Chemoselective esterification of α-hydroxyacids catalyzed by salicylaldehyde through induced intramolecularity

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SUPPLEMENTARY MATERIAL

Representative experimental procedures, analytical datas, spectral data (20 pages)

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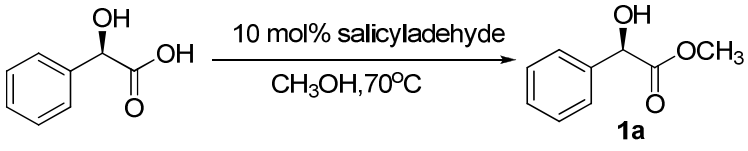
General.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Jeol JVMEX400 spectrometer (400 MHz, ^{1}H; 100 MHz, ^{13}C) and Bruker AVANCE 500 spectrometer (500 MHz, ^{1}H; 125 MHz, ^{13}C), respectly, with $CHCl_3$ as internal reference. Electron-impact (ESI) mass spectra were recorded using a Thermo Finnigan spectrometer equipped with LCQ Advantage ionization and Spectra System detector systems. Analytical GC was carried out using an Agilent 6890C GC system equipped with an Agilent DB-WAX column (30 m × 0.25 mm× 0.25 mm). Analytical TLC plates were visualized under UV light or by spraying with phosphomolybdic acid (PMA) and $KMnO_4$ staining agents. All the reactions were performed in nitrogen or argon atmosphere, and the end products were isolated as pure materials. Aldehyde **2,**[1] racemic *N*-Benzoyl-3-phenylisoserine,[2] 2-(4-nitrophenylamino)-2-phenylacetic acid,[3] and α-substituted α-hydroxyacids[4] were prepared according to the literature reports. (*R*)-Mandelic acid, racemic 4-bromomandelic acid, (*R*)-lactic acid, racemic 2-methyl-2-hydroxyl-propanoic acid, racemic tropic acid, *L*-tartaric acid, *L*-malic acid were purchased from ALDRICH or ACROS and used without further purification. All the liquid aldehydes and alcohols used in this study were distilled under reduced pressure from anhydrous $CaSO_4$ or activated magnesium metal before use.

Experimental:

Representative procedure for the esterification of α-hydroxyacids catalyzed by salicylaldehyde (Table 2):



1a

(*R*)-Mandelic acid (**1**, 153 mg, 1 mmol) was dissolved in methanol (1.0 mL) in a 5-mL single-neck round-bottom flask. Salicylaldehyde (12.2 mg, 11 μL, 0.10 mmol) was added to the flask via a syringe, at room temperature under nitrogen atmosphere. The resulting mixture was heated to 70°C, and the reaction progress was monitored by TLC, ^{1}H NMR spectroscopy, and GC analysis. After

completion of the reaction, the mixture was gradually cooled to room temperature, and the organic solvent was evaporated to give the crude product. The salicylaldehyde was recovered through vacuum distillation using a Kügelrohr apparatus (1 torr, 50°C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent provided pure methyl mandelate **1a** (153 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.33 (m, 5H), 5.18 (d, *J* = 5.2, 1H), 3.76 (s, 3H), 3.45 (d, *J* = 5.6, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.2, 128.6, 128.5, 126.6, 72.9, 53.0; MS $C_9H_{10}O_3$ (EI, 166) 166 (M^+, 13), 107 (100), 79 (51), 77 (43), 40 (12); TLC R_f 0.32 (EtOAc/hexane, 1/3); GC conditions: Agilent DB-WAX column (30 m × 0.25 mm × 0.25 mm), flow rate: 1 mL/min; 90°C, 1 min; 10°C/min to 140°C; retention time (t_R) 19.78 min; internal standard: 1,3,5-trimethylbenzene. HPLC for racemic methyl mandelate: t_R 27.4 min (*R*, 50%), 31.2 min (*S*, 50%) (CHIRALCEL AD-H, *i*-PrOH/hexane, 6/94, 1.0 mL/min, λ = 254 nm). $[\alpha]_D^{24}$ -142 (*c* 1.0, MeOH) for 99% ee (lit. $[\alpha]_D^{20}$ -144 (*c* 1.0, MeOH) for (*R*)). The absolute configuration was deduced to be *R* according to the sign of the optical rotation. [5a] Mp: 56-58°C.

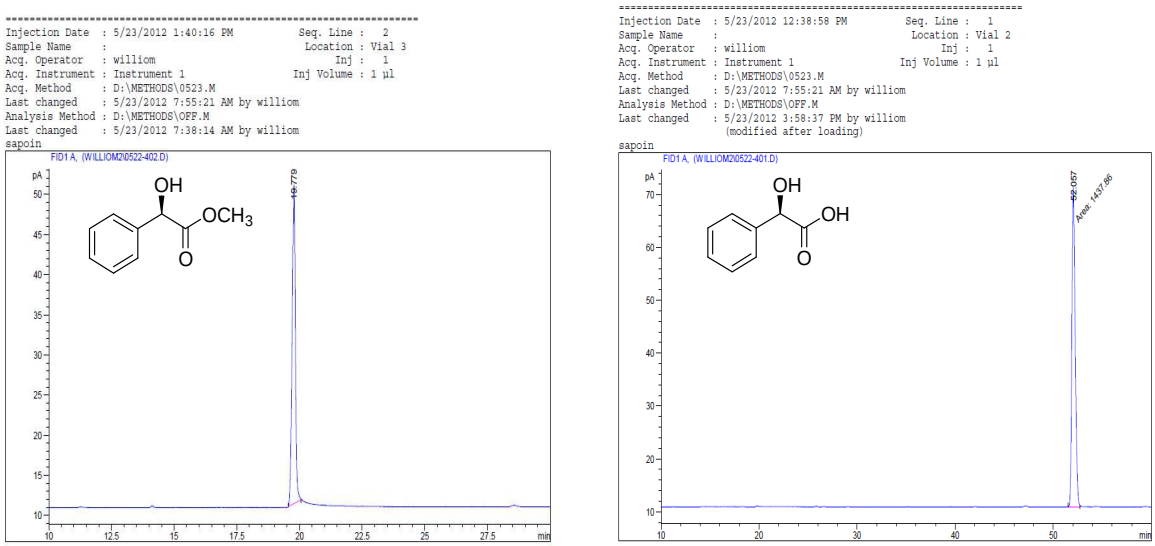


Figure S1. GC spectra of (*R*)-methyl mandelate and (*R*)-mandelic acid.

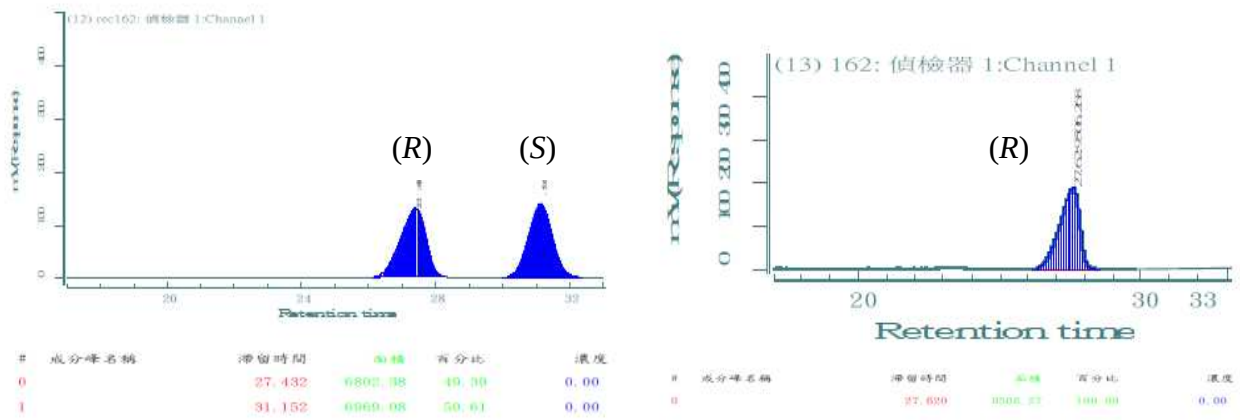
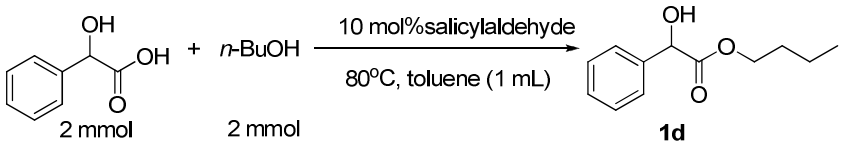


Figure S2. HPLC diagrams of racemic methyl mandelate and (*R*)-methyl mandelate.

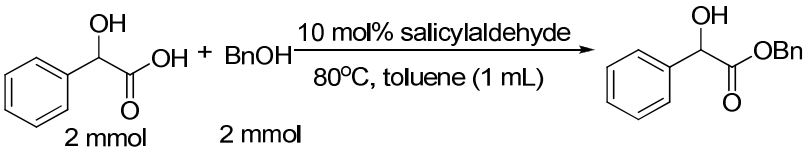
Representative procedure for the esterification of mandelic acid with *n*-butanol catalyzed by salicylaldehyde in toluene (concentration study, Table 3, entry 5):



To a 5-mL single-neck round-bottom flask was added mandelic acid (306 mg, 2 mmol) in 1 mL toluene at room temperature under nitrogen atmosphere. Solutions of *n*-butanol (149 mg, 184 μL, 2 mmol) and salicylaldehyde (24.4 mg, 22 μL, 0.20 mmol,10 mol%) were added successively via syringe. The resulting mixture was heated to 70°C and the reaction progress was monitored by TLC and ^{1}H NMR spectroscopy analysis. After completion of the reaction, the salicylaldehyde was recovered through vacuum distillation using a Kügelrohr apparatus (1 torr, 50°C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent provided pure *n*-butyl mandelate **1d (**387 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.34 (m, 5H), 5.16 (d, *J* = 5.2, 1H), 4.15 (m, 2H), 3.57 (d, *J* = 5.6, 1H, OH), 1.56 (m, 2H), 1.26 (m, 2H), 0.85 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.4, 128.5, 128.3, 126.5, 72.8, 66.0,

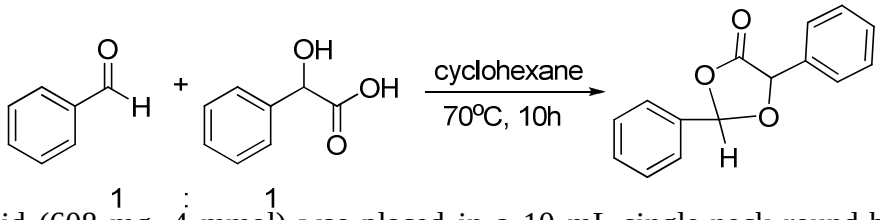
30.3, 18.8, 13.5; MS $C_{12}H_{16}O_3$ (EI, 208) 208 (M^+, 21), 191 (58), 107 (100), 79 (62), 77 (47); TLC R_f 0.28 (EtOAc/Hexane, 1/5).[5c]

Representative procedure for the esterification of α-hydroxyacids with benzyl alcohol catalyzed by salicylaldehyde in concentrated toluene (Table 4):



To a 5-mL single-neck round-bottom flask was added α-hydroxyacid (2 mmol) in 1 mL toluene at room temperature under nitrogen atmosphere. Solutions of benzyl alcohol (216mg, 208 μL, 2 mmol) and salicylaldehyde (24.4 mg, 22 μL, 0.20 mmol,10 mol%) were added successively via syringe. The resulting mixture was heated to 70°C and the reaction progress was monitored by TLC and ^{1}H NMR spectroscopy analysis. The salicylaldehyde was recovered through vacuum distillation using Kügelrohr apparatus (1 torr, 50°C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer waspurified by column chromatography on a shot pad of silica gel (hexane/EtOAc = 1/5) to provide the pure benzyl mandelate **1f** (455 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 7H), 7.21-7.19 (m, 2H), 5.24 (d, *J* = 12.0, 1H), 5.22 (d, *J* = 5.2, 1H), 5.14 (d, *J* = 12.0, 1H), 3.41 (d, *J* = 5.2,1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 138.2, 135.0, 128.6, 128.5, 128.4, 127.9, 126.6, 73.0, 67.6; MS $C_{15}H_{14}O_3$ (EI, 242) 242 (M^+, 4), 226 (12), 107 (100), 92(18), 90(24), 80(12), 79(19), 77(11); TLC R_f 0.34 (EtOAc/Hexane, 1/5); Mp: 96-98°C. [5a]

Synthesis of dioxolanone III from mandelic acid and benzaldehyde (equation 1):

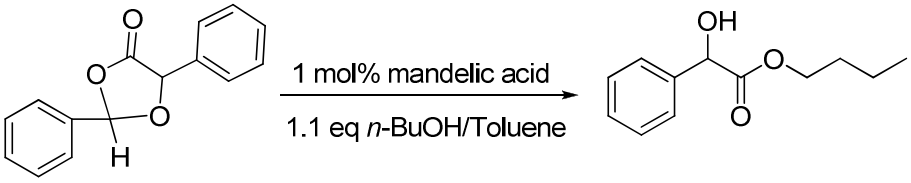


1 : 1

Mandelic acid (608 mg, 4 mmol) was placed in a 10 mL single-neck round-bottomed flask and

benzaldehyde (415 μL, 2 mmol) in cyclohexane (5 mL) was added to the flask via a syringe, at room temperature under nitrogen atmosphere. The resulting mixture was refluxed (70°C) for 10 h. The reaction mixture was gradually cooled to room temperature, and the organic solvent and unreacted benzaldehyde were evaporated under vacuum to give the crude product. The crude product was dissolved in ether (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL × 2) to remove the unreacted mandelic acid. The organic layer was dried with Na_2SO_4 and filtrated. Evaporation of the organic solvent provided pure 2,5-diphenyl-[1,3]dioxolan-4-one (dioxolanone **III**, 442 mg, 46% yield), with 99.6% of *cis* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.43 (m, 10H), 6.57 (s, H), 5.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 134.3, 133.3, 130.7, 129.3, 128.79, 128.75, 127.0, 126.8, 103.2, 77.19; MS $C_{15}H_{12}O_3$ (EI, 240) 240 (M^+, 16), 151(32) 105 (100), 93(23), 90(24), 79(43), 77(76); Mp: 102-104°C. [6]

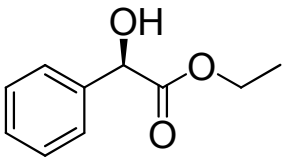
Synthesis of *n*-butyl mandelate 1d from dioxolanone III (equation 2):



To a dry 25 mL, two-neck round-bottom flask was added 2,5-diphenyl-[1,3]dioxolan-4-one (dioxolanone III, 240 mg, 1.0 mmol), *n*-butanol (82 mg, 102 μL, 1.1 mmol), and 1 mol% of mandelic acid (1.5 mg, 0.01 mmol) in anhydrous toluene (10 mL) under nitrogen atmosphere. The reaction mixture was heated at 70°C for 10 h. The mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent gave pure *n*-butyl mandelate 1d (196 mg, 94 % yield).

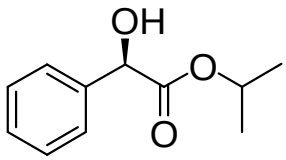
Analytical data for mandelate 1b, 1c, 1e, 1g-1i:

2-Hydroxy-2-phenyl-acetic acid ethyl ester[5a]-1b



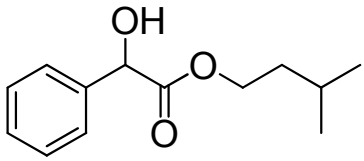
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.32 (m, 5H, ArH), 5.16 (d, *J* = 5.6, 1H), 4.31-4.14 (m, 2H), 3.44 (d, *J* = 5.6, 1H, OH), 1.23 (t, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 138.4, 128.5, 128.3, 126.5, 72.8, 62.1, 14.0 ; MS $C_{10}H_{12}O_3$ (EI, 70 eV, 180.2): 180 (M^+, 3), 107 (100), 79 (26), 77 (22), 32 (46); TLC R_f 0.31 (EtOAc/Hexane, 1/5); $[\alpha]^{32}$ -125.68 (*c* 1.0, $CHCl_3$) (lit.[5a] $[\alpha]^{25}$ -130 (*c* 1.0, $CHCl_3$); The absolute configuration was deduced to be *R* according to the sign of optical rotation.

2-Hydroxy-2-phenyl-acetic acid isopropyl ester[5a] -1c



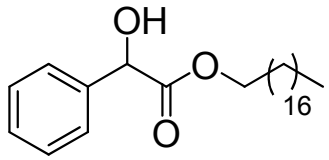
Data: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43-7.31 (m, 5H) 5.12-5.02 (m, 2H), 3.45 (bs, 1H, OH), 1.28 (d, *J* =6.4, 3H), 1.11 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.2, 138.6, 128.4, 128.2, 126.4, 72.9, 70.1, 21.6, 21.3; MS $C_{11}H_{14}O_3$ (EI, 70 eV, 194): 194 (M^+, 2), 107 (100), 79 (40), 77 (27), 43 (14); TLC R_f 0.38 (EtOAc/Hexane, 1/5); $[\alpha]^{21}$ -89.12 (*c* 1.0, MeOH) (lit.[5a] $[\alpha]^{20}$-91.6 (*c* 1.0, MeOH); The absolute configuration was deduced to be *R* according to the sign of optical rotation.

2-Hydroxy-2-phenyl-acetic acid isoarmyl ester[5c]-1e



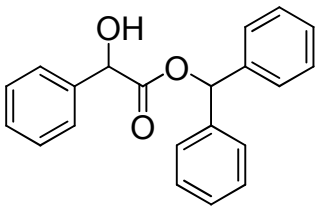
Data: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5H), 5.16 (d, *J* =5.6, 1H), 4.24-4.13 (m, 2H), 3.58 (bs, 1H, OH), 1.57-1.47 (m, 3H), 0.85 (d, *J* =6.4, 3H), 0.83 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7, 138.4, 128.5, 128.3, 126.5, 72.8, 64.8, 36.9, 24.8, 22.2; MS $C_{13}H_{18}O_3$ (EI, 70 eV, 222): 222 (M^+, 4), 107 (100), 87 (56), 77 (35); TLC R_f 0.32 (EtOAc/Hexane, 1/5);

2-Hydroxy-2-phenyl-acetic acid octadodecyl ester[7]-1g



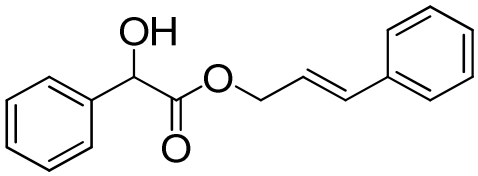
Data: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 5.16 (d, *J*) 5.7, 1H), 4.17-4.14 (m, 2H), 3.46 (d, *J*) 6.2, 1H), 1.57 (quint, *J*) 6.8, 2H), 1.30-1.20 (m, 30H), 0.88 (t, *J*) 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 138.5, 128.5, 128.4, 126.5, 72.8, 66.3, 31.9, 29.69, 29.65, 29.61, 29.5, 29.42, 29.35, 29.0, 28.4, 25.6, 22.7, 14.1; MS (FAB^+): calcd for $C_{26}H_{44}O_3$+Na: 427.3188, found: 427.3191; TLC R_f 0.26 (EtOAc/hexane, 1/10);

2-Hydroxy-2-phenyl-acetic acid benzhydryl ester[5a]-1h



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.31 (m, 10H), 7.21-7.15 (m, 3H), 6.94-6.90 (m, 3H), 5.30 (d, *J* = 5.6, 1H), 3.54 (d, *J* = 5.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 139.2, 139.1, 138.0, 128.53, 128.51, 128.45, 128.2, 127.7, 127.3, 126.8, 126.2, 78.6, 73.1; MS $C_{21}H_{18}O_3$ (EI, 318.): 318 (12), 277 (M^+, 100), 165 (66), 148 (70); TLC R_f 0.35 (EtOAc/Hexane, 1/5); mp: 56-57^{o}C.

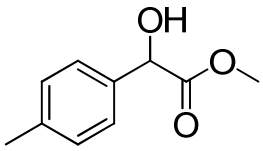
2-Hydroxy-2-phenyl-acetic acid cinnamyl ester-1i



Oil solid, Data: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0, 1H), 7.40-7.27 (m, 9H), 6.50 (dt, *J* = 16.0, 1.2, 1H), 6.19 (dt, *J* = 16.0, 6, 1H), 5.22 (d, *J* = 5.2, 1H), 4.85 (ddd, *J* = 12.8, 6.3, 1.2, 1H), 4.79 (ddd, *J* = 12.8, 6.4, 1.2, 1H), 3.47 (d, *J* = 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.5, 138.2, 135.9, 134.6, 128.63, 128.59, 128.52, 128.2, 126.6, 122.0, 73.0, 66.4; HR-MS (FAB^+) calcd for $C_{17}H_{16}O_3$+Na: 291.0997, found: 291.0994; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 75.92; H, 6.16; TLC R_f 0.36 (EtOAc/Hexane, 1/5).

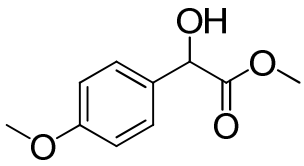
Analytical data for α-hydroxyacids 3a-3t:

2-Hydroxy-2-(*p*-tolyl)-acetic acid methyl ester[8]-3a



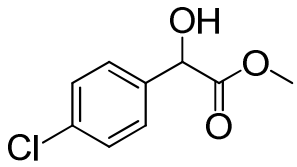
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0, 2H), 7.17 (d, *J* = 8.0, 2H), 5.16 (d, *J* = 5.6, 1H), 3.96 (d, *J* = 5.6, 1H, OH), 3.71 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 137.9, 135.3, 130.0, 126.3, 72.6, 52.4, 20.8; MS $C_{10}H_{12}O_3$ (ESI, 180): 204 ($M+Na^+$+H^+, 100), 504 ($2M+Na^+$+H^+, 72); TLC R_f 0.32 (EtOAc/Hexane, 1/5).

2-Hydroxy-2-(4-methoxy-phenyl)-acetic acid methyl ester[8]-3b



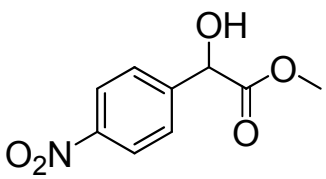
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.8, 2H), 6.88 (d, *J* = 8.8, 2H), 5.12 (d, *J* = 5.6, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.52 (m, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ174.2, 159.7, 130.4, 127.8, 114.0, 72.4, 55.2, 52.8; MS $C_{10}H_{12}O_4$: (EI, 70 eV, 196.2): 196 (M^+, 13), 137 (100), 109 (19), 77 (10); TLC R_f 0.31 (EtOAc/Hexane, 1/3).

2-(4-BromoChloro-phenyl)-2-hydroxy-acetic acid methyl ester[9]-3c



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.32-7.30 (m, 2H), 5.14 (d, *J* = 5.2, 1H,), 3.77 (s, 3H), 3.44 (d, *J* = 5.2, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 137.2, 131.7, 128.2, 122.5, 72.2, 53.0; MS $C_9H_9BrClO_3$ (EI, 70 eV, 200.6): 200 (M^+, 31), 227 (44), 79 (51), 187 (100), 77 (83), 43 (100); TLC R_f 0.32 (EtOAc/Hexane, 1/5).

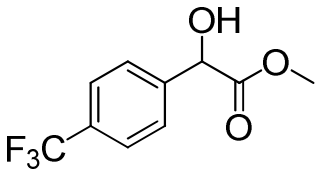
2-Hydroxy-2-(4-nitro-phenyl)-acetic acid methyl ester[8]-3d



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 5.31 (s, 1H), 3.80 (s, 3H), 3.65 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 164.4, 161.1, 133.9, 128.3, 115.6, 72.1, 53.1; MS $C_9H_9NO_5$: (EI, 70 eV, 211.2): 212 (M^++1, 2), 152 (96), 150 (50), 134 (48), 104 (100), 77 (54);

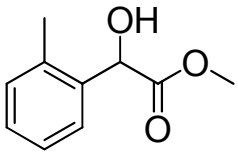
TLC R_f 0.28 (EtOAc/Hexane, 1/3). $C_9H_9NO_5$: 211.17.

2-Hydroxy-2-(4-trofluoromethyl-phenyl)-acetic acid methyl ester[10]-3e



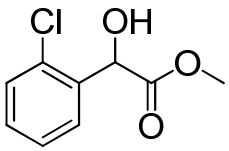
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0, 2H), 7.57 (d, *J* = 8.0, 2H), 5.26 (s, 1H), 3.79 (s, 3H,) 3.58 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.3, 142.0, 130.7, 126. 9, 125.45, 125.41, 72.3, 53.0; MS $C_{10}H_9F_3O_3$ (EI, 70 eV, 234.2): 234 (M^+, 16), 217 (35), 175 (23), 147 (100); TLC R_f 0.28 (EtOAc/Hexane, 1/3).

2-Hydroxy-2-(*o*-tolyl)-acetic acid methyl ester[11]-3f



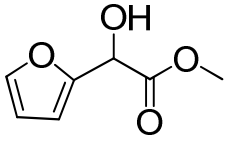
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5H), 5.38 (d, *J* = 5.2, 1H), 3.77 (s, 3H), 3.48 (d, *J* = 5.2, 1H, OH), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 136.5, 136.3, 130.8, 128.5, 126.8, 126.2, 70.4, 52.9, 19.2; MS $C_{10}H_{12}O_3$ (ESI, 180): 204 ($M+Na^+$+H^+, 66), 384 ($2M+Na^+$+H^+, 100); TLC R_f 0.36 (EtOAc/Hexane, 1/5).

2-(2-Chloro-phenyl)-2-hydroxy-acetic acid methyl ester[11]-3g



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.29-7.27 (m, 2H), 5.57 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 135.9, 133.3, 129.7, 129.6, 128.7, 127.0, 70.2, 50.3; MS $C_9H_9ClO_3$ (EI, 70 eV, 200.62): 200 (M^+, 5), 143 (25), 141 (96), 77 (100), 51 (23), 32 (49); TLC R_f 0.39 (EtOAc/Hexane, 1/5).

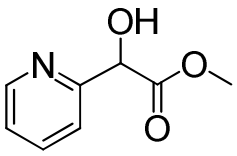
2-(Furan-2-yl)-2-hydroxy-acetic acid methyl ester[12]-3h



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.6, 1H), 6.35-6.32 (m, 2H), 5.19 (S, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 150.6, 142.9, 110.4, 108.6, 66.7, 53.0; MS $C_7H_8O_4$ (ESI, 156):

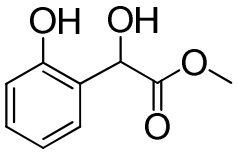
179 (M+Na^+,35), 335 (2M+Na^+, 100);TLC R_f 0.40 (EtOAc/Hexane, 1/19).

Hydroxy-2-pyridyl-acetic acid methyl ester[12]-3i



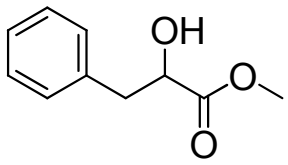
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.8, 1.2, 1H), 7.73 (td, *J* = 7.6, 1.6, 1H), 7.48 (d, *J* = 8.0, 1H), 7.26 (dd, *J* = 4.8, 1.2, 1H), 5.29 (s, 1H), 3.76 (S, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 141.1, 132.1, 128.2, 123.9, 113.7, 73.2, 52.9; MS $C_8H_9NO_3$ (ESI, 167.1): 190 (M+Na^+,29), 357 (2M+Na^+,100); TLC R_f 0.28 (EtOAc/Hexane, 1/3).

2-(2-Hydroxyl-phenyl)-2-hydroxy-acetic acid methyl ester[12]-3j



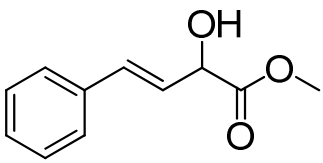
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.16 (m, 2H), 6.89-6.83 (m, 2H), 5.03 (S, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 154.8, 130.1, 129.1, 122.8, 120.4, 117.0, 72.2, 53.1; MS $C_9H_{10}O_4$ (ESI, 182.2): 205 (M+Na^+, 33), 423 (2M+Na^+, 100); TLC R_f 0.37 (EtOAc/Hexane, 1/2).

2-hydroxy-3-phenyl-propionic acid methyl ester[9]-3k



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 4.48-4.44 (m, 1H), 3.78 (s, 3H), 3.13 (dd, *J* = 14.0, 4.4, 1H), 2.97 (dd, *J* = 14.0, 7.2, 1H), 2.73 (d, *J* = 6.0, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 136.3, 129.3, 128.3, 126.7, 71.2, 52.2, 40.4; MS $C_{10}H_{12}O_3$ (EI, 70 eV, 180.2): 180 (M^+, 4), 162 (19), 103 (27), 91 (100), 32 (28); TLC R_f 0.30 (EtOAc/Hexane, 1/6).

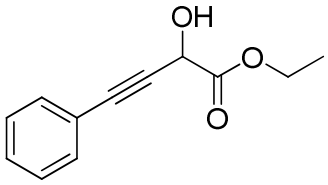
2-Hydroxy-4-phenyl-but-3-enoic acid methyl ester[13]-3l



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (d, *J* = 7.2, 2H), 7.35-7.31 (t, *J* = 7.2, 2H), 7.28-7.24 (t, *J* = 7.2, 1H), 6.81 (d, *J* = 16.0, 1H), 6.26 (dd, *J* = 16.0, 5.6, 1H), 4.86 (d, *J* = 5.6, 1H), 3.83 (s, 3H), 3.16 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.0, 132.3, 128.5, 128.0, 126.6, 125.2,

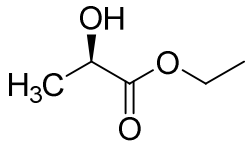
71.3, 52.9; MS $C_{11}H_{12}O_3$ (EI, 70 eV, 192.2): 192 (M^+, 2), 147 (28), 133 (15), 131 (100), 102 (41), 77 (34), 51 (21); TLC R_f 0.30 (EtOAc/Hexane, 1/3);

2-Hydroxy-4-phenyl-but-3-ynoic acid ethyl ester[5a]-3m



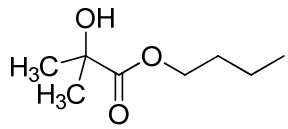
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.6, 2H), 7.34-7.31 (m, 3H), 5.06 (s, 1H), 4.36 (q, *J*= 7.2, 2H), 1.36 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.3, 131.8, 128.8, 128.2, 121.8, 85.3, 84.2, 62.8, 61.9, 14.0; MS $C_{12}H_{12}O_3$ (ESI, 204): 227 ($M+Na^+$, 28), 431 ($2M+Na^+$, 67), 635 ($3M+Na^+$, 100); TLC R_f 0.36 (EtOAc/Hexane, 1/5).

(*R*)-lactic acid ethyl ester[5b]-3n



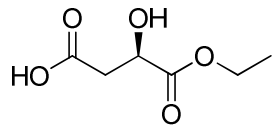
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (q, *J* = 7.2, 1H), 4.21 (q, *J*= 1.2, 2H), 2.86 (br, 1H, OH), 1.36 (d, *J* = 7.2, 3H), 1.24 (t, *J*= 1.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)δ175.2, 66.7, 61.6, 20.5, 14.0; MS $C_5H_{10}O_3$ (ESI, 118): 141 ($M+Na^++H^+$, 29), 259 ($2M+Na^+$, 63), 377 ($3M+Na^+$, 100); TLC R_f 0.36 (EtOAc/Hexane, 1/2); $[\alpha]^{28}$ -10.8 (*c* 3.0, CH_3CN); (lit. $[\alpha]^{24}$ -13.4 (*c* 3.0, CH_3CN) for (*R*))

2-Hydroxy-2-methyl-propanoic acid *n*-butyl ester[5b]-3o



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (t, *J* = 6.4, 2H), 1.61 (quin, *J* = 7.2, 2H), 1.39 (s, 3H), 1.32 (m, 2H),0.91 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 72.0, 65.6, 30.5, 27.1, 18.9, 13.5; MS $C_8H_{16}O_3$ (ESI, 160) 183 ($M+Na^+$, 30), 343 ($2M+Na^+$, 100); TLC R_f 0.35 (EtOAc/Hexane, 1/5).

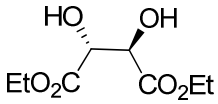
(*R*)-2-hydroxybutanedioic acid 1-methylester[5e]-3p



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (br, 1H, OH), 4.49 (dd, *J* = 6.4, 4.4, 1H), 4.25 (ddd, *J* = 14.4, 7.2, 2.4, 2H), 2.89 (dd, *J* = 16.8, 4.0, 2.4, 1H), 2.81 (dd, *J* = 16.8, 6.4, 2H), 1.28 (t, *J* = 6.8, 3H); ^{13}C NMR

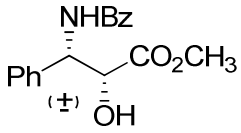
(100 MHz, $CDCl_3$) δ 175.3, 173.3, 67.1, 62.2, 38.4, 29.6, 14.0; MS $C_6H_{10}O_5$ (ESI, 162) 185 ($M+Na^+$, 19), 167 ($M+Na^+-H_2O$, 100); TLC R_f 0.23 (EtOAc/MeOH, 20/1); $[\alpha]^{27}$ -5.5 (*c* 2.0, CH_3OH); lit. $[\alpha]^{24}$ -5.2 (*c* 2.0, CH_3OH) for (*R*));

_D_-(-)-tartaric acid diethyl ester[5b]-3q



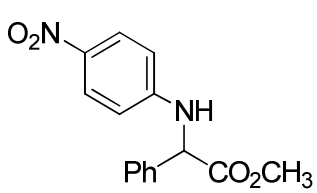
Data: ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2H), 4.25 (dd, *J* = 7.2, 1.2, 2H), 4.22 (dd, *J* = 6.8, 1.2, 2H), 3.97 (br, 1H, OH), 1.25 (t, *J*= 7.2, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 72.1, 62.1, 13.9; MS $C_8H_{14}O_6$ (ESI, 206.2): 229 ($M+Na^+$, 28), 435 ($2M+Na^+$, 100); TLC R_f 0.36 (EtOAc/Hexane, 1/2); $[\alpha]^{27}$ +8.9 (*c* 2.5, EtOH); (lit. $[\alpha]^{20}$ +8.5 (*c* 2.46, EtOH).

Racemic-methyl (2*R*, 3*S*)- *N*-Benzoylamino-2-hydroxy-3-phenyl-propanoate[5a]-3r



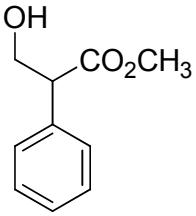
Data: ^1H NMR (400 MHz, CDCl3) δ 7.76 (d, *J* = 7.4, 2H), 7.53-7.30 (m, 8H), 7.01 (d, *J* = 8.8, 1H, NH), 5.74 (d, *J* = 8.8, 1.9, 1H), 4.63 (d, *J* = 1.9, 1H), 3.84 (s, 3H, OCH3), 3.41 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 166.9, 138.7, 134.1, 131.8, 128.7, 128.6, 127.9, 127.1, 127.0, 73.2, 55.8, 53.3; MS $C_{17}H_{17}NO_4$ (ESI, 299): 621 ($M2+Na^+$, 100), 323 ($M+Na^+$+1, 35); TLC R*f* 0.22 (EtOAc/hexane,1/2).

(4-Nitrophenylamino)-phenyl-acetic acid methyl ester[3]-3s



Data: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.2, 2H), 7.45-7.32 (m, 5H), 6.50 (d, *J* = 9.2, 2H), 5.84 (d, *J* = 5.2, 1H), 6.14 (d, *J* = 5.6, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 150.8, 135.9, 129.2, 128.9, 127.0, 126.2, 112.1, 59.8, 53.3; MS $C_{15}H_{14}N_2O_4$ (ESI, 286.2): 309 ($M+Na^+$, 21), 295 ($2M+Na^+$, 70), 881 ($3M+Na^+$, 100); TLC R_f 0.25 (EtOAc/MeOH, 2/1)

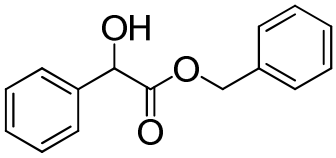
Methyl-2-phenyl-3-hydroxypropionate[14]-3t



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.14 (t, *J* = 9.6, 1H), 3.83 (dd, *J* = 8.8, 5.2, 2H), 3.7 (br, 1H, OH), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 135.5, 128.7, 128.0, 127.6, 64.4, 53.9, 52.1; MS $C_{10}H_{12}O_3$ (ESI, 180.2) 203 ($M+Na^+$, 43), 186 ($M+H_2O+Na^+$, 100), 635 ($3M+Na^+$, 100); TLC R_f 0.34 (EtOAc/Hexane, 1/5).

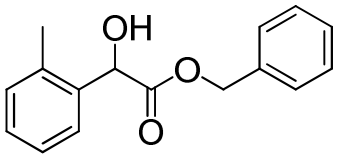
Analytical data for α-hydroxyacids 4a-4o:

2-Hydroxy-2-phenyl-acetic acid benzyl ester[5a]-4a



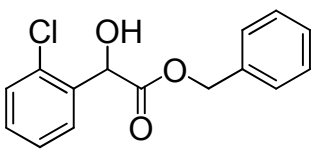
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 7H), 7.21-7.19 (m, 2H), 5.24 (d, *J* = 12.0, 1H), 5.22 (d, *J* = 5.2, 1H), 5.14 (d, *J* = 12.0, 1H), 3.41 (d, *J* =5.2,1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.5, 138.2, 135.0, 128.6, 128.5, 128.5, 128.4, 127.9, 126.6, 73.0, 67.6; MS $C_{15}H_{14}O_3$ (EI, 242): 242 (M^+, 4), 226 (12), 107 (100), 92(18), 90(24), 80(12), 79(19), 77(11); TLC R_f 0.34 (EtOAc/Hexane, 1/5); mp: 96-98^{o}C.

2-Hydroxy-2-(*o*-tolyl)-acetic acid benzyl ester[5a]-4b



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 4H), 7.23-7.17 (m, 5H), 5.42 (d, *J* = 5.2, 1H), 5.25 (d, *J* = 12.4, 1H), 5.15 (d, *J* = 5, 12.4, 1H), 3.35 (d, *J* = 5.2, 1H, OH), 2.40(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 136.5, 136.3, 135.0, 130.7, 128.44, 128.38, 128.3, 127.8, 126.7, 126.2, 70.4, 67.4, 19.2; TLC R_f 0.38 (EtOAc/Hexane, 1/6); MS $C_{16}H_{16}O_3$ (EI, 70eV, 256): 256 (M^+, 1), 120 (100), 90 (38).

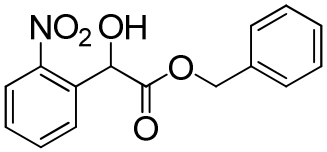
2-(2-Chloro-phenyl)-2-hydroxy-acetic acid benzyl ester[5a]-4c



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.20-7.10 (m, 7H), 5.53 (d, *J* = 5.2, 1H), 5.14 (d, *J* = 12.4, 1H), 5.07 (d, *J* = 12.4, 1H),

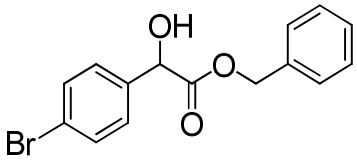
3.54 (d, *J* = 5.2, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 135.9, 134.9, 133.5, 129.9, 129.7, 128.7, 128.4, 128.3, 127.7, 127.1, 70.4, 67.7; MS $C_{15}H_{13}ClO_3$ (ESI, 275): 299 ($M+Na^+ + H^+$, 6), 572 ($2M+Na^+$, 51); TLC R_f 0.39 (EtOAc/Hexane, 1/4).

2-Hydroxy-2-(2-nitro-phenyl)-acetic acid benzyl ester[5d]-4d



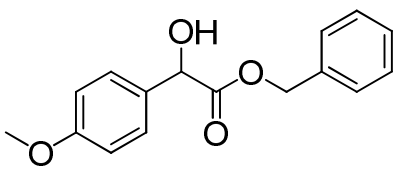
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0, 1H), 7.66-7.60 (m, 2H), 7.50 (td, *J* = 8.0, 1.6, 1H,), 7.32-7.30 (m, 3H), 7.22-7.20 (m, 2H), 5.89 (d, *J* = 4.8, 1H), 5.22 (d, *J* = 12.0, 1H), 5.16 (d, *J* = 12.0, 1H), 3.59 (d, *J* = 5.2, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 147.9, 134.6), 133.4, 132.9, 129.8, 129.3, 128.6, 128.1, 125.2, 70.2, 68.2; TLC R_f 0.36 (EtOAc/Hexane, 1/3); MS $C_{15}H_{15}NO_5$ (EI, 70 eV, 287.1): 287 (M^+, 3), 122 (100), 107 (65), 90 (33); mp: 89-91^{o}C.

2-(4-Bromo-phenyl)-2-hydroxy-acetic acid benzyl ester[5a]-4e



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.43-7.29 (m, 5H), 7.22-7.21 (m, 2H), 5.23(d, *J* = 12.0, 1H), 5.17 (d, *J* = 5.6, 1H), 5.14 (d, *J* = 12.0, 1H), 3.43 (d, *J* = 5.6, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.1, 134.7, 131.6, 128.5, 128.48, 128.0, 122.4, 72.3, 67.8; MS $C_{15}H_{13}BrO_3$ (EI, 70 eV, 320): 320 (M^+, 8), 186 (100), 107 (72), 90 (28); TLC R_f 0.38 (EtOAc/Hexane, 1/4); mp: 107-109^{o}C.

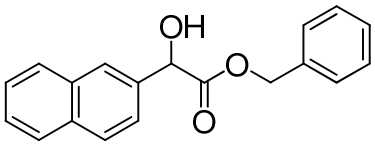
2-Hydroxy-2-(4-methoxy-phenyl)-acetic acid benzyl ester[5a]-4f



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 5H), 7.23-7.21 (m, 2H), 6.89-6.87 (m, 2H) , 5.24 (d, *J* = 12.4, 1H), 5.17 (d, *J* = 6.0, 1H), 5.13 (d, *J* = 12.4, 1H), 3.81(s, 3H), 3.42 (d, *J* = 6.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.7, 135.0, 130.4, 128.5, 128.4, 127.9, 127.85, 114.0, 72.5, 67.5, 55.2; TLC R_f 0.39 (EtOAc/Hexane, 1/3); MS $C_{16}H_{16}O_4$ (EI, 70 eV, 272.1): 272 (M^+, 8),

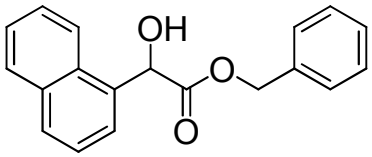
165 (21), 120 (100), 107 (60), 91 (30); mp: 94-96^{o}C.

2-Hydroxy-1-(naphthalen-1-yl)-acetic acid benzyl ester[5a]-4g



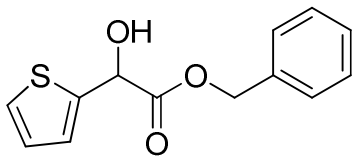
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91(s, 1H), 7.86-7.82 (m, 2H), 7.54-7.50 (m, 3H), 7.31-7.29 (m, 3H), 7.22-7.20 (m, 2H), 5.41 (s, 1H), 5.27 (d, *J* = 12.3, 1H), 5.15 (d, *J* = 12.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 135.5, 134.9, 133.3, 133.1, 128.5, 128.4, 128.39, 128.1, 128.0, 127.6, 126.28, 126.27, 125.9, 124.2, 73.1, 67.7; MS $C_{19}H_{16}O_3$ (ESI, 292): 315($M+Na^+$, 6), 607 ($2M+Na^+$); TLC R_f 0.32 (EtOAc/Hexane, 1/4); mp: 121-124^{o}C.

2-Hydroxy-2-(naphthalen-1-yl)-acetic acid benzyl ester[5a]-4h



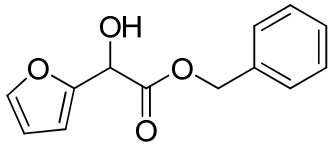
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.14 (m, 1H), 7.89-7.84 (m, 2H), 7.53-7.42 (m, 4H), 7.25-7.21 (m, 3H), 7.10-7.08 (m, 2H), 5.88 (d, *J* = 5.2, 1H), 5.25 (d, *J* = 12.4, 1H), 5.13 (d, *J* = 12.4, 1H), 5.48 (d, *J* = 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 134.8, 133.87, 133.86, 130.9, 129.3, 128.6, 128.3, 128.1, 127.7, 126.4, 125.7, 125.6, 125.1, 123.7, 71.3, 67.4; MS $C_{19}H_{16}O_3$ (EI, 292): 292 (M^+, 13), 157 (100), 129 (48), 128 (50), 91 (18); TLC R_f 0.34 (EtOAc/Hexane, 1/4); mp: 128-130^{o}C.

2-Hydroxy-2-(thiophen-2-yl)-acetic acid benzyl ester[5a]-4i



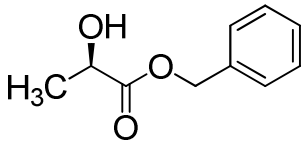
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 3H), 7.31-7.28 (m, 3H), 7.09 (dd, *J* = 6.6, 1.0, 1H), 6.98 (dd, *J* = 5.4, 4, 1H), 5.47 (s, 1H), 5.25 (q, *J* = 13.2, 2H), 3.47 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 141.2, 134.7, 128.6, 128.55, 128.17, 126.8, 125.7, 125.4, 69.1, 68.0; MS $C_{13}H_{12}O_3S$ (ESI, 248): 519 ($2M+Na^+$, 100); TLC R_f 0.22 (EtOAc/Hexane, 1/19).

2-(Furan-2-yl)-2-hydroxy-acetic acid benzyl ester[5a]-4j



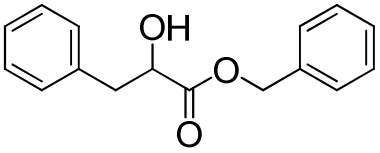
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.2, 1H), 7.37-7.32 (m,3H), 7.31-7.26 (m, 2H), 6.53 (d, *J* = 1.6, 2H), 5.27 (d, *J* = 12.4 H), 5.25 (s, 1H), 5.24 (d, *J* = 12.4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 150.6, 143.0, 134.8, 128.56, 128.5, 128.1, 110.5, 108.7, 67.9, 66.9; MS $C_{13}H_{12}O_4$ (ESI, 232): 255 ($M+Na^+$, 30), 487 ($2M+Na^+$, 100); TLC R_f 0.20 (EtOAc/Hexane, 1/19).

(*R*)-2-Hydroxy-propionic acid benzyl ester[5a]-4k



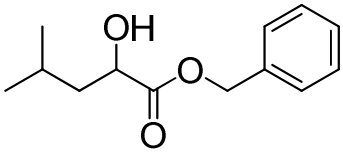
Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 5H), 5.21 (s, 2H), 4.32 (q, *J* = 6.8, 1H), 2.84 (bs, 1H, OH), 1.44 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 135.2, 128.6, 128.5, 128.2, 67.3, 66.8, 20.3; MS $C_{10}H_{12}O_3$ (ESI, 180) 204 ($M+Na^++H^+$, 100), 383 ($2M+Na^+$, 84); TLC R_f 0.30 (EtOAc/Hexane, 1/7). $[\alpha]^{30}$ -12.4 (*c* 1.02, $CHCl_3$); (lit. $[\alpha]^{23}$ -15.5 (*c* 1.02, $CHCl_3$)

2-hydroxy-3-phenyl-propionic acid benzyl ester[5a]-4l



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 5H), 7.31-7.28 (m, 3H), 7.20-7.19 (m, 2H), 5.23 (d, *J* = 12.0, 1H, 5.19 (d, *J* = 12.0, 1H), 4.52 (td, *J* = 4.8, 4.8, 1H), 3.16 (dd, *J* = 12.0, 4.8, 1H, OH) , 3.04-2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 136.1, 134.9, 129.4, 128.5, 128.48, 128.3, 126.7, 71.2, 67.2, 40.4; MS $C_{16}H_{16}O_3$ (EI,70 eV, 256.3): 256 (M^+, 2), 238 (25), 192 (38), 121 (84), 103 (26), 91 (100), 77 (15); TLC R_f 0.38 (EtOAc/Hexane, 1/5).

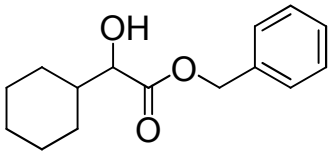
2-Hydroxyl-4-methyl-pentanoic acid benzyl ester[5a]-4m



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H), 5.21 (s, 2H), 4.25 (dt, *J* = 8.0, *J* = 5.6, 1H), 2.69-2.66 (m, 1H, OH), 1.89 (heptet, *J* = 6.8, 1H), 1.60-1.56 (m, 2H), 0.94 (s, *J* = 6.8, 3H), 0.93 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.7, 135.2, 128.6, 128.5, 128.3, 69.2, 67.3, 43.4, 24.4, 23.2,

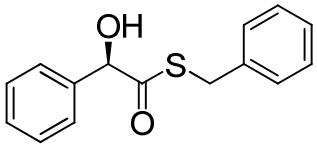
21.5; MS $C_{13}H_{18}O_3$ (EI, 222): 222 (M^+, 3), 91 (100), 87 (31), 69 (36); TLC R_f 0.30 (EtOAc/Hexane, 1/15).

2-Cyclohexyl-2-hydroxyl-acetic acid benzyl ester[5a]-4n



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38- 7.34 (m, 5H), 5.22 (s, 2H), 4.06 (dd, *J* = 6.0, 3.6, 1H), 2.74 (d, *J* = 6.0, 1H, OH), 1.77-1.63 (m, 5H), 1.38-1.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 135.2, 128.6, 128.5, 128.3, 74.8, 67.2, 42.0, 29.0, 26.2, 26.18, 26.0, 25.9; MS $C_{15}H_{20}O_3$ (EI, 248): 248 (M^+, 3), 113 (49), 95 (100) , 92 (13), 91 (61); TLC R_f 0.35 (EtOAc/Hexane, 1/15).

(*R*)-2-Hydroxy-2-phenyl-thioacetic acid S-benzyl ester.[15]-4o



Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 5H, ArH), 7.30-7.27 (m, 5H), 5.21 (s, 1H), 4.16 (d, *J* = 13.6, 1H), 4.10 (d, *J* = 13.6, 1H), 3.57 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 137.8, 136.7, 128.8, 128.79, 128.7, 128.6, 127.3, 127.0, 79.7, 33.2; MS $C_{15}H_{14}O_2S$ (EI, 70 eV, 258.3): 259 (M^++1, 5), 213 (23), 124 (26) , 107 (100), 91 (31) , 79 (25), 77 (16); TLC R_f 0.37 (EtOAc/Hexane, 1/6); mp: 83-85^{o}C.

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