A Practical New Chiral Controller for Asymmetric Diels-Alder and Alkylation Reactions

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Supporting Information:

(1*S, 2*S**)-2-(Naphthalene-2-ylsulfanyl)cyclohexanol (4).** A stirred solution of 2-naphthalenethiol (6.57 g, 41.0 mmol, Aldrich) in MeOH (100 mL) in a three-neck flask equipped with a reflux condenser, a glass stopper and a rubber septum was heated to ca. 50 °C and treated with a solution of NaOMe in MeOH (4.40 M, 2.75 mL, 12.1 mmol, Aldrich). Cyclohexene oxide (4.05 mL, 40.0 mmol, Aldrich) was introduced in the reaction via syringe over a period of 10 min. During the addition of the epoxide, the temperature of the oil bath was raised to 80 °C. After completion of the addition, the reaction mixture was heated at reflux for 30 min. Upon cooling to room temperature, 1M aq. HCl was added (15 mL) and MeOH was removed *in vacuo*. The residue was partitioned between water (200 mL) and ether (300 mL), the organic layer was separated, and the aqueous phase was extracted again with ether (200 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (ether-pentane 1:3) gave (±)-4 as a colorless solid (9.72 g, 94% yield). mp 49-50 °C; R_f=0.22 (EtOAc-hexanes 1:4); FTIR (film) ν 3439, 2932, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (m, 1H), 7.83-7.77 (m, 3H), 7.55-7.47 (m, 3H), 3.40 (tdd, *J* = 10.2, 4.4, 1.4 Hz, 1H), 3.06 (d, *J* = 1.5 Hz, 1H), 2.89 (ddd, *J* = 3.9, 9.9, 11.8 Hz, 1H), 2.17-2.13 (m, 2H), 1.75-1.66 (m, 2H), 1.40-1.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 133.6, 132.8, 132.6, 131.0, 130.1, 128.4, 127.7, 127.5, 126.6, 126.4, 72.2, 56.7, 33.9, 32.8, 26.2, 24.3; HRMS (EI+) *m/z* calcd for $[C_{16}H_{18}OS]^+$: 258.1078 found: 258.1060; resolution of enantiomers was achieved by using a Chiralcel OJ column (Daicel Chemical Industries, Ltd.), 2.5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 254 nm with elution times t_{fast} = 25 min, t_{slow} = 33 min.

Acetate of (1*S, 2*S**)-2-(Naphthalen-2-ylsulfanyl)-cyclohexanol (4-OAc).** A small sample of the acetate ester of (±)-4 was synthesized for analytical chiral HPLC purposes by reaction of (±)-4 with acetic anhydride, triethylamine (Et_3N) and DMAP in CH_2Cl_2 at 23 °C. R_f=0.46 (EtOAc-hexanes 1:4); FTIR (film) ν 2937, 1737, 1500, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, *J* = 0.7 Hz, 1H), 7.81-7.76 (m, 3H), 7.53 (dd, *J* = 1.4, 8.5 Hz, 1H), 7.50-7.26 (m, 2H), 4.88 (td, *J* = 9.2, 4.2 Hz, 1H), 3.29 (td, *J* = 9.8, 4.0 Hz, 1H), 2.17-2.08 (m, 2H), 1.89 (s, 3H), 1.73-1.70 (m, 2H), 1.51-1.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.3, 133.6, 132.2, 132.1, 130.7, 129.8, 128.2, 127.6, 127.3, 126.5, 126.0, 75.2, 50.1, 31.6, 31.3, 25.0, 23.5, 21.0; HRMS (EI+) *m/z* calcd for $[C_{18}H_{20}O_2S]^+$: 300.1184 found: 300.1187; resolution of enantiomers was achieved by using a Chiralcel OJ column, 5% *i*-PrOH in hexanes as eluent at a flow rate of 0.3 mL/min, detection wavelength of 254 nm with elution times t_{fast} = 37.5 min, t_{slow} = 42.0 min.

Lipase-catalyzed Enantioselective Acetylation of (4). A stirred solution of (±)-4 (9.67 g, 37.4 mmol) in *i*-Pr_2O (100 mL, Aldrich) at 23 °C was treated with Lipase PS (4.58 g, Amano Pharmaceutical Co., Inc.) and 2-propenyl acetate (8.24 mL, 74.8 mmol, Aldrich). The progress of the reaction was monitored by chiral phase analytical HPLC, using a Chiralcel OJ column, until one enantiomer of the starting material was completely consumed. After a total time of 54 h, the unsoluble enzyme was removed by filtration, washed with several portions of ether, dried in air for 5-10 min and stored at -20 °C under N_2 for reuse (recovered enzyme retains full activity and can be reused several times). The solvent, acetone (by-product) and unconsumed isopropenyl acetate were removed *in vacuo*. The unreacted alcohol (+)-4 (4.82 g, 49.8% yield) and acetate ester (+)-4-OAc (5.61, 49.9% yield) were separated by silica gel chromatography (ether-pentane gradient). (+)-4 is a colorless solid. $[\alpha]^{24}_D$ +53.1 (*c* 1.93, $CHCl_3$); mp 46-47 °C; >99% ee determined by chiral HPLC, elution time t_{major} = 33 min. (+)-4-OAc is a colorless solid. $[\alpha]^{24}_D$ +13.4 (*c* 2.27, $CHCl_3$); mp 52.5-53.5 °C; >99% ee determined by chiral HPLC, elution time t_{major} = 37.5 min.

(+)-(1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)cyclohexanol ((+)-2). A vigorously stirred solution of (+)-4 (4.82 g, 18.7 mmol) in $CHCl_3$ (50 mL, Mallinckrodt) at 0 °C (ice bath) was treated with peroxyacetic acid (35% w/w in acetic acid, 7.90 mL, 41.1 mmol, Eastman) dropwise via an addition funnel, over a period of 30 min. The reaction mixture was stirred at 0 °C for 2 h, the cooling bath was removed and the mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and quenched by slow addition of sat. aq. Na_2SO_3 (75 mL) and sat. aq. $NaHCO_3$ (150 mL). The organic phase was diluted with CH_2Cl_2 (100 mL), separated, washed with sat. aq. $NaHCO_3$ (150 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* gave (+)-2 as a colorless solid (5.38 g, 98% yield). $[\alpha]^{24}_D$ +10.1 (*c* 1.92, $CHCl_3$); mp 102-103 °C; R_f=0.27 (EtOAc-hexanes 2:3); FTIR (film) ν 3509, 2939, 1301, 1291, 1141, 1125 cm^{-1}; ^1H NMR ($CDCl_3$,

500 MHz) δ 8.46 (d, *J* = 0.7 Hz, 1H), 8.03-8.00 (m, 2H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.87 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.70 (dt, *J* = 0.8, 7.5 Hz, 1H), 7.65 (dt, *J* = 0.9, 7.3 Hz, 1H), 4.38 (s, 1H), 3.97 (td, *J* = 10.2, 4.9 Hz, 1H), 3.07 (m, 1H), 2.15-2.12 (m, 1H), 1.96-1.92 (m, 1H), 1.70-1.68 (m, 2H), 1.36-1.30 (m, 2H), 1.18-1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.5, 133.8, 132.1, 131.0, 129.6, 129.5, 129.5, 128.0, 127.9, 123.5, 69.1, 68.3, 34.2, 25.8, 24.6, 23.6; HRMS (EI+) *m/z* calcd for $[C_{16}H_{18}O_3S]^+$: 290.0977 found: 290.0978.

(–)-(1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)cyclohexanol ((+)-2). A solution of (+)-4-OAc (2.183 g, 7.267 mmol) in MeOH (23 mL) at room temperature was treated with a solution of NaOMe in MeOH (4.40 M, 0.825 mL, 3.63 mmol, Aldrich) for 4 h. Analysis of an aliquot of the product by chiral HPLC using an OJ column indicated that the alcohol obtained after the methanolysis of (+)-4-OAc was of >99% ee (t_{major} = 25 min). The solution was cooled to 0 °C, diluted with MeOH (10 mL) and treated with peroxyacetic acid (35% w/w in acetic acid, 3.074 mL, 15.99 mmol, Eastman) over 5 min. The milky reaction mixture was stirred at 0 °C for 4 h, and then allowed to warm to room temperature over the next 5 h. The reaction mixture was stirred vigorously for an additional period of 12 h, cooled back down to 0 °C and quenched by slow addition of aq. sat. Na_2SO_3 (25 mL) and sat. aq. $NaHCO_3$ (75 mL). After gas evolution had ceased, MeOH was removed *in vacuo*, and the residual aqueous phase was extracted with CH_2Cl_2 (2 X 150 mL). The combined organic layers were washed with water (2 X 100 mL) and dried over anhydrous K_2CO_3. Filtration and evaporation of the solvent *in vacuo* gave product (–)-2 as a colorless solid (2.095 g, 99% yield). $[\alpha]^{24}_D$ -10.0 (*c* 1.73, $CHCl_3$); mp 102-103 °C.

(+)-4-Bromo-benzoic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester. A solution of (+)-2 (82.0 mg, 0.282 mmol) and DMAP (51.7 mg, 0.423 mmol, Aldrich) in CH_2Cl_2 (2 mL) at room temperature was treated with 4-bromobenzoyl chloride (92.8 mg, 0.423 mmol, Aldrich). Within min, a white precipitate formed. The reaction mixture was stirred for 24 h. The product was isolated after silica gel chromatography (EtOAc-hexanes 2:3) as colorless crystals (97.8 mg, 73% yield). $[\alpha]^{24}_D$ +151.5 (*c* 1.20, $CHCl_3$); mp 164-165 °C; R_f=0.48 (EtOAc-hexanes 2:3); FTIR (film) ν 2940, 1719, 1590, 1308, 1267, 1145, 1125, 1101, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (s, 1H), 7.80-7.70 (m, 3H), 7.62-7.58 (m, 2H), 7.48-7.44 (m, 1H), 7.14-7.11 (m, 2H), 7.00-6.97 (m, 2H), 5.34 (td, *J* = 10.4, 4.9 Hz, 1H), 3.55 (ddd, *J* = 4.1, 10.1, 12.5 Hz, 1H), 2.61-2.57 (m, 1H), 2.23-2.20 (m, 1H), 2.01-1.97 (m, 1H), 1.81-1.76 (m, 2H), 1.50-1.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.0, 137.2, 135.0, 132.1, 131.0, 130.5, 129.7, 129.4, 129.1, 128.9, 128.1, 127.9, 127.7, 127.6, 122.7, 72.0, 65.9, 31.7, 24.5, 24.0, 23.6; HRMS (FAB+, $[M+H]^+$) *m/z* calcd for $[C_{23}H_{22}BrO_4S]^+$: 473.0422 found: 473.0445.

(+)-Acrylate of (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexanol (5). A solution of (+)-2 (1.104 g, 3.803 mmol), Et_3N (2.120 mL, 15.21 mmol) and acrylic acid (0.444 mL, 6.46 mmol, Avocado) in CH_2Cl_2 (4 mL) was rapidly transferred via cannula to a suspension of 2-chloro-1-methylpyridinium iodide (1.749 g, 6.845 mmol, Aldrich) in CH_2Cl_2 (5 mL) at room temperature. The yellow reaction mixture was stirred for 1.5 h, during which time most of the salt dissolved and then quenched with 1 M aq. HCl (100 mL). The product was extracted into ether (300 mL). The organic phase was washed successively with water (150 mL), sat. aq. $NaHCO_3$ (150 mL) and brine (150 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo*, followed by silica gel chromatography (EtOAc-hexanes 15:85) gave (+)-5 as a solid (1.192 g, 91% yield). $[\alpha]^{24}_D$ +48.1 (*c* 1.08, $CHCl_3$); mp 86 °C; R_f= 0.41 (EtOAc-hexanes 2:3); FTIR (film) ν 2943, 1724, 1308, 1266, 1188, 1145, 1127 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 8.50 (d, *J* = 1.3 Hz, 1H), 7.83 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.49-7.42 (m, 3H), 7.20-7.09 (m, 2H), 5.94 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.36 (td, *J* = 10.3, 4.4 Hz, 1H), 5.33 (dd, *J* = 10.4, 17.4 Hz, 1H), 4.90 (dd, *J* = 1.5, 10.4 Hz, 1H), 3.21 (ddd, *J* = 4.2, 9.9, 12.1 Hz, 1H), 2.34-2.30 (m, 1H), 1.98-1.94 (m, 1H), 1.55-1.51 (m, 1H), 1.34-1.14 (m, 2H), 0.99-0.69 (m, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.4, 136.8, 135.2, 132.2, 130.7, 130.1, 129.4, 129.3, 129.1, 127.8, 127.7, 127.5, 123.2. 70.9, 65.7, 31.4, 24.3, 24.2, 23.3; HRMS (EI+) *m/z* calcd for $[C_{19}H_{20}O_4S]^+$: 344.1082 found: 344.1071. (–)-5 was synthesized similarly from (–)-2; $[\alpha]^{23}_D$ -47.9 (*c* 1.57, $CHCl_3$).

General Protocol for the Diels-Alder Reactions of (+)- or (–)-5. A solution of (+)- or (–)-5 in $PhCH_3$ or CH_2Cl_2 (ca. 0.3 M) at -20 °C was treated with a solution of BCl_3 in heptane (1.0 M, Aldrich). As soon as the ester-BCl_3 complex dissolved (within a few min) the solution was further cooled to -78 °C and stirred at that temperature for 15 min. The diene was added via syringe down the wall of the flask and the reaction mixture was stirred at the appropriate temperature and monitored by TLC. When no acrylate ester remained, the reaction mixture was quenched with sat. aq. $NaHCO_3$, allowed to warm to room temperature, and was poured into more sat. aq. $NaHCO_3$. The products were extracted into EtOAc (for the case of 6a) or ether (for all other cases) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo*, gave the products. For purification procedures see below.

(–)-(1*S*, 4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (6a). A solution of (+)-5 (314 mg, 0.913 mmol) in $PhCH_3$ (3.5 mL) at -20 °C was treated with a solution of BCl_3 in heptane (1.0 M, 0.14 mL, 0.14 mmol, Aldrich). Within 5 min, the ester-BCl_3 complex dissolved and the solution was further cooled to -78 °C, and was stirred at that temperature for 15 min. Cyclopentadiene (0.301 mL, 3.65 mmol) was added via syringe down the wall of the flask and the reaction mixture was stirred for 30 min, before being quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was allowed to warm to room temperature, and was poured into sat. aq. $NaHCO_3$ (20 mL). The products were extracted into EtOAc (2 X 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo*, gave 6a (372 mg, 99% yield) as a colorless solid. The *endo:exo* ratio (98.5:1.5) and de (97%) were determined by chiral phase analytical HPLC, using a Chiralpak AD column,

20% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 226 nm and elution times: t_{major} = 24 min, t_{exo} = 30 min, t_{minor} = 35 min. The major adduct (–)-6a was purified by recrystallization from 1:4 EtOAc-hexanes (ca. 55 mL) in 83% yield based on (+)-5. $[\alpha]^{24}_D$ -6.5 (*c* 1.97, $CHCl_3$); mp 175 °C; R_f= 0.24 (EtOAc-hexanes 1:4); FTIR (film) ν 2943, 1728, 1310, 1173, 1144, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.43 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.68-7.61 (m, 2H), 6.08 (AA'X, *J* = 5.6, 3.0 Hz, 1H), 6.00 (AA'X', *J* = 5.6, 2.8 Hz, 1H), 5.04 (td, *J* = 9.5, 4.9 Hz, 1H), 3.37 (ddd, *J* = 4.1, 9.6, 11.7 Hz, 1H), 3.10 (br s, 1H), 2.73 (br s, 1H), 2.39 (dt, *J* = 9.3, 4.1 Hz, 1H), 2.20-2.05 (m, 2H), 1.83-1.78 (m, 1H), 1.67-1.55 (m, 2H), 1.39 (ddd, *J* = 3.6, 9.4, 11.8 Hz, 1H), 1.30-1.20 (m, 4H), 1.01 (ddd, *J* = 2.7, 4.2, 11.8 Hz, 1H), 0.98 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.4, 137.1, 136.1, 135.2, 133.0, 132.2, 130.4, 129.5, 129.3, 129.3, 127.9, 127.7, 123.5, 70.2, 65.5, 49.4, 45.6, 43.4, 42.5, 31.4, 29.3, 25.1, 24.1, 23.2; HRMS (EI+) *m/z* calcd for $[C_{24}H_{26}O_4S]^+$: 410.1552 found: 410.1557.

(+)-(1*S*, 4*S*)-Bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (7a). The de of 7a (97%) was determined by chiral phase analytical HPLC, using a Chiralpak AD column, 20% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 226 nm and elution times: t_{major} = 26.5 min, t_{minor} = 35.5 min. Purification of the inseparable mixture of *endo* products was achieved by silica gel chromatography (EtOAc-hexanes, 15:85) (333.9 mg, 94% yield). Diastereomerically pure (+)-7a was obtained by recrystallization from 1:4 EtOAc-hexanes. $[\alpha]^{24}_D$ +32.5 (*c* 0.61, $CHCl_3$); mp 127 °C; R_f= 0.52 (EtOAc-hexanes 2:3); FTIR (film) ν 2941, 2845, 1731, 1310, 1186, 1169, 1161, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, *J* = 1.4 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.82 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.70-7.62 (m, 2H), 6.21-6.15 (m, 2H), 5.01 (td, *J* = 9.6, 4.6 Hz, 1H), 3.37 (ddd, *J* = 4.2, 9.8, 11.9 Hz, 1H), 2.76-2.74 (m, 1H), 2.41-2.40 (m, 1H), 2,32-2.25 (m, 1H), 2.04-2.00 (m, 1H), 1.86-1.82 (m, 2H), 1.67-1.52 (m, 2H), 1.32-1.10 (m, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.9, 136.2, 135.3, 134.5, 132.2, 132.1, 130.3, 129.5, 129.3, 129.3, 128.0, 127.7, 123.4, 70.1, 65.5, 42.5, 31.6, 31.4, 30.3, 29.3, 25.2, 24.9, 24.2, 24.1, 23.2; HRMS (EI+) *m/z* calcd for $[C_{24}H_{28}O_4S]^+$: 424.1709 found: 424.1705.

(–)-4-Methyl-cyclohex-3-enecarboxylic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (8a). The de of 8a (93.5%) was determined by chiral phase analytical HPLC, using a Chiralpak AD column, 20% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 226 nm and elution times: t_{major} = 37 min, t_{minor} = 43 min. Purification of the inseparable mixture of products was achieved by silica gel chromatography (EtOAc-hexanes, 1:4). Diastereomerically pure (–)-8a was obtained by semi-preparative chiral phase HPLC, using a 2 cm X 25 cm Chiralpak AD column, 50% *i*-PrOH in hexanes as eluent at a flow rate of 8 mL/min, detection wavelength of 226 nm. Elution time t_{major} = 40 min. $[\alpha]^{24}_D$ -11.5 (*c* 0.96, $CHCl_3$); mp 114-116 °C; R_f= 0.47 (EtOAc-hexanes 2:3); FTIR (film) ν 2937, 2863, 1730, 1309, 1168, 1144, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.55 (d, *J* = 1.3 Hz, 1H), 7.87 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.51-7.48 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.19-7.09 (m, 2H), 5.33 (td, *J* = 10.1, 4.8 Hz, 1H), 5.20 (br d, *J* = 1.5 Hz, 1H), 3.22 (ddd, *J* = 4.1, 9.8, 12.0 Hz, 1H), 2.40-2.20 (m, 2H), 2.11-1.88 (m, 3H), 1.66-1.40 (m, 5H), 1.45 (s, 3H), 1.35-1.29 (m, 1H), 1.17-1.12 (m, 1H), 1.04-0.94 (m, 1H), 0.81-0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.4, 136.2, 135.2, 133.2, 132.1, 130.2, 129.4, 129.2, 129.2, 127.9, 127.7, 123.3, 119.1, 70.1, 65.6, 38.8, 31.4, 29.1, 26.9, 25.3, 24.8, 24.2, 23.4, 23.2; HRMS (EI+) *m/z* calcd for $[C_{24}H_{28}O_4S]^+$: 412.1709 found: 412.1700.

(–)-Cyclohex-3-enecarboxylic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (9a). The de of 9a (94%) was determined by chiral phase analytical HPLC, using a Chiralpak AD column, 20% *i*-PrOH in hexanes as eluent at a flow rate of 0.7 mL/min, detection wavelength of 226 nm and elution times: t_{major} = 57 min, t_{minor} = 63 min. Analytically pure (–)-9a was obtained by semi-preparative chiral phase HPLC, using a 2 cm X 25 cm Chiralpak AD column, 40% *i*-PrOH in hexanes as eluent at a flow rate of 7 mL/min, detection wavelength of 226 nm. Elution time t_{major} = 57 min. $[\alpha]^{24}_D$ -15.7 (*c* 0.30, $CHCl_3$); mp 102-103 °C; R_f= 0.51 (EtOAc-hexanes 2:3); FTIR (film) ν 2939, 1731, 1309, 1165, 1145, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.43 (d, *J* = 1.4 Hz, 1H), 8.00-7.98 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.69-7.60 (m, 2H), 5.52 (AB, 2H), 5.11 (td, *J* = 9.7, 4.9 Hz, 1H), 3.38 (ddd, *J* = 4.2, 9.8, 11.9 Hz, 1H), 2.28-2.33 (m, 1H), 2.11-2.08 (m, 2H), 1.98-1.84 (m, 4H), 1.73-1.58 (m, 4H), 1.45-1.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.3, 136.2, 135.2, 132.1, 130.2, 129.4, 129.3, 129.2, 127.9, 127.7, 126.2, 125.1, 123.3, 70.1, 65.6, 38.9, 31.5, 26.7, 24.9, 24.9, 24.2, 24.2, 23.2; HRMS (EI+) *m/z* calcd for $[C_{23}H_{26}O_4S]^+$: 398.1552 found: 398.1550.

(–)-4-Chloro-cyclohex-3-enecarboxylic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (10a). The de of 10a (93.5%) was determined by chiral phase analytical HPLC, using a Chiralpak AD column, 40% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 226 nm and elution times: t_{major} = 36.0 min, t_{minor} = 45.5 min. Analytically pure (–)-10a was obtained by semi-preparative chiral phase HPLC, using a 2 cm X 25 cm Chiralpak AD column, 70% *i*-PrOH in hexanes as eluent at a flow rate of 7 mL/min, detection wavelength of 226 nm. Elution time t_{major} = 92 min. $[\alpha]^{24}_D$ -7.1 (*c* 1.35, $CHCl_3$); mp 91 °C; R_f= 0.51 (EtOAc-hexanes 2:3); FTIR (film) ν 2940, 1732, 1349, 1309, 1169, 1144, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, *J* = 1.3 Hz, 1H), 8.01-7.98 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.71-7.62 (m, 2H), 5.65-5.63 (m, 1H), 5.11 (td, *J* = 9.8, 5.1 Hz, 1H), 3.37 (ddd, *J* = 4.1, 9.9, 12.1 Hz, 1H), 2.30-2.00 (m, 6H), 1.95-1.83 (m, 2H), 1.72-1.65 (m, 2H), 1.62-1.50 (m, 2H), 1.35-1.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.2, 135.3, 132.1, 131.0, 130.3, 129.4, 129.4, 129.3, 128.0, 128.0, 127.9, 123.4, 122.6, 70.4, 65.7, 37.9, 31.6, 31.6, 27.7, 25.9, 25.1, 24.2, 23.3; HRMS (EI+) *m/z* calcd for $[C_{23}H_{25}ClO_4S]^+$: 432.1168 found: 432.1165.

(–)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Isopropyl Ester (6b). To a stirred

suspension of (–)-6a (212 mg, 0.518 mmol) in *i*-PrOH (3.5 mL, HPLC grade) was added Ti(*i*-PrO)$_4$ (0.500 mL, 1.69 mmol) and the reaction mixture was heated at 85 °C. The substrate dissolved completely within 5 h. The reaction mixture was stirred for a total time of 52 h. It was then allowed to cool to room temperature and was poured into 0.5 M aq. HCl (30 mL). The products were extracted into 1:1 ether-pentane (3 X 40 mL). The combined organic layers were washed with water (60 mL), 0.5 M aq. HCl (2 X 30 mL), sat. aq. NaHCO$_3$ (60 mL), brine (60 mL) and dried over MgSO$_4$. Filtration and evaporation of the solvent *in vacuo* at 5 °C afforded the crude product mixture which was analyzed by ^{1}H NMR. No trace of the *exo* ester could be detected. The *endo* isopropyl ester (–)-6b was obtained as a colorless, volatile liquid (85.0 mg, 91% yield) after silica gel chromatography (ether-pentane 15:85). $[\alpha]^{19}_D$ -120.5 (*c* 0.84, CHCl$_3$); R_f= 0.45 (ether-pentane 1:9); FTIR (film) ν 2979, 1731, 1195, 1100 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.18 (AA'X, *J* = 5.6, 3.0 Hz, 1H), 5.92 (AA'X', *J* = 5.6, 2.8 Hz, 1H), 4.94 (sep, *J* = 6.3 Hz, 1H), 3.19, (bs s, 1H), 2.93-2.89 (m, 2H), 1.91-1.84 (m, 1H), 1.44-1.40 (m, 2H), 1.26 (d, *J* = 7.9 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 174.3, 137.7, 132.3, 67.3, 49.7, 45.8, 43.6, 42.6, 29.2, 21.9, 21.9; HRMS (EI+) *m/z* calcd for $[C_{11}H_{16}O_2]^+$: 180.1150 found: 180.1154. Continued elution (ether-pentane 4:1) gave the chiral auxiliary (+)-2 (132 mg, 88% yield) as a colorless solid.

(–)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid Isopropyl Ester (7b). For a procedure, see above for 6b. No trace of the *exo* ester could be detected by ^{1}H NMR. The *endo* isopropyl ester (–)-7b was obtained as a colorless oil after silica gel chromatography (ether-pentane 15:85). $[\alpha]^{19}_D$ -42.0 (*c* 1.56, CHCl$_3$); R_f= 0.40 (ether-pentane 1:9); FTIR (film) ν 2943, 1731, 1193, 1175, 1145 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.32-6.28 (m, 1H), 6.15-6.11 (m, 1H), 4.95 (sep, *J* = 6.3 Hz, 1H), 2.93-2.89 (m, 1H), 2.60-2.55 (m, 2H), 1.74-1.67 (m, 2H), 1.59-1.44 (m, 2H), 1.32-1.20 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (CDCl$_3$, 101 MHz) δ 175.1, 135.2, 131.4, 67.3, 43.0, 32.6, 29.8, 29.5, 25.4, 24.5, 21.9, 21.8; HRMS (EI+) *m/z* calcd for $[C_{12}H_{18}O_2]^+$: 194.1307 found: 194.1298. Continued elution (ether-pentane 4:1) gave the chiral auxiliary (+)-2 (102 mg, 85% yield) as a colorless solid.

(–)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (6c). A vigorously stirred solution of isopropyl ester (–)-6b (84.0 mg, 0.467 mmol) in MeOH (3 mL) was treated with 0.7 M aq. LiOH (3 mL) at room temperature. The oily substrate was not completely miscible initially but as transesterification to the methyl ester and partial hydrolysis occurred, the solution became homogeneous. Additional 1 mL portions of 1 M aq. LiOH were added periodically. After a total time of 36 h, only carboxylic acid could be seen by TLC. The organic solvents were evaporated *in vacuo*, and the residual aqueous phase was acidified to pH 1 with 1 M aq. HCl. The carboxylic acid was extracted into ether (2 X 40 mL) and the combined organic layers were dried over MgSO$_4$. Filtration and evaporation of the solvent *in vacuo* afforded the known carboxylic acid (–)-6c[18] as a colorless oil (58.0 mg, 90% yield). ^{1}H NMR analysis in CDCl$_3$ revealed that no epimerization to the *exo* acid had occurred.

(–)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (7c). For a procedure, see above for 6c. The known carboxylic acid (–)-7c[19] was obtained as a colorless solid. mp 42-44 °C. ^{1}H NMR analysis in CDCl$_3$ revealed that no epimerization to the *exo* acid had occurred.

(+)-(1*R*)-4-Methyl-cyclohex-3-enecarboxylic Acid (8b). LiOMe was freshly prepared by adding slowly a solution of *n*-BuLi in hexanes (3.9 M, 1.0 mL, 3.9 mmol) to MeOH (2 mL) at -30 °C. The solvents were removed *in vacuo*. To a stirred solution of LiOMe (0.15 g, 3.9 mmol) in MeOH (1.5 mL) at -10 °C, a solution of 8a (10 mg, 0.249 mmol, 93.5% de) in THF (1.8 mL) was added via cannula. The reaction mixture was stirred for 24 h at -10 °C, and then treated with 0.50 M aq. LiOH (0.50 mL, 0.25 mmol) at room temperature for 2 h. The organic solvents were removed *in vacuo*, and the residue was partitioned between 1 M aq. NaOH (40 mL) and ether (40 mL). The organic phase was separated and the aqueous phase was extracted again with ether (40 mL). The combined organic layers were washed with water (40 mL), brine (40 mL) and dried over anhydrous MgSO$_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (EtOAc-hexanes gradient) afforded the chiral auxiliary (-)-2 as a colorless solid (75.2 mg, 92% yield). The aqueous phase was acidified with 6 M aq. HCl to pH 0. The carboxylic acid was extracted into ether (2 X 40 mL) and the combined organic layers were dried over anhydrous MgSO$_4$. Filtration and evaporation of the solvent *in vacuo* afforded the known carboxylic acid (+)-8b[20] as a colorless solid (34.2 mg, 98% yield). mp 94-96.5 °C.

(+)-(1*R*)-Cyclohex-3-enecarboxylic Acid (9b). For a procedure, see above for 8b, except that the final hydrolysis was carried out at 0 °C instead of 23 °C. The chiral auxiliary (–)-2 was recovered after silica gel chromatography as a colorless solid. The known carboxylic acid (+)-9b[21] was obtained as a colorless liquid.

(+)-(1*R*)-4-chloro-cyclohex-3-enecarboxylic Acid Propyl Ester (10b). A solution of 10a (88.2 mg, 0.204 mmol, 93.5% de) in *n*-PrOH (2.5 mL) was treated with MeSO$_3$H (0.500 mL, 7.70 mmol, Aldrich) and the reaction mixture was stirred at 85 °C (oil bath temperature) for 20 h. The reaction mixture was allowed to cool to room temperature and quenched by pouring it into sat. aq. NaHCO$_3$ (50 mL). The products were extracted into CH$_2$Cl$_2$ (2 X 50 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous MgSO$_4$. Filtration and evaporation of the solvent *in vacuo*, followed by silica gel chromatography (ether-pentane 1:49) gave the propyl ester (+)-10b as a colorless oil (37.2 mg, 90% yield). $[\alpha]^{23}_D$ +69.0 (*c* 1.81, CHCl$_3$); R_f= 0.47 (ether-pentane 1:9); FTIR (film) ν 2968, 1733, 1175 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.80-5.79 (m, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 2.59-2.53 (m, 1H), 2.43-2.34 (m, 4H), 2.11-2.06 (m, 1H), 1.90-1.81 (m, 1H), 1.65 (qt, *J* = 7.5, 6.8 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CDCl$_3$, 101 MHz) δ 174.9, 131.4, 122.7, 66.2, 38.3, 31.9, 28.3, 26.1, 22.0, 10.4; HRMS (CI+, [M+NH$_4$]$^+$) *m/z* calcd for $[C_{10}H_{19}ClNO_2]^+$: 220.1104 found: 220.1107. Continued elution (EtOAc-hexanes 1:4) afforded the chiral auxiliary (-)-2 as a colorless solid (55.5 mg, 94% yield).

General Protocol for the Preparation of Racemic Benzyl Amides. The racemic benzyl amides corresponding to products 8b, 9b and 10b were prepared according to the protocol that follows. Enantiomeric separation was achieved by chiral HPLC. A solution of dry benzylamine in THF (ca. 0.5 M) at 0 °C was treated with a solution of Me_3Al in $PhCH_3$ (2.0 M, 1.0 equiv, Aldrich). The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 25 min, and then treated with a solution of the racemic ethyl ester (prepared by the Diels-Alder reaction of ethyl acrylate and isoprene, 1,3-butadiene or 2-chloro-1,3-dutadiene under catalysis by BCl_3) corresponding to 8b, 9b or 10b. The reaction mixture was heated at 85 °C (oil bath temperature) for 2 h. After the reaction mixture had cooled to room temperature, it was poured into ice-cold 2 M aq. HCl. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Filtration and concentration of the solvent *in vacuo*, followed by re-filtration through a short silica gel plug and evaporation of the solvent *in vacuo* afforded the amide as a colorless solid.

(±)-4-Methyl-cyclohex-3-enecarboxylic Acid Benzylamide. mp 117-119 °C; R_f= 0.33 (EtOAc-hexanes 2:3); FTIR (film) ν 3288, 1639, 1552, 1548, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.26 (m, 5H), 5.78 (br s, 1H), 5.40-5.39 (m, 1H), 4.46 (d, J = 5.7 Hz, 2H), 2.38-2.18 (m, 3H), 2.02-1.94 (m, 3H), 1.82-1.75 (m, 1H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.7, 138.6, 134.1, 128.8, 127.8, 127.5, 119.3, 43.5, 41.3, 29.5, 28.4, 26.2, 23.5; HRMS (EI+) *m/z* calcd for $[C_{15}H_{19}NO]^+$: 229.1467 found: 229.1466. Resolution of the enantiomers was achieved by using a Chiralcel OJ column, 5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 215 nm with elution times t_{fast} = 21.5 min, t_{slow} = 25.0 min.

(±)-Cyclohex-3-enecarboxylic Acid Benzylamide. mp 102.5-103 °C; R_f= 0.33 (EtOAc-hexanes 2:3); FTIR (film) ν 3281, 2925, 1640, 1556, 1494, 1454, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.26 (m, 5H), 5.78 (br s, 1H), 5.72-5.68 (m, 2H), 4.50-4.42 (m, 2H), 2.43-2.05 (m, 5H), 1.97-1.93 (m, 1H), 1.80-1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.6, 138.5, 128.8, 127.8, 127.6, 126.9, 125.4, 43.6, 41.4, 28.2, 25.8, 24.7; HRMS (EI+) *m/z* calcd for $[C_{14}H_{17}NO]^+$: 215.1310 found: 215.1311. Resolution of the enantiomers was achieved by using a Chiralcel OJ column, 3.5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 215 nm with elution times t_{fast} = 44 min, t_{slow} = 48 min.

(±)-4-Chloro-cyclohex-3-enecarboxylic Acid Benzylamide. mp 154.5-155 °C; R_f= 0.31 (EtOAc-hexanes 2:3); FTIR (film) ν 3299, 1635, 1540 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.26 (m, 5H), 5.82-5.81 (m, 1H), 5.75 (br s, 1H), 4.50-4.41 (m, 2H), 2.45-2.27 (m, 4H), 2.04-1.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.4, 138.3, 131.5, 128.9, 127.8, 127.7, 122.8, 43.7, 40.3, 32.1, 29.1, 27.0; HRMS (EI+) *m/z* calcd for $[C_{14}H_{16}ClNO]^+$: 249.0920 found: 249.0921. Resolution of the enantiomers was achieved by using a Chiralcel OJ column, 5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 215 nm with elution times t_{fast} = 51.5 min, t_{slow} = 57.5 min.

(1*R*)-4-Methyl-cyclohex-3-enecarboxylic Acid Benzylamide. To a suspension of 2-chloro-1-methylpyridinium iodide (24.5 mg, 0.0959 mmol, Avocado) in CH_2Cl_2 (0.5 mL) was added a solution of carboxylic acid (+)-8b (8.9 mg, 0.064 mmol), benzylamine (0.024 mL, 0.22 mmol) and tri-*n*-propylamine (*n*-Pr_3N) (0.061 mL, 0.32 mmol) in CH_2Cl_2 (1.3 mL). The reaction mixture was heated at reflux for 1 h. It was then poured into 1 M aq. HCl (30 mL) and the product was extracted into ether (60 mL). The organic layer was washed with water (30 mL), 0.5 M aq. NaOH (30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. Filtration, concentration of the solvent *in vacuo*, re-filtration through a short plug of silica gel followed by evaporation of the solvent *in vacuo*, afforded the product as a colorless solid. 92.5% ee, elution time t_{major} = 25 min.

(1*R*)-Cyclohex-3-enecarboxylic Acid Benzylamide. Synthesized from carboxylic acid (+)-9b. For a procedure, see above for formation of amide from (+)-8b. 93% ee, elution time t_{major} = 48 min.

(1*R*)-4-chloro-cyclohex-3-enecarboxylic Acid Benzylamide. Synthesized from *n*-propyl ester (+)-10b, according to the protocol described above for the racemic benzylamide. 93% ee, elution time t_{major} = 57.5 min.

(–)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl Methanol (6d). To a stirred solution of (–)-6a (200 mg, 0.488 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added a solution of DIBAL-H in CH_2Cl_2 (1.0 M, 0.98 mL, 0.98 mmol, Aldrich) via syringe to the flask over a period of 5 min. The reaction mixture was stirred for an additional period of 1 h, and then quenched by the addition of solid Na_2SO_4•$10H_2O$ (1.58 g, 4.90 mmol, Aldrich). The cooling bath was removed and when the mixture warmed to room temperature, Celite was added. Filtration and removal of the solvent at 45-50 °C using a Vigreaux column afforded the crude product mixture which was analyzed by ^1H NMR. No trace of the *exo* alcohol could be detected. Silica gel chromatography (ether-pentane 1:9) afforded the known volatile alcohol (–)-6d[23] as a colorless oil (54.0 mg, 88%). Continued elution (ether-pentane 4:1) gave the chiral auxiliary (+)-2 as a colorless solid (132 mg, 93% yield).

(+)-(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.1]oct-5-en-2-yl Methanol (7d). To a stirred solution of 7a (230 mg, 0.542 mmol, 97% de) in CH_2Cl_2 (2.5 mL) at -30 °C was added a solution of DIBAL-H in $PhCH_3$ (0.60 M, 1.8 mL, 1.1 mmol, Aldrich) via syringe over a period of 20 min. The reaction mixture was stirred for an additional period of 10 min, and then quenched by the addition of solid Na_2SO_4•$10H_2O$ (1.76 g, 5.46 mmol, Aldrich). The mixture was allowed to warm to room temperature. It was then diluted with ether and filtered through Celite. Evaporation of the solvent *in vacuo* afforded the crude product mixture which was analyzed by ^1H NMR. No trace of the *exo* alcohol could be detected. Silica gel chromatography (ether-pentane 1:9) gave the known alcohol (+)-7d[24] (71.1 mg, 95% yield). Continued elution (ether-pentane 4:1) gave the chiral auxiliary (+)-2 as a colorless solid (154 mg, 98% yield).

(–)-Phenyl-acetic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (11). Crushed, oven-dried (110 °C) 4 Å molecular sieves (0.555 g) were flame-dried in a flask at 2 mm Hg, and cooled to room temperature under argon. Phenylacetic acid (0.312 g, 2.29

mmol, Aldrich) was then introduced, followed by CH_2Cl_2 (6 mL). As soon as the carboxylic acid dissolved, neat DMAP (0.258 g, 2.29 mmol) and (–)-2 (0.604 g, 2.08 mmol) were added and the flask was cooled to 0 °C. DCC (0.473 g, 2.29 mmol, Aldrich) was added neat and 5 min later the cooling bath was removed, and the reaction mixture was stirred at room temperature for 4.5 h. The reaction mixture was then poured into CH_2Cl_2 (100 mL) and filtered under suction through a pad of Celite. The filtrate was passed through Celite again to remove some precipitate that appeared as the solution got cold under the vacuum. The filtrate was washed with 1 M aq. HCl (50 mL), water (50 mL), sat. aq. $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (acetone-PhH 1:49) gave (–)-11 (0.761 g, 89% yield) as a colorless solid. $[\alpha]^{20}_D$ -23.1 (*c* 1.28, $CHCl_3$); mp 125-126 °C; R_f= 0.46 (EtOAc-hexanes 2:3); FTIR (film) ν 2941, 1738, 1306, 1144, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (d, *J* = 1.3 Hz, 1H), 8.02-7.93 (m, 3H), 7.84 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.70-7.62 (m, 2H), 7.25-7.20 (m, 3H), 7.00-6.98 (m, 2H), 5.11 (td, *J* = 9.7, 4.7 Hz, 1H), 3.38 (ddd, *J* = 4.2, 9.8, 11.9 Hz, 1H), 3.03 (AB, *J* = 15.4 Hz, 2H), 2.36-2.33 (m, 1H), 206-2.03 (m, 1H), 1.87-1.84 (m, 1H), 1.70-1.57 (m, 2H), 1.33-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.1, 136.3, 135.2, 133.6, 132.2, 130.2, 129.5, 129.4, 129.3, 129.1, 128.4, 128.0, 127.8, 127.0, 123.4, 70.7, 65.5, 40.8, 31.3, 24.6, 24.1, 23.2; HRMS (EI+) *m/z* calcd for $[C_{24}H_{24}O_4S]^+$: 408.1396 found: 408.1377.

(+)-(6-Methoxy-naphthalen-2-yl)-acetic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (12). Crushed, oven-dried (110 °C) 4 Å molecular sieves (0.428 g) were flame-dried in a flask at 2 mm Hg, and cooled to room temperature under argon. 6-Methoxynaphthylacetic acid[25] (0.199 g, 0.921 mmol) was then introduced, followed by CH_2Cl_2 (3.5 mL). As soon as the carboxylic acid dissolved, neat DMAP (0.112 g, 0.921 mmol) and (+)-2 (0.243 g, 0.837 mmol) were added and the flask was cooled to 0 °C. DCC (0.190 g, 0.921 mmol, Aldrich) was added neat and 5 min later the cooling bath was removed, and the reaction mixture was stirred at room temperature for 3.5 h. The reaction mixture was then poured into CH_2Cl_2 (100 mL) and filtered under suction through a pad of Celite. The filtrate was passed through Celite again to remove some precipitate that appeared as the solution got cold under the vacuum. The filtrate was washed with 1 M aq. HCl (50 mL), water (50 mL), sat. aq. $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (acetone-PhH 1:24) gave (+)-12 (0.349 g, 85% yield) as a colorless solid. $[\alpha]^{22}_D$ +27.8 (*c* 0.62, $CHCl_3$); mp 134-135 °C; R_f= 0.37 (EtOAc-hexanes 2:3); FTIR (film) ν 2941, 1737, 1609, 1309, 1267, 1144, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.45 (s, 1H), 8.02-7.94 (m, 3H), 7.86 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.69 (t, *J* = 7.1 Hz, 1H), 7.65-7.59 (m, 3H), 7.28 (s, 1H), 7.12-7.07 (m, 3H), 5.13 (td, *J* = 9.8, 4.7 Hz, 1H), 3.90 (s, 3H), 3.39 (ddd, *J* = 4.1, 9.8, 11.9 Hz, 1H), 3.15 (AB, *J* = 15.5 Hz, 2H), 2.37-2.35 (m, 1H), 2.06-2.04 (m, 1H), 1.87-1.84 (m, 1H), 1.68-1.58 (m, 2H), 1.31-1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3, 157.6, 136.4, 135.3, 133.5, 132.2, 130.3, 129.6, 129.4, 129.3, 129.1, 128.8, 128.7, 128.0, 127.8, 127.8, 127.7, 126.9, 123.5, 119.0, 105.6, 70.9, 65.6, 55.3, 40.9, 31.3, 24.7, 24.2, 23.2; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{29}H_{28}NaO_5S]^+$: 511.1555 found: 511.1549.

(+)-(4-Isobutyl-phenyl)-acetic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (13). Crushed, oven-dried (110 °C) 4 Å molecular sieves (0.847 g) were flame-dried in a flask at 2 mm Hg, and cooled to room temperature under argon. 4-Isobutylphenylacetic acid[25] (0.188 g, 0.979 mmol) was then introduced, followed by CH_2Cl_2 (3.6 mL). As soon as the carboxylic acid dissolved, neat DMAP (0.120 g, 0.979 mmol) and (+)-2 (0.258 g, 0.890 mmol) were added and the flask was cooled to 0 °C. DCC (0.202 g, 0.979 mmol, Aldrich) was added neat and 5 min later the cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then poured into CH_2Cl_2 (100 mL) and filtered under suction through a pad of Celite. The filtrate was passed through Celite again to remove some precipitate that appeared as the solution got cold under the vacuum. The filtrate was washed with 1 M aq. HCl (50 mL), water (50 mL), aq. sat $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (EtOAc-hexanes 15:85) gave (+)-13 (0.373 g, 90% yield) as a colorless solid. $[\alpha]^{22}_D$ +22.0 (*c* 1.35, $CHCl_3$); mp 86-87 °C; R_f= 0.22 (EtOAc-hexanes 1:4); FTIR (film) ν 2952, 1739, 1453, 1310, 1144, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, *J* = 1.3 Hz, 1H), 8.01-7.93 (m, 3H), 7.85 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.70-7.61 (m, 2H), 6.95 (AB, *J* = 8.0 Hz, 4H), 5.10 (td, *J* = 9.7, 4.7 Hz, 1H), 3.39 (ddd, *J* = 4.2, 9.8, 11.9 Hz, 1H), 2.97 (AB, *J* = 15.4 Hz, 2H), 2,41 (d, *J* = 7.2 Hz, 2H), 2.37-2.34 (m, 1H), 2.06-2.04 (m, 1H), 2.07-2.03 (m, 1H), 1.88-1.83 (m, 1H), 1.81 (m, 1H), 1.70-1.57 (m, 2H), 1.32-1.23 (m, 3H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4, 140.5, 136.4, 135.3, 132.2, 130.8, 130.3, 129.5, 129.4, 129.3, 129.2, 128.9, 128.0, 127.8, 123.4, 70.7, 65.5, 45.1, 40.5, 31.3, 30.2, 24.6, 24.1, 23.2, 22.4; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{28}H_{32}NaO_4S]^+$: 487.1919 found: 487.1931.

General Protocol for the Akylation Reactions of (–)-11 or (+)-13. The substrate was dried azeotropically with $PhCH_3$ at 2 mm Hg. A pre-cooled (-78 °C) solution of this material in 4:1 DME-DMPU (ca. 0.2 M) was added via cannula (dry ice jacket) to a stirred solution of Ph_3CK (ca. 0.1 M) in 4:1 DME-DMPU at -78 °C. An additional volume of 4:1 DME-DMPU was used to transfer via cannula residual substrate into the reaction flask. After stirring for 15 min, a solution of the electrophile R-X (ca. 2.5 equiv) in DME was introduced into the reaction mixture via syringe down the wall of the flask. The reaction mixture lost color and sat. aq. NH_4Cl was immediately added. The mixture was allowed to warm up to room temperature and the organic solvents were evaporated *in vacuo*. The residue was partitioned between water and EtOAc. The organic phase was separated, washed with brine and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the crude product. The de was determined by ^1H NMR analysis. Silica gel chromatography (*t*-BuOMe-hexanes or EtOAc-hexanes gradient) gave the inseparable diastereomeric mixture.

(–)-(*R*)-2-Phenyl-propionic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (14). Diastereomerically pure (–)-14 was obtained by recrystallization from acetic acid-water. $[\alpha]^{20}_D$ -50.4 (*c* 0.27, $CHCl_3$); mp 105-106 °C; R_f= 0.52 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2940, 1733, 1309, 1144, 1127 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 8.48 (s, 1H), 7.80 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.43-7.38 (m, 3H), 7.29-7.27 (m, 2H), 7.17-7.04 (m, 5H), 5.16 (td, *J* = 9.3, 4.5 Hz, 1H), 3.45 (q, *J* = 7.2 Hz, 1H), 3.23 (ddd, *J* = 4.3, 9.2, 10.9 Hz, 1H), 2.01-1.97 (m, 1H), 1.90-1.85 (m, 1H), 1.38-1.26 (m, 2H), 1.35 (d, *J* = 7.3 Hz, 3H), 1.15-1.04 (m, 2H), 0.71-0.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.3, 140.1, 135.4, 135.3, 132.2, 130.6, 129.6, 129.3, 128.5, 128.0, 127.8, 127.7, 127.2, 123.5, 70.5, 65.1, 45.6, 30.8, 25.1, 23.8, 22.9, 18.5; HRMS (CI+, $[M+NH_4]^+$) *m/z* calcd for $[C_{25}H_{30}NO_4S]^+$: 440.1896 found: 440.1898.

(–)-(*R*)-2-Phenyl-butyric Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (15). Diastereomerically pure (–)-15 was obtained by recrystallization from MeOH. $[\alpha]^{22}_D$ -65.4 (*c* 0.56, $CHCl_3$); mp 122 °C; R_f= 0.50 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2939, 1733, 1310, 1144, 1127, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, *J* = 1.2 Hz, 1H), 7.92-7.81 (m, 3H), 7.68-7.59 (m, 3H), 7.34-7.23 (m, 5H), 4.91 (td, *J* = 9.2, 4.4 Hz, 1H), 3.38 (ddd, *J* = 4.3, 9.1, 11.0 Hz, 1H), 3.15 (t, *J* = 7.6 Hz, 1H), 2.22-2.09 (m, 2H), 1.95-1.82 (m, 2H), 1.75-1.62 (m, 2H), 1.60-1.50 (m, 1H), 1.40-1.22 (m, 3H). 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.9, 138.5, 135.3, 135.2, 132.1, 130.5, 129.6, 129.3, 128.5, 128.4, 128.0, 127.6, 127.2, 123.5, 70.7, 65.2, 53.3, 30.9, 26.8, 25.2, 23.9, 22.9, 12.0; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{26}H_{28}NaO_4S]^+$: 459.1606 found: 459.1591.

(–)-(*R*)-2-Phenyl-pentanoic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (16). Diastereomerically pure (–)-16 was obtained by recrystallization from MeOH. $[\alpha]^{21}_D$ -57.0 (*c* 0.56, CHCl3); mp 111.5-112 °C; R_f= 0.48 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2956, 1733, 1310, 1144, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.68-7.65 (m, 2H), 7.61-7.58 (m, 1H), 7.33-7.30 (m, 2H), 7.27-7.23 (m, 3H), 4.90 (td, *J* = 9.3, 4.5 Hz, 1H), 3.39 (ddd, *J* = 10.9, 9.2, 4.3 Hz, 1H), 3.22 (t, *J* = 7.7 Hz, 1H), 2.23-2.20 (m, 1H), 2.13-2.11 (m, 1H), 1.84-1.78 (m, 2H), 1.69-1.61 (m, 2H), 1.60-1.50 (m, 1H), 1.39-1.26 (m, 3H). 1.13-1.06 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.0, 138.6, 135.3, 135.3, 132.1, 130.5, 129.6, 129.3, 128.5, 128.4, 128.0, 127.6, 127.2, 123.5, 70.7, 65.2, 51.3, 35.6, 30.9, 25.1, 23.9, 22.9, 20.6, 13.7; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{27}H_{30}NaO_4S]^+$: 473.1763 found: 473.1769.

(–)-(*R*)-2,3-Diphenyl-propionic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (17). Diastereomerically pure (–)-17 was obtained by recrystallization from EtOAc-MeOH. $[\alpha]^{22}_D$ -72.7 (*c* 0.65, $CHCl_3$); mp 159 °C; R_f= 0.50 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2938, 1732, 1494, 1306, 1204, 1147, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.21 (s, 1H), 7.88 (d, *J* = 6.5 Hz, 1H), 7.80-7.75 (m, 2H), 7.66 (td, *J* = 7.5, 0.9 Hz, 1H), 7.60-7.57 (m, 2H), 7.32-7.28 (m, 5H), 7.19-7.13 (m, 3H), 7.00-6.99 (m, 2H), 4.81 (td, *J* = 9.3, 4.4 Hz, 1H), 3.63 (dd, *J* = 7.1, 8.8 Hz, 1H), 3.28-3.23 (m, 2H), 2.99 (dd, *J* = 7.0, 13.6 Hz, 1H), 2.18-2.15 (m, 1H), 1.89-1.86 (m, 1H), 1.79-1.77 (m, 1H), 1.56-1.46 (m, 2H), 1.24-1.18 (m, 2H), 1.10-1.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.3, 138.6, 138.0, 135.3, 135.0, 132.1, 130.5, 129.6, 129.3, 129.2, 129.0, 128.6, 128.4, 128.2, 128.0, 127.6, 127.5, 126.4, 123.5, 70.8, 65.2, 53.4, 40.2, 30.5, 25.2, 23.8, 22.8; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{31}H_{30}NaO_4S]^+$: 521.1763 found: 521.1768.

(–)-(*R*)-2-Phenyl-pent-4-enoic Acid (1*R*, 2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (18). Diastereomerically pure (–)-18 was obtained by recrystallization from MeOH. $[\alpha]^{24}_D$ -62.5 (*c* 0.12, $CHCl_3$); mp 111-113 °C; R_f= 0.52 (EtOAc-hexanes 2:3); FTIR (film) ν 2939, 1734, 1310, 1144, 1127 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 8.41 (d, *J* = 1.4 Hz, 1H), 7.73 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.39-7.33 (m, 5H), 7.18-7.06 (m, 5H), 5.60 (tdd, *J* = 6.9, 10.2, 17.1 Hz, 1H), 5.11 (td, *J* = 9.3, 4.5 Hz, 1H), 4.94 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.87 (m, 1H), 3.49 (t, *J* = 7.7 Hz, 1H), 3.22 (ddd, *J* = 4.3, 9.2, 10.8 Hz, 1H), 2.79 (m, 1H), 2.47 (m, 1H), 2.05-1.94 (m, 2H), 1.37-1.27 (m, 3H), 1.12-1.02 (m, 2H), 0.72-0.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.3, 138.0, 135.3, 135.2, 135.0, 132.1, 130.5, 129.6, 129.3, 128.6, 128.4, 128.4, 128.0, 127.6, 127.4, 123.5, 117.1, 70.9, 65.2, 51.2, 37.7, 30.9, 25.2, 23.8, 22.9; HRMS (CI+, $[M+NH_4]^+$) *m/z* calcd for $[C_{27}H_{32}NO_4S]^+$: 466.2052 found: 466.2043.

(+)-(*S*)-2-(6-Methoxy-naphthalen-2-yl)-propionic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (19). (+)-12 (132 mg, 0.271 mmol) was dried azeotropically with $PhCH_3$ at 2 mm Hg. A pre-cooled (-78 °C) solution of this material in 4:1 DME-DMPU (2 mL) was added via cannula (dry ice jacket) to a stirred solution of Ph_3CK (76.5 mg, 0.271 mmol) in 4:1 DME-DMPU (4.75 mL) at -78 °C. An additional volume of 4:1 DME-DMPU (0.75 mL) was used to transfer via cannula residual substrate into the reaction flask. After stirring for 15 min, a solution of MeI (0.042 mL, 0.68 mmol, EM Science) in DME (0.1 mL) was introduced into the reaction mixture via syringe down the wall of the flask. The reaction mixture lost color within 30 sec and sat. aq. NH_4Cl (3 mL) was immediately added. The mixture was allowed to warm up to room temperature and the organic solvents were evaporated *in vacuo*. The residue was partitioned between water (30 mL) and EtOAc (100 mL). The organic phase was separated, washed with brine (30 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the crude product of ca. 95% de (^1H NMR analysis). Silica gel chromatography (EtOAc-hexanes gradient) gave the inseparable diastereomeric mixture (166 mg, 90% yield). Diastereomerically pure (+)-19 was obtained by recrystallization from EtOAc-MeOH. $[\alpha]^{24}_D$ +45.2 (*c* 0.50, $CHCl_3$); mp 153-154 °C; R_f= 0.32 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2939, 1732, 1607, 1310, 1144, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), 7.90-7.81 (m, 3H), 7.73-7.64 (m, 4H), 7.58-7.55 (m, 2H), 7.36 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.15-7.11 (m, 2H), 5.00 (td, *J* = 9.3, 4.5 Hz, 1H), 3.91 (s, 3H), 3.51 (q, *J* = 7.2 Hz, 1H), 3.40 (ddd, *J* = 4.3, 9.2,

11.0 Hz, 1H), 2.21-2.17 (m, 1H), 2.10-2.07 (m, 1H), 1.83-1.80 (m, 1H), 1.66-1.52 (m, 2H), 1.42 (d, *J* = 7.3 Hz, 3H), 1.38-1.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.4, 157.7, 135.5, 135.3, 135.2, 133.8, 132.1, 130.5, 129.6, 129.4, 129.3, 129.3, 128.9, 128.0, 127.6, 127.0, 126.6, 126.2, 123.5, 118.9, 105.7, 70.6, 65.2, 55.4, 45.5, 30.8, 25.1, 23.8, 22.9, 18.6; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{30}H_{30}NaO_5S]^+$: 525.1712 found: 525.1710.

(+)-(*S*)-2-(4-Isobutyl-phenyl)-propionic Acid (1*S*, 2*S*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (20). Diastereomerically pure (+)-20 was obtained by recrystallization from MeOH. $[\alpha]^{24}_D$ +53.3 (*c* 0.67, $CHCl_3$); mp 115-116 °C; R_f= 0.50 (*t*-BuOMe-hexanes 1:1); FTIR (film) ν 2952, 1734, 1311, 1145, 1127 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 8.49 (d, *J* = 1.1 Hz, 1H), 7.81 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.44-7.40 (m, 3H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.19-7.09 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.16 (td, *J* = 9.1, 4.5 Hz, 1H), 3.49 (q, *J* = 7.2 Hz, 1H), 3.25 (ddd, *J* = 4.3, 9.0, 10.6 Hz, 1H), 2.32 (d, *J* = 7.2 Hz, 2H), 2.01-1.90 (m, 2H), 1.72 (m, 1H), 1.38 (d, *J* = 7.3 Hz, 3H), 1.35-1.30 (m, 2H), 1.13-1.08 (m, 2H), 0.82 (d, *J* = 1.8 Hz, 3H), 0.80 (d, *J* = 1.8 Hz, 3H), 0.74-0.67 (m, 2H); ^{13}C NMR (CD_2Cl_2, 126 MHz) δ 173.6, 141.0, 137.9, 136.2, 135.7, 132.6, 130.6, 129.8, 129.6, 129.6, 129.5, 128.3, 128.0, 127.8, 123.7, 70.6, 65.3, 45.5, 45.3, 31.1, 30.6, 25.3, 24.1, 23.2, 22.5, 18.6; HRMS (FAB+, $[M+Na]^+$) *m/z* calcd for $[C_{29}H_{34}NaO_4S]^+$: 501.2076 found: 501.2063.

General Protocol for the Preparation of Samples of Racemic Methyl Esters 21 to 27 for Chiral HPLC Analysis. The appropriate methyl ester [methyl phenylacetate, methyl 6-(methoxyphenyl)naphthylacetate or 4-(isobutylphenyl)acetate] was added to a solution of KHMDS (0.5 M in $PhCH_3$, 1 equiv, Aldrich) in DME-DMPU (4:1) at -78 °C. The enolate was stirred for 30 min to 1 h and the electrophile was added (MeI, EtI, *n*-PrI, BnBr or Allyl Br). The reaction mixture was stirred at -78 °C for 15 to 30 min and then allowed to warm to room temperature. Quenching with sat. aq. NH_4Cl, followed by aqueous work-up and silica gel chromatography gave the racemic methyl esters 21 to 27. For HPLC conditions, see below the corresponding enantiomerically enriched product.

General Protocol for the Acid Catalyzed Methanolysis of Products 14 to 20. A solution of the α-alkylated product (diastereomeric mixture) in MeOH and $MeSO_3H$ (ca. 4 M, 50-200 equiv, Aldrich) was heated at reflux until TLC showed that transesterification was complete. The reaction mixture was allowed to cool to room temperature and then poured into sat. aq. $NaHCO_3$. The products were extracted into CH_2Cl_2 and the combined organic layers were washed with water and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo*, followed by silica gel chromatography (ether-pentane or *t*-BuOMe-hexanes for 26) gave the methyl esters 21 to 27. Continued elution (EtOAc-hexanes) gave the chiral auxiliary (+)- or (–)-2.

(–)-(*R*)-2-Phenyl-propionic Acid Methyl Ester 21. Oil, $[\alpha]^{18}_D$ -81.6 (*c* 1.54, $CHCl_3$); lit.: $[\alpha]_D$ -96 ($CHCl_3$) for *R* enantiomer;[1] 92% ee, determined by using a Chiralcel OJ column, 5% *i*-PrOH in hexanes as eluent at a flow rate of 0.8 mL/min, detection wavelength of 230 nm with elution times t_{minor} = 11 min, t_{major} = 14.5 min.

(–)-(*R*)-2-Phenyl-butyric Acid Methyl Ester (22). Oil, $[\alpha]^{25}_D$ -78.3 (*c* 1.51, $CHCl_3$); lit.: $[\alpha]^{19}_D$ +82.3 (*c* 1.0, $CHCl_3$) for *S* enantiomer;[2] 96% ee, determined by using a Chiralcel OD column (Daicel Chemical Industries, Ltd.), 0.5% *i*-PrOH in hexanes as eluent at a flow rate of 0.7 mL/min, detection wavelength of 230 nm with elution times t_{major} = 8 min, t_{minor} = 9.5 min.

(–)-(*R*)-2-Phenyl-pentanoic Acid Methyl Ester (23). Oil, $[\alpha]^{25}_D$ -65.0 (*c* 1.55, $CHCl_3$); lit.: $[\alpha]^{23}_D$ -72 (*c* 2.11, MeOH) for *R* enantiomer;[3] 95% ee, determined by using a Chiralcel OD column, 4% *t*-BuOMe in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 230 nm with elution times t_{major} = 9.5 min, t_{minor} = 12 min.

(–)-(*R*)-2,3-Diphenyl-propionic Acid Methyl Ester (24). Oil, $[\alpha]^{23}_D$ -101.5 (*c* 2.28, $CHCl_3$); lit.: $[\alpha]^{23}_D$ +123.9 (*c* 0.223, $CHCl_3$) for *S* enantiomer;[4] 90% ee, determined by using a Chiralcel OD column, 0.5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 230 nm with elution times t_{major} = 11 min, t_{minor} = 13.5 min.

(–)-(*R*)-2-Phenyl-pent-4-enoic Acid Methyl Ester 25.[5] Oil, $[\alpha]^{25}_D$ -89.0 (*c* 1.49, $CHCl_3$); 95% ee, determined by using a Chiralcel OD column, 4% *t*-BuOMe in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 230 nm with elution times t_{major} = 13 min, t_{minor} = 15 min.

(+)-(*S*)-2-(6-Methoxy-naphthalen-2-yl)-propionic Acid Methyl Ester (26). Oil, $[\alpha]^{24}_D$ +72.5 (*c* 0.69, $CHCl_3$); lit.: $[\alpha]_D$ +75.0 ($CHCl_3$) for *S* enantiomer;[6] 94% ee, determined by using a Chiralcel OD column, 1% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection wavelength of 230 nm with elution times t_{minor} = 10.5 min, t_{major} = 12.5 min.

(+)-(*S*)-2-(4-Isobutyl-phenyl)-propionic Acid Methyl Ester (27). Oil, $[\alpha]^{26}_D$ +59.4 (*c* 0.99, $CHCl_3$); lit.: $[\alpha]_D$ +63.6 ($CHCl_3$) for *S* enantiomer;[33] 93% ee, determined by using a Chiralcel OJ column, 1% *i*-PrOH in hexanes as eluent at a flow rate of 0.8 mL/min, detection wavelength of 230 nm with elution times t_{major} = 11 min, t_{minor} = 13.5 min.

(–)-(*R*)-2-Phenyl-pent-4-enoic Acid Isopropyl Ester (28). To a stirred solution of 18 (95.0 mg, 0.212 mmol, 95% de) in *i*-PrOH (2 mL, HPLC grade) was added Ti(*i*-PrO)$_4$ (0.300 mL, 1.02 mmol) and the reaction mixture was stirred at 85 °C for 27 h, then allowed to cool to room temperature and poured into 1 M aq. HCl (30 mL). The products were extracted into ether (2 X 60 mL). The combined organic layers were washed with water (60 mL), sat. aq. $NaHCO_3$ (60 mL), brine (60 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* followed by silica gel chromatography (ether-pentane 15:85) gave the isopropyl ester (–)-28 as a colorless liquid (44.1 mg, 95% yield). $[\alpha]^{20}_D$ -43.4 (*c* 0.70, $CHCl_3$); R_f= 0.46 (ether-pentane 1:9); FTIR (film) ν 2360, 1731, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.24 (m, 5H), 5.73 (dddd, *J* = 6.8, 10.2, 13.6, 17.0 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.02-4.96 (m, 2H), 3.59 (dd, *J* = 6.7, 8.8 Hz, 1H), 2.85-2.78 (m, 1H), 2.53-2.45 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.0, 138.9, 135.4, 128.6, 127.9, 127.2, 116.9, 68.1, 51.7, 37.7, 21.9, 21.6; HRMS (EI+) *m/z* calcd for $[C_{14}H_{18}O_2]^+$:

218.1307 found: 218.1309. 95% ee, determined by using a Chiralcel OJ column, 0.2 % *i*-PrOH in hexanes as eluent, a flow rate of 1 mL/min, detection wavelength of 230 nm with elution times t_{major} = 7 min, t_{minor} = 8 min. Continued elution (ether-pentane 4:1) gave the chiral auxiliary (-)-2 (55.8 mg, 91% yield) as a colorless solid.

References:

(1) Miyamoto, K.; Tsuchiya, S.; Ohta, H. *J. Fluorine Chem.* **1992**, *59*, 225.

(2 Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1992**, *57*, 2166.

(3) Kawazu, K.; Fujita, T.; Mitsui, T. *J. Am. Chem. Soc.* **1959**, *81*, 932.

(4) Berova, N.; Kurtev, B.J. *Tetrahedron* **1969**, *25*, 2301.

(5) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825.

(6) Svoboda, J.; Capek, K.; Palecek, J. *Collect. Czech. Chem. Commun.* **1987**, *52*, 766.