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Highly Enantioselective Desymmetrization of Anhydrides by Carbon Nucleophiles: Reactions of Grignard Reagents in the Presence of (–)-Sparteine

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I. General

All air- and moisture-sensitive manipulations were carried out under argon with standard Schlenk techniques.

THF was distilled from sodium benzophenone ketyl under nitrogen. Toluene was purified by passing through a neutral alumina column under argon.

(–)-Sparteine (Aldrich), (1*S*, 2*S*)-(+)-*N*-methylpseudoephedrine (Aldrich), (*R*)-(+)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) (Aldrich), and (+)-quinidine (Avocado) were used without purification. (1*R*, 2*R*)-1,2-Dimethoxy-1,2-diphenylethane was prepared according to a literature procedure.[1]

Phenylmagnesium chloride (2.0 M in THF; Aldrich), 4-methoxyphenylmagnesium bromide (0.5 M in THF; Aldrich), 4-fluorophenylmagnesium bromide (2.0 M in Et_2O;

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(1) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351–9357.

Aldrich), and *o*-tolylmagnesium chloride (1.0 M in THF; Aldrich) were used as received.

3-Phenylglutaric anhydride[2] and 3-isopropylglutaric anhydride[3] were prepared by literature procedures. *o*-Tolualdehyde (Avocado), 3-thiophenemalonic acid (Acros), diethyl benzylmalonate (Aldrich), diethyl propylmalonate (Aldrich), diethyl isobutylmalonate (TCI), diethyl *tert*-butylmalonate (Aldrich), 3-(*tert*-butyldimethylsilyloxy)glutaric anhydride (Aldrich), and 1,3-cyclohexanedicarboxylic acid (Aldrich, mixture of *cis* and *trans*) were used as received.

All the other chemicals and solvents were purchased from Aldrich, Mallinckrodt, EM Science, or J. T. Baker and used as received.

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(2) Tokoroyama, T.; Kusaka, H. *Can. J. Chem.* **1996**, *74*, 2487–2502.

(3) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142–146.

II. Synthesis of Anhydrides

The yields have not been optimized.

3-(*o*-Tolyl)glutaric anhydride (Table 3, entry 2). This was prepared by the literature procedure for the synthesis of 3-isopropylglutaric anhydride,[3] starting with *o*-tolualdehyde, in 13% overall yield. Pale-yellow solid.

^{1}H NMR ($CDCl_3$): δ 7.29-7.22 (m, 3H), 7.11-7.09 (m, 1H), 3.68-3.58 (m, 1H), 3.05 (dd, $^2J_{HH}$ = 17.4 Hz and $^3J_{HH}$ = 4.5 Hz, 2H), 2.83 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 11.4 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.3, 137.3, 135.8, 131.5, 128.1, 127.3, 124.3, 36.8, 30.2, 19.5. FTIR (neat) 3066, 3022, 2974, 2922, 1813, 1761, 1493, 1463, 1420, 1409, 1373, 1282, 1248, 1209, 1175, 1096, 1071, 952, 760 cm^{-1}. M.p. 106-109 °C. HRMS (EI) calcd for $C_{12}H_{12}O_3$ (M^+) 204.0781, found 204.0776.

3-Propylglutaric anhydride (Table 3, entry 5) (CAS registry number: 4166-54-5). Diethyl propylmalonate (4.1 mL, 20 mmol) in Et_2O (20 mL) was added to $LiAlH_4$ (1.52 g, 40.0 mmol) in Et_2O (30 mL) at 0 °C. The mixture was stirred for 7 h at room temperature and then quenched with water. The white precipitate was removed by filtration, and the solvent was removed under vacuum to afford 2.07 g (88%) of 2-propyl-1,3-propanediol (CAS registry number: 2612-28-4) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 3.82 (dd, $^2J_{HH}$ = 10.7 Hz and $^3J_{HH}$ = 3.9 Hz, 2H), 3.65 (dd, $^2J_{HH}$ = 10.7 Hz and $^3J_{HH}$ = 7.7 Hz, 2H), 2.33 (br s, 2H), 1.83-1.76 (m, 1H), 1.40-1.29 (m, 2H), 1.27-1.17 (m, 2H), 0.92 (t, $^3J_{HH}$ = 6.9 Hz, 3H).

n-BuLi (1.61 M solution in hexane; 22.0 mL, 35.4 mmol) was added to a solution of 2-propyl-1,3-propanediol (2.02 g, 17.1 mmol) in THF (60 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, and then a solution of *p*-toluenesulfonyl chloride (6.70 g, 35.1 mmol) in THF (20 mL) was added to it by cannula. The mixture was stirred for 18.5 h at room temperature, and then the solvent was removed. DMSO (30 mL) and NaCN (3.36

g, 68.6 mmol) were added to the residual white solid, and the mixture was stirred for 17.5 h at 75 °C. After cooling to room temperature, water was added to the reaction mixture, which was extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (Et_2O / hexane = 3 / 1) to afford 1.22 g (52% from 2-propyl-1,3-propanediol) of 3-propylpentanedinitrile as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 2.62-2.46 (m, 4H), 2.20-2.11 (m, 1H), 1.59-1.51 (m, 2H), 1.43-1.35 (m, 2H), 0.97 (t, $^3J_{HH}$ = 7.2 Hz, 3H).

NaOH (6 N, aqueous; 12 mL) was added to a solution of 3-propylpentanedinitrile (1.20 g, 8.81 mmol) in MeOH (36 mL), and the resulting mixture was refluxed for 14 h. After removing the MeOH, the residue was acidified with HCl (6 N, aqueous) and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a pale-yellow oil. Ac_2O (8 mL) was added to this oil, and the mixture was stirred for 21 h at 125 °C. The volatiles were removed, and the residue was distilled under reduced pressure to afford 1.03 g of 3-propylglutaric anhydride as a colorless oil (6.61 mmol, 34% overall yield).

^{1}H NMR ($CDCl_3$): δ 2.88 (dd, $^2J_{HH}$ = 17.4 Hz and $^3J_{HH}$ = 4.5 Hz, 2H), 2.42 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 10.2 Hz, 2H), 2.24-2.09 (m, 1H), 1.45-1.34 (m, 4H), 0.94 (t, $^3J_{HH}$ = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 166.7, 36.8, 36.2, 28.6, 19.7, 13.9.

3-(3-Thiophene)glutaric anhydride (Table 3, entry 3) (CAS registry number: 154227-48-2). Synthesized from 3-thiophenemalonic acid, according to the procedure described for 3-propylglutaric anhydride. White solid, 8% overall yield.

^{1}H NMR ($CDCl_3$): δ 7.41-7.38 (m, 1H), 7.09 (s, 1H), 7.00-6.99 (m, 1H), 3.59-3.02 (m, 1H), 3.14 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 4.4 Hz, 2H), 2.90 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 9.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 166.0, 140.2, 127.8, 125.8, 121.1, 37.0, 29.9.

3-Benzylglutaric anhydride (Table 3, entry 4) (CAS registry number: 91963-19-8).

Synthesized from diethyl benzylmalonate, according to the procedure described for 3-propylglutaric anhydride. White solid, 13% overall yield.

^{1}H NMR ($CDCl_3$): δ 7.36-7.24 (m, 3H), 7.18-7.11 (m, 2H), 2.84-2.78 (m, 2H), 2.70-2.67 (m, 2H), 2.50-2.41 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 166.4, 136.9, 129.1, 129.1, 127.3, 40.7, 35.7, 30.7.

3-Isobutylglutaric anhydride (Table 3, entry 6) (CAS registry number: 185815-59-2). Synthesized from diethyl isobutylmalonate, according to the procedure described for 3-propylglutaric anhydride. Colorless oil, 37% overall yield.

^{1}H NMR ($CDCl_3$): δ 2.74-2.65 (m, 2H), 2.29-2.19 (m, 3H), 1.71-1.62 (m, 1H), 1.30-1.24 (m, 2H), 0.91 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 173.2, 44.3, 38.2, 28.2, 25.0, 22.7.

3-(*tert*-Butyl)glutaric anhydride (Table 3, entry 8) (CAS registry number: 145610-08-8). Synthesized from diethyl *tert*-butylmalonate, according to the procedure described for 3-propylglutaric anhydride. White solid, 30% overall yield.

^{1}H NMR ($CDCl_3$): δ 2.93-2.86 (m, 2H), 2.42-2.32 (m, 2H), 1.99-1.87 (m, 1H), 0.95 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 167.3, 38.9, 32.5, 32.2, 26.6.

***cis*-1,3-Cyclohexanedicarboxylic anhydride (eq 2)** (CAS registry number: 4355-31-1). 1,3-Cyclohexanedicarboxylic acid (mixture of cis and trans; 2.00 g, 11.6 mmol) in acetic anhydride (20 mL) was stirred for 15 h at 120 °C. The solvent was removed under vacuum, and the residual white solid was dissolved in CH_2Cl_2, filtered, and concentrated. The residue was distilled under vacuum to afford 1.01 g of a white solid (6.57 mmol, 57% yield).

^{1}H NMR ($CDCl_3$): δ 3.08-3.06 (m, 2H), 2.29-2.21 (m, 1H), 2.15-2.09 (m, 2H), 1.88-1.72 (m, 4H), 1.59-1.43 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 170.2, 36.6, 28.8, 27.5, 20.2.

III. Enantioselective Desymmetrization Reactions

Because the yields that are reported in the paper are the average of two runs, the yields that are given below for a specific experiment may differ from the values in the paper.

General procedure for Table 1. A solution of 3-phenylglutaric anhydride (76.1 mg, 0.40 mmol) in toluene (2.5 mL) was added by syringe to a mixture of the chiral ligand (0.40 mmol) and PhMgCl (2.0 M solution in THF; 200 μL, 0.40 mmol) in toluene (1.5 mL) at –78 °C. The reaction mixture was stirred for 9 h at –78 °C, and then it was quenched with NH_4Cl (saturated, aqueous; 1 mL). NaOH (2 N, aqueous; 4 mL) was added to the mixture, and the aqueous layer was washed with Et_2O. The aqueous layer was acidified with HCl (6 N, aqueous) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (acetone / hexane = 3 / 2) to afford 5-oxo-3,5-diphenylpentanoic acid (CAS registry number: 5456-53-1) as a white solid.

^{1}H NMR (acetone-d_6): δ 8.00-7.96 (m, 2H), 7.62-7.57 (m, 1H), 7.52-7.46 (m, 2H), 7.38-7.34 (m, 2H), 7.29-7.23 (m, 2H), 7.18-7.12 (m, 1H), 3.88-3.80 (m, 1H), 3.48 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 2.85 (dd, $^2J_{HH}$ = 16.0 Hz and $^3J_{HH}$ = 6.7 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.8 Hz and $^3J_{HH}$ = 8.3 Hz, 1H). ^{13}C NMR (acetone-d_6): δ 198.7, 173.3, 145.0, 138.1, 133.8, 129.5, 129.2, 128.9, 128.6, 127.3, 45.1, 40.9, 38.4.

Ee analysis of the methyl ester. 1,3-Dicyclohexylcarbodiimide (26.8 mg, 0.13 mmol) was added to a mixture of 5-oxo-3,5-diphenylpentanoic acid (26.8 mg, 0.10 mmol), 4-dimethylaminopyridine (6.0 mg, 4.9 μmol), and methanol (41 μL, 1.01 mmol) in THF (1.0 mL) / CH_2Cl_2 (2.0 mL) at 0 °C. This was stirred for 3 h at room temperature, and then the solvent was removed under vacuum. The residue was chromatographed on silica gel (hexane / Et_2O = 2 / 1) to afford methyl 5-oxo-3,5-diphenylpentanoate (CAS

registry number: 77565-69-6) as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.94-7.90 (m, 2H), 7.57-7.52 (m, 1H), 7.47-7.41 (m, 2H), 7.32-7.17 (m, 5H), 3.93-3.84 (m, 1H), 3.59 (s, 3H), 3.41 (dd, $^{2}J_{HH}$ = 17.1 Hz and $^{3}J_{HH}$ = 7.2 Hz, 1H), 3.33 (dd, $^{2}J_{HH}$ = 16.8 Hz and $^{3}J_{HH}$ = 7.2 Hz, 1H), 2.82 (dd, $^{2}J_{HH}$ = 15.6 Hz and $^{3}J_{HH}$ = 7.2 Hz, 1H), 2.69 (dd, $^{2}J_{HH}$ = 15.3 Hz and $^{3}J_{HH}$ = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 198.4, 172.5, 143.5, 137.0, 133.3, 128.83, 128.79, 128.3, 127.5, 127.0, 51.8, 44.7, 40.7, 37.6.

The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 95 : 5, flow = 1 mL / min. Retention times: 14.6 min [(*R*)-enantiomer], 18.5 min [(*S*)-enantiomer].

General procedure for Table 2. A solution of 3-phenylglutaric anhydride (76.1 mg, 0.40 mmol) in toluene (2.5 mL) was added by syringe to a mixture of (–)-sparteine (120 μL, 0.52 mmol) and the Grignard reagent (0.52 mmol) in toluene (1.5 mL) at –78 °C. The reaction mixture was stirred for 24 h at –78 °C, and then it was quenched with NH_4Cl (saturated, aqueous; 1 mL). NaOH (2 N, aqueous; 4 mL) was added to the mixture, and the aqueous layer was washed with Et_2O. The aqueous layer was acidified with HCl (6 N, aqueous) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (acetone / hexane = 3 / 2) to afford the 5-aryl-5-oxo-3-phenylpentanoic acid.

(*S*)-(+)-5-Oxo-3,5-diphenylpentanoic acid (Table 2, entry 1) (CAS registry number: 5456-53-1). White solid; 91% yield. $[\alpha]^{20}_{D}$ +14.7 (*c* 1.00, CH_2Cl_2).

For ee analysis, the acid was derivatized to its methyl ester (white solid). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 95 : 5, flow = 1 mL / min. Retention times: 14.6 min [(*R*)-enantiomer], 18.5 min [(*S*)-enantiomer]. 92% ee. $[\alpha]^{20}_{D}$ +1.8 (*c* 0.85, $CHCl_3$).

The absolute configuration of this ester was determined by comparison of the optical

rotation with a literature value.[4]

(*S*)-(+)-5-Oxo-3-phenyl-5-(4-methoxyphenyl)pentanoic acid (Table 2, entry 2). The general procedure was followed, except that the THF of the 4-methoxyphenylmagnesium bromide solution (purchased as a THF solution from Aldrich) was removed under vacuum in the presence of toluene, before the reaction was started. White solid; 88% yield. $[\alpha]^{20}_{D}$ +17.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 7.99-7.94 (m, 2H), 7.37-7.34 (m, 2H), 7.28-7.23 (m, 2H), 7.17-7.12 (m, 1H), 7.01-6.96 (m, 2H), 3.86 (s, 3H), 3.89-3.80 (m, 1H), 3.47-3.33 (m, 2H), 2.84 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 7.8 Hz, 1H). ^{13}C NMR (acetone-d_6): δ 197.1, 173.4, 164.4, 145.1, 131.1, 129.2, 128.6, 127.2, 114.6, 55.9, 44.8, 40.9, 38.5. FTIR (neat) 3197, 3030, 2967, 2929, 2875, 1734, 1698, 1677, 1602, 1575, 1511, 1496, 1455, 1420, 1374, 1263, 1219, 1181, 1108, 1082, 1065, 1020, 989, 845, 813, 762, 698 cm^{-1}. M.p. 139-140 °C. HRMS (EI) calcd for $C_{18}H_{18}O_4$ (M^+) 298.1200, found 298.1206.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its (–)-menthyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 95 : 5, flow = 1 mL / min. Retention times: 14.6 min [(*S*)-enantiomer], 19.5 min [(*R*)-enantiomer]. 89% ee. $[\alpha]^{20}_{D}$ –29.7 (*c* 1.02, $CHCl_3$).

^{1}H NMR ($CDCl_3$): (major diastereomer) δ 7.93-7.88 (m, 2H), 7.30-7.24 (m, 4H), 7.22-7.15 (m, 1H), 6.93-6.88 (m, 2H), 4.62-4.54 (m, 1H), 3.91-3.81 (m, 1H), 3.85 (s, 3H), 3.31 (dd, $^2J_{HH}$ = 16.2 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 3.25 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 7.2 Hz, 1H),

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(4) Díaz-Ortiz, A.; Díez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 259–263.

2.81 (dd, $^2J_{HH}$ = 15.3 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 8.4 Hz, 1H), 1.76-1.22 (m, 7H), 1.02-0.73 (m, 2H), 0.83 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 0.80 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 0.61 (d, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): (major diastereomer) δ 197.0, 171.8, 163.6, 143.4, 130.6, 130.2, 128.7, 127.6, 126.9, 113.9, 74.4, 55.7, 47.0, 44.8, 41.0, 40.8, 38.0, 34.3, 31.5, 26.0, 23.3, 22.1, 21.0, 16.2. FTIR (neat) 3062, 3029, 2955, 2869, 1724, 1676, 1601, 1576, 1510, 1455, 1419, 1369, 1311, 1260, 1221, 1170, 1148, 1081, 1029, 987, 834, 762, 699 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{36}O_4$ (M^+) 436.2608, found 436.2627.

(*S*)-(+)-5-Oxo-3-phenyl-5-(4-fluorophenyl)pentanoic acid (Table 2, entry 3). White solid; 81% yield. $[\alpha]^{20}_D$ +8.6 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.10-8.03 (m, 2H), 7.38-7.34 (m, 2H), 7.29-7.13 (m, 5H), 3.90-3.80 (m, 1H), 3.48 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 2.85 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.70 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 8.1 Hz, 1H). ^{13}C NMR (acetone-d_6): δ 197.3, 173.4, 166.4 (d, $^1J_{CF}$ = 252.1 Hz), 144.9, 134.8 (d, $^4J_{CF}$ = 2.9 Hz), 131.8 (d, $^3J_{CF}$ = 9.4 Hz), 129.2, 128.6, 127.3, 116.3 (d, $^2J_{CF}$ = 22.0 Hz), 45.0, 40.9, 38.4. FTIR (neat) 3064, 3030, 2918, 1707, 1684, 1598, 1506, 1496, 1454, 1410, 1369, 1297, 1276, 1232, 1156, 1082, 991, 836, 762, 700 cm^{-1}. M.p. 104-107 °C. HRMS (EI) calcd for $C_{17}H_{15}FO_3$ (M^+) 286.1000, found 286.1014.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99.4 : 0.6, flow = 1 mL / min. Retention times: 48.5 min [(*R*)-enantiomer], 52.0 min [(*S*)-enantiomer]. 80% ee. $[\alpha]^{20}_D$ –1.2 (*c* 0.88, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.98-7.91 (m, 2H), 7.30-7.17 (m, 5H), 7.14-7.07 (m, 2H), 3.91-3.82 (m, 1H), 3.59 (s, 3H), 3.39 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 3.30 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.82 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.3 Hz and $^3J_{HH}$ = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 196.8, 172.5, 165.9 (d, $^1J_{CF}$ = 254.8

Hz), 143.3, 133.4 (d, $^4J_{CF}$ = 2.9 Hz), 130.9 (d, $^3J_{CF}$ = 9.3 Hz), 128.8, 127.5, 127.1, 115.9 (d, $^2J_{CF}$ = 21.7 Hz), 51.8, 44.6, 40.7, 37.7. FTIR (neat) 3029, 2952, 2849, 1734, 1684, 1597, 1506, 1436, 1410, 1364, 1268, 1228, 1156, 1081, 1012, 836, 762, 700 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{17}FO_3$ (M^+) 300.1156, found 300.1165.

(*S*)-(+)-5-Oxo-3-phenyl-5-(*o*-tolyl)pentanoic acid (Table 2, entry 4). White solid; 69% yield. $[\alpha]^{20}_D$ +2.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 10.61 (br s, 1H), 7.70-7.68 (m, 1H), 7.39-7.14 (m, 8H), 3.84-3.74 (m, 1H), 3.44 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 3.32 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 8.7 Hz, 1H), 2.82(dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 8.1 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (acetone-d_6): δ 203.2, 173.3, 144.7, 139.4, 138.2, 132.5, 131.9, 129.2, 128.6, 127.3, 126.6, 48.2, 40.9, 38.8, 20.9. FTIR (neat) 3062, 3029, 2965, 2926, 1707, 1685, 1601, 1570, 1495, 1454, 1412, 1295, 1269, 1220, 1156, 1080, 1030, 982, 756, 700 cm^{-1}. M.p. 114-116 °C. HRMS (EI) calcd for $C_{18}H_{18}O_3$ (M^+) 282.1250, found 282.1237.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 95 : 5, flow = 1 mL / min. Retention times: 12.4 min [(*R*)-enantiomer], 15.7 min [(*S*)-enantiomer]. 38% ee. $[\alpha]^{20}_D$ –0.4 (*c* 0.92, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.57-7.54 (m, 1H), 7.37-7.16 (m, 8H), 3.87-3.77 (m, 1H), 3.60 (s, 3H), 3.35 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.23 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 2.77 (dd, $^2J_{HH}$ = 15.3 Hz and $^3J_{HH}$ = 7.2 Hz, 1H), 2.67 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 202.7, 172.5, 143.2, 138.3, 138.1, 132.1, 131.4, 128.8, 128.4, 127.6, 127.0, 125.8, 51.8, 47.6, 40.9, 38.0, 21.1. FTIR (neat) 3063, 3027, 2952, 2917, 2849, 1733, 1683, 1600, 1570, 1494, 1453, 1435, 1366, 1261, 1216, 1152,

1080, 1029, 754, 699 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{20}O_3$ (M^+) 296.1407, found 296.1403.

General procedure for Table 3 and eq 2. A solution of the anhydride (0.40 mmol) in toluene (2.5 mL) was added by syringe to a mixture of (–)-sparteine (120 μL, 0.52 mmol) and PhMgCl (2.0 M solution in THF; 260 μL, 0.52 mmol) in toluene (1.5 mL) at –78 °C. The reaction mixture was stirred for 24 h at –78 °C, and then it was quenched with NH_4Cl (saturated, aqueous; 1 mL). NaOH (2 N, aqueous; 4 mL) was added to the mixture, and the aqueous layer was washed with Et_2O. The aqueous layer was acidified with HCl (6 N, aqueous) and extracted with Et_2O or EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (acetone / hexane = 4 / 3 or 3 / 2) to afford the 3-substituted 5-oxo-5-phenylpentanoic acid.

(*S*)-(+)-5-Oxo-3-(*o*-tolyl)-5-phenylpentanoic acid (Table 3, entry 2). Pale-yellow oil; 87% yield. $[\alpha]^{20}_D$ +22.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 7.99-7.96 (m, 2H), 7.61-7.55 (m, 1H), 7.50-7.45 (m, 2H), 7.40-7.37 (m, 1H), 7.15-7.10 (m, 2H), 7.06-7.01 (m, 1H), 4.22-4.13 (m, 1H), 3.52 (dd, $^2J_{HH}$ = 17.4 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 3.42 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.82 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.71 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (acetone-d_6): δ 198.9, 173.6, 143.3, 138.1, 137.0, 133.8, 131.1, 129.4, 128.8, 127.0, 126.9, 126.6, 45.0, 40.7, 33.1, 20.0. FTIR (neat) 3062, 3023, 2969, 2918, 1707, 1684, 1597, 1579, 1491, 1448, 1411, 1362, 1276, 1214, 1180, 1158, 1001, 990, 754, 727, 689 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}NaO_3$ (M^+ + Na) 305.1154, found 305.1141.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 95 : 5, flow = 1 mL / min. Retention times: 11.8 min [(*R*)-enantiomer], 21.6 min [(*S*)-

enantiomer]. 84% ee. $[\alpha]^{20}_{D}$ +12.7 (*c* 0.85, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.93-7.90 (m, 2H), 7.57-7.52 (m, 1H), 7.46-7.41 (m, 2H), 7.21-7.06 (m, 4H), 4.21-4.11 (m, 1H), 3.58 (s, 3H), 3.39 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.32 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 7.2 Hz, 1H), 2.78 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 7.2 Hz, 1H), 2.67 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 198.4, 172.6, 141.8, 137.0, 136.2, 133.3, 130.9, 128.8, 128.2, 126.6, 126.4, 125.6, 51.8, 44.5, 40.4, 32.5, 19.9. FTIR (neat) 3062, 3021, 2951, 2917, 2849, 1734, 1684, 1597, 1579, 1491, 1447, 1436, 1361, 1267, 1208, 1153, 1109, 1001, 753, 727, 689 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NaO_3$ (M^+ + Na) 319.1310, found 319.1302.

(*S*)-(+)-5-Oxo-3-(3-thiophene)-5-phenylpentanoic acid (Table 3, entry 3). White solid; 76% yield. $[\alpha]^{20}_{D}$ +4.6 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.01-7.97 (m, 2H), 7.62-7.56 (m, 1H), 7.52-7.46 (m, 2H), 7.35-7.32 (m, 1H), 7.22-7.21 (m, 1H), 7.16-7.14 (m, 1H), 4.06-3.96 (m, 1H), 3.47 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 2.83 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.71 (dd, $^2J_{HH}$ = 15.9 Hz and $^3J_{HH}$ = 8.1 Hz, 1H). ^{13}C NMR (acetone-d_6): δ 198.8, 173.5, 145.8, 138.1, 133.8, 129.5, 128.9, 128.2, 126.2, 121.3, 44.9, 40.7, 33.6. FTIR (neat) 3084, 3057, 2957, 2919, 1695, 1681, 1596, 1578, 1448, 1412, 1363, 1272, 1226, 1214, 1161, 1064, 990, 950, 909, 861, 781, 754, 686, 646 cm^{-1}. M.p. 120-122 °C. HRMS (EI) calcd for $C_{15}H_{14}O_3S$ (M^+) 274.0658, found 274.0652.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 98 : 2, flow = 1 mL / min. Retention times: 27.8 min [(*R*)-enantiomer], 30.8 min [(*S*)-enantiomer]. 91% ee. $[\alpha]^{20}_{D}$ +0.4 (*c* 1.03, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.95-7.91 (m, 2H), 7.58-7.53 (m, 1H), 7.47-7.42 (m, 2H), 7.26-7.23 (m, 1H), 7.07-7.00 (m, 2H), 4.08-3.98 (m, 1H), 3.61 (s, 3H), 3.40 (dd, $^2J_{HH}$ = 16.8 Hz and

$^3J_{HH}$ = 6.9 Hz, 1H), 3.31 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.80 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.69 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 198.4, 172.5, 144.1, 137.0, 133.4, 128.8, 128.2, 126.9, 126.0, 120.8, 51.8, 44.5, 40.5, 33.0. FTIR (neat) 3103, 3061, 2996, 2950, 2917, 2848, 1733, 1684, 1596, 1580, 1448, 1436, 1411, 1360, 1278, 1214, 1159, 1080, 1001, 857, 782, 755, 689, 647 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{16}O_3S$ (M^+) 288.0815, found 288.0822.

(*S*)-(+)-5-Oxo-3-benzyl-5-phenylpentanoic acid (Table 3, entry 4). Colorless oil; 90% yield. $[\alpha]^{20}_D$ +16.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 7.98-7.94 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.45 (m, 2H), 7.33-7.18 (m, 5H), 3.17 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 3.06 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 6.1 Hz, 1H), 2.87-2.75 (m, 3H), 2.49-2.36 (m, 2H). ^{13}C NMR (acetone-d_6): δ 199.7, 174.2, 141.0, 138.2, 133.8, 130.2, 129.5, 129.2, 128.8, 127.1, 42.4, 40.4, 37.8, 34.2. FTIR (neat) 3085, 3061, 3027, 3004, 2918, 2671, 1706, 1684, 1598, 1580, 1496, 1448, 1408, 1370, 1288, 1221, 1180, 1159, 1075, 1030, 1001, 912, 746, 701, 690 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{18}O_3$ (M^+) 282.1250, found 282.1254.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oily solid). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 98 : 2, flow = 1 mL / min. Retention times: 14.7 min [(*R*)-enantiomer], 17.1 min [(*S*)-enantiomer]. 92% ee. $[\alpha]^{20}_D$ +10.5 (*c* 0.91, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.91-7.88 (m, 2H), 7.58-7.52 (m, 1H), 7.46-7.41 (m, 2H), 7.31-7.20 (m, 5H), 3.63 (s, 3H), 3.06 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 2.97 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 5.7 Hz, 1H), 2.91-2.82 (m, 1H), 2.74-2.71 (m, 2H), 2.42 (d, $^3J_{HH}$ = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 199.5, 173.3, 139.7, 137.2, 133.3, 129.6, 128.8, 128.6, 128.3, 126.5, 51.7, 42.0, 40.4, 37.9, 33.5. FTIR (neat) 3061, 3027, 2948, 2926, 2849, 1733, 1684, 1623, 1597,

1580, 1496, 1448, 1436, 1372, 1218, 1158, 1074, 1029, 1001, 745, 690, 668 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}O_3Na$ ($M+Na^+$) 319.1310, found 319.1296.

(*S*)-(+)-5-Oxo-3-propyl -5-phenylpentanoic acid (Table 3, entry 5). Colorless oil; 76% yield. $[\alpha]^{20}_D$ +0.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.03-8.00 (m, 2H), 7.64-7.58 (m, 1H), 7.53-7.48 (m, 2H), 3.14 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.05 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 2.59-2.51 (m, 1H), 2.40 (d, $^3J_{HH}$ = 6.9 Hz, 2H), 1.40-1.32 (m, 4H), 0.90-0.85 (m, 3H). ^{13}C NMR (acetone-d_6): δ 199.9, 174.4, 138.4, 133.8, 129.5, 128.9, 43.3, 38.7, 37.1, 31.8, 20.5, 14.6. FTIR (neat) 3208, 3062, 2958, 2930, 2873, 1706, 1687, 1597, 1580, 1448, 1409, 1372, 1292, 1218, 1180, 1001, 753, 690 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1250, found 234.1254.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its phenyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99 : 1, flow = 1 mL / min. Retention times: 16.0 min [(*R*)-enantiomer], 18.0 min [(*S*)-enantiomer]. 91% ee. $[\alpha]^{20}_D$ +5.4 (*c* 0.86, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 8.00-7.98 (m, 2H), 7.58-7.34 (m, 5H), 7.25-7.19 (m, 1H), 7.08-7.04 (m, 2H), 3.19 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.04 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 5.8 Hz, 1H), 2.74-2.66 (m, 3H), 1.50-1.36 (m, 4H), 0.94 (t, $^3J_{HH}$ = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 199.7, 171.7, 150.8, 137.2, 133.3, 129.6, 128.8, 128.3, 126.0, 121.8, 42.8, 38.7, 36.6, 31.5, 20.2, 14.4. FTIR (neat) 3063, 3043, 2958, 2930, 2872, 1754, 1684, 1595, 1580, 1493, 1448, 1410, 1373, 1316, 1292, 1267, 1194, 1162, 1126, 1099, 1023, 1002, 936, 752, 689 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{22}NaO_3$ (M^+ + Na) 333.1461, found 333.1458.

(*S*)-(+)-5-Oxo-3-isobutyl-5-phenylpentanoic acid (Table 3, entry 6). Colorless oil; 75% yield. $[\alpha]^{20}_D$ +1.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.04-8.00 (m, 2H), 7.64-7.58 (m, 1H), 7.54-7.48 (m, 2H), 3.16 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.03 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 2.66-2.58 (m, 1H), 2.43-2.38 (m, 2H), 1.75-1.63 (m, 1H), 1.31-1.26 (m, 2H), 0.88 (d, $^3J_{HH}$ = 6.6 Hz, 6H). ^{13}C NMR (acetone-d_6): δ 199.9, 174.3, 138.4, 133.8, 129.5, 128.9, 44.4, 43.6, 38.9, 29.9, 26.0, 23.2, 22.9. FTIR (neat) 3062, 2957, 2931, 2871, 1706, 1686, 1597, 1580, 1467, 1448, 1409, 1367, 1296, 1220, 1180, 1112, 1001, 922, 752, 690 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{20}O_3$ (M^+) 248.1407, found 248.1415.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its phenyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99 : 1, flow = 1 mL / min. Retention times: 11.0 min [(*R*)-enantiomer], 13.9 min [(*S*)-enantiomer]. 91% ee. $[\alpha]^{20}_D$ +4.7 (*c* 0.81, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 8.01-7.97 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.43 (m, 2H), 7.40-7.34 (m, 2H), 7.26-7.19 (m, 1H), 7.09-7.04 (m, 2H), 3.21 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 7.2 Hz, 1H), 3.02 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 5.5 Hz, 1H), 2.81-2.70 (m, 1H), 2.66 (d, $^3J_{HH}$ = 5.8 Hz, 2H), 1.77-1.65 (m, 1H), 1.43-1.32 (m, 2H), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 199.8, 171.6, 150.8, 137.3, 133.3, 129.6, 128.8, 128.3, 126.0, 121.8, 43.8, 43.0, 38.8, 29.5, 25.6, 23.0, 22.7. FTIR (neat) 3064, 2956, 2930, 2870, 1754, 1684, 1595, 1493, 1448, 1410, 1368, 1296, 1194, 1162, 1130, 1109, 1023, 1001, 934, 752, 689 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{24}NaO_3$ (M^++ Na) 347.1618, found 347.1611.

(*S*)-(+)-5-Oxo-3-isopropyl-5-phenylpentanoic acid (Table 3, entry 7). Colorless oil; 70% yield. $[\alpha]^{20}_D$ +0.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.05-8.02 (m, 2H), 7.63-7.58 (m, 1H), 7.54-7.48 (m, 2H), 3.10 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 3.03 (dd, $^2J_{HH}$ = 16.8 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 2.61-2.50 (m, 1H), 2.41 (dd, $^2J_{HH}$ = 15.7 Hz and $^3J_{HH}$ = 6.1 Hz, 1H), 2.31 (dd, $^2J_{HH}$ =

16.0 Hz and $^3J_{HH}$ = 7.7 Hz, 1H), 1.90-1.79 (m, 1H), 0.93 (d, $^3J_{HH}$ = 6.9 Hz, 6H). ^{13}C NMR (acetone-d_6): δ 200.0, 174.8, 138.3, 133.7, 129.5, 128.9, 40.4, 37.5, 36.0, 30.8, 19.5, 19.3. FTIR (neat) 3061, 2961, 2875, 1706, 1684, 1597, 1580, 1448, 1411, 1388, 1370, 1335, 1283, 1213, 1180, 1101, 1001, 933, 751, 690 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1250, found 234.1260.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its phenyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99.4 : 0.6, flow = 1 mL / min. Retention times: 16.1 min [(*R*)-enantiomer], 17.4 min [(*S*)-enantiomer]. 92% ee. $[\alpha]^{20}_D$ +5.4 (*c* 0.87, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 8.00-7.98 (m, 2H), 7.58-7.53 (m, 1H), 7.48-7.43 (m, 2H), 7.40-7.33 (m, 2H), 7.25-7.18 (m, 1H), 7.09-7.05 (m, 2H), 3.12 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 6.9 Hz, 1H), 3.05 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 5.7 Hz, 1H), 2.74-2.53 (m, 3H), 1.97-1.87 (m, 1H), 0.99 (d, $^3J_{HH}$ = 6.9 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 199.8, 172.0, 150.8, 137.2, 133.3, 129.6, 128.8, 128.3, 126.0, 121.8, 40.1, 37.2, 36.2, 30.6, 19.6, 19.2. FTIR (neat) 3064, 2961, 2930, 2874, 1755, 1684, 1595, 1493, 1448, 1412, 1371, 1336, 1272, 1195, 1162, 1128, 1099, 1070, 1024, 932, 752, 689 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{22}NaO_3$ (M^+ + Na) 333.1461, found 333.1462.

(*S*)-(–)-5-Oxo-3-(*tert*-butyl)-5-phenylpentanoic acid (Table 3, entry 8). White solid; 84% yield. $[\alpha]^{20}_D$ –2.1 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.04-8.00 (m, 2H), 7.62-7.57 (m, 1H), 7.52-7.47 (m, 2H), 3.27 (dd, $^2J_{HH}$ = 17.4 Hz and $^3J_{HH}$ = 4.5 Hz, 1H), 2.94 (dd, $^2J_{HH}$ = 17.7 Hz and $^3J_{HH}$ = 7.5 Hz, 1H), 2.67-2.59 (m, 1H), 2.51 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 5.1 Hz, 1H), 2.19 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 7.8 Hz, 1H), 0.95 (s, 9H). ^{13}C NMR (acetone-d_6): δ 199.9, 175.3, 138.4, 133.6, 129.4, 128.9, 40.7, 40.6, 36.2, 34.1, 27.7. FTIR (neat) 3064, 2962, 1706, 1684, 1597,

1581, 1472, 1448, 1418, 1397, 1368, 1300, 1219, 1159, 1055, 1018, 1001, 753, 689, 668 cm^{-1}. M.p. 65-68 °C. HRMS (ESI) calcd for $C_{15}H_{20}NaO_3$ (M^+ + Na) 271.1310, found 271.1307.

The absolute configuration of the product was assigned by analogy with 5-oxo-3,5-diphenylpentanoic acid (Table 2, entry 1).

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99.4 : 0.6, flow = 1 mL / min. Retention times: 11.0 min [(*S*)-enantiomer], 11.9 min [(*R*)-enantiomer]. 91% ee. $[\alpha]^{20}_D$ +2.1 (*c* 0.81, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.98-7.95 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.43 (m, 2H), 3.56 (s, 3H), 3.13 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 3.9 Hz, 1H), 2.91 (dd, $^2J_{HH}$ = 17.1 Hz and $^3J_{HH}$ = 8.1 Hz, 1H), 2.66-2.58 (m, 1H), 2.53 (dd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 4.8 Hz, 1H), 2.19 (dd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 8.4 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 199.9, 174.3, 137.4, 133.1, 128.7, 128.2, 51.8, 40.4, 40.0, 36.1, 33.6, 27.6. FTIR (neat) 3063, 2960, 2916, 2872, 1734, 1686, 1597, 1581, 1472, 1448, 1436, 1368, 1297, 1261, 1212, 1157, 1058, 1019, 1002, 894, 752, 690, 667 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{22}NaO_3$ (M^+ + Na) 285.1467, found 285.1464.

(*S*)-(–)-5-Oxo-3-(*tert*-butyldimethylsilyloxy)-5-phenylpentanoic acid (Table 3, entry 9). White solid; 51% yield. $[\alpha]^{20}_D$ –7.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.03-8.00 (m, 2H), 7.65-7.59 (m, 1H), 7.55-7.49 (m, 2H), 4.87-4.79 (m, 1H), 3.38 (dd, $^2J_{HH}$ = 16.2 Hz and $^3J_{HH}$ = 7.2 Hz, 1H), 3.22 (dd, $^2J_{HH}$ = 16.5 Hz and $^3J_{HH}$ = 4.8 Hz, 1H), 2.67 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 5.7 Hz, 1H), 2.57 (dd, $^2J_{HH}$ = 15.6 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 0.80 (s, 9H), 0.10 (s, 3H), –0.01 (s, 3H). ^{13}C NMR (acetone-d_6): δ 198.7, 172.8, 138.4, 133.9, 129.5, 129.0, 67.3, 46.6, 43.0, 26.2, 18.6, –4.5, –4.6. FTIR (neat) 3063, 2955, 2929, 2897, 2857, 1712, 1685, 1598, 1581, 1472, 1449, 1410, 1362, 1298, 1255, 1212, 1159, 1087, 965, 835, 778, 689 cm^{-1}. M.p. 60-62 °C. HRMS (ESI) calcd for $C_{17}H_{26}NaO_4Si$ (M^+ + Na) 345.1498, found 345.1486.

For ee analysis, the acid was derivatized to its methyl ester (colorless oily solid). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99.4 : 0.6, flow = 1 mL / min. Retention times: 7.9 min [(*R*)-enantiomer], 8.9 min [(*S*)-enantiomer]. 87% ee. $[\alpha]^{20}_{D}$ –7.7 (*c* 0.99, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.99-7.95 (m, 2H), 7.60-7.54 (m, 1H), 7.49-7.44 (m, 2H), 4.81-4.73 (m, 1H), 3.69 (s, 3H), 3.29 (dd, $^2J_{HH}$ = 16.2 Hz and $^3J_{HH}$ = 6.6 Hz, 1H), 3.17 (dd, $^2J_{HH}$ = 16.2 Hz and $^3J_{HH}$ = 6.0 Hz, 1H), 2.66 (dd, $^2J_{HH}$ = 14.7 Hz and $^3J_{HH}$ = 5.7 Hz, 1H), 2.56 (dd, $^2J_{HH}$ = 14.7 Hz and $^3J_{HH}$ = 6.3 Hz, 1H), 0.80 (s, 9H), 0.07 (s, 3H), –0.02 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 198.6, 171.8, 137.4, 133.4, 128.8, 128.5, 66.5, 51.8, 46.1, 42.8, 25.9, 18.1, –4.6, –4.8. FTIR (neat) 2952, 2929, 2855, 1739, 1684, 1623, 1598, 1581, 1472, 1463, 1448, 1436, 1372, 1254, 1208, 1156, 1085, 1002, 834, 778, 689 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{28}O_4SiNa$ ($M+Na^+$) 359.1649, found 359.1635.

The absolute configuration of this ester was determined by converting it to 5-phenyl-1,3-pentanediol (see next paragraph; CAS registry number: 115346-88-8 for *R* enantiomer, 115346-55-9 for *S* enantiomer) and comparing the optical rotation with the literature value.[5]

Methyl 5-oxo-3-(*tert*-butyldimethylsilyloxy)-5-phenylpentanoate (18.6 mg, 55 μmol) was dissolved in AcOH (1.5 mL) / MeOH (1.5 mL), and then Pd / C (10%; 60 mg, 56 μmol Pd) was added. The mixture was purged with H_2 gas (~1 atm) and stirred for 13 h at room temperature. The Pd / C was then removed by passing the reaction mixture through celite, and the solvent was evaporated. The residue was dissolved in Et_2O (3 mL), and then $LiAlH_4$ (~90 mg) was added. The mixture was stirred for 30 min at room temperature and then quenched with water. The precipitate was removed by filtration through celite. The solvent was evaporated, and the residue was chromatographed on

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([5]) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

silica gel (EtOAc / MeOH = 20 / 1) to afford 5.0 mg of 5-phenyl-1,3-pentanediol as a colorless oil (28 μmol, 50%).

^{1}H NMR ($CDCl_3$): δ 7.32-7.17 (m, 5H), 3.95-3.80 (m, 3H), 2.79-2.64 (m, 2H), 2.40 (br s, 2H), 1.90-1.63 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 142.1, 128.7, 128.6, 126.1, 71.9, 62.1, 39.6, 38.5, 32.1. $[\alpha]^{20}_D$ –8.8 (*c* 0.50, EtOH).

(1*S*,3*R*)-(+)-3-Benzoylcyclohexanecarboxylic acid (eq 2). Colorless oil; 78% yield. $[\alpha]^{20}_D$ +19.7 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (acetone-d_6): δ 8.06-8.00 (m, 2H), 7.64-7.49 (m, 3H), 3.58-3.48 (m, 1H), 2.61-2.50 (m, 1H), 2.18-2.02 (m, 2H), 1.95-1.87 (m, 2H), 1.63-1.50 (m, 2H), 1.44-1.28 (m, 2H). ^{13}C NMR (acetone-d_6): δ 203.0, 177.9, 137.1, 133.8, 129.6, 129.1, 45.0, 42.8, 32.3, 29.8, 29.6, 25.7. FTIR (neat) 3060, 2938, 2861, 1705, 1680, 1597, 1580, 1448, 1420, 1376, 1282, 1263, 1212, 1181, 1129, 1024, 980, 940, 921, 798, 767, 699 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{16}O_3$ (M^+) 232.1094, found 232.1093.

The absolute configuration of the product was determined by X-ray crystallography (crystallization from acetone of the brucine salt of the (+) enantiomer). CCDC deposition number: 175589.

For ee analysis, the acid was derivatized to its methyl ester (colorless oil). The ee of this ester was determined on a Daicel Chiralcel OD column with hexanes : isopropanol = 99.4 : 0.6, flow = 1 mL / min. Retention times: 17.8 min [(1*S*,3*R*)-enantiomer], 23.1 min [(1*R*,3*S*)-enantiomer]. 82% ee. $[\alpha]^{20}_D$ +22.4 (*c* 1.13, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ 7.95-7.92 (m, 2H), 7.59-7.54 (m, 1H), 7.50-7.44 (m, 2H), 3.67 (s, 3H), 3.36-3.27 (m, 1H), 2.53-2.43 (m, 1H), 2.19-1.92 (m, 4H), 1.74-1.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 202.8, 175.8, 136.2, 133.2, 128.9, 128.5, 51.9, 44.9, 43.0, 31.5, 29.0, 28.6, 25.3. FTIR (neat) 2938, 2860, 1733, 1680, 1596, 1580, 1558, 1447, 1435, 1375, 1312, 1280, 1259, 1206, 1168, 1130, 1073, 1036, 964, 698, 668 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{18}O_3$ (M^+) 246.1250, found 246.1248.