Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z53364

69451 Weinheim, Germany

Highly Enantio- and Diastereoselective Organocatalytic Asymmetric Tandem Michael-Aldol Reaction of β-Ketoesters and α,β-Unsaturated Ketones

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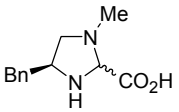
General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ = 7.26) for ^{1}H and relative to the central $CDCl_3$ resonance (δ = 77.0) or $(CD_3)_2SO$ (δ = 39.52) for ^{13}C-NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotation was measured on a Perkin-Elmer 241 polarimeter. All diastereoselectivities were measured by ^{1}H NMR spectroscopy on crude reaction mixtures. The enantiomeric excess (ee) of the products were determined by chiral HPLC using Daicel Chiralpak or Daicel Chiralcel columns with hexane/2-propanol or hexane/EtOH as eluent as indicated in the respective entries.

Materials. Benzylideneacetone **2a**, 4-chlorobenzylideneacetone **2c**, 4-hydroxybenzylideneacetone **2d**, furfurylideneacetone (*cis*-*trans* mixture) **2f**, *trans*-4-(2-thienyl)-3-butene-2-one **2g**, ethyl benzoylacetate **3a**, methyl 4-fluorobenzoylacetate **3c**, ethyl 4-metoxybenzoylacetate **3d**, were purchased commercially and used as received. 2-Naphthylideneacetone[1] **2b**, 2-nitro-benzylidenacetone[2] **2e**, 2-pyrimidalacetone[3] **2h**, 1-phenyl-pent-1-en-3-one[4] **2i**, 4-methoxy-benzylideneacetone[5] **2j**, benzyl benzoylacetate[6] **3b** were prepared according to literature procedures.

Procedure for the synthesis of imidazolidine catalyst 1. Imidazolidine catalyst **1** was synthesized by condensation of the diamine with an equimolar amount of glyoxylic acid monohydrate in CH_2Cl_2 at ambient temperature for 15 h, after which the solvent was evaporated and the resulting solid dried thoroughly under vacuum.



4-Benzyl-1-methyl-imidazolidine-2-carboxylic acid (1a). Isolated as a colorless solid in a 2:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$, major diastereomer) δ 2.52-2.93 (m, 2H), 2.89 (s, 3H), 3.21 (dd, *J* = 5.8, 13.4 Hz, 1H), 3.41-3.48 (m, 1H), 3.74 (quintet, *J* = 6.8 Hz, 1H), 4.19 (s, 1H), 7.20-7.31 (m, 5H); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 38.4, 40.6, 58.1, 58.8, 85.6, 126.9, 128.8, 128.7, 137.4, 168.8; ^{1}H-NMR ($CDCl_3$, minor diastereomer) δ 2.52-2.93 (m, 2H), 2.84 (s, 2H), 3.01 (dd, *J* = 6.3, 13.4 Hz, 1H), 3.64-3.71 (m, 1H), 4.01 (quintet, *J* = 6.7 Hz, 1H), 4.12 (s 1H), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, minor diastereomer) δ 39.3, 40.3, 57.3, 58.9, 82.3, 126.8, 128.6, 129.2, 137.3, 169.4; HRMS m/z 243.1100 ($M+Na^+$), calc. for $C_{12}H_{16}O_2N_2Na^+$ 243.1109.

General procedure for the tandem Michael-aldol reaction of β-ketoesters. To a solution of 0.5 mmol of α,β-unsaturated ketone **2** in 1.0 mL of ethanol in a glass tube equipped with a magnetic stirring bar, is added 1.0 mmol of β-ketoester **3**, 0.05 mmol of catalyst **1** and the mixture was stirred at ambient temperature for the time indicated in the tables. The reaction mixture was diluted with Et_2O (2 mL), filtered by suction and the precipitate washed with 2 mL of Et_2O.

During our investigation of the imidazolidine catalyzed tandem Michael-aldol reaction, the reaction rate was found to be very concentration dependent as yields decreased dramatically upon dilution as shown for the formation cyclohexanone **5b** (Figure S1).

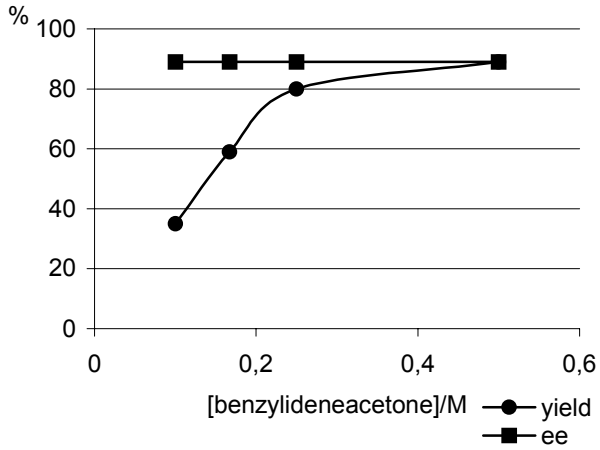
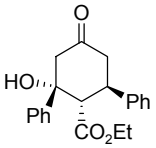
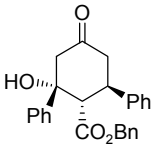


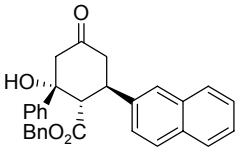
Figure S1 Concentration dependence of yield and enantiomeric excess for the tandem Michael-aldol reaction of benzylideneacetone **2a** with benzyl benzoylacetate **3b** catalyzed by **1** (10 mol%) in EtOH at ambient temperature for 44h.[7]



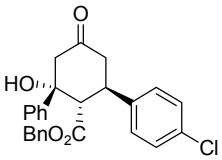
2-Hydroxy-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid ethyl ester (5a). Isolated as a colorless solid. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA. ^{1}H NMR ($CDCl_3$) δ 0.52 (t, J = 7.6 Hz, 3H, CH_3), 2.68-2.80 (m, 4H, CH_2COCH_2), 3.50-3.58 (m, 3H, OCH_2 and C*HCO_2Et), 4.44 (d, J = 2.8 Hz, 1H, OH), 7.24-7.37 (m, 8H, ArH), 7.50 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.2, 43.2, 47.3, 53.9, 56.6, 60.6, 77.3, 124.5, 127.4, 127.5, 127.6, 128.4, 128.7, 140.2, 144.0, 174.2, 206.0; HRMS m/z ($M+Na^+$) 361.1414, calc. for $C_{21}H_{22}O_4Na^+$ 361.1416.



2-Hydroxy-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (5b). Isolated as a colorless solid, mp. 179-181 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralcel OD-R chiral stationary phase in MeOH/MeCN 88/12; $[\alpha]^{rt}_D$ = -13.8^{o} (c = 1.0, $CHCl_3$, 89% ee); ^{1}H NMR ($CDCl_3$) δ 2.66-2.78 (m, 4H, CH_2COCH_2), 3.62 (d, J = 12.1 Hz, 1H, C*HCO_2Bn), 3.77-3.84 (m, 1H, PhC*H), 4.37 (s, 1H, OH), 4.39 (d, J = 12.1 Hz, 1H, CO_2CH_2Ph), 4.49 (d, J = 14.0 Hz, 1H, CO_2CH_2Ph) 6.51 (d, J = 7.0 Hz, 2H, ArH), 7.08-7.48 (m, 13H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.4, 47.4, 54.0, 56.7, 66.5, 77.4, 124.5, 127.5, 127.6, 127.7, 128.0, 128.3, 128.6, 128.9, 134.5, 140.2, 143.9, 174.2, 205.9; HRMS m/z ($M+Na^+$) 423.1580, calc. for $C_{26}H_{24}O_4Na^+$ 423.1572.

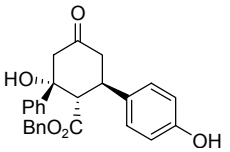


2-Hydroxy-6-naphthalen-2-yl-4-oxo-2-phenyl-cyclohexanecarboxylic acid benzyl ester (5c). Isolated as a colorless solid, mp. 245-246.5 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralcel OD-R chiral stationary phase in MeOH/MeCN 95/5; $[\alpha]^{rt}_D$ = +4.3^{o} (c = 1.0, $CHCl_3$, 91% ee); ^{1}H NMR ($CDCl_3$) δ 2.70-2.87 (m, 4H, CH_2COCH_2), 3.77 (d, J = 10.5 Hz, 1H, C*HCO_2Bn), 4.00 (td, J = 11,7, 5.5 Hz, 1H, 2-Np-C*H), 4.35 (d, J = 12.5 Hz, 1H, CO_2CH_2Ph), 4.40 (d, J = 12.1 Hz, 1H, CO_2CH_2Ph), 4.46 (s, 1H, OH), 6.25 (d, J = 7.4 Hz, 2H, ArH), 6.76-7.83 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$) δ 43.5, 47.5, 54.0, 56.4, 66.5, 77.5, 124.6, 125.0, 126.1, 126.4, 126.6, 127.4, 127.6, 127.7, 127.8, 128.0, 128.6, 128.8, 132.9, 133.5, 134.2, 137.5, 144.0, 174.2, 205.8; HRMS m/z ($M+Na^+$) 473.1711, calc. for $C_{30}H_{26}O_4Na^+$ 473.1729.

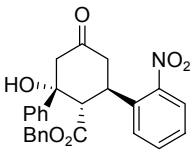


6-(4-Chloro-phenyl)-2-hydroxy-4-oxo-2-phenyl-cyclohexane-carboxylic acid benzyl ester (5d). Isolated as a colorless solid, mp. 224-225 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralcel OD-R chiral stationary phase in MeOH/MeCN 95/5; $[\alpha]^{rt}_D$ = -3.1^{o} (c = 1.0, $CHCl_3$, 97% ee); ^{1}H NMR ($CDCl_3$) δ 2.56-2.72(m, 4H, CH_2COCH_2), 3.52 (d, J = 12.1 Hz, 1H, C*HCO_2Bn), 3.70-3.77 (m, 1H, 4-Cl-Ph_4-C*H), 4.28 (d, J = 2.7 Hz, 1H, OH), 4.39 (d, J = 12.5, Hz, 1H, CO_2C**H**HPh), 4.49 (d, J = 12.1, Hz, 1H, CO_2CH**H**Ph) 6.50-6.52

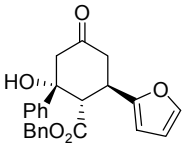
(m, 2H, ArH), 7.07-7.30 (m, 10H, ArH), 7.39-7.42 (m, 2H, ArH), ^{13}C NMR ($CDCl_3$) δ 42.7, 47.3, 53.9, 56.5, 66.7, 77.3, 124.5, 127.8, 127.9, 128.2, 128.3, 128.6, 128.8, 129.0, 133.4, 134.3, 138.6, 143.7, 173.9, 205.3; HRMS m/z ($M+Na^+$) 457.1170, calc. for $C_{26}H_{23}ClO_4Na^+$ 457.1183.



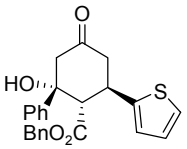
2-Hydroxy-6-(4-hydroxy-phenyl)-4-oxo-2-phenyl-cyclohexanecarboxylic acid benzyl ester (5e). Isolated as a colorless solid, mp. 222-225 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralcel AD chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA); $[\alpha]^{rt}_D$ = -46.0^{o} (*c* = 1.0, $CHCl_3$, 99% ee); ^{1}H NMR ($CDCl_3$) δ 2.62-2.76 (m, 4H, CH_2COCH_2), 3.56 (d, *J* = 11.7 Hz, 1H, C*HCO_2Bn), 3.71-3.78 (m, 1H, 4-OH-Ph-C***H**), 4.35 (d, *J* = 2.7 Hz, 1H, OH), 4.49 (s, 2H, CO_2CH_2Ph), 4.70 (s, 1H, HO-Ph), 6.56 (d, *J* = 6.6, 2H, ArH), 6.73 (d, *J* = 8.2 Hz, 2H, ArH), 7.11-7.35 (m, 8H, ArH), 7.46 (d, *J* = 7.41 Hz, 2H, ArH) HRMS m/z ($M+Na^+$) 439.1526, calc. for $C_{26}H_{24}O_5Na^+$ 439.1521.



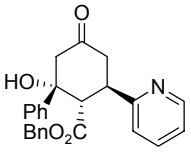
Hydroxy-6-(2-nitro-phenyl)-4-oxo-2-phenyl-cyclohexanecarboxylic acid benzyl ester (**5f).** Isolated as a colorless solid, mp. 164-166 ^{o}C. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/EtOH 70/30 containing 0.2% TFA; $[\alpha]^{rt}_D$ = +134.0^{o} (*c* = 1.0, $CHCl_3$, 96% ee); ^{1}H NMR ($CDCl_3$) δ 2.60-2.91 (m, 4H, CH_2OCH_2), 3.73 (br, 1H, C*HCO_2Bn), 4.13 (br, 1H, *2*-NO_2-Ph-C*H), 4.47-4.56 (m, 3H, CO_2CH_2Ph and OH), 6.62 (d, *J* = 7.0 Hz, 2H, ArH), 7.10-7.33 (m, 7H, ArH), 7.34-7.66 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 36.5, 47.0, 53.9, 55.6, 66.8, 77.1, 124.4, 127.8, 128.1, 128.2, 128.3, 128.6, 129.2, 132.7, 134.2, 143.6, 149.9, 174.2, 204.5; HRMS m/z ($M+Na^+$) 468.1426, calc. for $C_{26}H_{23}NO_6Na^+$ 468.1423.



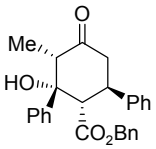
6-Furan-2-yl-2-hydroxy-4-oxo-2-phenyl-cyclohexanecarboxylic acid benzyl ester (5g). Isolated as a colorless solid, mp. 168-170 ^{o}C. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA; $[\alpha]^{rt}_D$ = -27.5^{o} (*c* = 1.0, $CHCl_3$, 80% ee); ^{1}H NMR ($CDCl_3$) δ 2.60-2.84 (m, 4H, CH_2COCH_2), 3.66 (d, *J* = 11.7 Hz, 1H, C*HCO_2Bn), 3.88-3.95 (td, *J* = 12.1, 4.7 Hz, 1H, 2-furyl-C*H), 4.30 (s, 1H, OH), 4.57 (d, *J* = 12.5, Hz, 1H, CO_2CH**H**Ph), 4.68 (d, *J* = 12.1, Hz, 1H, CO_2C**H**HPh), 6.04 (d, *J* = 3.1 Hz, 1H, ArH), 6.20-6-21 (m, 1H, ArH), 6.74-6.76 (m, 2H, ArH), 7.13-7.42 (m, 7H, ArH), 7.43 (d, *J* = 7.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 36.8, 44.4, 53.9, 54.8, 66.7, 76.7, 106.5, 110.2, 124.5, 127.7, 127.9, 128.2, 128.3, 128.6, 134.5, 142.3, 143.7, 153.3, 174.2, 205.3; HRMS m/z ($M+Na^+$) 413.1360 calc. for $C_{27}H_{26}O_5Na^+$ 413.1365.



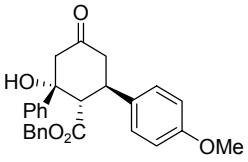
2-Hydroxy-4-oxo-2-phenyl-6-thiophen-2-yl-cyclohexanecarboxylic acid benzyl ester (5h). Isolated as a colorless solid, mp. 171-174 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralcel OD-R chiral stationary phase in MeOH/MeCN 95/5; $[\alpha]^{rt}_{D}$ = -19.7^{o} (*c* = 1.0, $CHCl_3$, 81% ee); ^{1}H NMR ($CDCl_3$) δ 2.64-2.76 (m, 3H, CH_2COCH_2), 2.85-2.90 (m, 1H, CH_2COCH_2), 3.57 (d, *J* = 11.7, 1H, C*HCO_2Bn), 4.17 (td, *J* = 12.5, 4.7, Hz, 1H, 2-thienyl-C*H), 4.31 (d, *J* = 2.7 Hz, 1H, OH), 4.54 (d, *J* = 12.1 Hz, 1H, CO_2C**H**HPh), 4.62 (d, *J* = 12.1 Hz, 1H, CO_2CH**H**Ph), 6.65 (d, *J* = 8.6 Hz, 2H, ArH), 6.85-6.89 (m, 2H, ArH), 7.12-7.33 (m, 7H, ArH), 7.43-7.46 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 38.7, 48.4, 53.8, 58.3, 66.7, 77.4, 124.7, 124.8, 125.3, 127.1, 128.0, 128.3, 128.6, 128.8, 134.8, 143.6, 144.1, 174.0, 204.8; HRMS m/z (M+Na^+) 429.1139, calc. for $C_{24}H_{22}O_4SNa^+$ 429.1136.



2-Hydroxy-4-oxo-2-phenyl-6-pyridin-2-yl-cyclohexanecarboxylic acid benzyl ester (5i). Isolated as a colorless solid, mp. 188-190 ^{o}C. The enantiomers were separated by HPLC using a Chiralpak AD-RH chiral stationary phase in MeOH/MeCN 95/5; $[\alpha]^{rt}_{D}$ = -9.0^{o} (*c* = 1.0, $CHCl_3$, 84% ee); ^{1}H NMR ($CDCl_3$) δ 2.62-2.67 (m, 2H, CH_2), 2.79 (dd, *J* = 15.2, 3.1 Hz, 1H, CH**H**), 3.08-3-15 (m, 1H, C**H**H), 3.84-3.93 (m, 2H, 2-pyridyl-C*H + C*HCO_2Bn), 4.32 (d, *J* = 3.1 Hz, 1H, OH), 4.48 (d, *J* = 2 Hz, 2H, CO_2CH_2Ph), 6.54 (d, *J* = 6.6 Hz, 2H, ArH), 6.96 (d, *J* = 7.4 Hz, 1H, ArH), 7.03-7.40 (m, 7H, ArH), 7.41-7.50 (m, 3H, ArH), 8.50-8.51 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 44.1, 45.5, 53.9, 55.2, 66.3, 77.6, 122.5, 123.1, 124.6, 127.6, 127.7,128.0, 128.2, 128.5, 134.5, 136.8, 143.9, 149.8, 159.1, 174.5, 206.7; HRMS m/z (M+Na^+) 424.1536, calc. for $C_{25}H_{23}NO_4Na^+$ 424.1525.

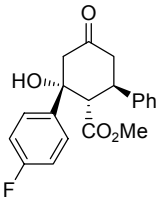


2-Hydroxy-3-methyl-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (5j). Isolated as a colorless solid, mp. 205-206 ^{o}C. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/EtOH 50/50 containing 0.15 % TFA; $[\alpha]^{rt}_{D}$ = -10.9^{o} (*c* = 1.0, $CHCl_3$, 95% ee); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 3H, CH_3), 2.68-2.84 (m, 3H, MeC*H$COCH_2$), 2.58 (d, *J* = 11.7 Hz, 1H, C*HCO_2Bn), 3.71 (sextet, *J* = 5.5 Hz, 1H, PhC*H), 4.23 (d, *J* = 2.0 Hz, 1H, OH), 4.30 (d, *J* = 12.1 Hz, 1H, CO_2CH_2Ph), 4.37 (d, *J* = 12.1 Hz, 1H, CO_2CH_2Ph), 6.40 (d, *J* = 8.2 Hz, 2H, ArH), 7.01-7.34 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.5, 43.5, 47.6, 53.6, 58.8, 66.3, 80.1, 127.4, 127.5, 127.6, 127.9, 128.2, 128.4, 128.9, 134.5, 140.2, 142.6, 174.1, 207.4; HRMS m/z (M+Na^+) 437.1738, calc. for $C_{27}H_{26}O_4Na^+$ 437.1729.

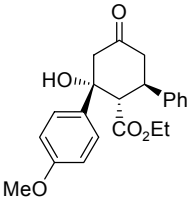


2-Hydroxy-6-(4-methoxy-phenyl)-4-oxo-2-phenyl-cyclohexanecarboxylic acid benzyl ester (5k). Isolated as a colorless solid, mp. 207-209 ^{o}C. The enantiomers

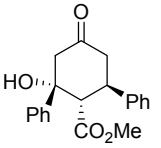
were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA; $[\alpha]^{rt}_D$ = -8.5° (*c* = 1.0, $CHCl_3$, 86% ee); ^{1}H NMR ($CDCl_3$) δ 2.64-2.77 (m, 4H, CH_2COCH_2), 3.57 (d, *J* = 11.7 Hz, 1H, C*HCO_2Bn), 3.73-3.80 (m, 4H, CH_3O and 4-CH_3O-Ph-C*H), 4.37 (d, *J* = 2.7 Hz, 1H, OH), 4.48 (s, 2H, CO_2CH_2Ph), 6.54 (d, *J* = 7.0 Hz, 2H, ArH), 6.79-6.82 (m, 2H, ArH), 7.09-7.33 (m, 8H, ArH), 7.47 (d, *J* = 7.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 42.6, 47.7, 53.9, 55.2, 56.9, 66.4, 77.3, 114.2, 124.6, 127.6, 128.0, 128.2, 128.5, 128.6, 132.2, 134.5, 144.0, 158.9, 174.3, 206.0; HRMS m/z (M+Na^+) 453.1706, calc. for $C_{27}H_{26}O_5Na^+$ 453.1678.



2-(4-Fluoro-phenyl)-2-hydroxy-4-oxo-6-phenyl-cyclohexanecarboxylic acid methyl ester (5l). Isolated as a colorless solid, mp. 215-216 °C. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA; $[\alpha]^{rt}_D$ = -12.5° (*c* = 1.0, $CHCl_3$, 92% ee); ^{1}H NMR ($CDCl_3$) δ 2.54-2.69 (m, 4H, CH_2COCH_2), 3.00 (s, 3H, CO_2CH_3), 3.49 (d, *J* = 11.7 Hz, 1H, C*HCO_2Me), 3.67-3.75 (m, 1H, PhCH), 4.34 (s, *J* = 2.7 Hz, 1H, OH), 6.93-6.99 (m, 2H, ArH), 7.18-7.29 (m, 5H, ArH), 7.37-7.42 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 43.2, 47.1, 51.7, 54.1, 56.8, 76.9, 115.4 (d, *J* = 21.5 Hz), 126.3 (d, *J* = 8.4 Hz), 127.3, 127.7, 128.8, 140.0, 162.0 (d, *J* = 246.9 Hz), 174.7, 205.6; HRMS m/z (M+Na^+) 365.1168, calc. for $C_{20}H_{19}FO_4Na^+$ 365.1165.

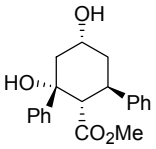


2-Hydroxy-2-(4-methoxy-phenyl)-4-oxo-6-phenyl-cyclohexanecarboxylic acid ethyl ester (5m). Isolated as a colorless solid, mp. 193-196 °C. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/EtOH 50/50 containing 0.15% TFA; $[\alpha]^{rt}_D$ = -6.0° (*c* = 1.0, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$) δ 0.54 (t, *J* = 7.0 Hz, 3H, CH_3CH_2O), 2.63-2.74 (m, 4H, CH_2COCH_2), 3.50-3.56 (m, 3H, C*HCO_2Et + $CO_2CH_2CH_3$), 3.59-3.77 (m, 4H, CH_3O,+ PhC*H), 4.37 (d, *J* = 2.7 Hz, 1H, OH), 6.83-6.86 (m, 2H, ArH), 7.22-7.33 (m, 5H, ArH), 7.38-7.40 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.3, 43.2, 47.4, 54.3, 55.2, 56.7, 60.6, 77.03, 113.7, 125.8, 127.5, 127.6, 128.7, 136.4, 140.3, 158.9, 174.3, 206.1; HRMS m/z (M+Na^+) 391.1522, calc. for $C_{22}H_{24}O_5Na^+$ 391.1521.



2-Hydroxy-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (5n). Prepared from **5b** by a transesterfication procedure. To a solution of **5b** in MeOH was added 10% Pd/C and the mixture was put under a H_2 atmosphere at ambient temperature and pressure for 2 h. After removal of the catalyst by filtration, $TMSCHN_2$ (2.0 M in hexane) was added slowly until the yellow color persisted. The mixture was stirred for another 15 min and a drop of CH_3COOH was added. After removal of the solvent the crude product obtained was a colorless solid

which was used directly for the next step; ^{1}H NMR ($CDCl_3$) δ 2.61-2.73 (m, 4H, CH_2COCH_2), 2.98 (s, 3H, OMe), 3.52 (d, *J* = 11.6 Hz, 1H, C*HCO_2Me), 3.70-3.78 (m, 1H, C*HPh) 4.37 (d, *J* = 2.7 Hz, 1H, OH), 7.15-7.31 (m, 8H, ArH), 7.41-7.43 (m, 2H, ArH).



2,4-Dihydroxy-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester (6a). Prepared by hydrogenation of the crude product **6n**. A mixture of **6n** and Raney-Nickel in MeOH was stirred under a H_2 atmosphere at ambient temperature and pressure until **6n** was consumed as judged by TLC (usually 10-15 h). After removal of the catalyst by filtration and evaporation of the solvent, the title compound was isolated as a colorless solid after purification by FC using Et_2O/CH_2Cl_2 as eluent. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/2-propanol 90/10. X-ray quality crystals were obtained by recrystallization from MeOH. ^{1}H NMR ($CDCl_3$) δ 1.82-1.94 (m, 2H, CH_2), 2.13-2.21 (m, 2H, CH_2), 2.95 (s, 3H, MeO), 3.12 (d, *J* = 11.6 Hz, 1H, C*HCO_2Me), 3.63 (dt, *J* = 2.8, 11.6 Hz, 1H, C*HPh), 4.12-4.17 (m, 1H, C*HOH), 4.79 (d, *J* = 10.0 Hz, 1H, C*HOH), 5.04 (d, *J* = 2.8 Hz, 1H, tertiary-OH), 7.14-7.28 (m, 8H, ArH), 7.36-7.39 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 38.1, 40.0, 43.0, 51.4, 57.1, 67.0, 76.7, 124.4, 127.1, 127.3, 127.6, 128.4, 128.5, 141.8, 145.4, 175.7; HRMS m/z ($M+Na^+$) 349.1418, calc. for $C_{20}H_{22}O_4Na^+$ 349.1416.

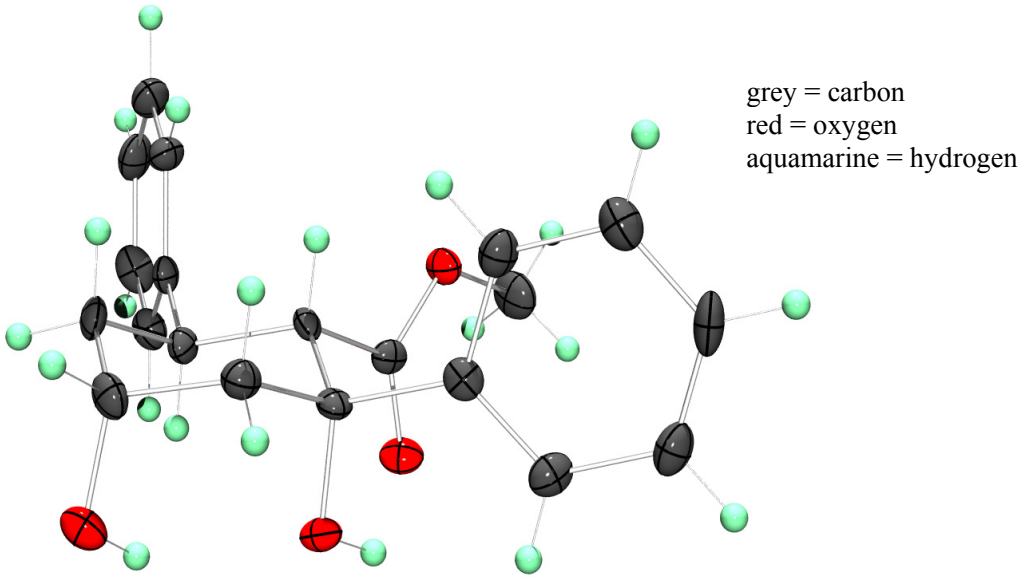
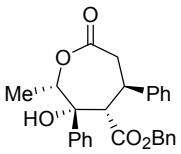
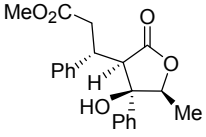


Figure S2. X-ray crystal structure compound **6a**.



3-Hydroxy-2-methyl-7-oxo-3,5-diphenyl-oxepane-4-carboxylic acid benzyl ester (6b). Prepared by Baeyer-Villiger oxidation of compound **5j**. To a solution of **5j** (92 mg, 0.22 mmol) in CH_2Cl_2 at ambient temperature was added urea-hydrogen peroxide complex (UHP) (206 mg, 10 equiv.) and trifluoroacetic anhydride (120 μL, 4.2 equiv.) and the reaction mixture was stirred for 1h after which it was quenched with a $NaHCO_3$ solution (sat., aq.). The organic phase was separated and the aqueous layer was extracted once with CH_2Cl_2. After the absence of peroxides in the organic phase was confirmed (peroxide strip test) the organic phase was evaporated to afford a 2:1 mixture regioisomers, the title compound being the minor regioisomer. Lactone **6b** was isolated as a colorless solid following purification by FC using using Et_2O/CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.4 Hz, 1H, CH_3), 2.60 (d, *J* = 7.6 Hz, 1H, OH), 2.65 (dd, *J* = 11.2, 18.4 Hz, 1H, C**H**H), 2.89 (dd, *J* = 6.4, 18.4 Hz, 1H, CH**H**), 3.20 (dt, *J* = 6.4, 11.6 Hz, 1H, C*HPh), 4.12 (d, *J* = 12.8 Hz, 1H, C*HCO_2Bn), 4.49 (quintet, *J* = 7.2 Hz, 1H, C*HMe), 4.67 (d, *J* = 12.4 Hz, 1H, CO_2C**H**HBn), 4.79 (d, *J* = 12.4 Hz, 1H, CO_2CH**H**Bn), 6.89 (d, *J* = 6.4 Hz, 2H, ArH), 7.05-7.08 (m, 4H, ArH), 7.17-7.31 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.9, 36.6, 37.8, 51.7, 67.0, 71.1, 89.7, 125.8, 127.1, 127.2, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 128.9, 134.5, 137.9, 141.4, 169.6, 170.6; HRMS m/z ($M+Na^+$) 453.1674, calc. for $C_{27}H_{26}O_5Na^+$ 453.1678.



3-(4-Hydroxy-5-methyl-2-oxo-4-phenyl-tetrahydro-furan-3-yl)-3-phenyl-propionic acid methyl ester (6c). Prepared by translactonization of compound **6b.** To a solution of LiOH in MeOH (1 mg/mL) was added **6b** and the mixture stirred for 20-30 min. After dilution with H_2O the reaction mixture was acidified with 5M HCl and extracted with CH_2Cl_2. The pure title compound was obtained as a colorless solid after FC in Et_2O/pentane. X-ray quality crystals were obtained after recrystallization from MeOH. ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.8 Hz, 3H, CH_3), 2.71 (dd, *J* = 6.4, 15.6 Hz, 1H, C**H**HCO), 3.40-3.56 (m, 3H, CH**H**CO and C*HPh and C*HCO), 3.52 (s, 3H, OCH_3), 4.45 (q, *J* = 6.8 Hz, 1H, C*HMe), 6.87-6.96 (m, 5H, ArH), 7.09-7.16 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.4, 37.5, 38.0, 51.9, 56.0, 81.7, 83.7, 124.9, 126.9, 127.5, 127.8, 128.4, 128.5, 138.9, 142.0, 174.2, 175.1; HRMS m/z ($M+Na^+$) 377.1371, calc. for $C_{21}H_{22}O_5Na^+$ 377.1365.

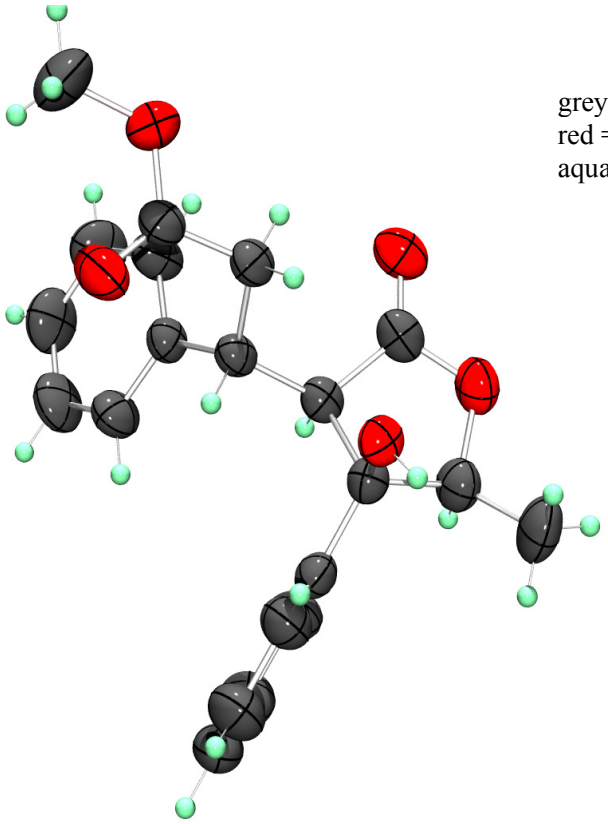
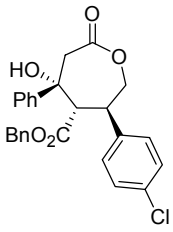
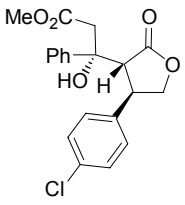


Figure S3. X-ray crystal structure compound **6c**.



3-(4-Chloro-phenyl)-5-hydroxy-7-oxo-5-phenyl-oxepane-4-carboxylic acid benzyl ester (6d). Prepared by Baeyer-Villiger oxidation of compound **5d**. To a solution of **5d** in CH_2Cl_2 at ambient temperature was added urea-hydrogen peroxide complex (UHP) (10 equiv.) and trifluoroacetic anhydride (4.2 equiv.) and the reaction mixture was stirred for 1h at ambient temperature after which it was quenched with a $NaHCO_3$ solution (sat., aq.). The organic phase was separated and the aqueous layer was extracted once with CH_2Cl_2. After the absence of peroxides in the organic phase was confirmed (peroxide strip test) the organic phase was evaporated to afford the crude lactone **6d** which was further purified by FC using Et_2O/CH_2Cl_2 to afford the title compound as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 3.11 (d, J = 14.4 Hz, 1H, C**H**HCO), 3.42-3.47 (m, 2H, CH**H**CO and C*HCO_2Bn), 3.73-3.78 (m, 1H, C*HAr), 4.29-4.33 (m, 2H, OC**H**HPh and C**H**HOCO), 4.42 (d, J = 12.0 Hz, 1H, OCH**H**Ph), 4.60 (dd, J = 9.2, 13.2 Hz, 1H, CH**H**OCO), 4.63 (d, J = 2.4 Hz, 1H, OH), 6.52 (d, J = 7.2 Hz, 2H, ArH), 7.08-7.42 (m, 12H, ArH); HRMS m/z (M+Na^+) 450.1239, calc. for $C_{26}H_{23}O_5ClNa^+$ 450.1234.



3-[4-(4-Chloro-phenyl)-2-oxo-tetrahydro-furan-3-yl]-3-hydroxy-3-phenyl-propionic acid methyl ester (6e). Prepared by translactonization of compound **6d** as

described for compound **6f**. The enantiomers were separated by HPLC using a Chiralcel OD chiral stationary phase in hexane/2-propanol 90/10. X-ray quality crystals were obtained by recrystallization in hexane/2-propanol. $[\alpha]^{rt}_D$ = -95.8° (*c* = 1.0, $CHCl_3$, 97% ee); ^{1}H NMR ($CDCl_3$) δ 2.76 (dd, *J* = 2.0, 4.4 Hz, 1H, C*HCO), 2.99 (d, *J* = 16.4 Hz, 1H, C**H**HCO), 3.35 (dt, *J* = 8.4, 4.4 Hz, 1H, C*HAr), 3.49 (s, 3H, OMe), 3.83 (d, *J* = 16.4 Hz, 1H, CH**H**CO), 4.20 (dd, *J* = 3.6, 8.8 Hz, 1H, OC**H**H), 4.69 (dd, *J* = 8.4, 8.8 Hz, 1H, OCH**H**), 5.11 (d, *J* = 2.0 Hz, 1H, OH), 6.51 (d, *J* = 8.0 Hz, 2H, ArH), 7.07 (d, *J* = 8.0 Hz, 2H, ArH), 7.24-7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 42.0, 42.6, 51.8, 58.4, 73.5, 76.2, 125.4, 127.6, 127.7, 128.4, 128.5, 128.9, 132.6, 141.0, 142.4, 173.4, 176.0; HRMS m/z ($M+Na^+$) 397.0813, calc. for $C_{20}H_{19}O_5ClNa^+$ 397.0819.

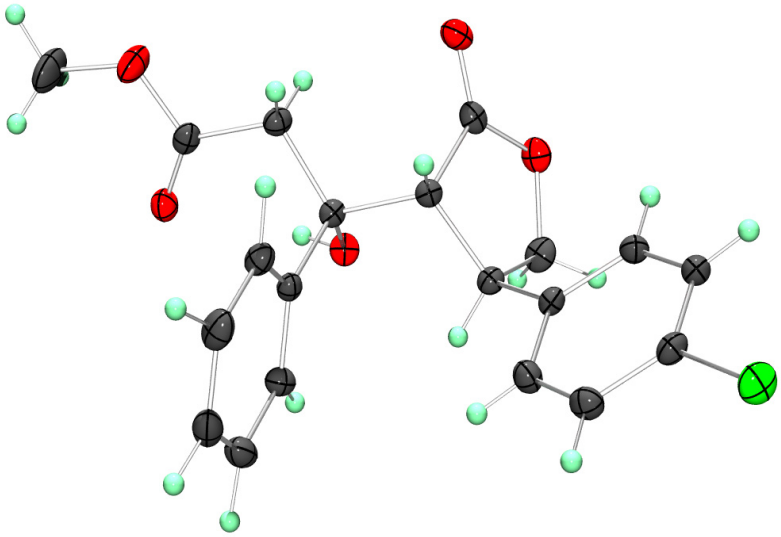
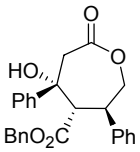
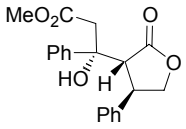


Figure S4. X-ray crystal structure compound **6e**.

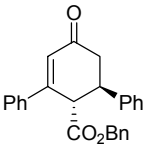


5-Hydroxy-7-oxo-3,5-diphenyl-oxepane-4-carboxylic acid benzyl ester (6f). Prepared by Baeyer-Villiger oxidation of compound **5b**. To a solution of **5b** (400 mg, 1.0 mmol) in CH_2Cl_2 at ambient temperature was added urea-hydrogen peroxide complex (UHP) (940 mg, 10 equiv.) and trifluoroacetic anhydride (0.6 mL, 4.2 equiv.) and the reaction mixture was stirred for 1h after which it was quenched with a $NaHCO_3$ solution (sat., aq.). The organic phase was separated and the aqueous layer was extracted once with CH_2Cl_2. After the absence of peroxides in the organic phase was confirmed (peroxide strip test) the organic phase was evaporated to afford the crude lactone **6f** which was further purified by FC using Et_2O/CH_2Cl_2 to afford the title compound as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/EtOH 50/50. ^{1}H NMR ($CDCl_3$) δ 3.04 (d, *J* = 14.4 Hz, 1H, C**H**HCO), 3.41 (dd, *J* = 2.8, 14.4 Hz, 1H, CH**H**CO), 3.45 (d, *J* = 12.0 Hz, 1H, C*HCO_2Bn), 3.69-75 (m, 1H, C*HPh), 4.19 (d, *J* = 12.8

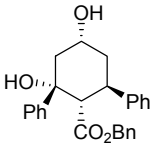
Hz, 1H, OC**H**HPh), 4.30 (d, *J* = 12.8 Hz, 1H, OCH**H**Ph), 4.28-4.32 (m, 1H, C**H**HOCO), 4.60 (dd, *J* = 9.6, 13.2 Hz, 1H, CH**H**OCO), 4.63 (d, *J* = 2.8 Hz, 1H, OH), 6.39 (d, *J* = 7.2 Hz, 2H, ArH), 7.01-7.37 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 44.8, 46.8, 61.1, 66.4, 71.1, 72.9, 124.1, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.6, 129.1, 134.2, 138.3, 144.9, 170.2, 173.5; HRMS m/z ($M+Na^+$) 439.1526, calc. for $C_{26}H_{24}O_5Na^+$ 439.1521.



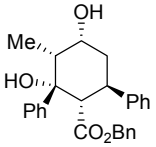
3-Hydroxy-3-(2-oxo-4-phenyl-tetrahydro-furan-3-yl)-3-phenyl-propionic acid methyl ester (6g). Prepared by translactonization of compound **6f.** To 10 mL a solution of LiOH in MeOH (1 mg/mL) was added **6f** (50 mg, 0.12 mmol), and the mixture stirred for 20-30 min. After dilution with H_2O the reaction mixture was acidified with 5M HCl and extracted with CH_2Cl_2. The pure title compound was obtained as a colorless solid after FC in Et_2O/pentane. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 90/10. $[\alpha]^{rt}_D$ = -100.8^o (*c* = 1.0, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$) δ 2.75 (dd, *J* = 2.0, 4.0 Hz, 1H, C*HCO), 2.93 (d, *J* = 16.4 Hz, 1H, C**H**HCO), 3.35 (dt, *J* = 8.0, 3.6 Hz, 1H, C*HPh), 3.41 (s, 3H, OMe), 3.76(d, *J* = 16.4 Hz, 1H, CH**H**CO), 4.20 (dd, *J* = 3.6, 8.0 Hz, 1H, OC**H**H), 4.64 (dd, *J* = 8.2, 8.0 Hz, 1H, OCH**H**), 5.04 (d, *J* = 2.0 Hz, 1H, OH), 6.52-6.55 (m, 2H, ArH), 7.02-7.05 (m, 3H, ArH), 7.14-7.26 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 42.2, 43.2, 51.8, 58.6, 73.9, 76.4, 125.5, 126.2, 126.9, 127.6, 128.4, 128.8, 142.5, 142.6, 173.4, 176.5; HRMS m/z ($M+Na^+$) 363.1205, calc. for $C_{20}H_{20}O_5Na^+$ 363.1208.



4-Oxo-2,6-diphenyl-cyclohex-2-enecarboxylic acid benzyl ester (6h). Prepared by elimination from compound **5b**. Compound **5b** (100.0 mg, 0.26 mmol) was added to a commercially available solution of HCl (5 mL) in Et_2O (1.0 M) and the mixture was stirred for 1-2 h until quenched with H_2O and extracted with CH_2Cl_2. The solvent was removed and the title compound was obtained as a colorless solid after FC in Et_2O/pentane. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -124.9^o (*c* = 1.0, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$) δ 2.75 (d, *J* = 2.4 Hz, 1H), 2.77 (s, 1H), 3.75 (q, *J* = 11.2 Hz, 1H), 4.18 (dd, *J* = 1.6, 7.2 Hz, 1H), 4.74 (d, *J* = 2.4 Hz, 2H), 6.36 (d, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 2H), 7.13-7.34 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 41.8, 44.3, 52.2, 66.9, 126.3, 127.2, 127.5, 128.1, 128.2, 128.4, 128.6, 128.9, 129.9, 134.9, 137.9, 140.8, 155.6, 171.1, 197.3; HRMS m/z ($M+Na^+$) 405.1470, calc. for $C_{27}H_{26}O_5Na^+$ 405.1467.



2,4-Dihydroxy-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (6i). Prepared by diastereoselective reduction of compound **5b**. To a solution of **5b** in dry THF at –78 °C was added L-selectride (3 equiv.) and the reaction mixture was stirred under an N_2 atmosphere and slowly allowed to warm up. At –10 °C the reaction mixture was quenched with H_2O, poured into a saturated aqueous sodium perborate solution at 60 °C and stirred for 4 h. After extraction with CH_2Cl_2 the solvent was removed and the title compound was obtained as a colorless solid after purification by FC using CH_2Cl_2/Et_2O. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/2-propanol 90/10; ^{1}H NMR ($CDCl_3$) δ 1.83-1.93 (m, 2H, CH_2), 2.13-2.20 (m, 2H, CH_2), 3.18 (d, *J* = 11.6 Hz, 1H, C*HCO_2Bn), 3.66 (dt, *J* = 3.6, 13.2 Hz, 1H, PhC*H), 4.14 (m, 1H, C***H**OH), 4.32 (d, *J* = 12.8 Hz, 1H, OC**H**HPh), 4.35 (d, *J* = 12.8 Hz, 1H, OCH**H**Ph), 4.79 (d, *J* = 10.0 Hz, 1H, C*HO**H**), 5.05 (d, *J* = 2.4 Hz, 1H, tertiary OH), 6.42 (d, *J* = 7.2 Hz, 2H, ArH), 7.01-7.39 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 37.6, 40.3, 42.9, 56.8, 66.4, 66.8, 124.5, 127.4, 127.7, 128.1, 128.3, 128.4, 128.7, 129.1, 134.4, 140.3, 145.0, 174.8; HRMS m/z ($M+Na^+$) 425.1717, calc. for $C_{26}H_{26}O_4Na^+$ 425.1729.



2,4-Dihydroxy-3-methyl-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (6j). Prepared by diastereoselective reduction of compound **5j** as described for compound **6i**. ^{1}H NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.8 Hz, 3H, CH_3), 1.91-1.99 (m, 2H, C*HMe + C**H**H), 2.24 (dt, *J* = 14.0, 3.6 Hz, 1H, CH**H**), 3.12 (d, *J* = 12.0 Hz, 1H, C*HCO_2Bn), 3.61 (dt, *J* = 3.6, 12.0 Hz, 1H, PhC*H), 3.93-3.97 (m, 1H, C***H**OH), 4.26 (d, *J* = 12.4 Hz, 1H, OC**H**HPh), 4.38 (d, *J* = 12.4 Hz, 1H, OCH**H**Ph), 4.49 (d, *J* = 9.6 Hz, 1H, C*HO**H**), 4.97 (d, *J* = 1.6 Hz, 1H, tertiary OH), 6.35 (d, *J* = 7.2 Hz, 2H, ArH), 6.99-7.47 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.9, 38.0, 41.3, 42.3, 59.0, 66.0, 71.8, 79.0, 124.2, 125.6, 127.1, 127.3, 127.7, 127.8, 128.2, 128.3, 128.6, 134.6, 141.7, 143.5, 175.1; HRMS m/z ($M+Na^+$) 439.1888, calc. for $C_{27}H_{28}O_4Na^+$ 439.1885.

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[7] A similar dilution effect was observed for the imidazolidine catalyzed formation of warfarin.