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Supporting Information

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Organocatalytic Conjugate Addition of Malonates to α,ß-Unsaturated Aldehydes: Asymmetric Formal Synthesis of (-)-Paroxetine, Chiral Lactams and Lactones

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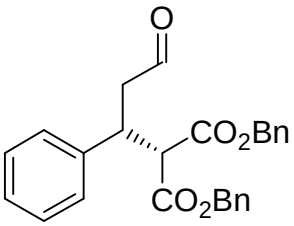
General. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ (δ = 77.0) for ^{13}C NMR. Chromatography was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh) using mixtures of Et_2O and *n*-pentane or EtOAc and *n*-pentane as eluents. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. NMR data of known compounds are in agreement with literature values.

Materials. All solvent were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. α,ß-Unsaturated aldehydes (**7e**, **7f**, **7g**, **7h**, **7i**, **7j**) were prepared following the procedure described in the literature.[1] Cinnamylaldehyde (**7a**) was purified by distillation before usage and stored under nitrogen. Catalysts **(*R*)-10** and **(*S*)-10** were prepared as described in the literature.[2]

General procedure for the organocatalytic addition of malonates to a,ß-unsaturated aldehydes: The catalyst 15.0 mg (0.025 mmol, 0.1 equiv.) **10** was added to a stirred ice-cooled (0 °C) solution of the α,ß-unsaturated aldehyde (0.50 mmol, 2.0 equiv.) **7** in 1.0 mL solvent followed by the addition of (0.25 mmol, 1.0 equiv.) malonate **8**. The reaction mixture was stirred for 96 h at 0 °C and then filtered through 1-2 cm bed of silica washing through with Et_2O and CH_2Cl_2. The solvents were evaporated under vacuum. The crude product was subjected to FC on silica gel (Et_2O/*n*-pentane/CH_2Cl_2 1:10:0.1) to yield the desired addition product.

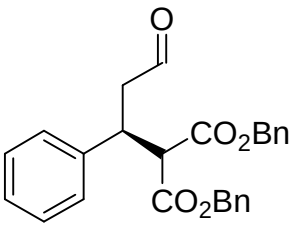
(*R*)-2-(3-Oxo-1-phenylpropyl)malonic acid dibenzyl ester (6a)



(*R*)-6a

Yellow solid. Yield: 80% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.59 (t, ^3J = 1.5 Hz, 1H), 7.43–7.09 (m, 15H), 5.20 (s, 1H), 5.19 (s, 1H), 4.95 (s, 1H), 4.94 (s, 1H), 4.10 (m, 1H), 3.89 (d, ^3J = 9.0 Hz, 1H), 2.92 (dd, ^3J = 1.5 Hz, ^3J = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 199.9, 167.7, 167.1, 139.5, 135.0, 134.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.5, 67.5, 67.2, 57.4, 47.2, 39.5. HRMS: $C_{26}H_{24}O_5$ $[M+Na]^+$ calcd: 439.1521, found: 439.1507. $[\alpha]_D^{23}$ = -15.7 (c = 1.03, $CHCl_3$, 84% *ee* (*R*)).

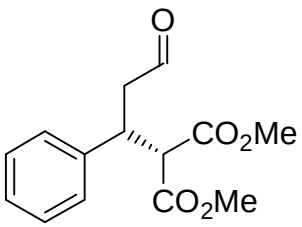
(*S*)-2-(3-Oxo-1-phenylpropyl)malonic acid dibenzyl ester (6a)



(*S*)-6a

Yellow solid. Yield: 75% using catalyst **(*R*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.59 (t, ^3J = 1.5 Hz, 1H), 7.43–7.09 (m, 15H), 5.20 (s, 1H), 5.19 (s, 1H), 4.95 (s, 1H), 4.94 (s, 1H), 4.10 (m, 1H), 3.89 (d, ^3J = 9.0 Hz, 1H), 2.92 (dd, ^3J = 1.5 Hz, ^3J = 6.3 Hz, 2H). $[\alpha]_D^{23}$ = +16.8 (c = 0,81, $CHCl_3$, 90% *ee* (*S*)).

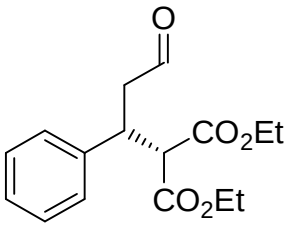
(*R*)-2-(3-Oxo-1-phenylpropyl)malonic acid dimethyl ester (6b)



6b

Colourless liquid. Yield: 85% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.61 (t, ^{3}J = 1.6 Hz, 1H), 7.33–7.22 (m, 5H), 4.04 (m, 1H), 3.78 (d, ^{3}J = 2.5 Hz, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 2.94 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.8, 168.2, 167.6, 139.5, 128.6, 127.8, 127.4, 57.0, 52.6, 52.3, 47.2, 39.3. HRMS: $C_{14}H_{16}O_5$ [M+Na]$^+$ calcd: 287.0895, found: 287.0882. $[\alpha]_D^{23}$ = -29.8 (c = 0.56, $CHCl_3$, 93% *ee* (*R*)).

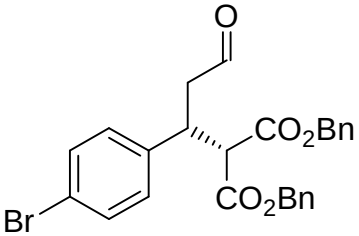
(*R*)-2-(3-Oxo-1-phenylpropyl)malonic acid diethyl ester (6c)



6c

Colourless liquid. Yield: 42% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.58 (t, ^{3}J = 1.5 Hz, 1H), 7.30–7.19 (m, 5H), 4.20 (q, ^{3}J = 7.1 Hz, 2H), 4.01 (dt, ^{3}J = 9.7 Hz, ^{3}J = 5.3 Hz, 1H), 3.93 (q, ^{3}J = 7.1 Hz, 2H), 3.70 (d, ^{3}J = 10.1 Hz, 1H), 2.90 (m, 2H), 1.25 (t, ^{3}J = 7.1 Hz, 3H), 0.99 (t, ^{3}J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 200.0, 167.9, 167.3, 139.6, 128.6, 128.0, 127.4, 61.7, 61.3, 57.4, 47.3, 39.4, 13.9, 13.6. HRMS: $C_{16}H_{20}O_5$ [M+Na]$^+$ calcd: 315.1208, found: 315.1210. $[\alpha]_D^{23}$ = -25.8 (c = 1.02, $CHCl_3$, 89% *ee* (*R*)).

(*R*)-2-(3-Oxo-1-(4-bromophenyl)propyl)malonic acid dibenzyl ester (6f)

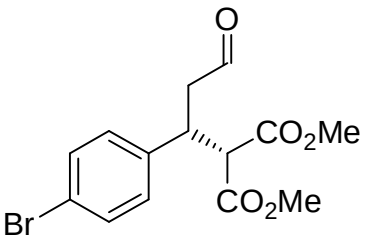


6f

White solid. Yield: 84% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.53 (dd, ^{3}J = 1.0 Hz, ^{3}J = 1.5 Hz, 1H), 7.36–7.26 (m, 10H), 7.06–7.04 (m, 4H), 5.15 (s, 2H), 4.92 (s, 2H), 4.00 (dt, ^{3}J = 9.4 Hz, ^{3}J = 5.3 Hz, 1H), 3.78 (d, ^{3}J = 9.4 Hz, 1H), 2.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.2, 167.6, 138.6, 134.8, 134.7, 131.8, 129.8, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 67.6, 67.4, 57.0, 47.1, 38.7. HRMS: $C_{26}H_{23}BrO_5$ [M+Na]$^+$ calcd:

517.0627, found: 517.0637. $[\alpha]_D^{23}$ = -14.9 (c = 0.53, $CHCl_3$, 90% *ee* (*R*)).

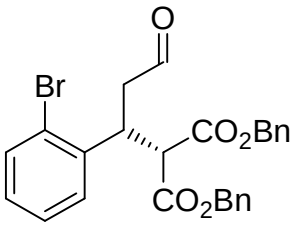
(*R*)-2-(3-Oxo-1-(4-bromophenyl)propyl)malonic acid dimethyl ester (6g)



6g

Yellow liquid. Yield: 40% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H), 7.41 (d, ^3J = 8.4 Hz, 2H), 7.12 (d, ^3J = 8.4 Hz, 2H), 3.99 (dt, ^3J = 9.1 Hz, ^3J = 5.1 Hz, 1H), 3.72 (s, 3H), 3.71 (d, ^3J = 9.1 Hz, 1H), 3.53 (s, 3H), 2.95 (ddd, ^2J = 17.5 Hz, ^3J = 5.1 Hz, ^3J = 0.8 Hz, 1H), 2.88 (ddd, ^2J = 17.5 Hz, ^3J = 9.1 Hz, ^3J = 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 199.3, 168.1, 167.6, 138.8, 131.8, 129.7, 121.4, 56.8, 52.8, 52.6, 47.0, 38.7. HRMS: $C_{14}H_{15}BrO_5$ $[M+Na]^+$ calcd: 365.0001, found: 365.0016. $[\alpha]_D^{23}$ = -20.0 (c = 0.30, $CHCl_3$, 95% *ee* (*R*)).

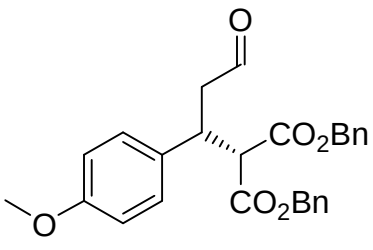
(*R*)-2-(3-Oxo-1-(2-bromophenyl)propyl)malonic acid dibenzyl ester (6h)



6h

Colourless liquid. Yield: 34% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.52 (dd, ^3J = 8.0 Hz, ^4J = 0.6 Hz, 1H), 7.37–7.04 (m, 13H), 5.12 (s, 1H), 5.11 (s, 1H), 5.01 (s, 2H), 4.56 (m, 1H), 4.06 (m, 1H), 2.97 (d, ^3J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 199.7, 167.5, 167.1, 138.6, 134.9, 133.5, 128.9, 128.5, 128.4, 128.3, 128.2, 127.7, 124.6, 67.4, 67.3, 55.2, 45.9, 38.1. HRMS: $C_{26}H_{23}BrO_5$ $[M+Na]^+$ calcd: 517.0627, found: 517.0615. $[\alpha]_D^{23}$ = -0.1 (c = 0.46, $CHCl_3$, 88% *ee* (*R*)).

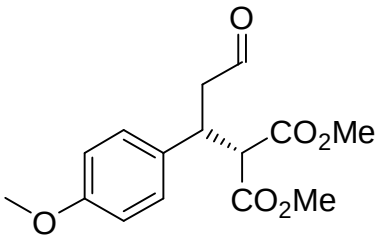
(*R*)-2-(3-Oxo-1-(4-methoxyphenyl)propyl)malonic acid dibenzyl ester (6i)



6i

Yellow solid. Yield: 93% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.53 (t, ^{3}J = 1.4 Hz, 1H), 7.34–7.24 (m, 8H), 7.10 (d, ^{3}J = 8.7 Hz, 2H), 7.05 (dd, ^{3}J = 7.5 Hz, ^{4}J = 1.8 Hz, 2H), 6.75 (d, ^{3}J = 8.6 Hz, 2H), 5.15 (s, 2H), 4.91 (s, 2H), 3.99 (dt, ^{3}J = 9.6 Hz, ^{3}J = 5.5 Hz, 1H), 3.78 (d, ^{3}J = 9.6 Hz, 1H), 3.76 (s, 3H), 2.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 200.1, 167.7, 158.7, 134.9, 131.3, 129.1, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 114.1, 67.4, 67.2, 57.6, 47.3, 38.8. HRMS: $C_{26}H_{26}O_6$ $[M+Na]^+$ calcd: 469.1627, found: 469.1607. $[\alpha]_D^{23}$ = -28.4 (c = 0.96, $CHCl_3$, 81% *ee* (*R*)).

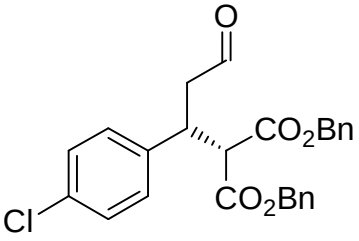
(*R*)-2-(3-Oxo-1-(4-methoxyphenyl)propyl)malonic acid dimethyl ester (6j)



6j

Yellow liquid. Yield: 73% from using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1H), 7.13 (d, ^{3}J = 8.6 Hz, 2H), 6.80 (d, ^{3}J = 8.6 Hz, 2H), 3.96 (dt, ^{3}J = 9.6 Hz, ^{3}J = 5.4 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.68 (d, ^{3}J = 9.6 Hz, 1H), 3.49 (s, 3H), 2.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 200.1, 168.3, 167.8, 158.7, 131.4, 128.9, 114.0, 57.3, 55.0, 52.6, 52.4, 47.2, 38.7. HRMS: $C_{15}H_{18}O_6$ $[M+Na]^+$ calcd: 317.1001, found: 317.1000. $[\alpha]_D^{23}$ = -22.3 (c = 0.65, $CHCl_3$, 92% *ee* (*R*)).

(*R*)-2-(3-Oxo-1-(4-chlorophenyl)propyl)malonic acid dibenzyl ester (6k)

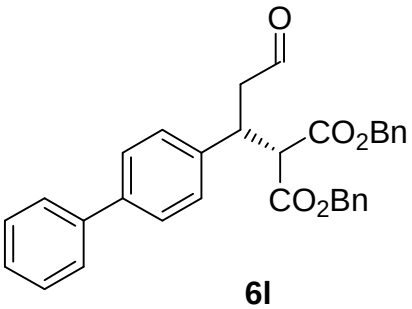


6k

White solid. Yield: 85% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.52 (t, ^{3}J = 1.6 Hz, 1H), 7.35–7.04 (m, 14H), 5.14 (s, 2H), 4.91 (s, 2H),

4.07 (m, 1H), 3.78 (d, ^{3}J = 10.0 Hz, 1H), 2.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.3, 167.4, 166.9, 138.0, 134.8, 134.7, 133.2, 129.4, 128.8, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 67.7, 67.3, 57.0, 47.1, 38.6. $[\alpha]_D^{23}$ = -15.4 (c = 1.00, $CHCl_3$, 86% *ee*).

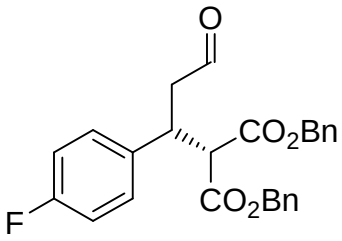
(*R*)-2-(1-(Biphenyl-4-yl)-3-oxopropyl) malonic acid dibenzyl ester (6l)



6l

White solid. Yield: 76% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.57 (t, ^{3}J = 1.6 Hz, 1H), 7.55–7.03 (m, 19H), 5.16 (s, 2H), 5.92 (s, 2H), 4.10 (m, 1H), 3.86 (d, ^{3}J = 10.0 Hz, 1H), 2.91 (dd, ^{3}J = 6.4 Hz, ^{3}J = 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 199.8, 167.6, 167.1, 140.3, 140.1, 138.5, 134.9, 134.8, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 127.3, 126.9, 67.4, 67.2, 57.3, 47.1, 39.0. $[\alpha]_D^{23}$ = -12.3 (c = 1.00, $CHCl_3$, 86% *ee* (*R*)).

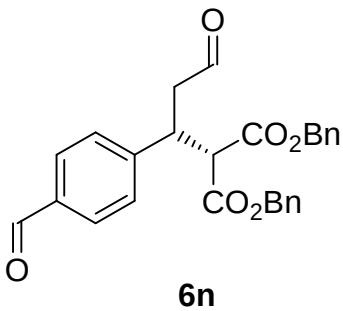
(*R*)-2-(3-Oxo-1-(4-fluorophenyl)propyl)malonic acid dibenzyl ester (6m)



6m

White solid. Yield: 72% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H), 7.35–7.23 (m, 8H), 7.11 (dd, ^{3}J = 5.3 Hz, ^{3}J = 8.6 Hz, 1H), 7.03 (dd, ^{3}J = 7.1 Hz, ^{4}J = 1.8 Hz, 1H), 6.86 (t, ^{3}J = 8.6 Hz, 1H), 5.12 (s, 2H), 4.88 (s, 2H), 4.00 (dt, ^{3}J = 9.5 Hz, ^{3}J = 5.2 Hz, 1H), 3.76 (d, ^{3}J = 9.5 Hz, 1H), 2.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.5, 167.0, 134.9, 129.7, 129.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 115.7, 115.5, 67.5, 67.3, 57.3, 47.3, 38.6. HRMS: $C_{26}H_{23}FO_5$ $[M+Na]^+$ calcd: 457.1427, found: 457.1445. $[\alpha]_D^{23}$ = -15.0 (c = 0.56, $CHCl_3$, 86% *ee* (*R*)).

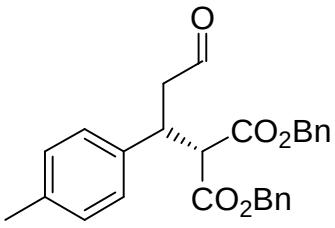
(*R*)-2-(3-Oxo-1-(4-formylphenyl)propyl)malonic acid dibenzyl ester (6n)



6n

White solid. Yield: 95% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 9.55 (t, ^{3}J = 1.2 Hz, 1H), 7.70 (d, ^{3}J = 8.3Hz, 2H), 7.34 (m, 2H), 7.28–7.21 (m, 10H), 7.05 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, 2H), 5.15 (s, 2H), 4.91 (s, 2H), 4.11 (m, 1H), 3.84 (d, ^{3}J = 9.8 Hz, 1H), 2.94 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 198.8, 191.6, 167.3, 166.8, 146.6, 135.4, 134.8, 134.6, 130.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 67.6, 67.3, 56.7, 47.0, 39.2. HRMS: $C_{27}H_{24}O_6$ $[M+Na]^+$ calcd: 467.1471, found: 467.1481. $[\alpha]_D^{23}$ = -16.8 (c = 0.37, $CHCl_3$, 86% *ee* (*R*)).

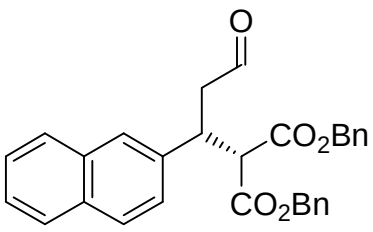
(*R*)-2-(3-Oxo-1-(4-methylphenyl)propyl)malonic acid dibenzyl ester (6o)



6o

Colourless oil. Yield: 95% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.53 (t, ^{3}J = 1.6 Hz, 1H), 7.39–7.02 (m, 14H), 5.14 (s, 2H), 4.90 (s, 2H), 4.01 (m, 1H), 3.80 (d, ^{3}J = 10.0 Hz, 1H), 2.83 (dd, ^{3}J = 6.4 Hz, ^{3}J = 1.6 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 200.0, 167.6, 167.1, 137.0, 136.3, 134.9, 134.8, 129.4, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.8, 67.3, 67.1, 57.5, 47.2, 39.1, 21.0. $[\alpha]_D^{23}$ = -18.6 (c = 1.00, $CHCl_3$, 88% *ee* (*R*)).

(*R*)-2-(1-(naphthalen-2-yl)-3-oxopropyl) malonic acid dibenzyl ester (6p)

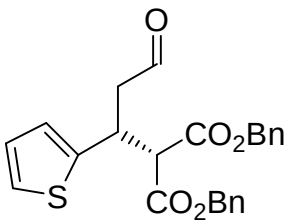


6p

White solid. Yield: 69% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.56 (t, ^{3}J = 1.6 Hz, 1H), 7.79–6.81 (m, 17H), 5.16 (s, 2H), 4.83 (s, 2H), 4.22 (m, 1H), 3.94 (d, ^{3}J = 10.0 Hz, 1H),

2.96 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 199.7, 167.6, 167.1, 136.9, 134.9, 134.6, 133.2, 132.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 126.2, 126.0, 125.7, 67.4, 67.2, 57.3, 47.1, 39.6. $[\alpha]_D^{23}$ = -13.1 (c = 1.00, $CHCl_3$, 88% *ee* (*R*)).

(*R*)-2-(3-Oxo-1-thiophen-2-ylpropyl)malonic acid dibenzyl ester (6q)



6q

Yellow Liquid. Yield: 83% using catalyst **(*S*)-10**. ^{1}H NMR ($CDCl_3$) δ 9.59 (t, ^3J = 1.4 Hz, 1H), 7.38–7.26 (m, 8H), 7.15 (m, 3H), 6.86 (m, 2H), 5.15 (s, 1H), 5.15 (s, 1H), 5.00 (s, 2H), 4.39 (dt, ^3J = 7.0 Hz, ^3J = 8.8 Hz, 1H), 3.87 (d, ^3J = 8.8 Hz, 1H), 2.93 (dd, ^3J = 1.4 Hz, ^3J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 199.4, 167.3, 167.0, 142.5, 134.9, 128.5, 128.5, 128.3, 128.3, 128.2, 126.8, 126.0, 124.6, 67.5, 67.4, 57.8, 47.7, 34.7. $[\alpha]_D^{23}$ = -13.5 (c = 0.51, $CHCl_3$, 92% *ee* (*R*)).

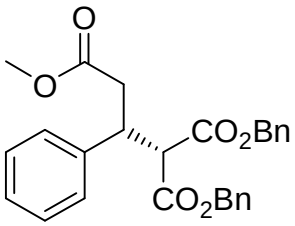
Oxidation of the aldehydes to the carboxylic esters:

General method A: Representative procedure: 50 mg (0.10 mmol) **6h** were diluted with 3.0 mL *t*-BuOH and 3.0 mL 1 M NaH_2PO_4 (aq.). 3.0 mL 1 M $KMnO_4$ were added successively. After 5 min of vigorous stirring 5.0 mL saturated $NaHSO_3$ was added and the pH was adjusted to approximately 3 with 1 M HCl. The resulting mixture was extracted 3 times with 10 mL EtOAc, the combined organic layers were washed with 10 mL of water and 10 mL brine, and dried over $MgSO_4$. The organic layer was concentrated in vacuum and the resiual acid was dissolved in 2.0 mL toluene and 5.0 mL MeOH. $TMSCHN_2$ (2.0 M in *n*-hexane) was added dropwise until the yellow colour persisted. The solution was stirred for an additional 10 min and quenched with a drop of concentrated AcOH. The solvents were evaporated under vacuum. The crude product was subjected to FC on

silica gel (Et_2O/*n*-pentane/CH_2Cl_2 1:10:0.1) to give **11h** (29 mg, 0.06 mmol, 60%) as a yellow liquid.

General method B: Representative procedure: 84 mg (0.17 mmol, 1.0 equiv.) **6l** were dissolved in 1.0 mL MeOH, 1.0 mL CH_3CN, and 1.0 mL water. The solution was cooled down to 0 °C and 63 mg (0.46 mmol, 2.7 equiv.) KH_2PO_4 and 46 mg (0.43 mmol, 2.5 equiv.) $NaClO_2$ were added. After the injection of 0.5 mL H_2O_2 (35%) the mixture was warmed up to rt and stirred for 2 h. The pH was adjusted to 3 with 1 M HCl and 5 mL saturated Na_2SO_3 solution were added. The resulting mixture was extracted 3 times with 10 mL CH_2Cl_2, the combined organic layers were washed with 10 mL of water, and dried over $MgSO_4$. The organic layer was concentrated in vacuum and the resiual acid was dissolved in 2.0 mL toluene and 5.0 mL MeOH. $TMSCHN_2$ (2.0 M in *n*-hexane) was added dropwise until the yellow colour persisted. The solution was stirred for an additional 10 min and quenched with a drop of concentrated AcOH. The solvents were evaporated under vacuum. The crude product was subjected to FC on silica gel (EtOAc/*n*-pentane 1:9) to give **11l** (80 mg, 0.15 mmol, 90%) as a yellow liquid.

(*R*)-2-Benzyloxycarbonyl-3-phenylpetanedioic acid 1-benzyl ester 5-methyl ester (11a)

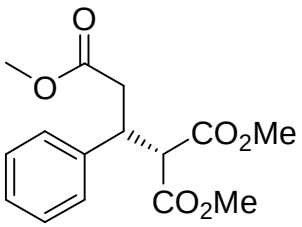


11a

Yellow solid. Yield: 50% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.33–7.19 (m, 13H), 7.04 (dd, ^4J = 2.0 Hz, ^3J = 7.0 Hz, 2H), 5.16 (s, 2H), 4.87 (s, 1H), 4.86 (s, 1H), 3.96 (dt, ^3J = 4.6 Hz, ^3J = 9.9 Hz, 1H), 3.87 (d, ^3J = 9.9 Hz, 1H), 3.50 (s, 3H), 2.83 (dd, ^3J = 4.6 Hz, ^2J = 15.7 Hz, 1H), 2.73 (dd, ^3J = 9.9 Hz, ^2J = 15.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 167.7, 167.2, 139.6, 135.1, 134.9, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.4, 67.3, 67.1, 57.2, 51.6, 41.4, 38.3. HRMS: $C_{27}H_{26}O_6$ $[M+Na]^+$

calcd: 469.1627, found: 469.1632. $[\alpha]_D^{23}$ = -7.1 (c = 0.58, $CHCl_3$, 86% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 19.1 min. (major enantiomer); τ_2 = 25.4 min. (minor enantiomer)).

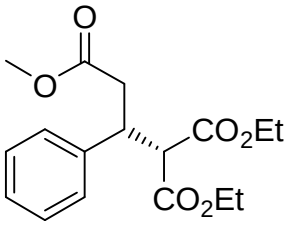
(*R*)-2-Methyloxycarbonyl-3-phenylpetanedioic acid 1,5-dimethyl ester (11b)



11b

Yellow solid. Yield: 40% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.30–7.19 (m, 5H), 3.92 (dt, ^3J = 4.9 Hz, ^3J = 9.9 Hz, 1H), 3.78 (d, ^3J = 9.9 Hz, 1H), 3.74 (s, 3H), 3.53 (s, 3H), 3.48 (s, 3H), 2.85 (dd, ^3J = 4.9 Hz, ^2J = 15.7 Hz, 1H), 2.75 (dd, ^3J = 9.5 Hz, ^2J = 15.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 168.4, 167.9, 139.7, 128.5, 127.9, 127.4, 57.0, 52.7, 52.4, 51.6, 41.4, 38.3. HRMS: $C_{15}H_{18}O_6$ $[M+Na]^+$ calcd: 317.1001, found: 317.0994. $[\alpha]_D^{23}$ = -16.5 (c = 0.37, $CHCl_3$, 91% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 0.5 mL/min (τ_1 = 20.1 min. (major enantiomer); τ_2 = 23.3 min. (minor enantiomer)).

(*R*)-2-Ethyloxycarbonyl-3-phenylpetanedioic acid 5-ethyl ester 1-methyl ester (11c)

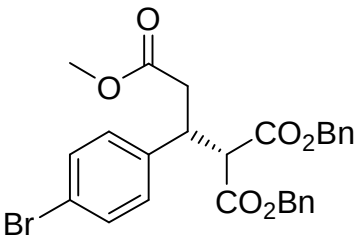


11c

Colourless liquid. Yield: 59% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.28–7.18 (m, 5H), 4.12 (q, ^3J = 7.1 Hz, 2H), 3.91 (m, 3H), 3.73 (d, ^3J = 10.3 Hz, 1H), 3.52 (s, 3H), 2.85 (dd, ^3J = 4.6 Hz, ^2J = 15.6 Hz, 1H), 2.74 (dd, ^3J = 9.9 Hz, ^2J = 15.6 Hz, 1H), 1.26 (t, ^3J = 7.1 Hz, 3H), 0.98 (t, ^3J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.6, 168.0, 167.5, 139.8, 128.4, 128.1, 127.3, 61.7, 61.4, 57.3, 51.6, 41.4, 38.5, 14.0, 13.7. HRMS: $C_{17}H_{22}O_6$ $[M+Na]^+$ calcd: 345.1314, found: 345.1320. $[\alpha]_D^{23}$ = -29.0 (c = 0.10, $CHCl_3$, 89% *ee* (*R*)). HPLC: Daicel Chiralpak AD,

hexane/2-propanol (80/20), flow rate = 0.5 mL/min (τ_1 = 18.5 min. (major enantiomer); τ_2 = 27.4 min. (minor enantiomer)).

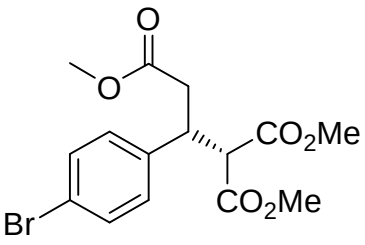
(*R*)-2-Benzyloxycarbonyl-3-(4-bromophenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11f)



11f

White solid. Yield: 72% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.34–7.26 (m, 10H), 7.06–7.03 (m, 4H), 5.16 (s, 2H), 4.90 (s, 2H), 3.91 (dt, ^3J = 10.0 Hz, ^3J = 4.4 Hz, 1H), 3.82 (d, ^3J = 10.0 Hz, 1H), 3.51 (s, 3H), 2.80 (dd, ^3J = 15.8 Hz, ^3J = 4.3 Hz, 1H), 2.67 (dd, ^3J = 15.8 Hz, ^3J = 9.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 167.7, 167.3, 138.8, 135.2, 135.0, 131.9, 130.1, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 121.6, 67.7, 67.5, 57.1, 52.0, 41.1, 38.3. HRMS: $C_{27}H_{25}BrO_6$ $[M+Na]^+$ calcd: 547.0732, found: 547.0728. $[\alpha]_D^{23}$ = -3.7 (c = 0.59, $CHCl_3$, 90% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 22.5 min. (major enantiomer); τ_2 = 35.2 min. (minor enantiomer)).

(*R*)-2-Methyloxycarbonyl-3-(4-bromophenyl)petanedioic acid 1,5-dimethyl ester (11g)

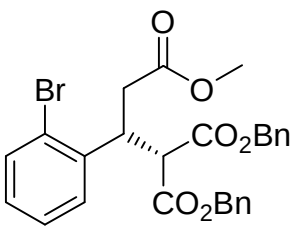


11g

Colourless liquid. Yield: 51% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, ^3J = 8.5 Hz, 2H), 7.12 (d, ^3J = 8.5 Hz, 2H), 3.90 (dt, ^3J = 10.0 Hz, ^3J = 4.8 Hz, 1H), 3.75 (s, 3H), 3.73 (d, ^3J = 10.0 Hz, 1H), 3.55 (s, 3H), 3.52 (s, 3H), 2.83 (dd, ^2J = 15.9 Hz, ^3J = 4.7 Hz, 1H), 2.72 (dd, ^2J = 15.9 Hz, ^3J = 9.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.4, 168.2, 138.8, 131.6, 129.7, 121.4, 56.7, 52.8, 52.6, 51.7, 40.8, 38.0. HRMS: $C_{15}H_{17}BrO_6$ $[M+Na]^+$ calcd: 395.0106, found: 395.0099. $[\alpha]_D^{23}$ = -3.5 (c = 0.01, $CHCl_3$, 95% *ee* (*R*)). HPLC: Daicel

Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 9.8 min. (major enantiomer); τ_2 = 12.7 min. (minor enantiomer)).

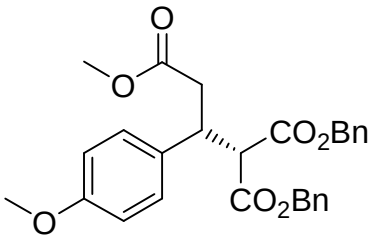
(*R*)-2-Benzyloxycarbonyl-3-(2-bromophenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11h)



11h

Yellow liquid. Yield 60% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.51 (dd, ^3J = 8.1 Hz, ^4J = 0.8 Hz, 1H), 7.34–7.03 (m, 13H), 5.30 (s, 1H), 5.13 (s, 1H), 5.12 (s, 1H), 4.99 (s, 2H), 4.47 (m, 1H), 4.12 (d, ^3J = 8.4 Hz, 1H), 3.52 (s, 3H), 2.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.4, 167.5, 167.2, 138.7, 135.0, 133.4, 128.7, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 127.5, 67.3, 67.2, 55.0, 51.6, 36.2. $[\alpha]_D^{23}$ = -10.0 (c = 0.01, $CHCl_3$, 88% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 17.5 min. (major enantiomer); τ_2 = 21.7 min. (minor enantiomer)).

(*R*)-2-Benzyloxycarbonyl-3-(4-methoxyphenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11i)

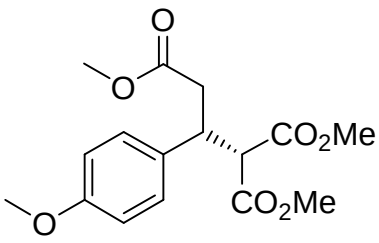


11i

Yellow solid. Yield: 90% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.34–7.22 (m, 8H), 7.11 (d, ^3J = 8.7 Hz, 2H), 7.04 (dd, ^3J = 7.9 Hz, ^4J = 1.6 Hz, 2H), 6.74 (d, ^3J = 8.7 Hz, 2H), 5.15 (s, 2H), 4.88 (s, 2H), 3.90 (dt, ^3J = 9.8 Hz, ^3J = 4.5 Hz, 1H), 3.82 (d, ^3J = 9.8 Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 2.79 (dd, ^3J = 15.6 Hz, ^3J = 4.5 Hz, 1H), 2.68 (dd, ^3J = 15.6 Hz, ^3J = 9.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 167.7, 167.3, 158.6, 135.0, 131.4, 129.0, 128.5, 128.4, 128.2, 128.1, 113.8, 67.3, 67.1, 57.4, 51.2, 40.7, 38.5. HRMS: $C_{28}H_{28}O_7$ $[M+Na]^+$ calcd: 499.1733, found: 499.1728. $[\alpha]_D^{23}$ = -6.7 (c = 0.56, $CHCl_3$, 81% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol

(80/20), flow rate = 1.0 mL/min (τ_1 = 23.7 min. (major enantiomer); τ_2 = 38.2 min. (minor enantiomer)).

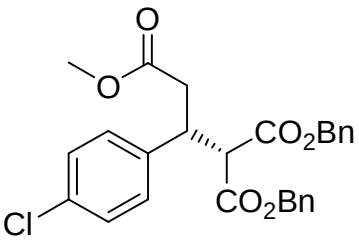
(*R*)-2-Methyloxycarbonyl-3-(4-methoxyphenyl)petanedioic acid 1,5-dimethyl ester (11j)



11j

Yellow liquid. Yield: 84% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.12 (d, ^3J = 8.7 Hz, 2H), 6.78 (d, ^3J = 8.7 Hz, 2H), 3.86 (dt, ^3J = 9.9 Hz, ^3J = 4.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.72 (d, ^3J = 9.8 Hz, 1H), 3.51 (s, 3H), 3.47 (s, 3H), 2.80 (dd, ^3J = 15.6 Hz, ^3J = 4.8 Hz, 1H), 2.70 (dd, ^3J = 15.6 Hz, ^3J = 9.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 168.4, 167.9, 158.6, 131.5, 128.9, 113.7, 57.1, 55.0, 52.6, 52.3, 51.5, 40.6, 38.4. HRMS: $C_{16}H_{20}O_7$ $[M+Na]^+$ calcd: 347.1107, found: 347.1112. $[\alpha]_D^{23}$ = -12.9 (c = 1.21, $CHCl_3$, 92% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 0.5 mL/min (τ_1 = 24.3 min. (major enantiomer); τ_2 = 32.3 min. (minor enantiomer)).

(*R*)-2-Benzyloxycarbonyl-3-(4-chlorophenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11k)

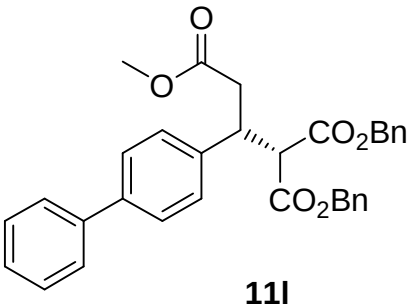


11k

White solid. Yield: 81% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.35-7.03 (m, 14H), 5.16 (s, 2H), 4.90 (s, 2H), 3.90 (m, 1H), 3.81 (d, ^3J = 10.2 Hz, 1H), 3.51 (s, 3H), 2.79 (dd, ^3J = 16.0 Hz, ^3J = 4.4 Hz, 1H), 2.67 (dd, ^3J = 16.0 Hz, ^3J = 10.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.2, 167.4, 167.0, 138.0, 134.9, 134.8, 133.1, 129.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 67.5, 67.2, 56.9, 51.7, 40.8, 38.2. HRMS: $C_{27}H_{25}ClO_6$ $[M+Na]^+$ calcd: 503.1237, found: 503.1237. $[\alpha]_D^{23}$ = -6.4 (c = 1.00, $CHCl_3$, 86% *ee* (*R*)). HPLC: Daicel

Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 15.3 min. (major enantiomer); τ_2 = 18.1 min. (minor enantiomer)).

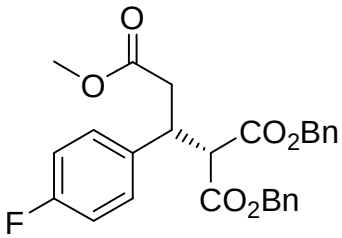
(*R*)-1,1-dibenzyl 3-methyl 2-(biphenyl-4-yl)propane-1,1,3-tricarboxylate (11l)



11l

Yellow oil. Yield: 90% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.57-7.02 (m, 19H), 5.17 (s, 3H), 4.90 (s, 3H), 4.00 (m, 1H), 3.90 (d, ^3J = 10.0 Hz, 1H), 3.53 (s, 3H), 2.85 (dd, ^3J = 16.0 Hz, ^3J = 4.8 Hz, 1H), 2.77 (dd, ^3J = 16.0 Hz, ^3J = 10.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.5, 167.6, 167.2, 140.5, 140.0, 138.6, 135.0, 134.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 127.1, 126.9, 67.4, 67.2, 57.1, 51.6, 41.0, 38.2. HRMS: $C_{33}H_{30}O_6$ $[M+Na]^+$ calcd: 545.1940, found: 545.1941. $[\alpha]_D^{23}$ = -2.3 (c = 1.00, $CHCl_3$, 89% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 22.7 min. (major enantiomer); τ_2 = 44.1 min. (minor enantiomer)).

(*R*)-2-Benzyloxycarbonyl-3-(4-fluorophenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11m)

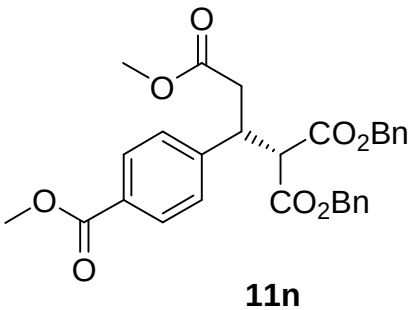


11m

White solid. Yield: 16% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.27–7.19 (m, 8H), 7.07 (dd, ^3J = 5.3 Hz, ^3J = 8.6 Hz, 1H), 6.98 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H), 6.81 (t, ^3J = 8.6 Hz, 1H), 5.09 (s, 2H), 4.82 (s, 2H), 3.86 (dt, ^3J = 10.1 Hz, ^3J = 5.7 Hz, 1H), 3.75 (d, ^3J = 10.1 Hz, 1H), 3.44 (s, 3H), 2.73 (dd, ^2J = 15.8 Hz, ^3J = 4.4 Hz, 1H), 2.60 (dd, ^2J = 15.8 Hz, ^3J = 9.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.3, 167.5, 167.1, 135.1, 135.0, 134.8, 129.7, 129.6, 128.6, 128.5, 128.4, 128.3, 128.2, 115.5, 115.2, 67.4, 67.2, 57.1, 51.6, 40.7, 38.4. HRMS: $C_{26}H_{23}FO_5$ $[M+Na]^+$ calcd: 487.1533, found: 487.1513. $[\alpha]_D^{23}$ =

-4.6 (c = 0.20, $CHCl_3$, 86% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 19.7 min. (major enantiomer); τ_2 = 30.7 min. (minor enantiomer)).

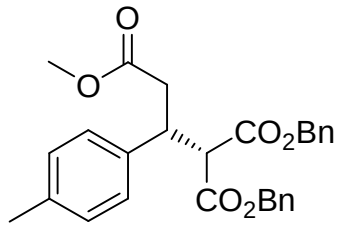
(*R*)-2-Benzyloxycarbonyl-3-(4-methoxycarbonylphenyl)pentanedioic acid 1-benzyl ester 5-methyl ester (11n)



11n

White solid. Yield: 70% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, ^3J = 8.4Hz, 2H), 7.33 (m, 2H), 7.28–7.22 (m, 10H), 7.03 (dd, ^3J = 7.4 Hz, ^4J = 1.4 Hz, 2H), 5.16 (s, 2H), 4.87 (s, 2H), 4.00 (dt, ^3J = 9.9 Hz, ^3J = 4.5 Hz, 1H), 3.90 (s, 3H), 3.87 (d, ^3J = 9.9 Hz, 1H), 2.84 (dd, ^3J = 16.0 Hz, ^3J = 4.6 Hz, 1H), 2.72 (dd, ^3J = 16.0 Hz, ^3J = 9.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.1, 167.4, 166.9, 166.7, 144.8, 134.8, 134.7, 134.6, 129.8, 129.2, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 67.5, 67.2, 52.1, 51.7, 41.2, 38.0. HRMS: $C_{29}H_{28}O_8$ $[M+Na]^+$ calcd: 527.1682, found: 527.1678. $[\alpha]_D^{23}$ = -4.2 (c = 0.26, $CHCl_3$, 86% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 31.2 min. (major enantiomer); τ_2 = 63.7 min. (minor enantiomer)).

(*R*)-2-Benzyloxycarbonyl-3-(4-methylphenyl)petanedioic acid 5-benzyl ester 1-methyl ester (11o)

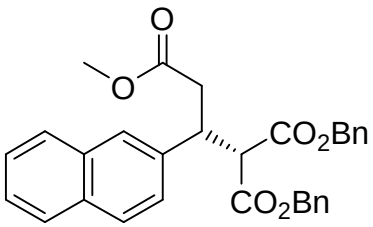


11o

Colourless oil. Yield: 92% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.32-7.00 (m, 14H), 5.15 (s, 2H), 4.87 (s, 2H), 3.91 (m, 1H), 3.84 (d, ^3J = 10.0 Hz, 1H), 3.50 (s, 3H), 2.79 (dd, ^3J = 15.6 Hz, ^3J = 4.4 Hz, 1H), 2.70 (dd, ^3J = 15.6 Hz, ^3J = 10.0 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$) δ171.8, 168.0, 167.5, 137.1, 136.7, 135.3, 135.2, 129.4, 128.8, 128.6, 128.4, 128.4, 128.3, 128.0, 67.6, 67.3, 57.5, 51.8, 41.3, 38.6, 21.3. HRMS: $C_{28}H_{28}O_6$ $[M+Na]^+$ calcd: 483.1783, found: 483.1786.

$[\alpha]_D^{23}$ = -6.2 (c = 1.00, $CHCl_3$, 88% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 15.5 min. (major enantiomer); τ_2 = 21.6 min. (minor enantiomer)).

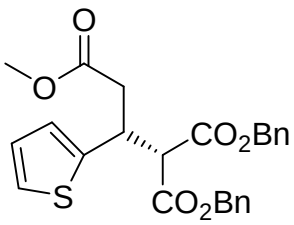
(*R*)-1,1-dibenzyl 3-methyl 2-(naphthalen-2-yl)propane-1,1,3-tricarboxylate (11p)



11p

Colourless oil. Yield: 86% using general oxidation method B. ^{1}H NMR ($CDCl_3$) δ 7.93-6.86 (m, 17H), 5.17 (s, 2H), 4.82 (s, 2H), 4.14 (m, 1H), 3.98 (d, ^3J = 10.4 Hz, 1H), 3.74 (s, 3H), 2.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.4, 167.6, 167.2, 137.1, 135.0, 134.7, 133.2, 132.7, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.6, 127.0, 126.0, 125.9, 125.8, 67.4, 67.1, 57.2, 51.6, 41.5, 38.3. HRMS: $C_{31}H_{28}O_6$ $[M+Na]^+$ calcd: 519.1783, found: 519.1791. $[\alpha]_D^{23}$ = -2.1 (c = 1.00, $CHCl_3$, 88% *ee*). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 21.6 min. (major enantiomer); τ_2 = 30.1 min. (minor enantiomer)).

(*R*)-2-Benzyloxycarbonyl-3-thiophen-2-ylpentanedioic acid 1-benzyl ester 5-methyl ester (11q)

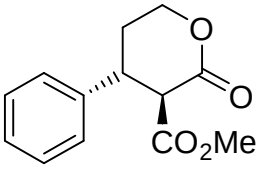


11q

Yellow Liquid. Yield: 40% using general oxidation method A. ^{1}H NMR ($CDCl_3$) δ 7.33–7.26 (m, 8H), 7.13 (m, 3H), 6.85 (m, 2H), 5.16 (s, 1H), 5.15 (s, 1H), 4.98 (s, 2H), 4.27 (dt, ^3J = 9.1 Hz, ^3J = 4.9 Hz, 1H), 3.91 (d, ^3J = 9.1 Hz, 1H), 3.57 (s, 3H), 2.87 (dd, ^3J = 16.0 Hz, ^3J = 4.8 Hz, 1H), 2.78 (dd, ^3J = 16.0 Hz, ^3J = 9.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.3, 167.1, 142.5, 135.0, 128.5, 128.5, 128.3, 128.2, 128.2, 126.7, 125.8, 124.4, 67.4, 67.2, 57.6, 51.7, 40.0, 36.7. HRMS: $C_{25}H_{24}O_6S$ $[M+Na]^+$ calcd: 475.1191, found: 475.1197. $[\alpha]_D^{23}$ = -11.0 (c = 0.26, $CHCl_3$, 92% *ee* (*R*)). HPLC: Daicel

Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 20.7 min. (major enantiomer); τ_2 = 23.8 min. (minor enantiomer)).

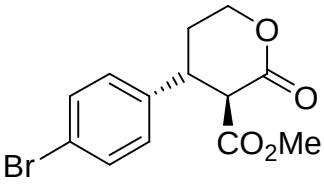
(*R*,*R*)-2-Oxo-4-phenyltetrahydropyran-3-carboxylic acid methyl ester (9a)



9a

299 mg (1.13 mmol, 1.0 equiv.) **6b** were solved in 5 mL THF. The solution was cooled to 0 °C and 1.25 mL concentrated AcOH and 112 mg (1.70 mmol, 1.5 equiv.) $NaCNBH_3$ (95%) were subsequently added. The reaction mixture was warmed up to rt overnight. 5 mL brine were added and the pH was adjusted to 7 with saturated $NaHCO_3$ solution. The aqueous layer was extracted 3 times with 10 mL Et_2O and the combined organic layers were dried over $MgSO_4$. After evapouration of the solvents under vacuum the crude product was dissolved in 8.1 mL CH_2Cl_2. 1.21 g of silica were added and the mixture was stirred slowly for 4 d. After filtration the solvent was evapourated under vacuum and the crude product was subjected to FC on silica gel (Et_2O/*n*-pentane/CH_2Cl_2 1:1:0.1) to give diastereomerically pure **9a** (151 mg, 0.64 mmol, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37 (tt, ^3J = 7.4 Hz, ^4J = 1.4 Hz, 2H), 7.32 (tt, ^3J = 7.4 Hz, ^4J = 1.4 Hz, 1H), 7.25 (dd, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 2H), 4.55 (m, 2H), 3.75 (d, ^3J = 10.5 Hz, 1H), 3.68 (s, 3H), 3.64 (dt, ^3J = 5.5 Hz, ^3J = 10.5 Hz, 1H), 2.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 168.5, 168.0, 140.8, 129.0, 127.6, 126.7, 68.8, 55.0, 52.7, 41.0, 29.7. HRMS: $C_{13}H_{14}O_4$ $[M+Na]^+$ calcd: 257.0790, found: 275.0781. $[\alpha]_D^{23}$ = -52.3 (c = 0.39, $CHCl_3$, 90% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (70/30), flow rate = 1.0 mL/min (τ_1 = 8.4 min. (major enantiomer); τ_2 = 10.6 min. (minor enantiomer)).

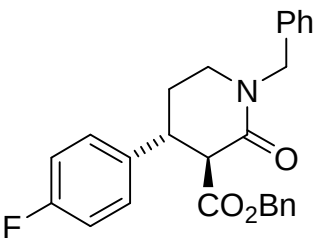
(*R*,*R*)-2-Oxo-4-(4-bromophenyl)tetrahydropyran-3-carboxylic acid methyl ester (9b)



9b

70 mg (0.20 mmol, 1.0 equiv.) **6g** were solved in 2 mL THF. The solution was cooled to 0 °C and 0.50 mL concentrated AcOH and 22 mg (0.35 mmol, 1.5 equiv.) $NaCNBH_3$ (95%) were subsequently added. The reaction mixture was warmed up to rt overnight. 5 mL brine were added and the pH was adjusted to 7 with saturated $NaHCO_3$ solution. The aqueous layer was extracted 3 times with 10 mL Et_2O and the combined organic layers were dried over $MgSO_4$. After evapouration of the solvents under vacuum the crude product was dissolved in 1.4 mL CH_2Cl_2. 272 mg of silica were added and the mixture was stirred slowly for 28 h. After filtration the solvent was evapourated under vacuum and the crude product was subjected to FC on silica gel (Et_2O/*n*-pentane/CH_2Cl_2 1:1:0.1) to give diastereomerically pure **9b** (31 mg, 0.10 mmol, 49%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, ^3J = 8.4 Hz, 2H), 7.09 (d, ^3J = 8.4 Hz, 2H), 4.54 (dt, ^3J = 4.9 Hz, ^2J = 11.3 Hz, 1H), 4.47 (td, ^3J = 4.0 Hz, ^2J = 11.3 Hz, 1H), 3.66 (s, 3H), 3.64 (d, ^3J = 10.9 Hz, 1H), 3.57 (dt, ^3J = 5.1 Hz, ^3J = 10.9 Hz, 1H), 2.16 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 168.3, 166.6, 139.8, 132.2, 128.5, 121.6, 68.7, 54.8, 52.9, 40.6, 29.7. HRMS: $C_{13}H_{13}BrO_4$ $[M+Na]^+$ calcd: 334.9895, found: 334.9897. $[\alpha]_D^{23}$ = -56.5 (c = 0.26, $CHCl_3$, 93% *ee* (*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (70/30), flow rate = 1.0 mL/min (τ_1 = 15.7 min. (major enantiomer); τ_2 = 22.1 min. (minor enantiomer)).

(*R*,*S*)-1-Benzyl-4-(4-fluorophenyl)-2-oxo-piperidine-3-carboxylic acid benzyl ester (12)

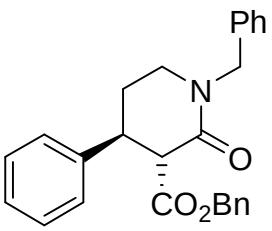


12

To a solution of 136 mg (0.31 mmol, 1.0 equiv.) (*R*)-2-[1-(4-fluoro-phenyl)-3-oxo-propyl]malonic acid dibenzyl ester **6m** and benzylamine 34 mg (0.31 mmol, 1.0 eq) in 3.0 mL dioxane at 0 °C was added 86 mg sodium triaacetoxyborohydride (0.40

mmol, 1.3 eq). The resulting mixture was stirred at rt for 24 h. After this time, the reaction mixture was quenched by adding 10 mL aq. saturated $NaHCO_3$ and the product was extracted three times with 10 mL EtOAc each. The organic extract was dried over Na_2SO_4 and the solvent was evaporated in vacuum to give the crude product, which was purified by FC on silica gel (EtOAc/*n*-pentane 1:5) giving **14** (91 mg, 0.22 mmol, 70% overall yield, dr = 13:1) as a yellow oil. Major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 7.34-6.90 (m, 14H), 5.16 (d, ^2J = 12.4 Hz, 1H), 5.05 (d, ^2J = 12.4 Hz, 1H), 4.75 (d, ^2J = 14.4 Hz, 1H), 4.55 (d, ^2J = 14.4 Hz, 1H), 3.63(d, ^3J = 11.2 Hz, 1H), 3.44-3.36 (m, 2H), 3.28 (m, 1H), 2.04-1.96 (m, 2H). ^{13}C NMR ($CDCl_3$) δ169.7, 165.5, 161.8 (J_{C-F} = 244.4 Hz), 136.8, 136.4, 135.4, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 115.6 (J_{C-F} = 21.2 Hz), 66.7, 56.8, 50.3, 46.2, 41.9, 29.3. HRMS: $C_{26}H_{24}FNaNO_3$ $[M+Na]^+$ calcd: 440.1638, found: 440.1640.

(*S*,*R*)-1-Benzyl-4-phenyl-2-oxo-piperidine-3-carboxylic acid benzyl ester (14)

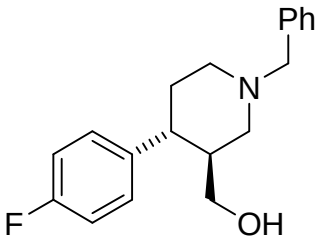


14

To a solution of 129 mg (0.31 mmol, 1.0 equiv.) (*S*)-2-[1-phenyl-3-oxo-propyl]malonic acid dibenzyl ester **6a** and benzylamine 33 mg (0.31 mmol, 1.0 eq) in 3.0 mL dioxane at 0 °C was added 85 mg sodium triacetoxyborohydride (0.40 mmol, 1.3 eq). The resulting mixture was stirred at rt for 24 h. After this time, the reaction mixture was quenched by adding 10 mL aq. saturated $NaHCO_3$ and the product was extracted three times with 10 mL EtOAc each. The organic extract was dried over Na_2SO_4 and the solvent was evaporated in vacuum to give the crude product, which was purified by FC on silica gel (EtOAc/*n*-pentane 1:5) giving **15** (83 mg, 0.21 mmol, 67% overall yield, dr = 12:1) as a yellow oil. Mayor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 7.33-7.05 (m, 15H), 5.14 (d, ^2J = 12.4 Hz, 1H), 5.04 (d, ^2J = 12.4 Hz, 1H), 4.75 (d, ^2J = 14.6

Hz, 1H), 4.57 (d, ^{2}J = 14.6 Hz, 1H), 3.71(d, ^{3}J = 11.2 Hz, 1H), 3.47-3.37 (m, 2H), 3.29 (m, 1H), 2.06-2.03 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.9, 165.7, 141.0, 136.4, 135.4, 128.7, 128.6, 128.3, 128.0, 127.8, 126.7, 66.7, 56.5, 50.2, 46.2, 42.5, 29.2. HRMS: $C_{26}H_{25}NaNO_3$ $[M+Na]^+$ calcd: 422.1732, found: 422.1733.

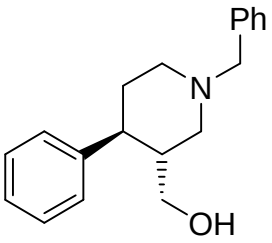
[1-Benzyl-4-(4-fluoro-phenyl)-piperidin-3-yl]-methanol (13)



13

(*R*,*S*)-1-Benzyl-4-(4-fluorophenyl)-2-oxo-piperidine-3-carboxylic acid benzyl ester **12** (28 mg, 0.07 mmol, 1.0 equiv.) dissolved in THF (2 mL) was added dropwise to a stirred solution of $LiAlH_4$ (65 mg, 1.71 mmol) in THF (3 mL), whilst being cooled by an ice bath. The reaction mixture was then warmed to rt and then heated at reflux overnigth. After this time the flask was cooled to rt, water (1 mL) was added dropwise and the mixture was stirred for 10 min. 2M NaOH (3 mL) was then added and the reaction mixture was left to stir for a further 10 min. The mixture was then poured into saturated Rochelle´s salt solution (30 mL) and extracted with EtOAc (4 x 20 mL). The organic extracts were combined, washed with brine (3 x 20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo to give the crude product, which was purified by FC on silica gel (EtOAc/*n*-pentane 1:1) giving **15** (18 mg, 0.06 mmol, 85% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.40-6.96 (m, 9H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.58 (d, *J* = 13.4 Hz, 1H), 3.37 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.30-3.12 (m, 2H), 2.99 (m, 1H), 2.35 (m, 1H), 2.13-1.65 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 161.3 (J_{C-F} = 244.1 Hz), 140.1 (J_{C-F} = 3.0 Hz), 137.9, 129.3, 128.8, 128.2, 127.1, 115.4 (J_{C-F} = 21.2 Hz), 63.8, 63.4, 57.2, 53.8, 44.2, 44.1, 34.4. HRMS: $C_{19}H_{22}FNaNO$ $[M+Na]^+$ calcd: 322.1583, found: 322.1584. $[\alpha]_D^{23}$ = -20.1 (c = 1.00, $CHCl_3$, 87% *ee*).

(1-Benzyl-4-phenyl-piperidin-3-yl)-methanol 15.



15

(*S*,*R*)-1-Benzyl-4-phenyl-2-oxo-piperidine-3-carboxylic acid benzyl ester **14** (83 mg, 0.21 mmol, 1.0 equiv.) dissolved in THF (3 mL) was added dropwise to a stirred solution of $LiAlH_4$ (38 mg, 1.0 mmol) in THF (10 mL), whilst being cooled by an ice bath. The reaction mixture was then warmed to rt and then heated at reflux overnigth. After this time the flask was cooled to rt, water (1 mL) was added dropwise and the mixture was stirred for 10 min. 2M NaOH (3 mL) was then added and the reaction mixture was left to stir for a further 10 min. The mixture was then poured into saturated Rochelle´s salt solution (30 mL) and extracted with EtOAc (4 x 20mL). The organic extracts were combined, washed with brine (3 x 20mL), dried with $MgSO_4$, filtered and concentrated in vacuo to give the crude product, which was purified by FC on silica gel (EtOAc/*n*-pentane 1:1) giving **15** (46.1 mg, 0.16 mmol, 79% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.38-7.20 (m, 10H), 3.63 (m, 2H), 3.39 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.24 (m, 2H), 3.03 (m, 1H), 2.36(m, 1H), 2.11 (m, 3H), 1.08 (m. 1H), 0.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 144.2, 129.4, 128.6, 128.2, 127.4, 127.2, 126.5, 64.0, 63.4, 57.2, 53.8, 45.0, 43.8, 34.0. HRMS: $C_{19}H_{24}NO$ $[M+H]^+$ calcd: 282.1857, found: 282.1857. $[\alpha]_D^{23}$ = +15.1 (c = 1.0, $CHCl_3$, 90% *ee*).

References

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[2] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797.