, 6H), 1.29 (s, 9H), 3.18 (d, J = 7.6 Hz, 2H), 3.63 (t, J = 7.0 Hz, 1H), 4.15 (q, J = 7.0 Hz, 4H), 7.11 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H).

^{13}C NMR ($CDCl_3$/TMS): δ = 13.83, 31.45, 33.97, 34.20, 53.67, 61.18, 125.17, 128.27, 134.60, 149.32, 168.74.

2-(4-*tert*-Butylbenzyl)-1,3-propanediol (4):
To dry THF (10 mL) was added portionwise $LiAlH_4$ (500 mg, 13 mmol). The resulting suspension was heated to 50–55 °C, and a solution of **3** (2.8 g, 8.7 mmol) in THF (7.0 mL) was added over 20 min. Thereafter stirring was continued for 3 h at r.t. and then ice-water (2 × 50 mL) was added. The pH was adjusted to 2 by adding 10% H_2SO_4 (~ 10 mL) and the resulting suspension was extracted with diisopropyl ether (3 × 30 mL). Organic extracts were dried, filtered and evporated. Crude product (1.82 g, 93%) was crystallized from light petroleum/hexane (1:1) affording 1.67 g (86%) of pure **4**; mp 68–70 °C.

IR (KBr): ν = 3350 (br), 2960, 1510, 1360, 1025 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.29 (s, 9H), 1.99–2.04 (m, 1H), 2.54 (d, J = 7.4 Hz, 4H), 3.06 (s, 2H), 3.39 (dd, J = 10.6, 7.2 Hz, 1H), 3.75 (dd, J = 10.7, 3.9 Hz, 1H), 7.10 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 31.23, 33.57, 34.20, 43.67, 65.03, 125.13, 128.48, 136.56.

(+)-[2-(4-*tert*-Butylbenzyl)-2-hydroxymethyl]ethyl Acetate [(*R*)-5]:
Compound **4** (1.0 g, 4.6 mmol) was slurried in a mixture of hexane/diisopropyl ether (1:1, 50 mL), and *Pseudomonas sp.* lipase (100 mg) was added at 30 °C. The reaction was initiated by injecting vinyl acetate (5 mL) and was followed by HPLC on reverse phase C_8 column (250 × 4.6 mm, Altech), injecting the 50 µL samples taken at regular time intervals. After 2.4 h, complete conversion to monoacetate was observed. The mixture was filtered, the filtrate evaporated to dryness, and the crude product (1.12 g, 98.6% HPLC assay) was purified by flash chromatography on silica gel (60 g); yield: (1.05 g, 87%); $[\alpha]_D$ + 27.6 (c = 2.97, $CHCl_3$), bp 132–135 °C/0.07 Torr.

IR (film): ν = 3450, 2955, 1760, 1360, 1240, 1030 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (s, 9H), 2.07 (s, 3H), 2.08–2.14 (m, 1H), 2.16 (s, 1H), 2.55–2.70 (m, 2H), 3.51 (dd, J = 11.3, 6.2 Hz, 1H), 3.61 (dd, J = 11.3, 4.6 Hz), 1H), 4.08 (dd, J = 10.3, 6.4 Hz, 1H), 4.19 (dd, J = 11.2, 4.6 Hz, 1H), 7.11 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 20.72, 31.21, 33.62, 34.21, 42.22, 61.97, 63.97, 125.20, 128.54, 136.05, 148.88, 171.54.

(+)-[2-(4-*tert*-Butylbenzyl)-2-chloromethyl]ethyl Acetate [(*S*)-6]:
To a solution of Ph_3P (439 mg, 1.67 mmol) in anhydr. CH_2Cl_2 (10 mL), was added triphosgene (191 mg, 0.64 mmol) at 0 °C. When the gas evolution had ceased, the mixture was stirred for an additional 15 min. Thereafter solvent was evaporated, and to the crystalline residue was immediately added a solution of **5** (402 mg, 1.52 mmol) in anhydr. CH_2Cl_2 (10 mL). The resulting slurry was stirred at 40–45 °C for 2.5 hrs and the progress of reaction was followed by TLC with CH_2Cl_2 acetone (9.5:0.5) as the eluent. On addition of water (20 mL) the resulting slurry was extracted with light petroleum (3 × 15 mL), the organic extract dried, and evaporated. Crude product (390 mg, 98%) was purified by flash chromatography using CH_2Cl_2/cyclohexane (1:1) as eluent; pale yellow oil; $[\alpha]_D$ + 4.6 (c = 3.0, MeOH).

IR (film): ν = 2960, 1735, 1370, 1235 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 9H), 2.06 (s, 3H), 2.27–2.38 (m, 1H), 2.66–2.77 (m, 2H), 3.50 (dd, J = 11.1, 5.1 Hz, 1H), 3.60 (dd, J = 11.1, 4.5 Hz, 1H), 4.08 (dd, J = 11.1, 7.2 Hz, 1H), 4.16 (dd, J = 11.1, 5.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 20.86, 31.38, 34.25, 34.41, 41.56, 44.96, 64.07, 125.49, 128.73, 135.24, 149.38, 170.85.

(+)-[2-(4-*tert*-Butylbenzyl)-2(4-tolylsulfonyloxymethyl)]ethyl Acetate [(*S*)-8]:
To a solution of the monoacetate (+)-**5** (293 mg, 1.11 mmol) in anhydr. pyridine (5 mL) was added freshly crystallized TsCl (377 mg, 1.98 mmol) at 0 °C. After stirring briefly at 0–5 °C, the mixture was kept on ice for 48 h. Then crushed ice and water (30 mL) were added, and the resulting emulsion was extracted with diisopropyl ether (3 × 35 mL). The collected organic extracts were washed with water (2 × 20 mL), dried, filtered and evaporated. The crude product was purified by flash chromatography using CH_2Cl_2/cyclohexane (1:1) as eluent; yellow viscous oil; yield: 4–28 mg (93%); $[\alpha]_D$ + 4.32 (c = 3, $CHCl_3$).

IR (film): ν = 2960, 1745, 1370, 1240, 1175 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.29 (s, 9H), 1.95 (s, 3H), 1.98–2.28 (m, 1H), 2.46 (s, 3H), 2.60 (dd, J = 7.8, 2.5 Hz, 2H), 3.91–4.05 (m, 4H), 6.98 (d, J = 7.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 20.45, 21.42, 31.11, 33.07, 39.18, 39.25, 62.92, 68.87, 125.43, 127.97, 128.58, 129.83, 132.67, 134.75, 144.84, 149.40, 170.73.

(−)-2-(Chloromethyl)-2-(4-*tert*-butylbenzyl)propanol [(*S*)-7]:
To a solution of (+)-**6** (437 mg, 1.55 mmol) in MeOH (5 mL) was added a solution of KOH (114 mg, 2.03 mmol) in MeOH (5 mL), and the mixture stirred for 1 h at r.t. Then water (30 mL) was added and the resulting suspension extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried, filtered and evaporated. The crude product (367 mg, 98%) was crystallized from CH_2Cl_2; mp 39–41 °C, $[\alpha]_D$ − 28.3 (c = 2.0, $CHCl_3$).

IR (KBr): ν = 3395, 2970, 2110, 1370, 1030 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 9H), 1.63 (b, 1H), 2.15–2.19 (m, 1H), 2.68 (d, J = 7.4 Hz, 2H), 3.55 (dd, J = 10.9, 5.4 Hz, 1H), 3.67 (dd, J = 10.8, 4.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 31.16, 33.95, 34.19, 44.29, 45.25, 62.41, 125.40, 128.71, 135.93, 149.22.

(−)-2-(4-*tert*-Butylbenzyl)propanol [(*S*)-9]:
Method A: A solution of (−)-**7** (132 mg, 0.55 mmol) in absolute MeOH (5 mL) was purged with N_2, and 10% Pd/C (400 mg) and HCO_2NH_4 (420 mg, 6.6 mmol) were added. The mixture was heated at 45 °C under N_2, and the hydrogenolysis was followed by GC on a HP-17 column. After complete conversion (25 h), the mixture was filtered through silica gel (5 g, 0.063–0.2 mm, Merck), and the filtrate evaporated. The residual oil was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were dried, filtered and evaporated. The crude product was distilled at 85–88 °C/0.07 Torr to afford 99 mg (85%) of pure (−)-**9**; $[\alpha]_D$ − 4.9 (c = 2.5, $CHCl_3$).

IR (film): ν = 3350, 2960, 1460, 1370, 1040 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.93 (d, J = 6.7 Hz, 3H), 1.31 (s, 9H), 1.46 (s, 1H), 1.88–2.00 (m, 1H), 2.40 (dd, J = 13.6, 7.9 Hz, 1H), 2.70 (dd, J = 13.6, 6.4 Hz, 1H), 3.47 (dd, J = 10.6, 6.0 Hz, 1H), 3.55 (dd, J = 10.7, 5.8 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H).

^{13}CNMR ($CDCl_3$/TMS): δ = 16.37, 20.59, 31.21, 37.56, 39.02, 67.67, 125.13, 128.75, 137.46, 148.71.

Method B: To a solution of (+)-**8** (360 mg, 8.7 mmol) in anhydr. THF (7 mL) was added $LiAlH_4$ (130 mg, 3.5 mmol) in small portions. The reaction was continued under stirring at 20 °C, and formation of the product was followed by TLC (CH_2Cl_2, R_f 0.35). After 18 h, the mixture was poured onto ice-water (20 mL) and the resulting emulsion extracted with diisopropyl ether (3 × 20 mL). The organic extracts were dried, evaporated and the crude product purified by distillation; viscous oil (150 mg, 82%, 92.4% e.e.); $[\alpha]_D$ −6.2 (c = 2.5, $CHCl_3$).

(+)-2-(4-*tert*-Butylbenzyl)-1-chloropropane (10):
To a solution of Ph_3P (880 mg, 3.3 mmol) in anhydr. CH_2Cl_2 (12 mL) was added BTC (380 mg, 1.3 mmol) at 0 °C. After the evolution of gas had ceased, the solution was stirred for an additional 15 min. Thereafter the solvent was evaporated, and a solution of (+)-**9** (3.0 mmol) in anhydr. CH_2Cl_2 (15 mL) was added to the crystalline residue immediately. The mixture was stirred at r.t. for 6 h. After addition of water (30 mL), the resulting slurry was extracted with light petroleum (3 × 25 mL), the organic extract was dried and evaporated, and the crude product was purified by flash chromatography using CH_2Cl_2/cyclohexane (1:2) as eluent. The chromatographically pure product, a pale yellow oil (95%) was used in the next step without further purification; $[\alpha]_D$ +17.1 (c = 1.9, $CHCl_3$).

1-[3-(4-*tert*-Butylmethyl)-2-methyl]propyl-*cis*-3,5-dimethylmorpholine [(*S*)-1]:
Compound (+)-**10** (674 mg, 3.0 mmol) was dissolved in freshly distilled DMF (8 mL) and *cis*-3,5-dimethylmorpholine (1.04 g, 9.0 mmol, 98% *cis*-isomer) was added. The mixture was heated under an N_2 atmosphere at 120 °C for 3 h. Then the solvent was evaporated and the crude product mixture slurried in water (10 mL), pH adjusted to 9–10, and extracted with CH_2Cl_2 (3 × 10 mL). The dried organic extracts were evaporated and the crude product separated from excess of *cis*-3,5-dimethylmorpholine by distillation. First *cis*-3,5-dimethylmorpholine was recovered (bp 81–84 °C/100 Torr), followed by **1** (801 mg, 88%); bp 126–130 °C/0.02 Torr.

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