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Highly Enantioselective Organocatalysed Conjugate Addition of Malonate to Acyclic α,β Unsaturated Enones

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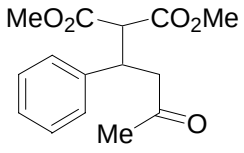
General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ=0) for ^{1}H and relative to the central $CDCl_3$ resonance (δ=77) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products were determined by chiral HPLC using Daicel Chiralpak AS/AD or Daicel Chiralcel OD columns with hexane/2-propanol as eluent.

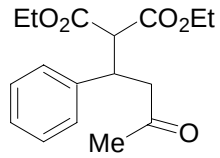
Materials. Furfurylideneacetone (*cis*+*trans* mixture), 4-hydroxybenzylideneacetone, 4-chlorobenzylideneacetone, 3-octen-2-one, dibenzyl malonate were purchased from Lancaster and used as received. Methyl *trans*-4-oxo-2-pentenoate, 4-methyl-1-phenyl-pent-1-en-3-one, benzylideneacetone, 5-methyl-3-hexen-2-one, *trans*-4-(2-thienyl)-3-butene-2-one, 2-cyclohexen-1-one, dimethyl malonate, diethyl malonate, benzyl ethyl malonate, benzyl methyl malonate and diisopropyl malonate were purchased from Aldrich and used as received. Diallyl malonate was purchased from ABCR GmbH KG and used as received. 4-(4-Dimethylamino-phenyl)-3-butene-2-one were purchased from Maybridge Chemicals and used as received. 2-Nitro-benzylidenacetone,[1] 4-nitro-benzylideneacetone,[2] 4-pyridin-2-yl-buten-3-en-2-one,[3] 4-naphthalen-2-yl-3-buten-2-one,[4] 1-phenyl-pent-1-en-3-one[5] were prepared according to literature procedures.

General procedure for catalytic addition of dialkyl malonate α,β-unsaturated enones.

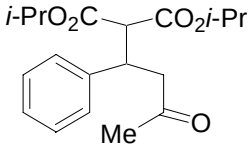
To a glass tube with a magnetic stirring bar is added 7 mmol of malonate (3), 1 mmol of enone (2), 0.1 mmol of catalyst (1) and stirred at ambient temperature for the time indicated in the table. The reaction mixture was purified by flash chromatography (FC).



2-(3-Oxo-1-phenyl-butyl)-malonic acid dimethyl ester (4a). Purified by FC using EtOAc/pentane and isolated as a colorless solid, mp. 44-46 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_{D}$ = -9.7^{o} (*c* = 1.0 g/100mL, $CHCl_3$, 73% ee); ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H, C**H**$_3$CO), 2.81-2.93 (m, 2H, COC**H**$_2$), 3.42 (s, 3H, CO_2C**H**$_3$), 3.64 (s, 3H, CO_2C**H**$_3$), 3.67 (d, *J* = 2.0 Hz, 1H, CO_2C**H**CO_2), 3.87-3.93 (m, 1H, C***H**), 7.10-7.22 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ, 30.2, 40.3, 47.0, 52.3, 52.6, 57.0, 127.2, 127.9, 128.5, 140.3, 167.9, 168.5, 205.9; HRMS m/z 301.1050 (M+Na^+), calc. for $C_{15}H_{18}O_5Na^+$ 301.1052.

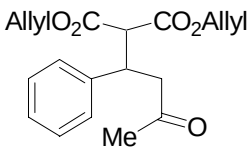


2-(3-Oxo-1-phenyl-butyl)-malonic acid diethyl ester (4b). Purified by FC using Et_2O/pentane and isolated as a colorless solid, mp. 42-43 ^{o}C. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_{D}$ = -12.1^{o} (*c* = 1.0 g/100mL, $CHCl_3$, 91% ee); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3H, OCH_2C**H**$_3$), 1.17 (t, *J* = 7.0 Hz, 3H, OCH_2C**H**$_3$), 1.94 (s, 3H, C**H**$_3$CO), 2.84-2.87 (m, 2H, COC**H**$_2$), 3.62 (d, *J* = 10.1 Hz, 1H, CO_2C**H**CO_2), 3.83-3.89 (m, 3H, 1H, from C***H**, 2H from OC**H**$_2CH_3$), 4.11 (q, *J* = 7 Hz, 2H, OC**H**$_2CH_3$), 7.11-7.20 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 30.2, 40.4, 47.3, 57.3, 61.2, 61.6, 127.1, 128.3, 140.3, 167.6, 168.1, 206.0; HRMS m/z 329.1367 (M+Na^+), calc. for $C_{17}H_{22}O_5$ Na^+ 329.1365.

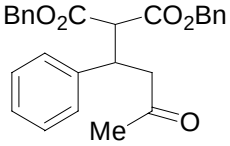


2-(3-Oxo-1-phenyl-butyl)-malonic acid isopropyl ester (4c). Purified by FC using EtOAc/pentane and isolated as a colorless oil. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_{D}$ = -13.6^{o} (*c* = 1.0 g/100mL, $CHCl_3$, 71% ee); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6 Hz, 3H, C**H**$_3$CH), 0.96 (d, *J* = 6.0 Hz, 3H, C**H**$_3$CH), 1.16

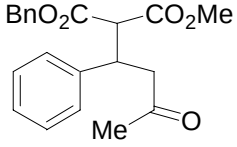
(dd, *J* =2.3, 6.2, H, 2 C**H**$_3$CH), 1.94 (s, 3H, C**H**$_3$CO), 2.77-2.90 (m, 2H, COC**H**$_2$), 3.56 (d, *J* = 10.1 Hz, 1H CO_2C**H**CO_2), 3.84-3.90 (m, 1H, C***H**), 4.67-4.73 (m, 1H, CH_3C**H**), 4.94-5.01 (m, 1H, CH_3C**H**), 7.09-7.20 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.3, 21.5, 21.6, 30.3, 40.4, 47.7, 57.7, 68.8, 69.2, 127.1, 128.2, 128.4, 140.4, 167.1, 167.7, 206.2; HRMS m/z 357.1671 (M+Na^+), calc. for $C_{19}H_{26}O_5$ Na^+ 357.1678.



2-(3-Oxo-1-phenyl-butyl)-malonic acid diallyl ester (4e). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -12.0^o (*c* = 1.0 g/100mL, $CHCl_3$, 89% ee); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H, C**H**$_3$CO), 2.86-3.74 (m, 2H, COC**H**$_2$), 3.75 (d, *J* = 9.8 Hz, 1H, CO_2C**H**CO_2), 3.93-3.99 (m, 1H, C***H**), 4.34 (dt, *J* = 2.0, 6.0 Hz, 2H, CH_2=CHC**H**$_2$), 4.59 (d, *J* = 6.0 Hz, 2H, CH_2=CHC**H**$_2$), 5.07-5.12 (m, 2H, C**H**$_2$=CH), 5.19-5.30 (m, 2H, C**H**$_2$=CH), 5.55-5.64 (m, 1H, CH_2=C**H**), 5.79-5.89 (m, 1H, CH_2=C**H**), 7.14-7.25 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.2, 40.4, 47.1, 57.2, 65.8, 66.1, 118.5, 118.8, 127.2, 128.0, 128.4, 131.2, 131.3, 140.2, 167.1, 167.6, 205.9; HRMS m/z 353.1368 (M+Na^+), calc. for $C_{19}H_{22}O_5Na^+$ 353.1365.

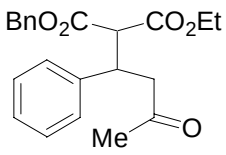


2-(3-Oxo-1-phenyl-butyl)-malonic acid dibenzyl ester (4f). Purified by FC using Et_2O/pentane and isolated as a colorless solid mp. 84-86 ^{o}C The enantiomers were determined by HPLC using a Daicel Chiralpak AS chiral stationary phase hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -7.1^o (*c* = 1.0 g/100mL, $CHCl_3$, 99% ee); ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, C**H**$_3$CO), 2.80 (d, *J* =6.6 Hz, 2H, COC**H**$_2$), 3.75 (d, *J* = 9.8 Hz, 1H, CO_2C**H**CO_2), 3.90-3.96 (m, 1H, C***H**), 4.81 (s, 2H, OC**H**$_2$), 5.06 (d, *J* = 2.7 Hz, 2H, OC**H**$_2$), 6.97-7.30 (m, 15H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.2, 40.4, 47.0, 57.3, 67.1, 67.2, 126.9, 127.2, 128.0, 128.1, 128.18, 128.2, 128.4, 128.5, 134.9, 135.1, 140.2, 167.3, 167.8, 205.9; HRMS m/z 453.1682 (M+Na^+) calc. for $C_{27}H_{26}O_5Na$ 453.1678.



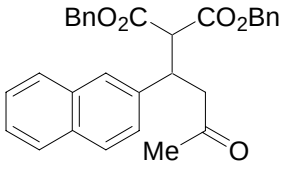
2-(3-Oxo-1-phenyl-butyl)-malonic acid benzyl ester methyl ester (4g). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The diastereomeric ratio was determined to be 1:1.5 by NMR. Major diastereomer ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H, C**H**$_3$CO), 2.83-2.94 (m, 2H, COC**H**$_2$), 3.67 (s, 3H, CO_2C**H**$_3$), 3.76 (d *J* = 9.7, 1H, CO_2C**H**CO_2), 3.94-4.00 (m, 1H, C***H**), 4.89

(s, 2H, OC**H**$_2$), 7.05-7.35 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.2, 40.4, 47.2, 52.5, 57.1, 67.0, 127.24, 128.0, 128.1, 128.39, 128.53, 134.9, 140.21, 167.4, 168.4, 205.95. Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H, C**H**$_3$CO), 2.83-2.94 (m, 2H, COC**H**$_2$), 3.45 (s, 3H, CO_2C**H**$_3$), 3.74 (d, *J* = 9.4, 1H, CO_2C**H**CO_2), 3.94-4.00 (m, 1H, C***H**), 5.14 (s, 2H, OC**H**$_2$), 7.05-7.35 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.1, 40.3, 46.8, 52.3, 57.2, 67.2, 127.21, 127.94, 128.20, 128.25, 128.50, 135.1, 140.26, 167.8, 168.3, 205.90; HRMS m/z 377.1364 (M+Na^+), calc. for $C_{21}H_{22}O_5Na^+$ 377.1365. After decarboxylation of the diastereomeric mixture of **4g**, the enantiomers were separated by HPLC using a Daicel Chiralcel OD chiral stationary phase in hexane/2-propanol 95/5, 96% ee. **Decarboxylation procedure**: To a solution of **4g** (0.354 g, 1 mmol) in 5 mL of MeOH was added 47 mg of 10% of Pd/C and the mixture was stirred under H_2 atmosphere at room temperature for 2.5 hrs. Filtration and concentration gave the crude acid which was used directly in the following reaction without further purification. The crude acid was dissolved in 3 mL of MeOH, 3 drops of TEA were added and heated over night at 60 ^{o}C. The final product **6** was purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless oil (50% yield over two steps).

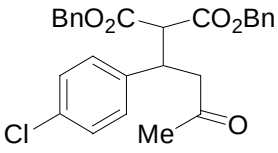


2-(3-Oxo-1-phenyl-butyl)-malonic acid benzyl ester ethyl ester (4h). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The diastereomeric ratio was determined to be 1:1 by NMR; ^{1}H NMR ($CDCl_3$) δ 0.95, 1.18 (t,t, *J* = 7.0 Hz, *J* = 7.0 Hz, 3H, C**H**$_3$CH_2O), 1.96, 1.99 (s,s, 3H, C**H**$_3$CO), 2.84-2.92 (m, 2H, COC**H**$_2$), 3.74, 3.76 (d,d, *J* = 4.7 Hz *J* = 4.7 Hz, 1H, CO_2C**H**CO_2), 3.91, 4.15(q,q, *J* = 7.0 Hz, *J* = 7.0 Hz, 2H, CH_3C**H**$_2$O), 3.93-3.99 (m, 1H, C***H**), 4.91, 5.17 (s, d, *J* = 3.0 Hz, 2H, OC**H**$_2$), 7.01-7.29 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.9, 30.2, 30.3, 40.3, 40.4, 47.1,47.2, 57.3, 61.3, 61.6, 67.0, 67.2, 127.17, 127.19, 128.04, 128.07, 128.13, 128.18, 128.2, 128.37, 128.43, 128.50, 135.1, 135.2, 140.3, 167.4, 167.5, 168.0, 205.91, 205.97. HRMS m/z 391.1523 (M+Na^+), calc. for $C_{22}H_{24}O_5Na^+$ 391.1521. After decarboxylation of the diastereomeric mixture of **4h**, the enantiomers were separated by HPLC using Daicel Chiralcel OD chiral stationary phase in hexane/2-propanol 95/5. **Decarboxylation procedure**: To a solution of **4h** (0.368 g, 1 mmol) in 5 mL of MeOH was added 47 mg of 10% of Pd/C and the mixture was stirred under H_2 atmosphere at room temperature for 2.5 hrs. Filtration and concentration gave the crude acid which was used directly in the following reaction without further purification. The crude acid was dissolved in 3 mL of MeOH, 3 drops of TEA were added and heated over night at 80 ^{o}C. The final product was purified by FC using Et_2O/CH_2Cl_2. and isolated as a colorless oil (78% yield over

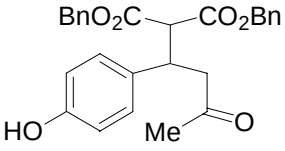
two steps). $[\alpha]^{rt}_D$ = +5.7° (*c* = 1.0 g/100mL, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH$_2$O), 2.04 (s, 3H, C**H**$_3$CO), 2.54-2.68 (octet, *J* = 7.8 Hz, 2H, COC**H**$_2$), 2.77-2.82 (m, 2H, C**H**$_2$CO$_2$Et), 3.64-3.69 (m, 1H, C***H**), 4.02 (q, *J* = 7.2 Hz, 2H, CH$_3$C**H**$_2$O), 7.17-7.29 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 14.0, 30.3, 37.3, 40.8, 49.4, 60.3, 126.8, 127.2, 128.5, 143.0, 172.0, 206.8, HRMS m/z 257.1149 (M+Na$^+$), calc. for $C_{14}H_{18}O_3Na^+$ 257.1154.



2-(1-Naphthalen-2-yl-3-oxo-butyl)-malonic acid dibenzyl ester (4j). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_D$ = -5.3° (*c* = 1.0 g/100mL, $CHCl_3$, 90% ee); ^{1}H-NMR ($CDCl_3$) δ1.95 (s, 3H, C**H**$_3$), 2.91-3.04 (m, 2H, C**H**$_2$), 3.95 (d, *J* = 10.0 Hz, 1H, CO$_2$C**H**CO$_2$), 4.16-4.22 (m, 1H, C***H**), 4.85 (s, 2H, OC**H**$_2$), 5.16 (d, *J* = 2.0 Hz, 2H, OC**H**$_2$), 6.91 (dd, *J* = 1.2, 7.6 Hz, 2H, Ar**H**), 7.10 (t, *J* = 7.6 Hz, 2H, Ar**H**), 7.17-7.20 (m, 1H, Ar**H**), 7.25-7.36 (m, 6H, Ar**H**), 7.43-7.48 (m, 2H, Ar**H**), 7.65 (d, *J* = 1.2 Hz, 1H, Ar**H**), 7.71-7.79 (m, 3H, Ar**H**); ^{13}C-NMR ($CDCl_3$) δ30.2, 40.5, 47.1, 57.3, 67.1, 67.3, 125.8, 126.0, 126.1, 127.0, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 132.6, 133.3, 134.8, 135.1, 137.7, 167.4, 167.8, 205.8; HRMS m/z 503.1842 (M+Na$^+$), calc. for $C_{31}H_{28}O_5Na^+$ 503.1834.

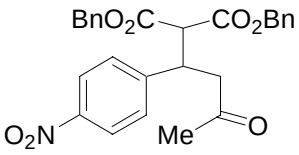


(*R*)-2-[1-(4-Chloro-phenyl)-3-oxo-butyl]-malonic acid dibenzyl ester (4k). Purified by FC using Et_2O/pentane and isolated as a colorless solid, mp. 83-85° C. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -8.1° (*c* = 1.0 g/100mL, $CHCl_3$, 98% ee); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3H, C**H**$_3$CO), 2.81 (d, *J* = 6.2 Hz, 2H, COC**H**$_2$), 3.75 (d, *J* = 9.4 Hz, 1H, CO$_2$C**H**CO$_2$), 3.91-3.97 (m, 1H, C***H**), 4.90 (d, *J* = 2 Hz, 2H, C**H**$_2$O), 5.11 (s, 2H C**H**$_2$O), 7.02-7.33 (m, 14H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.2, 39.7, 46.8, 57.0, 67.2, 67.3, 128.26, 128.28, 128.3, 128.4, 128.5, 128.6, 129.5, 132.9, 134.8, 135.0, 138.7, 167.2, 167.6, 205.4; HRMS m/z 487.1280 (M+Na$^+$), calc. for $C_{27}H_{25}ClO_5Na^+$ 487.1288.

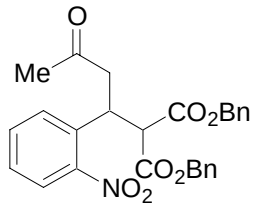


2-[1-(4-Hydroxy-phenyl)-3-oxo-butyl]-malonic acid dibenzyl ester (4l). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid, mp. 118-119 °C. The enantiomers were separated by HPLC using a Daicel

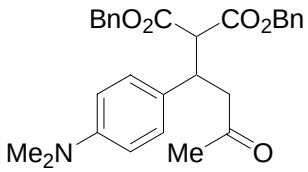
Chiralcel OD chiral stationary in hexane/2-propanol 80/20; $[\alpha]^{rt}_D$ = -13.5° (*c* = 1.0 g/100mL, $CHCl_3$, 93% ee); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3H, C**H**$_3$CO), 2.80 (d, *J* = 7.0 Hz, 2H, COC**H**$_2$), 3.72 (d, 9.7 Hz, 1H, CO_2C**H**CO_2), 3.85-3.91 (m, 1H, C***H**), 4.87 (s, 2H OC**H**$_2$), 5.11 (d, *J* = 5.0 Hz, 2H, OC**H**$_2$), 6.05 (s, 1H, **H**O), 6.50 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.95 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.01-7.31 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.1, 40.0, 47.4, 57.6, 67.2, 67.3, 115.5, 128.1, 128.2, 128.3, 128.4, 128.6, 129.1, 134.9, 135.0, 155.1, 167.5, 167.8, 207.4; HRMS m/z 469.1628 (M+Na$^+$), calc. for $C_{27}H_{26}O_7Na^+$ 469.1627.



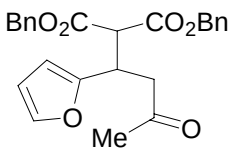
2-[1-(4-Nitro-phenyl)-3-oxo-butyl]-malonic acid dibenzyl ester (4m). Purified by FC using Et_2O/EtOAc/pentane and isolated as a yellow solid mp. 68-70 °C. The enantiomers were separated by HPLC using a Daicel Chiralcel OD chiral stationary phase in hexane/2-propanol 80/20; $[\alpha]^{rt}_D$ = -9.3° (*c* = 1.0 g/100mL, $CHCl_3$, 89% ee); ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H, C**H**$_3$CO), 2.84-2.91 (m, 2H, COC**H**$_2$), 3.80 (d, *J* = 9.7 Hz, 1H, CO_2C**H**CO_2), 4.02-4.09 (m, 1H, C***H**), 4.91 (d, *J* = 2.3 Hz, 2H, OC**H**$_2$), 5.13 (s, 2H, OC**H**$_2$), 7.07 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.21-7.35 (m, 10H, Ar**H**), 7.93 (d, *J* = 8.6 Hz, 2H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.1, 39.8, 46.5, 56.4, 67.3, 67.5, 123.5, 128.4, 128.43, 128.5, 128.6, 129.1, 134.6, 134.9, 146.8, 147.8, 166.9, 167.3, 204.8; HRMS m/z 498.1514 (M+Na$^+$), calc. for $C_{27}H_{25}NO_7Na^+$ 498.1529.



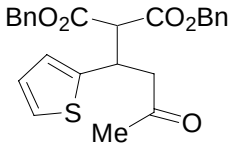
2-[1-(2-Nitro-phenyl)-3-oxo-butyl]-malonic acid dibenzyl ester (4n). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_D$ = -9.8° (*c* = 1.0 g/100mL, $CHCl_3$, 86% ee); ^{1}H-NMR ($CDCl_3$) δ 1.98 (s, 3H, COC**H**$_3$), 3.02 (s, 1H, COC**H**H), 3.04 (d, *J* = 1.6 Hz, 1H, COCH**H**), 4.13 (d, *J* = 8.0 Hz, 1H, CO_2C**H**CO_2), 4.49 (br q, *J* = 8.0 Hz, 1H, C*H), 5.01 (d, *J* = 4.4 Hz, 2H, OC**H**$_2$), 5.11 (s, 2H, OC**H**$_2$), 7.14-7.17 (m, 2H, Ar**H**), 7.23-7.39 (m, 11H, Ar**H**), 7.53 (dd, *J* = 1.2, 8.0 Hz, 1H, Ar**H**); ^{13}C-NMR ($CDCl_3$) δ 29.6, 34.5, 45.5, 55.3, 67.1, 67.2, 124.5, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.8, 132.5, 134.7, 134.8, 135.0, 149.9, 167.1, 167.5, 205.3; HRMS m/z 419.1526 (M+Na$^+$), calc. for $C_{27}H_{25}O_7NNa^+$ 419.1529.



2-[1-(4-Dimethylamino-phenyl)-3-oxo-butyl]-malonic acid dibenzyl ester (4o). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 80/20; $[\alpha]^{rt}_D$ = -2.9° (*c* = 1.0 g/100mL, $CHCl_3$, 77% ee); ^{1}H-NMR ($CDCl_3$) δ1.95 (s, 3H, COC**H**$_3$), 2.82 (s, 1H, COC**H**H), 2.84 (d, *J* = 1.6 Hz, 1H, COCH**H**), 2.91 (s, 6H, (C**H**$_3$)$_2$N), 3.77 (d, *J* = 9.6 Hz, 1H, CO_2C**H**CO_2), 3.88-3.94 (m, 1H, C***H**), 4.91 (d, *J* = 2.4 Hz, 2H, OC**H**$_2$), 5.14 (d, *J* = 2.4 Hz, 2H, OC**H**$_2$), 6.58 (d, *J* = 9.2 Hz, 2H, Ar**H**), 7.04-7.08 (m, 4H, Ar**H**), 7.23-7.33 (m, 8H, Ar**H**); ^{13}C-NMR ($CDCl_3$) δ30.1, 39.8, 40.4, 47.3, 57. 7, 66.9, 67.1, 112.4, 126.9, 127.4, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.1, 135.2, 149.5, 167.5, 168.0, 206.4; HRMS m/z 496.2086 (M+Na$^+$), calc. for $C_{29}H_{31}O_5NNa^+$ 496.2100.

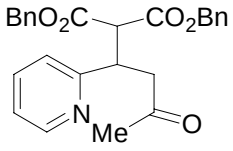


2-(1-Furan-2-yl-3-oxo-butyl)-malonic acid dibenzyl ester (4p). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The enantiomers were separated by HPLC using a Daicel Chiralpak AD chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -6.3° (*c* = 1.0 g/100mL, $CHCl_3$, 92% ee); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H, C**H**$_3$CO), 2.85 (dd, *J* = 4.7, 17.5, Hz, 1H, COC**H**H), 2.97 (dd, *J* = 9.0, 17.5, Hz, 1H, COCH**H**), 3.92 (d, *J* = 7.8 Hz, 1H, CO_2C**H**CO_2), 4.12-4.17 (m, 1H, C***H**), 5.05 (s, 2H, OC**H**$_2$), 5.13 (d, *J* = 1.6 Hz, 2H, OC**H**$_2$), 6.03 (d, *J* = 3.1 Hz, 1H, C_4**H**$_3$O), 6.20 (dd, *J* = 2.0, 3.1 Hz, 1H, C_4**H**$_3$O), 7.21-7.34 (m, 11H, Ar**H**, C_4**H**$_3$O); ^{13}C NMR ($CDCl_3$) δ 29.9, 33.8, 44.2, 54.7, 67.1, 67.2, 106.9, 110.2, 128.2, 128.21, 128.26, 128.3, 128.4, 128.5, 134.9, 135.0, 141.6, 153.1, 167.3, 167.5, 205.6, ; HRMS m/z 4431478, calc. for $C_{25}H_{24}O_6Na^+$ 443.1471.

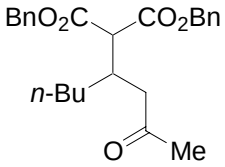


2-(3-Oxo-1-thiophen-2-yl-butyl)-malonic acid dibenzyl ester (4q). Purified by FC using Et_2O/pentane and isolated as a colorless solid, mp. 39-40 °C. The enantiomers were separated by HPLC using a Daicel Chiralpak AD chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -6.6° (*c* = 1.0 g/100mL, $CHCl_3$, 92% ee); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, C**H**$_3$CO), 2.90-2.96 (m, 2H, COC**H**$_2$), 3.87 (d, *J* = 8.6 Hz, 1H, CO_2C**H**CO_2), 4.31-4.37 (m, 1H, C***H**), 5.00 (s, 2H, OC**H**$_2$), 5.13 (d, *J* = 4.3 Hz, 2H, OC**H**$_2$), 6.84 (d, *J* = 3.5 Hz, 2H, C_4**H**$_3$S), 7.12 (t, *J* = 3.5 Hz, 1H, C_4**H**$_3$S), 7.14-34 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.2, 35.6, 47.6, 57.6, 67.2, 67.3, 124.2, 125.8, 126.6, 128.2, 128.24,

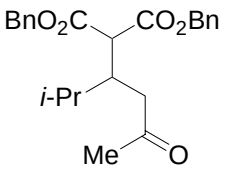
128.26, 128.3, 128.4, 128.5, 134.9, 135.0, 143.3, 167.2, 167.5, 205.5; HRMS m/z 459.1248 ($M+Na^+$), calc. for $C_{25}H_{24}O_5SNa^+$ 459.1242.



2-(3-Oxo-1-pyridin-2-yl-butyl)-malonic acid dibenzyl ester (4r). Purified by FC using Et_2O/pentane and isolated as a dark color oil. The enantiomers were separated by HPLC using a Daicel Chiralpak AD chiral stationary phase in hexane/2-propanol 80/20; $[\alpha]^{rt}_D$ = -1.5° (*c* = 1.0 g/100mL, EtOH, 79% ee); ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, C**H**$_3$CO), 2.72 (dd, *J* = 3.5, 17.5 Hz, 1H, COC**H**H), 3.06 (dd, *J* = 8.6, 17.5 Hz, 1H, COCH**H**), 3.97-4.04 (m, 2H, CO_2C**H**CO_2, C***H**), 4.85 (s, 2H, OC**H**$_2$), 5.06 (d, *J* = 1.6 Hz, 2H, OC**H**$_2$), 6.93-6.93 (m, 1H C_5**H**$_4$N), 7.01-7.25 (m, 11H, C_5**H**$_4$N, Ar**H**), 7.36-7.41 (m, 1H, C_5**H**$_4$N), 8.31 (d, *J* = 2.0 Hz, 1H, C_5**H**$_4$N); ^{13}C NMR ($CDCl_3$) δ 30.0, 41.2, 45.8, 55.7, 66.8, 67.1, 121.8, 124.6, 128.0, 128.09, 128.1, 128.2, 128.3, 128.4, 135.0, 135.2, 136.1, 148.9, 160.0, 167.5, 168.0, 206.0; HRMS m/z 454.1629 ($M+Na^+$), calc. for $C_{26}H_{25}NO_5Na^+$ 454.1630.

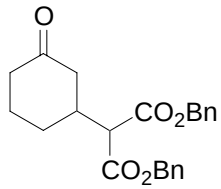


2-[1-(2-Oxo-propyl)-pentyl]-malonic acid dibenzyl ester (4s). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The enantiomers were separated by HPLC using a Chiralcel OD chiral stationary phase in hexane/2-propanol 99/1; $[\alpha]^{rt}_D$ = -7.1° (*c* = 0.45 g/100mL, $CHCl_3$, 91% ee); ^{1}H-NMR ($CDCl_3$) δ0.79-84 (m, 3H, C**H**$_3$), 1.15-1.36 (m, 6H, 3 C**H**$_2$), 2.03 (s, 3H, C**H**$_3$CO), 2.45 (dd, *J* = 6.4, 17.6 Hz, 1H, COC**H**H), 2.61-2.70 (m, 2H, COCH**H** and C***H**), 3.65 (d, *J* = 5.6 Hz, 1H, CO_2C**H**CO_2), 5.11-5.14 (m, 4H, 2 OC**H**$_2$), 7.28-7.34 (m, 5H, Ar**H**); ^{13}C-NMR ($CDCl_3$) δ 13.9, 22.6, 29.1, 30.2, 31.8, 33.7, 45.1, 53.9, 66.9, 67.0, 128.2, 128.3, 128.4, 128.5, 135.3, 135.4, 168.4, 168.7, 207.4; HRMS m/z 433.2000 ($M+Na^+$), calc. for $C_{25}H_{30}O_5Na^+$ 433.1991.

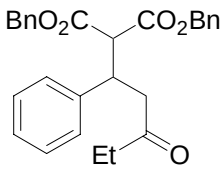


2-(1-Isopropyl-3-oxo-butyl)-malonic acid dibenzyl ester (4t). Purified by FC using Et_2O/pentane and isolated as a colorless oil. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 98/2; $[\alpha]^{rt}_D$ = -9.7° (*c* = 1.0 g/100mL, $CHCl_3$, 84% ee); ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, *J* = 7.2 Hz, 3H, C**H**$_3$CH), 0.87 (d, *J* = 7.2 Hz, 3H, C**H**$_3$CH), 1.68 (octet, *J* = 6.4 Hz, 1H, $(CH_3)_2$C**H**), 2.07 (s, 3H, COC**H**$_3$), 2.48 (dd, *J* = 5.6, 18.0 Hz, 1H, COC**H**H), 2.66 (dd, *J* = 5.6, 18.0 Hz, 1H, COCH**H**), 2.73 (quintet, *J* = 6.4 Hz, 1H, C***H**), 3.63 (d, *J* = 6.4 Hz, 1H, CO_2C**H**CO_2), 5.10 (d, *J* = 3.6 Hz, 4H, 2 OC**H**$_2$), 7.26-7.34 (m, 10H, Ar**H**); ^{13}C-NMR ($CDCl_3$)

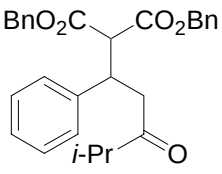
δ18.8, 20.5, 29.8, 30.1, 38.9. 42.8, 53.5, 67.0, 67.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.2, 135.3, 168.6, 168.9, 207.2; HRMS m/z 419.1834 ($M+Na^+$), calc. for $C_{24}H_{28}O_5Na^+$ 419.1834.



2-(3-Oxo-cyclohexyl)-malonic acid dibenzyl ester (4u). Purified by FC using EtOAc/pentane and isolated as a colorless solid, mp. 42-44 °C. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = -1.4° (*c* = 1.0 g/100mL, MeOH, 83% ee); ^{1}H NMR ($CDCl_3$) δ 1.24-16.3 (m, 2H, C**H**$_2$), 1.84-2.02 (m, 2H, C**H**$_2$), 2.13-2.25 (m, 2H, C**H**$_2$), 2.32-2.44 (m, 2H, C**H**$_2$), 2.50-2.55 (m, 1H, C***H**), 3.39 (d, *J* = 8.6 Hz, 1H, CO_2C**H**CO_2), 5.12 (s, 3H, OC**H**$_2$), 5.13 (s, 2H, OC**H**$_2$), 7.24-7.35 (m, 10H Ar**H**); ^{13}C NMR ($CDCl_3$) δ 24.4, 28.6, 38.1, 40.9, 45.0, 56.7, 67.2, 67.3, 128.2, 128.4, 128.6, 135.0, 135.1, 167.4, 167.5, 209.4; HRMS m/z 403.1513 ($M+Na^+$), calc. for $C_{23}H_{24}O_5Na^+$ 403.1521.

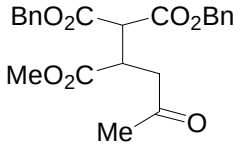


2-(3-Oxo-1-phenyl-pentyl)-malonic acid dibenzyl ester (4v). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_D$ = +1.5° (*c* = 1.0 g/100mL, EtOH, 95% ee). ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.6 Hz, 3H, C**H**$_3$CH$_2$), 2.20 (qq, *J* = 7.6, 22.4 Hz, 2H, CH$_3$C**H**$_2$), 2.79-2.91 (m, 2H, COC**H**$_2$), 3.84 (d, *J* = 10.0 Hz, 1H, CO_2C**H**CO_2), 3.99-4.05 (m, 1H, C*H), 4.89 (s, 2H, OC**H**$_2$), 5.13 (d, *J* = 2.8 Hz, 2H, OC**H**$_2$), 7.04-7.07 (m, 2H, Ar**H**), 7.17-7.33 (m, 13H, Ar**H**); ^{13}C-NMR ($CDCl_3$) δ 7.4, 36.2, 40.5, 45.8, 57.3, 67.1, 67.2, 127.2, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.0, 135.1, 140.3, 167.4, 167.9, 208.6; HRMS m/z 467.1836 ($M+Na^+$), calc. for $C_{28}H_{28}O_5Na^+$ 467.1834.

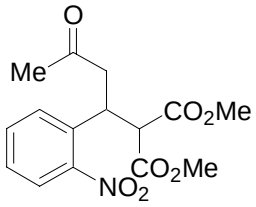


2-(4-Methyl-3-oxo-1-phenyl-pentyl)-malonic acid dibenzyl ester (4w). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless solid. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = +3.3° (*c* = 0.58 g/100mL, CH_2Cl_2, 94% ee); ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, *J* = 6.8 Hz, 3H, C**H**$_3$CH), 0.84 (d, *J* = 6.8 Hz, 3H, C**H**$_3$CH), 2.92 (septet, *J* = 6.8 Hz, 1H, C**H**$(CH_3)_2$), 2.77 (dd, *J* = 4.8, 16.8 Hz, 1H, COC**H**H), 2.87 (dd, *J* = 9.6, 16.8 Hz, 1H, COC**H**H), 3.78 (d, *J* = 9.6 Hz, 1H, CO_2C**H**CO_2), 3.92-3.99 (m, 1H, C*H), 4.82 (s, 2H, OC**H**$_2$), 5.06 (d, *J* = 2.0 Hz, 2H, OC**H**$_2$), 6.98-7.00 (m, 2H, Ar**H**), 7.10-7.29 (m, 13H, Ar**H**);

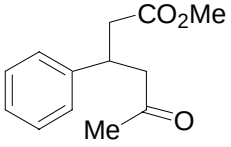
^{13}C-NMR ($CDCl_3$) δ 17.7, 17.8, 40.4, 41.0, 43.9, 57.2, 67.1, 67.2, 127.1, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 135.0, 135.2, 140.5, 167.5, 167.9, 211.7; HRMS m/z 481.1993 ($M+Na^+$), calc. for $C_{29}H_{30}O_5Na^+$ 481.1991.



2-Benzyloxycarbonyl-3-(2-oxo-propyl)-succinic acid 1-benzyl ester 4-methyl ester (4x). Purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless oil The enantiomers were separated by HPLC using a Daicel Chiralcel OD chiral stationary phase in hexane/2-propanol 90/10; $[\alpha]^{rt}_D$ = -2.9^o (*c* = 1.0 g/100mL, $CHCl_3$, 59% ee). ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, C**H**$_3$CO), 2.72 (dd, *J* = 4.7, 18.3 Hz, 1H, COC**H**$_2$), 2.94 (dd, *J* = 7.4, 18.3 Hz, 1H, COC**H**$_2$), 3.53 (s, 3H, CO_2C**H**$_3$), 3.61-3.66 (m, 1H, C***H**), 3.99 (d, *J* = 6.6 Hz 1H, CO_2C**H**CO_2), 5.12 (d, *J* = 1.6 Hz, 4H OC**H**$_2$), 7.24-7.33 (m, 10H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 29.7, 39.1, 41.7, 52.0, 52.3, 67.4, 67.5, 128.32, 128.36, 128.4, 128.44, 128.5, 134.9, 167.5, 167.7, 172.3, 205.4; HRMS m/z 435.1413 ($M+Na^+$), calc for $C_{23}H_{24}O_7Na^+$ 435.1420.

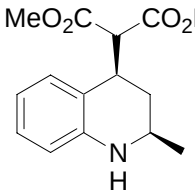


2-[1-(2-Nitro-phenyl)-3-oxo-butyl]-malonic acid dimethyl ester (4y). Prepared by transesterfication of **4n**. To a solution of 110.0 mg of the dibenzylester **4n** in 10 mL MeOH was added 1.0 mL of conc. HCl and the mixture was refluxed for 60 hrs or until all the starting material were consumed (TLC or GC). The solvent was evaporated and the mixture was diluted with water and extracted with CH_2Cl_2. After evaporation of the CH_2Cl_2 the crude product was purified by FC using Et_2O/CH_2Cl_2 and isolated as a colorless oil. The enantiomers were separated by HPLC using a Daicel Chiralpak AS chiral stationary phase in hexane/2-propanol 97/3; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, C**H**$_3$CO), 3.05-3.18 (m, 2H, C**H**$_2$CO), 5.58 (s, 3H, CO_2C**H**$_3$), 3.69 (s, 3H, CO_2C**H**$_3$), 4.01 (d, *J* = 8.2 Hz, 1H, CO_2C**H**CO_2), 4.43-4.49 (m, 1H, C***H**), 7.33-7.42 (m, 2H, Ar**H**), 7.51 (t, *J* = 8. Hz, 1H, Ar**H**), 7.79 (d, *J* = 8.2 Hz, 1H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 29.9, 34.5, 45.8, 52.6, 52.7, 55.3, 124.7, 128.0, 128.9, 132.6, 135.2, 150.2, 167.8,, 168.4, 205.5; HRMS m/z 346.0901, ($M+Na^+$) calc for $C_{15}H_{17}NO_7Na^+$ 346.0903.



5-Oxo-3-phenyl-hexanoic acid methyl ester 6. Prepared by the decarboxylation-transesterfication procedure of **4f** as shown in Scheme 2. To a solution of 120.4 mg of **4f** in MeOH was added 10 mg 10% Pd/C and the

mixture was stirred for 2.5 hrs at ambient temperature under a H_2 atmosphere to afford the crude diacid. After filtering off the catalyst, the solution was refluxed in H_2O overnight to afford the crude monoacid after evaporation of the solvent. The monoacid was redissolved in MeOH and toluene was added to give a 5/2 MeOH-toluene solution to which trimethylsilyldiazomethane (2.0 M in hexane) was added dropvise until the yellow color persisted and no more N_2 was evolved. After 5 minutes of stirring a drop of CH_3COOH was added to quench the excess of trimethylsilyldiazomethane and the mixture was stirred for another 5 minutes. After removal of the solvents the crude reaction mixture was purified by FC using Et_2O/pentane and 41.5 mg (67%) of **6** was isolated as a colorless oil. The enantiomers were separated by HPLC using a Daicel Chiralcel OD chiral stationary phase in hexane/2-propanol 95/5; $[\alpha]^{rt}_D$ = +6.8^o (*c* = 1.0 g/100mL, $CHCl_3$, 96% ee); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, C**H**$_3$CO), 2.65 (octet, *J* = 7.8 Hz, 2H, COC**H**$_2$), 2.75-2.85(m, 2H, C**H**$_2$CO$_2$CH$_3$), 3.57 (s, 3H, CO$_2$C**H**$_3$), 3.65-3.71 (m, 1H, C***H**), 7.23 (m, 5H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 30.4, 37.2, 40.5, 49.3, 51.6, 126.8, 127.2, 128.6, 143.0, 172.2, 206.8; HRMS m/z 243.0990 (M+Na$^+$), calc. for $C_{13}H_{16}O_3Na^+$ 243.0997.



(2*R*,4*R*,)-2-(2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-malonic acid dimethyl ester 7. Prepared by reductive amination of **4y** (unoptimised)**.** To 16.2 mg of **4y** in EtOH (10 mL) was added 15 mg 10% Pd/C and 1.0 mL acetic acid and the reaction mixture was stirred under a H_2 atmosphere (5 bar) for 30 min. After filtering off the catalyst and evaporating the solvent, the residue was dissolved in saturated $NaHCO_3$ and extracted with CH_2Cl_2. After removal of the solvent the product **7** was purified from the by products 2-methyl-quinoline and 2-methyl-quinoline-*N*-oxide by FC using Et_2O/pentane. This reductive amination was very sensitive to the conditions, for instance using MeOH instead of EtOH afforded no product, and longer reaction times at lower pressure also afforded decreased yields. The enantiomeric excess was determined by GC using a Chrompack Chirasil Dex-CB chiral stationary phase. $[\alpha]^{rt}_D$ = +1.1^o (*c* = 1.0 g/100mL, $CHCl_3$, 86% ee).; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.8 Hz, 3H, C**H**$_3$CH), 1.84 (m, 2H, C**H**$_2$), 3.32-3.44 (m, 1H), 3.57 (s, 3H, CO$_2$C**H**$_3$), 3.60-3.68 (m, 1H), 3.71 (s, 3H, CO$_2$C**H**$_3$), 4.03 (d, *J* = 6.0 Hz, 1H, C**H**(CO)$_2$), 6.41 (dd, *J* = 0.8, 8.0 Hz, 1H, Ar**H**), 6.54 (t, *J* = 7.4 Hz, 1H, Ar**H**), 6.87-6.93 (m, 2H, Ar**H**); ^{13}C NMR ($CDCl_3$) δ 22.9, 33.6, 36.7, 47.6, 52.5, 52.9, 54.6, 110.0, 114.8, 117.6, 126.3, 127.7, 145.8, 168.8, 169.8; HRMS m/z 300.1194 (M+Na$^+$), calc. for $C_{15}H_{19}O_4NNa^+$ 300.1212.

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