Supporting Information

for

Preparation of mono-substituted malonic acid half oxyesters (SMAHOs)

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Beilstein J. Org. Chem. 2021, 17, 2085–2094. doi:10.3762/bjoc.17.135

Experimental procedures, compound characterization data, and NMR spectra for all compounds
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1. General information

All commercially available reagents, including solvents (ethyl acetate = EA, petroleum ether = PE, cyclohexane = Cy, diethyl ether, dichloromethane, N,N-dimethylformamide = DMF, ethanol, methanol, and tetrahydrofuran = THF), were used as received. Room temperature means 18–25 °C. Melting points (mp) are uncorrected and were measured on a Büchi B-545 apparatus. Analytical thin layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator (Merck 60F254). Visualization was effected using ultraviolet light (λ = 254 nm) and/or a aqueous solution of KMnO₄. Flash chromatography (FC) was performed on 40–63 μm silica gel with mixtures of solvents. High-resolution mass spectra were obtained at the ICOA of the Université of Orléans by electrospray ionization using a Q-TOF analyzer. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer. H NMR chemical shifts were referenced to the residual solvent signal; 13C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. Data are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptuplet, m = multiplet, br = broad), coupling constant J (Hz), integration.

2. Preparation of substituted malonates 3

General procedure 1 (GP1) - alkylation: A RBF equipped with a stirring bar was charged with NaH 60% (1.0 equiv) and purged with argon. DMF (V mL) was added and the RBF was cooled to 0 °C (ice/water bath). Malonate 1 (1.1 equiv) was added dropwise with a syringe and the mixture was stirred for 15 min. The alkyl halide 2 (1.0 equiv) was then added dropwise with a syringe. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then, the resulting mixture was poured in sat aq NH₄Cl (3 V) and the resulting solution was extracted with EtO (3 × 2 V). The combined organic layers were washed with water (10 V) and brine (5 V), dried (Na₂SO₄), and evaporated. Purification by FC afforded the expected product 3.

Compound 3aa: Following GP1 performed with dimethyl malonate (1a, 1.0 mL, 8.8 mmol, 1.1 equiv), sodium hydride (0.32 g, 8.0 mmol, 1.0 equiv), and iodomethane (2a, 0.2 mL, 8.0 mmol, 1.0 equiv) in DMF (8 mL, c = 1 M) for 2 h, the desired product 3aa was obtained after purification by FC [V(SiO₂) = 50 mL, PE/EA (90 : 10, UV+KMnO₄) 10:25 (250 mL)], as a colorless oil (0.591 g, 50%).

1H NMR (400 MHz, CDCl₃) δ 3.71 (s, 6H), 3.44 (q, J = 7.3 Hz, 1H), 1.40 (d, J = 7.3 Hz, 3H).

13C[1H] NMR (100 MHz, CDCl₃) δ 170.6 (2 C), 52.5 (CH), 52.5 (2 CH₃).

Compound 3ba: Following GP1 performed with diethyl malonate (1b, 6.7 mL, 44.0 mmol, 1.1 equiv), sodium hydride (1.92 g, 48.0 mmol, 1.2 equiv), and iodomethane (2b, 5.6 mL, 50.0 mmol, 1.1 equiv) in DMF (40 mL, c = 1 M) for 16 h, the desired product 3ba was obtained after purification by FC [V(SiO₂) = 100 mL, PE/EA (90 : 10, UV+KMnO₄) 98:2 (1000 mL)] as a colorless oil (5.302 g, 76%).

1H NMR (400 MHz, CDCl₃) δ 4.14 (q, J = 7.2 Hz, 4H), 3.36 (q, J = 7.3 Hz, 1H), 1.35 (d, J = 7.3 Hz, 3H), 1.21 (t, J = 7.2 Hz, 6H).

13C[1H] NMR (100 MHz, CDCl₃) δ 170.2 (2 C), 61.3 (2 CH₂), 46.2 (CH), 14.1 (2 CH₃), 13.6 (CH₃).

Compound 3ab: Following GP1 performed with dimethyl malonate (1a, 0.60 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and ethyl bromide (2h, 0.37 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M) for 16 h, the desired product 3ab was obtained after purification by FC [V(SiO₂) = 50 mL, Cy/EA (95 : 5, 250 mL), 90:10 (250 mL)] as a colorless oil (318 mg, 40%).

1H NMR (400 MHz, CDCl₃) δ 3.72 (s, 6H), 3.28 (t, J = 7.4 Hz, 1H), 1.92 ( quint, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H).

13C[1H] NMR (100 MHz, CDCl₃) δ 70.0 (2 C), 53.3 (CH), 52.5 (2 CH₃), 22.4 (CH₂), 12.0 (CH₃).

Compound 3ac: Following GP1 performed with dimethyl malonate (1a, 0.63 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and 1-iodobutane (2c, 0.57 mL, 5.5 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M) for 16 h, the desired product 3ac was obtained after purification by FC [V(SiO₂) = 50 mL, Cy/EA (95 : 5, 250 mL), 90:10 (250 mL)] as a colorless oil (710 mg, 75%).

1H NMR (400 MHz, CDCl₃) δ 3.71 (s, 6H), 3.33 (t, J = 7.5 Hz, 1H), 1.87 (q, J = 7.5 Hz, 2H), 1.46–1.19 (m, 4H), 0.87 (t, J = 6.6 Hz, 3H).

13C[1H] NMR (100 MHz, CDCl₃) δ 70.1 (2 C), 52.5 (2 CH₃), 51.8 (CH), 29.6 (CH₂), 28.7 (CH₃), 22.4 (CH₂), 13.9 (CH₃).

1 Spectral analysis matches with a commercially available sample.
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4 Neimert-Andersson, K.; Blomberg, E.; Somfai, P. J. Org. Chem. 2004, 69, 3746-3752.
Compound 3bd: Following GPl performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and 1-iodooctane (2d, 0.90 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M), the desired product 3bd was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (1.329 g, 93%).

Rf (PE/EA : 90/10, UV+Kmno4): 0.63

1H NMR (400 MHz, CDCl3): δ 4.16 (q, J = 7.1 Hz, 4H), 3.28 (t, J = 7.5 Hz, 1H), 1.89–1.80 (m, 2H), 1.31–1.18 (m, 18H), 0.84 (t, J = 6.6 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3): δ 169.7 (2 C), 61.3 (2 CH2), 52.2 (CH), 31.9 (CH2), 29.4 (CH2), 29.3 (CH2), 28.8 (CH2), 27.4 (CH2), 22.7 (CH2), 14.2 (3 CH3).

Compound 3be: Following GPl performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and 2-isopropanol (2e, 0.50 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M), the desired product 3be was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (524 mg, 52%).

Rf (Cy/EA : 90/10, UV+Kmno4): 0.37

1H NMR (400 MHz, CDCl3): δ 4.15 (q, J = 7.1 Hz, 4H), 3.06 (d, J = 8.7 Hz, 1H), 2.41–2.28 (m, 1H), 1.22 (t, J = 7.1 Hz, 6H), 0.96 (d, J = 6.9 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 168.9 (2 C), 61.2 (2 CH2), 59.2 (CH), 28.8 (CH), 20.4 (2 CH3), 14.2 (2 CH3).

Compound 3bf: Following GPl performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and allyl bromide (2f, 0.43 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M), the desired product 3bf was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (807 mg, 81%).

Rf (Cy/EA : 90/10, UV+Kmno4): 0.29

1H NMR (400 MHz, CDCl3): δ 5.76 (ddt, J = 17.1, 10.3, 7.2 Hz, 1H), 5.10 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 4H), 3.40 (t, J = 7.2 Hz, 1H), 2.63 (t, J = 7.2 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 169.0 (2 C), 134.2 (CH), 117.6 (CH2), 61.5 (2 CH2), 51.8 (CH), 32.9 (CH2), 14.2 (2 CH3).

Compound 3bg: Following GPl performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and propargyl bromide (2g, 0.74 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M), the desired product 3bg was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (572 mg, 58%).

Rf (Cy/EA : 90/10, UV+Kmno4): 0.34

1H NMR (400 MHz, CDCl3): δ 4.20 (q, J = 7.2 Hz, 4H), 3.53 (t, J = 7.5 Hz, 1H), 2.78–2.71 (m, 2H), 2.02–1.97 (m, 1H), 1.25 (t, J = 7.2 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 167.9 (2 C), 80.0 (C), 70.5 (CH), 61.8 (2 CH3), 51.2 (CH), 18.5 (CH2), 14.1 (2 CH3).

Compound 3bh: Following GPl performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and benzyl bromide (2h, 0.59 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M), the desired product 3bh was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (959 mg, 76%).

Rf (Cy/EA : 90/10, UV+Kmno4): 0.25

1H NMR (400 MHz, CDCl3): δ 7.33–7.27 (m, 2H), 7.26–7.21 (m, 3H), 4.19 (q, J = 7.2 Hz, 4H), 3.67 (t, J = 7.9 Hz, 1H), 3.24 (d, J = 7.9 Hz, 2H), 1.23 (t, J = 7.2 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 169.0 (2 C), 138.0 (C), 128.9 (2 CH2), 128.6 (2 CH), 126.8 (CH), 61.5 (2 CH2), 54.0 (CH), 34.8 (CH2), 14.1 (2 CH3).

Compound 3bi: Following GPl performed with diethyl malonate (1b, 0.46 mL, 3.0 mmol, 1.0 equiv), sodium hydride (0.12 g, 3.0 mmol, 1.0 equiv), and 2-(bromomethyl)thiophene (2i, 0.53 g, 3.0 mmol, 1.0 equiv) in DMF (3 mL, c = 1 M) for 16 h, the desired product 3bi was obtained by purification by FC [V(SiO2) = 50 mL, Cy/EA: 95:5 (500 mL)] as a yellow oil (229 mg, 30%).

Rf (Cy/EA : 80/20, UV+Kmno4): 0.53

1H NMR (400 MHz, CDCl3): δ 7.25–7.21 (m, 1H), 7.03–7.00 (m, 1H), 6.93 (d, J = 4.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 4H), 3.63 (t, J = 7.8 Hz, 1H), 3.24 (d, J = 7.8 Hz, 2H), 1.22 (t, J = 7.1 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 169.0 (2 C), 138.2 (C), 128.3 (CH), 125.8 (CH), 122.1 (CH), 61.6 (CH2), 53.3 (CH3), 29.3 (CH2), 14.1 (CH3).

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Compound 3bj: Following GP1 performed with diethyl malonate (1b, 0.84 mL, 5.5 mmol, 1.1 equiv), sodium hydride (0.20 g, 5.0 mmol, 1.0 equiv), and 1-bromo-3-chloropropane (2j, 0.49 mL, 5.0 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M) for 16 h, the desired product 3bj was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA:95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (1.077 g, 91%).

Rf (PE/EA: 90/10, UV+KMnO4): 0.48

1H NMR (400 MHz, CDCl3): δ 4.17 (q, J = 7.1 Hz, 4H), 3.51 (t, J = 6.5 Hz, 2H), 3.31 (t, J = 7.5 Hz, 1H), 2.01 (q, J = 7.5 Hz, 2H), 1.84–1.75 (m, 2H), 1.24 (t, J = 7.1 Hz, 6H).

13C[1H] NMR (100 MHz, CDCl3): δ 169.1 (2 C), 61.5 (2 CH2), 51.3 (CH), 44.2 (CH2), 30.2 (CH2), 26.2 (CH2), 14.1 (2 CH3).

Compound 3ak: Following GP1 performed with dimethyl malonate (1a, 0.56 mL, 4.9 mmol, 1.1 equiv), sodium hydride (0.18 g, 4.5 mmol, 1.0 equiv), and tert-butyl (2-bromoethoxy)carbamate (2k, 1.00 g, 4.5 mmol, 1.0 equiv) in DMF (10 mL, c = 0.5 M) for 16 h, the desired product 3ak was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA:90:10 (250 mL), 80:20 (250 mL)] as a colorless oil (507 mg, 41%).

Rf (Cy/EA: 80/20, UV+KMnO4): 0.11

1H NMR (400 MHz, CDCl3): δ 4.68 (br s, 1H), 3.72 (s, 6H), 3.42 (t, J = 7.1 Hz, 1H), 3.19 - 3.13 (m, 2H), 2.07 (q, J = 6.6 Hz, 2H), 1.40 (s, 9H).

13C[1H] NMR (100 MHz, CDCl3): δ 169.7 (2 C), 155.9 (C), 79.4 (C), 52.7 (2 CH3), 49.2 (CH), 38.5 (CH2), 29.1 (CH2), 28.4 (3 CH3).

Compound 3bl: Following GP1 performed with diethyl malonate (1b, 1.5 mL, 10.0 mmol, 1.0 equiv), sodium hydride (0.40 g, 10.0 mmol, 1.0 equiv), and 2-bromomethyl 4-methylbenzoate (2l, 2.431 g, 10.0 mmol, 1.0 equiv) in DMF (10 mL, c = 1 M) at 80 °C for 16 h, the desired product 3bl was obtained after purification by FC [V(SiO2) = 100 mL, PE/EA:98:2 (500 mL), 95:5 (250 mL), 90:10 (250 mL), 80/20 (250 mL)] as a colorless oil (1.425 g, 44%).

Rf (PE/EA: 90/10, UV+KMnO4): 0.34

HRMS (ESI+): [M+Na]+ Calcd. for C13H22NaO3: 345.1308. Found: 345.1309.

1H NMR (400 MHz, CDCl3): δ 7.88 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H), 4.35 (t, J = 6.1 Hz, 2H), 4.16 (t, J = 7.1 Hz, 4H), 3.55 (t, J = 7.3 Hz, 1H), 2.52–2.29 (m, 5H), 1.23 (t, J = 7.1 Hz, 6H).

13C[1H] NMR (100 MHz, CDCl3): δ 169.0 (2 C), 166.4 (C), 143.8 (C), 129.7 (2 CH), 129.1 (2 CH), 127.3 (C), 62.3 (CH2), 61.7 (2 CH2), 49.2 (CH), 28.0 (CH2), 21.7 (CH2), 14.1 (2 CH3).

Compound 3bm: Following GP1 performed with diethyl malonate (1b, 1.67 mL, 11.0 mmol, 1.1 equiv), sodium hydride (0.40 g, 10.0 mmol, 1.0 equiv), and (2-bromoethoxy)(tert-butyl)dimethylsilane (2m, 2.392 g, 10.0 mmol, 1.0 equiv) in DMF (10 mL, c = 1 M) for 16 h, the desired product 3bm was obtained after purification by FC [V(SiO2) = 50 mL, PE/EA:98:2 (250 mL), 95:5 (250 mL)] as a colorless oil (1.655 g, 51%).

Rf (PE/EA: 90/10, UV+KMnO4): 0.41

HRMS (ESI+): [M+Na]+ Calcd. for C19H30NaO3Si: 341.1754. Found: 341.1750.

1H NMR (400 MHz, CDCl3): δ 4.25–4.10 (m, 4H), 3.63 (t, J = 6.4 Hz, 2H), 3.56 (t, J = 6.4 Hz, 1H), 2.09 (q, J = 6.4 Hz, 2H), 1.25 (t, J = 7.7 Hz, 6H), 0.86 (s, 9H), 0.01 (s, 6H).

13C[1H] NMR (100 MHz, CDCl3): δ 169.7 (2 C), 61.4 (2 CH2), 60.4 (CH2), 48.6 (CH), 31.8 (CH2), 26.0 (3 CH3), 18.4 (C), 14.2 (2 CH3). [2 CH3 not detected]

Compound 3bn: Following GP1 performed with diethyl malonate (1b, 3.4 mL, 22.0 mmol, 1.1 equiv), sodium hydride (0.98 g, 24.0 mmol, 1.2 equiv), and bromoacetonitrile (2n, 1.4 mL, 20.0 mmol, 1.0 equiv) in THF (40 mL), the desired product 3bn was obtained after purification by FC [V(SiO2) = 100 mL, PE/EA:80:20 (500 mL), 70:30 (500 mL)] as a colorless oil (990 mg, 24%).

Rf (PE/EA: 80/20, UV+KMnO4): 0.15

HRMS (ESI+): [M+H]+ Calcd. for C14H14NO: 200.0917. Found: 200.0916.

1H NMR (400 MHz, CDCl3): δ 4.29–4.20 (m, 4H), 3.68 (t, J = 7.3 Hz, 1H), 2.90 (d, J = 7.3 Hz, 2H), 1.28 (d, J = 7.1 Hz, 6H).

13C[1H] NMR (100 MHz, CDCl3): δ 166.5 (2 C), 116.9 (C), 62.7 (2 CH2), 48.1 (CH), 17.0 (CH2), 14.0 (2 CH3).

Compound 3ao: Following GP1 performed with dimethyl malonate (1a, 0.47 mL, 4.1 mmol, 1.1 equiv), sodium hydride (0.15 g, 3.7 mmol, 1.0 equiv), and 2-(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2o, 1.00 g, 3.7 mmol, 1.0 equiv) in DMF (5 mL, c = 1 M), the desired product 3ao was obtained after purification by FC [V(SiO2) = 50 mL, PE/EA:80:20 (250 mL), 60:40 (250 mL)] as a colorless oil (714 mg, 70%).

Rf (PE/EA: 80/20, UV+KMnO4): 0.20

HRMS (ESI+): [M+H]+ Calcd. for C12H20BO3: 273.1503. Found: 273.1506.

1H NMR (400 MHz, CDCl3): δ 3.67 (s, 6H), 3.55 (t, J = 8.0 Hz, 1H), 1.27 (d, J = 8.0 Hz, 2H), 1.18 (s, 12H).

13C[1H] NMR (100 MHz, CDCl3): δ 171.0 (2 C), 83.6 (2 C), 52.5 (2 CH2), 47.4 (CH), 24.7 (4 CH3), 11.7 (br CH2).

11 Isaad, J.; Rolla, M.; Bianchini, R. *Eur. J. Org. Chem.* 2009, 2748-2764.
Compound 3ap: Following GPJ performed with dimethyl malonate (1a, 0.9 mL, 7.9 mmol, 1.1 equiv), sodium hydride (0.29 g, 7.2 mmol, 1.0 equiv), (chloromethyl)trimethylsilane (2p, 1.0 mL, 7.2 mmol, 1.0 equiv) and sodium iodide (3.2 g, 21.5 mmol, 3.0 equiv) in THF (15 mL, c = 0.5 M) at reflux for 24 h, the desired product 3ap was obtained after purification by FC [V(SiO2) = 50 mL, Cy/EA 95:5 (250 mL), 90:10 (250 mL)] as a colorless oil (333 mg, 21%).

Rf (PE/EA: 90:10, UV+KMNIO): 0.48

HRMS (ESI+): [M+Na]+ Calcd. for CaH5NaO5Si: 241.0866. Found: 241.0866.

1H NMR (400 MHz, CDCl3): δ 3.71 (s, 6H), 3.38 (t, J = 7.9 Hz, 1H), 1.18 (d, J = 7.9 Hz, 2H). 15C[1H] NMR (100 MHz, CDCl3): δ 171.2 (2 C), 52.7 (2 CH2), 47.6 (CH), 16.3 (CH2), –1.54 (3 CH3).

3. Preparation of substituted malonic acids 9

General procedure 2 (GP2) - saponification: A RBF equipped with a stirring bar was charged with malonate 3 (1.0 equiv) and MeOH (c = 2 M). After addition of a 6 M aqueous solution of NaOH (5.0 equiv), the reaction mixture was stirred at 70 °C for 1 h. The resulting mixture was then acidified to pH 1 with 1 M aq HCl, and extracted twice with EA (20 mL). The combined organic layers were dried (Na2SO4) and evaporated to afford the expected product 9.

Compound 9a: Following GP2 performed with 3aa (0.40 mL, 3.0 mmol, 1.0 equiv) and NaOH (0.60 g, 15.0 mmol, 5.0 equiv) in MeOH (2.5 mL, c = 2 M), the desired product 9a was obtained as an off-white solid (314 mg, 89%).

mp: 136–138 °C (lit.: 131–134°C)

1H NMR (400 MHz, CD3COCD3): δ 10.42 (br s, 2H), 3.47 (q, J = 7.2 Hz, 1H), 1.35 (d, J = 7.2 Hz, 3H).

13C[1H] NMR (100 MHz, CD3COCD3): δ 171.8 (2 C), 46.1 (CH), 14.0 (CH3).

Compound 9c: Following GP2 performed with 3ac (565 mg, 3.0 mmol, 1.0 equiv) and NaOH (0.60 g, 15.0 mmol, 5.0 equiv) in MeOH (2.5 mL, c = 2 M), the desired product 9c was obtained as a white solid (439 mg, 91%).

mp: 101–103 °C (lit.: 102–103°C)

1H NMR (400 MHz, CD3SOCD3): δ 12.62 (br s, 2H), 3.17 (t, J = 7.4 Hz, 1H), 1.69 (q, J = 7.4 Hz, 2H), 1.36–1.14 (m, 4H), 0.84 (t, J = 6.8 Hz, 3H).

13C[1H] NMR (100 MHz, CD3SOCD3): δ 171.1 (2 C), 51.7 (CH), 29.2 (CH2), 28.3 (CH2), 22.1 (CH2), 13.9 (CH3).

Compound 9d: Following GP2 performed with 3bd (817 mg, 3.0 mmol, 1.0 equiv) and NaOH (0.60 g, 15.0 mmol, 5.0 equiv) in MeOH (2.5 mL, c = 2 M), the desired product 9d was obtained as a white solid (647 mg, quantitative).

mp: 110–113 °C (lit.: 113–114°C)

1H NMR (400 MHz, CD3SOCD3): δ 12.64 (br s, 2H), 3.17 (t, J = 7.4 Hz, 1H), 1.68 (q, J = 7.4 Hz, 2H), 1.28–1.19 (m, 12H), 0.85 (t, J = 6.2 Hz, 3H).

13C[1H] NMR (100 MHz, CD3SOCD3): δ 171.0 (2 C), 51.7 (CH), 31.3 (CH2), 28.9 (CH2), 28.8 (CH2), 28.7 (CH2), 28.5 (CH2), 26.9 (CH2), 22.2 (CH2), 14.0 (CH3).

Compound 9f: Following GP2 performed with 3bf (100 mg, 0.5 mmol, 1.0 equiv) and NaOH (0.10 g, 2.5 mmol, 5.0 equiv) in MeOH (0.4 mL, c = 2 M), the desired product 9f was obtained as a white solid (61 mg, 85%).

mp: 101–104 °C (lit.: 102–105°C)

1H NMR (400 MHz, CD3COCD3): δ 9.90 (br s, 2H), 5.91–5.75 (m, 1H), 5.12 (dd, J = 17.1, 3.0 Hz, 1H), 5.02 (dd, J = 10.3, 3.0 Hz, 1H), 3.46 (t, J = 7.5 Hz, 1H), 2.59 (t, J = 7.5 Hz, 2H).

13C[1H] NMR (100 MHz, CD3COCD3): δ 170.5 (2 C), 135.7 (CH), 117.4 (CH2), 51.8 (CH), 33.6 (CH2).

Compound 9h: Following GP2 performed with 3bh (222 mg, 0.89 mmol, 1.0 equiv) and NaOH (0.18 g, 5.0 mmol, 5.0 equiv) in MeOH (0.8 mL, c = 2 M), the desired product 9h was obtained as an off-white solid (151 mg, 87%).

1H NMR (400 MHz, CD3COCD3): δ 9.78 (br s, 2H), 7.34–7.24 (m, 4H), 7.24–7.17 (m, 1H), 3.73 (d, J = 7.8 Hz, 1H), 3.19 (d, J = 7.8 Hz, 2H).

13C[1H] NMR (100 MHz, CD3COCD3): δ 170.4 (2 C), 139.5 (C), 129.7 (2 CH), 129.2 (2 CH), 127.3 (CH), 54.0 (CH), 35.4 (CH2).

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4. Preparation of substituted meldrum acid derivatives 7

Compound 7h:16 A flame-dried 100 mL RBF equipped with a stirring bar was charged with meldrum acid (5, 1.44 g, 10.0 mmol, 1.0 equiv), closed with a septum, and purged with argon. After the addition of benzaldehyde (6h, 1.00 mL, 10.0 mmol, 1.0 equiv) with a syringe, and abs. EtOH (20 mL, c = 0.5 M) by quick removal of the septum, the mixture was stirred (by heating with a heat gun, if necessary) until complete solubilization of the solid. Then, piperidine (99 µL, 1.0 mmol, 10 mol %) and acetic acid (57 µL, 1.0 mmol, 10 mol %) were added through the septum with syringes, and the reaction was stirred at rt for 30 min. NaBH(OAc)₃ (4.24 g, 20.0 mmol, 2.0 equiv) was added in 4 equal portions, one after the other on a 30 min interval by temporary removal of the septum and the reaction was stirred for 60 min at rt. Then, the resulting mixture was quenched with a sat. aq. NH₄Cl (50 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and evaporated. Purification by recrystallization (MeOH/H₂O) afforded the expected product 7h as an off-white solid (1.321 g, 56%).

1H NMR (400 MHz, CDCl₃): δ 7.39–7.22 (m, 5H), 3.75 (t, J = 4.7 Hz, 2H). 13C[1H] NMR (100 MHz, CDCl₃): δ 165.4 (2 C), 129.9 (2 CH), 128.8 (2 CH), 127.3 (CH), 105.4 (C), 48.3 (CH), 32.3 (CH₂), 28.6 (CH₃), 27.4 (CH₃).

General procedure 3 (GP3) - preparation of meldrum acid derivatives: A RBF equipped with a stirring bar was charged with the malonic acid derivative 9 (1.0 equiv) and Ac₂O (5–8 M), and cooled to 0 °C (ice/water bath). After the addition of 2–3 drops of concentrated H₂SO₄, acetone (1.1 equiv) was added dropwise to the stirred mixture with a pressure-equalizing dropping funnel. The reaction was allowed to warm to room temperature and stirred for 6 h. Then, the resulting mixture was placed in the refrigerator for 2 h, and the resulting solid was collected by filtration on a fritted funnel and rinsed with cold water (2 times) and Et₂O (3 times). Traces of water were removed by addition of toluene (10 mL) and evaporation (3 times) to afford the desired product 7.

Compound 7a:17 Following GP3 performed with methylnalonic acid 9a (2.95 g, 25.0 mmol, 1.5 equiv) and acetone (2.0 mL, 27.5 mmol, 1.1 equiv) in Ac₂O (3.2 mL, c = 8.0 M), the desired product 7a was obtained as a white solid (3.354 g, 84%).

mp: 114–116 °C (lit.: 113–114 °C)

1H NMR (400 MHz, CDCl₃): δ 1.80 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H).

13C[1H] NMR (100 MHz, CDCl₃): δ 166.2 (2 C), 105.0 (C), 41.4 (CH), 28.6 (CH₃), 26.5 (CH₃), 10.8 (CH₂).

Compound 7s:18 Following GP3 performed with phenylmalonic acid 9s (4.50 g, 25.0 mmol, 1.5 equiv) and acetone (2.0 mL, 27.5 mmol, 1.1 equiv) in Ac₂O (5.0 mL, c = 5.0 M), the desired product 7s was obtained as a pale yellow solid (4.690 g, 84%).

mp: 135–138 °C (lit.: 135–137 °C)

1H NMR (400 MHz, CDCl₃): δ 7.50–7.39 (m, 3H), 7.37–7.24 (m, 2H), 4.82 (s, 1H), 1.88 (s, 3H), 1.78 (s, 3H).

13C[1H] NMR (100 MHz, CDCl₃): δ 164.9 (2 C), 130.7 (C), 129.3 (2 CH), 129.2 (2 CH), 128.9 (CH), 105.9 (C), 52.9 (CH), 28.6 (CH₃), 27.5 (CH₃).

5. Preparation of SMAHOs 4

General procedure 4 (GP4) - monosaponification: In a manner similar to 19, a RBF equipped with a stirring bar was charged with the malonic acid derivative 3 (1.0 equiv) and the solvent (c = 0.5 M, V mL). A 5 M aqueous solution of KOH (1.0 equiv) was added with a syringe and the reaction mixture was stirred at rt for 2 h. Then, the mixture was concentrated, diluted with water (V mL), and the resulting aqueous layer was washed with Et₂O (3×V/4 mL), acidified to pH 1 by the addition of 1 M aq HCl, saturated with NaCl, and extracted with EA (3×V/4 mL). The combined organic layers were dried (Na₂SO₄) and evaporated to afford the expected product 4.

Compound 4aa:20 Following GP4 performed with 3aa (6.70 mL, 50.0 mmol, 1.0 equiv) and potassium hydroxide (3.37 g, 60.0 mmol, 1.2 equiv) in MeOH (100 mL), the desired product 4aa was obtained as a colorless oil (6.011 g, 91%).

Characterization date are in agreement with those reported in 19.

Compound 4ba:20 Following GP4 performed with 3ba (3.00 g, 17.2 mmol, 1.0 equiv) and potassium hydroxide (0.96 g, 17.2 mmol, 1.0 equiv) in EtOH (34 mL), the desired product 4ba was obtained as a colorless oil (1.818 g, 72%).

1H NMR (400 MHz, CDCl₃): δ 10.15 (br s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.45 (q, J = 7.4 Hz, 1H), 1.41 (d, J = 7.4 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H).

13C[1H] NMR (100 MHz, CDCl₃): δ 175.9 (C), 170.1 (C), 61.9 (CH₂), 46.1 (CH), 14.0 (CH₃), 13.6 (CH₂).

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Compound 4ab. Following GP4 performed with 3ab (1.28 g, 8.0 mmol, 1.0 equiv) and potassium hydroxide (0.54 g, 10.0 mmol, 1.2 equiv) in MeOH (15 mL), the desired product 4ab was obtained as a colorless oil (1.052 g, 90%).

1H NMR (400 MHz, CDCl3): δ 10.62 (br s, 1H), 3.75 (s, 3H), 3.32 (t, J = 7.4 Hz, 1H), 1.95 (quint, J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3): δ 175.4 (C), 169.8 (C), 53.2 (CH), 52.8 (CH2), 22.4 (CH3), 11.9 (CH3).

Compound 4ac. Following GP4 performed with 3ac (1.02 g, 6.4 mmol, 1.0 equiv) and potassium hydroxide (0.43 g, 7.7 mmol, 1.2 equiv) in MeOH (11 mL), the desired product 4ac was obtained as a colorless oil (0.871 g, 78%).

Characterization date are in agreement with those reported in 19.

Compound 4bd. Following GP4 performed with 3bd (5.50 g, 20.2 mmol, 1.0 equiv) and potassium hydroxide (1.13 g, 20.2 mmol, 1.0 equiv) in EtOH (40 mL), the desired product 4bd was obtained as a colorless oil (3.560 g, 72%).

Characterization date are in agreement with those reported in 19.

Compound 4be: Following GP4 performed with 3be (2.70 g, 13.3 mmol, 1.0 equiv) and potassium hydroxide (0.75 g, 13.3 mmol, 1.0 equiv) in EtOH (27 mL), the desired product 4be was obtained as a colorless oil (1.716 g, 74%).

HRMS (ESI+): m/z [M+Na]+ Calcd. for C12H11NaO4: 197.0784. Found: 197.0783.

1H NMR (400 MHz, CDCl3): δ 10.76 (br s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.05 (t, J = 8.3 Hz, 1H), 2.93 (m, 1H), 1.56 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.4 Hz, 6H).

13C{1H} NMR (100 MHz, CDCl3): δ 174.2 (C), 168.9 (C), 54.9 (CH), 58.7 (CH2), 29.1 (CH), 20.4 (CH3), 20.3 (CH3), 14.1 (CH3).

Compound 4bf: Following GP4 performed with 3bf (0.98 g, 4.9 mmol, 1.0 equiv) and potassium hydroxide (0.27 g, 4.9 mmol, 1.0 equiv) in EtOH (10 mL), the desired product 4bf was obtained as a colorless oil (0.603 g, 71%).

Characterization date are in agreement with those reported in 19.

Compound 4bg. Following GP4 performed with 3bg (1.70 g, 8.6 mmol, 1.0 equiv) and potassium hydroxide (0.48 g, 8.6 mmol, 1.0 equiv) in EtOH (18 mL), the desired product 4bg was obtained as a colorless oil (0.963 g, 65%).

Characterization date are in agreement with those reported in 19.

Compound 4bh: Following GP4 performed with 3bh (1.07 g, 4.3 mmol, 1.0 equiv) and potassium hydroxide (0.24 g, 4.3 mmol, 1.0 equiv) in EtOH (10 mL), the desired product 4bh was obtained as a colorless oil (0.657 g, 69%).

Characterization date are in agreement with those reported in 19.

Compound 4bi: Following GP4 performed with 3bi (0.19 g, 0.73 mmol, 1.0 equiv) and potassium hydroxide (49 mg, 0.88 mmol, 1.2 equiv) in EtOH (2 mL), the desired product 4bi was obtained as a colorless oil (0.118 g, 71%).

1H NMR (400 MHz, CDCl3): δ 9.03 (br s, 1H), 7.40–7.19 (m, 1H), 7.06 (m, 1H), 6.97 (d, J = 4.9 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.73 (t, J = 7.6 Hz, 1H), 3.29 (d, J = 7.6 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3): δ 174.1 (C), 168.8 (C), 137.7 (C), 128.1 (CH), 125.9 (CH), 122.2 (CH), 62.0 (CH2), 53.0 (CH), 29.2 (CH2), 14.0 (CH3).

Compound 4bj: Following GP4 performed with 3bj (1.62 g, 6.8 mmol, 1.0 equiv) and potassium hydroxide (0.38 g, 6.8 mmol, 1.0 equiv) in EtOH (14 mL), the desired product 4bj was obtained as a colorless oil (0.890 g, 62%).

HRMS (ESI+): m/z [M+Na]+ Calcd. for C12H11NaO4: 231.0394. Found: 231.0391.

1H NMR (400 MHz, CDCl3): δ 10.05 (br s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.54 (t, J = 6.4 Hz, 2H), 3.40 (t, J = 7.4 Hz, 1H), 2.11–2.02 (m, 2H), 1.89–1.79 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3): δ 174.8 (C), 169.0 (C), 62.0 (CH2), 51.1 (CH), 44.2 (CH2), 30.1 (CH2), 26.2 (CH2), 14.1 (CH3).

Compound 4ak: Following GP4 performed with 3ak (0.50 g, 1.8 mmol, 1.0 equiv) and potassium hydroxide (0.10 g, 1.8 mmol, 1.0 equiv) in MeOH (5 mL), the desired product 4ak was obtained as a colorless oil (0.366 g, 76%).

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HRMS (ESI)*: [M+K]+ Calcd. for C_{11}H_{10}KNO_3: 300.0843. Found: 300.0843.

\(^1\)H NMR (400 MHz, CD_2COCD_3): \( \delta \) 6.09 (br s, 1H), 3.71 (s, 3H), 3.48 (t, J = 7.2 Hz, 1H), 3.16 (q, J = 6.4 Hz, 2H), 2.10–2.06 (m, 2H), 1.40 (s, 9H). [CO$_2$H not detected]

\(^1^3^C\)(\(^1^H\)) NMR (100 MHz, CD_2COCD_3): \( \delta \) 170.5 (C), 170.4 (C), 156.7 (C), 78.6 (C), 52.4 (CH$_3$), 49.5 (CH), 38.9 (CH$_2$), 30.5 (CH$_2$), 28.5 (3 CH$_3$).

Compound 4bl: Following GP4 performed with 3bl (1.40 g, 4.4 mmol, 1.0 equiv) and potassium hydroxide (0.30 g, 5.3 mmol, 1.2 equiv) in EtOH (9 mL), the desired product 4bl was obtained as a colorless oil (0.825 g, 63%).

Characterization date are in agreement with those reported in 19.

Compound 4bn: Following GP4 performed with 3bn (0.94 g, 4.7 mmol, 1.0 equiv) and potassium hydroxide (0.26 g, 4.7 mmol, 1.0 equiv) in EtOH (20 mL), the desired product 4bn was obtained as a colorless oil (0.528 g, 65%).

HRMS (ESI)*: [M+Na]+ Calcd. for C$_3$H$_5$NaO$_3$Si: 313.1442. Found: 313.1444.

\(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 9.30 (br s, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.75–3.61 (m, 2H), 3.61 (t, J = 6.6 Hz, 1H), 2.13 (q, J = 6.0 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

\(^1^3^C\)(\(^1^H\)) NMR (100 MHz, CDCl$_3$): \( \delta \) 175.1 (C), 169.5 (C), 61.8 (CH$_2$), 60.4 (CH$_2$), 48.6 (CH), 31.7 (CH$_2$), 26.0 (3 CH$_3$), 18.4 (C), 14.1 (CH$_3$). [2 CH$_3$ not detected]

Compounds 4ao:

- Following GP4 performed with 3ao (0.41 g, 1.5 mmol, 1.0 equiv) and potassium hydroxide (0.10 g, 1.8 mmol, 1.2 equiv) in MeOH (3 mL), the desired product 4ao was obtained as a colorless oil (0.300 g, 77%).

HRMS (ESI)*: [M+Na]+ Calcd. for C$_7$H$_5$NaO$_2$: 281.1167. Found: 281.1165.

\(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 7.62 (br s, 1H), 3.72 (s, 3H), 3.61 (t, J = 7.9 Hz, 1H), 1.32 (d, J = 7.9 Hz, 2H), 1.20 (s, 12H).

\(^1^3^C\)(\(^1^H\)) NMR (100 MHz, CDCl$_3$): \( \delta \) 175.5 (C), 170.9 (C), 83.9 (2 C), 52.7 (CH$_3$), 47.4 (CH), 24.7 (4 CH$_3$), 11.5 (CH$_2$).

Compounds 4aq:

- Following GP4 performed with dimethyl chloromalonate 3aq (2.5 mL, 20.0 mmol, 1.0 equiv) and potassium hydroxide (1.12 g, 20.0 mmol, 1.0 equiv) in MeOH (40 mL), the desired product 4aq was obtained as a colorless oil (2.160 g, 70%).

HRMS (ESI)*: m/z [M+Na]+ Calcd. for C$_{19}$H$_{15}$NaO$_2$: 277.0710. Found: 277.0713.

\(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 10.16 (br s, 1H), 3.73 (s, 3H), 3.40 (t, J = 7.8 Hz, 1H), 1.18 (t, J = 7.8 Hz, 2H), 0.01 (s, 9H).

\(^1^3^C\)(\(^1^H\)) NMR (100 MHz, CDCl$_3$): \( \delta \) 176.7 (C), 170.8 (C), 52.8 (CH$_3$), 47.6 (CH), 16.2 (CH$_2$), –1.54 (3 CH$_3$).

Compounds 4br:

- Following GP4 performed with diethyl bromomalonate 3br (1.7 mL, 10.0 mmol, 1.0 equiv) and potassium hydroxide (0.56 g, 10.0 mmol, 1.0 equiv) in EtOH (20 mL), the desired product 4br was obtained as a colorless oil (1.001 g, 47%).

HRMS (ESI)*: m/z [M+Na]+ Calcd. for C$_{17}$H$_{14}$NaO$_2$: 232.9419. Found: 232.9418.

\(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 10.66 (br s, 1H), 4.91 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).

\(^1^3^C\)(\(^1^H\)) NMR (100 MHz, CDCl$_3$): \( \delta \) 169.8 (C), 164.7 (C), 63.9 (CH$_2$), 41.4 (CH), 13.9 (CH$_3$).

General procedure 5 (GP5) - monoesterification: A 50 mL RBF equipped with a stirring bar was charged with the methyl malonic acid (9a, 0.50 g, 4.2 mmol, 1.0 equiv), DMAP (26 mg, 0.21 mmol, 5 mol %), CH$_3$CN (10 mL), and the requisite alcohol 8 (1.1 equiv) and cooled at –15 °C (ice/salt bath). A solution of DCC (0.87 g, 4.2 mmol, 1.0 equiv) in CH$_2$CN (10 mL) was added dropwise to the stirred mixture with a pressure-equalizing dropping funnel. The reaction was allowed to warm to rt and stirred for 14 h. Then, the reaction mixture was filtered through a fritted funnel (rimmed with CH$_3$Cl$_2$), and the filtrate was evaporated. The resulting crude oil were added 30 mL of sat aq NaHCO$_3$. The resulting solution was washed with Et$_2$O (2 x 10 mL), acidified to pH 1 with 1 M aq HCl, and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated to afford the expected product 4.
Compound 4ca: Following GP5 performed with isopropanol (8c, 0.35 mL, 4.6 mmol, 1.1 equiv), the desired product 4ca was obtained as a colorless oil (0.341 g, 51%).

HRMS (ESI)^+: [M+Na]^+ Calcd. for C_{14}H_{20}NaO_3: 240.1220. Found: 240.1225.

^1H NMR (400 MHz, CDCl_3): δ 9.90 (br s, 1H), 7.05 (d, J = 6.5 Hz, 1H), 3.42 (q, J = 7.3 Hz, 1H), 1.40 (d, J = 7.3 Hz, 3H), 1.22 (d, J = 6.5 Hz, 6H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 175.9 (C), 169.7 (C), 69.5 (CH), 46.2 (CH), 21.6 (CH_3), 21.5 (CH_3), 13.5 (CH_3).

Compound 4da: Following GP5 performed with benzyl alcohol (8d, 0.48 mL, 4.6 mmol, 1.1 equiv), the desired product 4da was obtained as a colorless oil (0.462 g, 53%).

Characterization date are in agreement with those reported in 19.

Compound 4fa: Following GP5 performed with allyl alcohol (8f, 0.31 mL, 4.6 mmol, 1.1 equiv), the desired product 4fa was obtained as a colorless oil (0.345 g, 52%).

HRMS (ESI)^+: [M+Na]^+ Calcd. for C_{14}H_{20}NaO_3: 215.1031. Found: 215.1032.

^1H NMR (400 MHz, CDCl_3): δ 10.11 (br s, 1H), 7.44 (dt, J = 16.2, 6.7 Hz, 1H), 3.09 (t, J = 7.3 Hz, 1H), 1.65–1.78 (m, 2H), 1.32–1.33 (m, 3H), 0.68 (m, 6H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 176.4 (C), 169.6 (C), 135.3 (CH), 115.8 (CH), 46.8 (CH), 46.0 (CH), 13.6 (CH_3).

Compound 4ga: Following GP5 performed with tert-butanol 8g (0.44 mL, 4.6 mmol, 1.1 equiv), the desired product 4ga was obtained as a colorless oil (0.271 g, 37%).

^1H NMR (400 MHz, CDCl_3): δ 10.90 (br s, 1H), 3.37 (q, J = 7.3 Hz, 1H), 1.44 (d, J = 7.3 Hz, 3H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 176.5 (C), 169.3 (C), 82.4 (C), 47.0 (CH), 27.9 (3 CH_3), 13.7 (CH_3).

Compound 4ha: Following GP5 performed with 2,2,2-trifluoroethanol 8h (0.33 mL, 4.6 mmol, 1.1 equiv), the desired product 4ha was obtained as a colorless oil (0.285 g, 34%).

HRMS (ESI)^*: [M+Na]^+ Calcd. for C_{14}H_{20}NaO_3: 223.0188. Found: 223.0189.

^1H NMR (400 MHz, CDCl_3): δ 10.51 (br s, 1H), 4.59–4.49 (m, 2H), 3.62 (q, J = 7.2 Hz, 1H), 1.51 (d, J = 7.2 Hz, 3H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 175.4 (C), 168.3 (C), 122.7 (q, 3J_CF = 277.3 Hz, CF_3), 61.2 (q, 3J_CF = 37.0 Hz, CH_3), 45.7 (CH), 13.5 (CH_3).

^19F[^1]H NMR (377 MHz, CDCl_3): δ −73.8 (3 F).

Compound 4ea: Following GP5 performed with (−)-menthol (8e, 722 mg, 4.6 mmol, 1.1 equiv), the desired product 4ea was obtained as a colorless oil (0.297 g, 28%).

^1H NMR (400 MHz, CDCl_3): (2 diastereomers) δ 9.94 (br s, 2H), 4.76–4.66 (m, 2H), 3.51–3.40 (m, 2H), 2.60–1.95 (m, 2H), 1.92–1.79 (m, 2H), 1.72–1.62 (m, 4H), 1.53–1.35 (m, 10H), 1.12–0.92 (m, 4H), 0.93–0.82 (m, 14H), 0.78–0.68 (m, 6H).

^13C[^1]H NMR (100 MHz, CDCl_3): (2 diastereomers) δ 176.2 (C), 176.1 (C), 169.7 (C), 169.6 (C), 76.0 (CH), 76.0 (CH), 47.0 (CH), 46.3 (CH), 46.3 (CH), 40.6 (CH_3), 40.4 (CH_3), 34.3 (2 CH_2), 31.5 (2 CH), 26.3 (CH), 26.1 (CH), 23.4 (CH_2), 23.4 (CH_2), 22.1 (2 CH_2), 20.8 (2 CH_3), 16.3 (CH_3), 16.1 (CH_3), 13.8 (CH_3), 13.7 (CH_3).

Compound 4ia: Following GP5 performed with phenol (8i, 440 mg, 4.6 mmol, 1.1 equiv), the desired product 4ia was obtained as a colorless oil (0.136 g, 17%).

HRMS (ESI)^*: [M+Na]^+ Calcd. for C_{16}H_{20}NaO_3: 217.0471. Found: 217.0471.

^1H NMR (400 MHz, CDCl_3): δ 10.92 (br s, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 3.77 (q, J = 7.2 Hz, 1H), 1.61 (d, J = 7.2 Hz, 3H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 176.1 (C), 168.4 (C), 150.5 (C), 129.6 (2 CH), 126.3 (CH), 121.4 (2 CH), 46.2 (CH), 13.6 (CH_3).

Compound 4ja: Following GP5 performed with (+)-citronellol (8j, 0.85 mL, 4.6 mmol, 1.1 equiv), the desired product 4ja was obtained as a pale yellow oil (0.625 g, 58%).

HRMS (ESI)^*: [M+H]^+ Calcd. for C_{14}H_{18}O_2: 257.1747. Found: 257.1750.

^1H NMR (400 MHz, CDCl_3): δ 9.20 (br s, 1H), 5.07 (t, J = 6.4 Hz, 1H), 4.19 (br s, 2H), 3.47 (q, J = 7.3 Hz, 1H), 2.00–1.92 (m, 2H), 1.71–1.66 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56–1.40 (m, 2H), 1.44 (d, J = 7.3 Hz, 3H), 1.37–1.14 (m, 2H), 0.90 (d, J = 6.4 Hz, 3H).

^13C[^1]H NMR (100 MHz, CDCl_3): δ 175.9 (C), 170.1 (C), 131.5 (C), 124.6 (CH), 66.4 (CH_2), 46.1 (CH), 37.0 (CH_2), 35.3 (CH_2), 29.5 (CH), 25.8 (CH_2), 25.5 (CH_2), 19.4 (CH), 17.8 (CH_3), 13.7 (CH_3).

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26 Park, C.; Ha, M.W.; Kim, B.; Hong, S.; Kim, D.; Park, Y.; Kim, M.H.; Lee, J. K.; Lee, J.; Park, H.G. Adv. Synth. Catal. 2015, 357, 2841–2848.

27 Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K.; Kametani, T. J. Chem. Soc., Perkin Trans. 1, 1989, 897-903.
Compound 4ka: Following GP5 performed with (S)-ethyl lactate (8k, 0.58 mL, 4.6 mmol, 1.0 equiv), the desired product 4ka was obtained as a colorless oil (0.298 g, 32%).

HRMS (ESI\(^+\)): [M+H]\(^+\) Calcd. for C\(_{12}\)H\(_{20}\)O\(_2\): 219.0863. Found: 219.0864.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.51 (brs, 2H), 4.19 (q, J = 7.1 Hz, 4H), 3.62–3.51 (m, 2H), 1.50 (d, J = 7.2 Hz, 6H), 1.47 (d, J = 7.4 Hz, 6H), 1.26 (t, J = 7.1 Hz, 6H).

\(^{13}\)C\(^{\left[1\right]}\) NMR (100 MHz, CDCl\(_3\)): δ 174.9 (C), 174.6 (C), 170.6 (C), 170.5 (C), 169.6 (C), 169.4 (C), 69.7 (CH), 69.7 (CH), 61.7 (CH\(_2\)), 61.7 (CH\(_2\)), 46.0 (CH), 45.7 (CH), 16.8 (2 CH\(_3\)), 14.1 (CH\(_3\)), 14.1 (CH\(_3\)), 13.7 (CH\(_3\)), 13.6 (CH\(_3\)).

General procedure 6 (GP6) - opening of meldrum acid derivatives: In a manner similar to \(^{19}\), a RBF equipped with a stirring bar was charged with the substituted meldrum acid 7 (1.0 equiv), the alcohol 8 (1.0 equiv), and toluene (c = 0.25 M). The reaction mixture was stirred at reflux for 4h (or at 80 °C for 24 h). Then, the mixture was diluted with Et\(_2\)O (20 mL), and the resulting organic layer was extracted with saturated aqueous NaHCO\(_3\) (2 times). The combined aqueous layers were cooled to 0 °C (ice/water bath) and acidified to pH 1 with 1 M aq HCl, saturated with NaCl, and extracted with Et\(_2\)O (3 × 20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and evaporated to afford the expected product 4.

Compound 4ch: Following GP6 performed with 7h (0.50 g, 2.1 mmol, 1.0 equiv) and propan-2-ol (8c, 0.19 mL, 2.5 mmol, 1.0 equiv) in toluene at 80 °C for 24 h, the desired product 4ch was obtained as a pale yellow oil (0.462 g, 93%).

HRMS (ESI\(^{+}\)): m/z [M+Na]\(^+\) Calcd. for C\(_{17}\)H\(_{21}\)NaO\(_3\): 259.0940. Found: 259.0941.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 10.61 (brs, 1H), 7.35–7.29 (m, 2H), 7.28–7.23 (m, 3H), 5.05 (hept, J = 6.3 Hz, 1H), 3.72 (t, J = 7.8 Hz, 1H), 3.27 (d, J = 7.8 Hz, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H).

\(^{13}\)C\(^{\left[1\right]}\) NMR (100 MHz, CDCl\(_3\)): δ 174.8 (C), 168.3 (C), 137.5 (C), 128.9 (2 CH), 128.7 (2 CH), 127.0 (CH), 69.7 (CH), 53.8 (CH), 34.7 (CH\(_3\)), 21.6 (2 CH\(_3\)).

Compound 4dh: Following GP6 performed with 7h (0.50 g, 2.1 mmol, 1.0 equiv) and benzyl alcohol (8d, 0.22 mL, 2.1 mmol, 1.0 equiv) in refluxing toluene for 4 h, the desired product 4dh was obtained as a pale yellow oil contaminated by ca. 13% of the decarboxylated product (0.392 g, 57%).

HRMS (ESI\(^{+}\)): m/z [M+Na]\(^+\) Calcd. for C\(_{19}\)H\(_{21}\)NaO\(_3\): 307.0940. Found: 307.0941.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 10.71 (brs, 1H), 7.41–7.21 (m, 10H), 5.19 (s, 2H), 3.84 (t, J = 7.7 Hz, 1H), 3.31 (d, J = 7.7 Hz, 2H).

\(^{13}\)C\(^{\left[1\right]}\) NMR (100 MHz, CDCl\(_3\)): δ 174.6 (C), 168.6 (C), 137.3 (C), 135.1 (C), 128.9 (2 CH), 128.7 (2 CH), 128.5 (CH), 128.3 (2 CH), 127.0 (CH), 67.5 (CH\(_2\)), 53.7 (CH), 34. 8 (CH\(_2\)).

Compound 4da: Following GP6 performed with 7a (0.32 g, 2.0 mmol, 1.0 equiv) and benzyl alcohol (8d, 0.21 mL, 2.0 mmol, 1.0 equiv) in refluxing toluene for 8 h, the desired product 4da was obtained as a pale yellow oil (0.357 g, 85%).

Compound 4ea: Following GP6 performed with 7a (0.32 g, 2.0 mmol, 1.0 equiv) and (–)-menthol (8e, 0.312 g, 2.0 mmol, 1.0 equiv) in refluxing toluene for 5 h, the desired product 4ea was obtained as a colorless oil (0.375 g, 58%).

Compound 4bs: Following GP6 performed with 7s (0.440 g, 2.0 mmol, 1.0 equiv) in a refluxing mixture of toluene and EtOH 1:1 for 8 h, the desired product 4bs was obtained as white solid (0.272 g, 65%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 9.52 (brs, 1H), 7.46–7.29 (m, 5H), 4.65 (s, 1H), 4.30–4.15 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H).

\(^{13}\)C\(^{\left[1\right]}\) NMR (100 MHz, CDCl\(_3\)): δ 173.5 (C), 168.3 (C), 132.3 (C), 129.3 (2 CH), 128.9 (2 CH), 128.6 (CH), 62.3 (CH\(_2\)), 57.7 (CH), 14.1 (CH\(_3\)).

6. Copies of NMR spectra

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\(^{28}\) Bagum, H.; Christensen, K.E.; Genov, M.; Pretsch, A.; Pretsch, D.; Moloney, M. G. *Tetrahedron* 2019, 75, 130561.
$\text{3aa}$

$^1\text{H, CDCl}_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$\text{3ab}$

$^1H$, CDCl$_3$, 400 MHz
$\text{3ab}$

$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$\text{3ac}$

$^1\text{H, CDCl}_3$, 400 MHz
$^{13}$C-$^1$H, CDCl$_3$, 100 MHz

3ac
$^{1}$H, CDCl$_3$, 400 MHz
$\text{1^1C}[^1\text{H}], \text{CDCl}_3, 100 \text{ MHz}$
$3^\text{be}$

$^1\text{H, CDCl}_3, 400 \text{ MHz}$
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$3bf$

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C$\left[^1H\right]$, CDCl$_3$, 100 MHz
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{1}H, CDCl$_3$, 100 MHz

3bg
$^1$H, CDCl$_3$, 400 MHz

3bh
$^{13}$C\textsuperscript{1H}, CDCl$_3$, 100 MHz

3bh
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{[\textit{H}]} C\textsubscript{1}, CDCl\textsubscript{3}, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{1}H, CDCl\textsubscript{3}, 100 MHz
$^{1}\text{H}, \text{CDCl}_3, 400 \text{ MHz}$

3ak

$^{1}\text{H}, \text{CDCl}_3, 400 \text{ MHz}$
$^{13}$C-$^1$H, CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
3bm

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{1}H, CDCl\textsubscript{3}, 100 MHz

$3\text{bm}$
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}\text{C}[^1\text{H}], \text{CDCl}_3, 100 \text{ MHz}$
3ao

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{[1]H}, CDCl$_3$, 100 MHz
$\text{3ap}$

$^1\text{H, CDCl}_3, 400 \text{ MHz}$
$\text{3ap}$

$^{13}\text{C}[^1\text{H}], \text{CDCl}_3, 100\text{ MHz}$
$^{1}\text{H, CD}_{2}\text{COCD}_3$, 400 MHz
$\text{HO-} \begin{array}{c} \text{C} \\ \text{O} \end{array} \text{OH}$

$9a$

$^{13}\text{C}[^{1}\text{H}], \text{CD}_3\text{COCD}_3, 100 \text{ MHz}$
$9c$

$^1$H, CD$_3$SOCD$_3$, 400 MHz
$^1$C[¹H], CD$_3$SOCD$_3$, 100 MHz
$9d$

$^1$H, CD$_3$SOCD$_3$, 400 MHz
$^{13}\text{C}[^1\text{H}], \text{CD}_3\text{SOCD}_3, 100 \text{ MHz}$
9f
$^1$H, CD$_3$COCD$_3$, 400 MHz
$^{13}$C$^1$H, CD$_3$COCD$_3$, 100 MHz
$9h$

$^1$H, CD$_3$COCD$_3$, 400 MHz
$^{13}$C\textsuperscript{[\text{\text{H}}]}, CD$_3$COCD$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C(\textsuperscript{1}H), CDCl$_3$, 100 MHz

7h
$^1$H, CDCl$_3$, 400 MHz
$^1$C($^1$H), CDCl$_3$, 100 MHz
$\text{H, CDCl}_3$, 400 MHz
$\text{C}^1$ [H], CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C$^\text{1H}$, CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 100 MHz
$\text{4ba}$

$^{13}\text{C}[^1\text{H}], \text{CDCl}_3, 100 \text{ MHz}$
$\text{O} - \text{C} - \text{O}$

$\text{O}$

$\text{4ab}$

$^1\text{H}, \text{CDCl}_3, 100 \text{ MHz}$
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
4ac

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
\[ \text{4be} \]

\[ ^1H, \text{CDCl}_3, \text{400 MHz} \]
\[\text{O} \quad \text{O}\]

4be

$^{13}\text{C}[^1\text{H}], \text{CDCl}_3, 100 \text{ MHz}$
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}\text{C}[^1\text{H}]$, CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C[\textsuperscript{1}H], CDCl$_3$, 100 MHz
\(^1\text{H, CDCl}_3, 400 \text{ MHz}\)
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
4bi

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\textsuperscript{1}H, CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz

4bj
$^{13}$C{\textsuperscript{1}H}, CDCl$_3$, 100 MHz
4ak

$^1$H, CD$_3$COCD$_3$, 400 MHz
$^{13}$C[$^1$H], CD$_3$COCD$_3$, 400 MHz
$^{1}$H, CDCl$_3$, 400 MHz
$^{13}$C [$^1$H], CDCl$_3$, 100 MHz
$^{1}$H, CDCl$_3$, 400 MHz
$^1$C[$^1$H], CDCl$_3$, 100 MHz
4bn

$^1\text{H}, \text{CDCl}_3, 400 \text{ MHz}$
$^{13}$C[\textsuperscript{1}H], CDCl\textsubscript{3}, 100 MHz
$^{1}H$, CDCl$_3$, 400 MHz
4ao

$^{13}$C($^1$H), CDCl$_3$, 100 MHz
4ap

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C{'H}, CDCl$_3$, 100 MHz
$\text{Cl}$

$\text{4aq}$

$^1\text{H}, \text{CDCl}_3, 400 \text{ MHz}$
$^{13}$C\textsuperscript{[\textit{H}]} Cl, CDCl\textsubscript{3}, 100 MHz
$4\text{br}$

$^1\text{H, CDCl}_3, 400\text{ MHz}$
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$\text{O} - \text{O} - \text{C} = \text{O}$

$4\text{ca}$

$^1\text{H}, \text{CDCl}_3, 400 \text{ MHz}$
$^{13}$C($^1$H), CDCl$_3$, 400 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
$\text{4fa}$

$^1\text{H, CDCl}_3, 400 \text{ MHz}$
$^{13}$C\text{H}, CDCl$_3$, 400 MHz
4ga

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\(\text{[H]}\), CDCl$_3$, 400 MHz

4ga
$\text{F}_3\text{C}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{CCH}_3$

$4\text{ha}$

$^1\text{H}, \text{CDCl}_3, 400 \text{ MHz}$
$^{13}$C($^1$H), CDCl$_3$, 400 MHz

4ha

$\text{CH}_2\text{CO}_2\text{H}$
$^{19}$F\textsuperscript{[1]H}, CDCl$_3$, 377 MHz
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}\text{C}(^1\text{H})$, CDCl$_3$, 400 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}\text{C}[^1\text{H}], \text{CDCl}_3, 400 \text{ MHz}$

$4\text{ia}$
4ja

$^{1}$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 400 MHz
4ka (d.r. = 1:1)

$^1$H, CDCl$_3$, 400 MHz
$4ka$ (d.r. = 1:1)

$^{13}$C [$^1$H], CDCl$_3$, 400 MHz
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 100 MHz
4dh (ca. 17 mol% of decarboxylated byproduct)

$^1$H, CDCl$_3$, 400 MHz
4dh (ca. 17 mol% of decarboxylated byproduct)

$^{13}$C[1H], CDCl$_3$, 100 MHz
4bs

$^1$H, CDCl$_3$, 400 MHz
$^{13}$C$[^1]$H, CDCl$_3$, 100 MHz