Supporting Information

“A Highly Stereoselective Intermolecular Oxy-Michael Addition Reaction to α,β -Unsaturated Malonate Esters”

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2-[2-Methyl-1-(6-methyl-tetrahydro-pyran-2-yloxy)-propyl]-malonic acid dimethyl ester (3). To a stirred solution of (S)-6-methyltetrahydropyran-2-ol **1** (116mg, 1mmol) in THF (15ml) at -78°C was added KHMDS (2ml, 1mmol, 0.5 M solution in toluene) dropwise. The reaction mixture was then stirred for 15 mins at -78°C before a solution of 18-crown-6 (0.4ml, 1.0mmol, 2.48M in toluene) was added dropwise. Stirring was maintained for a further 30 minutes at -78°C before a solution of 2-isobutylidene malonic acid dimethyl ester **2** (125mg, 0.67mmol) in THF (5ml) was added dropwise. Stirring was maintained for 15 minutes at -78°C . The reaction was then quenched with glacial acetic acid (0.08ml, 2mmol) via syringe and the resulting mixture was allowed to warm to room temperature. Diethyl ether (15ml) and water (15ml) were added and the aqueous layer was separated and extracted with diethyl ether (3 x 15ml). The combined organic layers were washed with brine (15ml), dried

(MgSO₄), filtered and concentrated in vacuo. The crude de was determined as 94% by inspection of the crude 600MHz NMR spectrum. Purification by flash column chromatography eluting with 40–60 petroleum ether / diethyl ether (4:1) gave the title compound **3** (172mg, 85%) as an oil: $[\alpha]_D^{20} = +4.1$ (c 1.2, CHCl₃); IR (film) $\nu_{\max}$ 1737, 1435, 1156, 1128, 1066, 1035, 996, 960 cm⁻¹; ¹H NMR (CDCl₃: 600 MHz) δ 4.40 (dd, $J = 9.5, 2.1$ Hz, 1H), 4.20 (dd, $J = 9.0, 3.3$ Hz, 1H), 3.71 (s, 6H), 3.68 (d, $J = 9.0$ Hz, 1H), 3.45 (ddq, $J = 12.4, 6.2, 1.9$ Hz, 1H), 1.82 (dq, $J = 6.9, 6.9, 3.3$ Hz, 1H), 1.81–1.08 (m, 6H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H); ¹³C NMR (CDCl₃: 100 MHz) δ 168.3, 168.1, 103.3, 81.9, 72.1, 52.5, 52.3, 32.2, 31.7, 31.0, 22.4, 21.5, 19.1, 16.8; MS-EI m/z (rel int) 325 ([M+Na]⁺, 20), 187 (100), 133 (80), 116 (47), 100 (25); HRMS-EI (calcd for [M+NH₄]⁺) 320.2068, found 320.2071.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-thiophen-2-yl-methyl]-malonic acid dimethyl ester (5): ¹H NMR (CDCl₃: 600 MHz) δ 7.23 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.03 (m, 1H), 6.91 (dd, $J = 5.1, 3.6$ Hz, 1H), 5.50 (d, $J = 10.3$ Hz, 1H), 4.56 (dd, $J = 9.5, 2.2$ Hz, 1H), 4.02 (d, $J = 10.3$ Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.42 (ddq, $J = 12.4, 6.2, 2.1$ Hz, 1H), 1.80–1.06 (m, 6H), 1.08 (d, $J = 6.2$ Hz, 3H); ¹³C NMR (CDCl₃: 100 MHz) δ 167.3, 166.5, 142.6, 126.3, 125.7, 125.6, 103.2, 74.6, 72.4, 52.7, 52.6, 32.0, 30.4, 22.1, 21.3.

2-[(4-Methoxy-phenyl)-(6-methyl-tetrahydro-pyran-2-yloxy)-methyl]-malonic acid dimethyl ester (6): ¹H NMR (CDCl₃: 600 MHz) δ 7.29 (d, $J = 8.7$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 5.14 (d, $J = 10.3$ Hz, 1H), 4.48 (dd, $J = 9.5, 2.1$ Hz, 1H), 3.90 (d, $J = 10.3$ Hz, 1H), 3.76 (s, 6H), 3.47 (s, 3H),

3.35 (ddq, $J = 17.3, 12.4, 6.2, 2.1$ Hz, 1H), 1.78–1.02 (m, 6H), 0.99 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 167.8, 166.7, 159.3, 131.4, 128.7, 113.5, 103.2, 79.2, 72.3, 59.4, 55.1, 52.5, 52.3, 31.9, 30.4, 22.1, 21.3.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-phenyl-methyl]-malonic acid dimethyl ester (7): ^1H NMR (CDCl_3 : 600 MHz) δ 7.38–7.22 (m, 5H), 5.19 (d, $J = 10.2$ Hz, 1H), 4.51 (dd, $J = 9.5, 2.2$ Hz, 1H), 3.91 (d, $J = 10.2$ Hz, 1H), 3.77 (s, 3H), 3.45 (s, 3H), 3.35 (ddq, $J = 12.4, 6.2, 2.1$ Hz, 1H), 1.79–1.01 (m, 6H), 0.97 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 167.7, 166.7, 139.4, 128.0, 127.9, 127.3, 103.4, 79.6, 72.3, 59.5, 52.5, 52.3, 31.9, 30.5, 22.1, 21.3.

2-[1-(6-Methyl-tetrahydro-pyran-2-yloxy)-heptyl]-malonic acid dimethyl ester (8): ^1H NMR (CDCl_3 : 600 MHz) δ 4.44 (dd, $J = 9.5, 2.1$ Hz, 1H), 4.29 (ddd, $J = 10.9, 8.5, 5.4$ Hz, 1H), 3.72 (s, 3H), 3.62 (d, $J = 8.5$ Hz, 1H), 3.47 (ddq, $J = 12.4, 6.2, 2.1$ Hz, 1H), 1.80–1.08 (m, 16H), 1.17 (d, $J = 6.2$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 168.2, 167.9, 103.0, 77.6, 72.1, 57.0, 52.4, 52.3, 34.2, 32.2, 31.7, 30.9, 29.1, 24.6, 22.6, 22.3, 21.5, 14.1.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-thiophen-2-yl-methyl]-malonic acid dienzyl ester (9): ^1H NMR (CDCl_3 , 400 MHz) δ 7.36 – 7.26 (m, 10H), 7.21 (d, $J = 5.0$ Hz, 1H), 7.10 (m, 2H), 6.99 (d, $J = 2.4$ Hz, 1H), 6.87 (dd, $J = 3.6, 4.9$ Hz, 1H), 5.53 (d, $J = 10.3$ Hz, 1H), 5.22 (m, 1H), 5.00 (d, $J = 2.3$

Hz, 1H), 5.00 (d, $J = 2.3$ Hz, 1H), 4.97 (d, $J = 2.3$ Hz, 1H), 4.50 (dd, $J = 2.0, 9.3$ Hz, 1H), 4.14 (d, $J = 10.3$ Hz, 1H), 3.41 (m, 1H), 1.06 (d, $J = 6.2$ Hz, 3H), 0.89–1.72 (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.6, 166.9, 142.6, 135.4, 135.3, 128.6, 128.5, 128.4, 128.3, 128.1, 126.7, 126.4, 125.9, 125.7, 101.3, 74.7, 72.3, 67.4, 67.2, 60.1, 41.6, 32.0, 30.4, 22.2, 21.4.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-phenyl-methyl]-malonic acid dibenzyl ester (10): ^1H NMR (CDCl_3 , 400 MHz) δ 7.34 – 7.24 (m, 13H), 6.99 (m, 2H), 5.19 (m, 3H), 4.87 (dd, $J = 2.3, 22.3$ Hz, 2H), 4.46 (dd, $J = 1.8, 9.3$ Hz, 1H), 4.03 (d, $J = 10.2$ Hz, 1H), 3.30 (m, 1H), 0.99–1.70 (m, 6H), 0.95 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.0, 166.1, 139.5, 135.5, 135.0, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 103.5, 79.8, 72.2, 67.2, 67.1, 60.2, 32.0, 30.4, 22.2, 21.4.

2-[2-Methyl-1-(6-methyl-tetrahydro-pyran-2-yloxy)-propyl]-malonic acid dibenzyl ester (11): ^1H NMR (CDCl_3 , 400 MHz) δ 7.35 – 7.30 (m, 10H), 5.15 (m, 4H), 4.33 (dd, $J = 1.6, 9.3$ Hz, 1H), 4.28 (dd, $J = 3.3, 8.6$ Hz, 1H), 3.81 (d, $J = 8.7$ Hz, 1H), 3.41 (m, 1H), 1.89 – 1.80 (m, 1H), 1.17 (d, $J = 6.1$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.92–1.46 (m, 6H), 0.91 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.6, 167.5, 135.4, 135.3, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 104.0, 81.7, 72.1, 67.1, 67.0, 56.2, 32.3, 31.7, 29.7, 22.4, 21.6, 16.9, 16.2.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-thiophen-2-yl-methyl]-malonic acid diethyl ester (12):

^1H NMR (CDCl_3 : 600 MHz) δ 7.20 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.03 (m, 1H), 6.89 (dd, $J = 5.1, 3.5$ Hz, 1H), 5.48 (d, $J = 10.4$ Hz, 1H), 4.58 (dd, $J = 9.5, 2.2$ Hz, 1H), 4.23 (m, 2H), 4.01 (q, $J = 7.1$ Hz, 2H), 3.98 (d, $J = 10.4$ Hz, 1H), 3.42 (ddq, $J = 12.4, 6.2, 2.1$ Hz, 1H), 1.79–1.05 (m, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.07 (t, $J = 7.1$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 166.9, 166.1, 142.7, 126.2, 125.8, 125.5, 103.3, 74.7, 72.3, 61.7, 61.5, 60.0, 32.0, 30.4, 22.1, 21.3, 14.1, 13.7.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-furan-2-yl-methyl]-malonic acid diethyl ester (13):

^1H NMR (CDCl_3 : 600 MHz) δ 7.35 (d, $J = 1.8$ Hz, 1H), 6.33 (d, $J = 3.2$ Hz, 1H), 6.28 (dd, $J = 3.2, 1.8$ Hz, 1H), 5.24 (d, $J = 10.6$ Hz, 1H), 4.54 (dd, $J = 9.5, 2.2$ Hz, 1H), 4.22 (m, 2H), 4.13 (d, $J = 10.6$ Hz, 1H), 4.03 (m, 2H), 3.39 (ddq, $J = 12.4, 6.2, 2.1$ Hz, 1H), 1.79–1.25 (m, 6H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.09 (t, $J = 7.1$ Hz, 3H), 1.05 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 167.1, 166.1, 152.1, 142.2, 110.2, 108.7, 103.4, 72.9, 72.1, 61.6, 61.4, 56.7, 31.9, 30.4, 22.1, 21.3, 14.1, 13.8.

2-[(6-Methyl-tetrahydro-pyran-2-yloxy)-phenyl-methyl]-malonic acid diethyl ester (14):

^1H NMR (CDCl_3 : 600 MHz) δ 7.39–7.22 (m, 5H), 5.18 (d, $J = 10.3$ Hz, 1H), 4.54 (dd, $J = 9.6, 2.1$ Hz, 1H), 4.24 (m, 2H), 3.94 (m, 2H), 3.89 (d, $J = 10.3$ Hz, 1H), 3.36 (ddq, $J = 12.5, 6.2, 2.1$ Hz, 1H), 1.79–1.02 (m, 6H), 1.30 (t, $J = 7.1$ Hz, 3H), 0.97 (d, $J = 6.2$ Hz, 3H), 0.96 (t, $J = 7.1$ Hz, 3H); ^{13}C

NMR (CDCl₃: 100 MHz) δ 167.4, 166.3, 139.5, 128.0, 127.9, 127.7, 103.5, 79.8, 72.2, 61.5, 61.3, 59.7, 31.9, 30.5, 22.2, 21.3, 14.1, 13.7.

2-[(4-Methoxy-phenyl)-(6-methyl-tetrahydro-pyran-2-yloxy)-methyl]-malonic acid diethyl ester (15): ¹H NMR (CDCl₃: 600 MHz) δ 7.29 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.13 (d, J = 10.4 Hz, 1H), 4.50 (dd, J = 9.5, 2.1 Hz, 1H), 4.22 (m, 2H), 3.91 (m, 2H), 3.87 (d, J = 10.4 Hz, 1H), 3.76 (s, 3H), 3.35 (ddq, J = 12.4, 6.2, 2.1 Hz, 1H), 1.78–1.02 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃: 100 MHz) δ 167.4, 166.3, 159.3, 131.6, 128.9, 113.4, 103.2, 79.3, 72.2, 61.5, 61.3, 59.7, 55.2, 32.0, 30.4, 22.2, 21.3, 14.1, 13.7.

2-[2-Methyl-1-(6-methyl-tetrahydro-pyran-2-yloxy)-propyl]-malonic acid diethyl ester (16): ¹H NMR (CDCl₃: 600 MHz) δ 4.42 (dd, J = 9.5, 2.1 Hz, 1H), 4.17 (m, 5H), 3.63 (d, J = 9.0 Hz, 1H), 3.45 (ddq, J = 12.4, 6.2, 1.9 Hz, 1H), 1.82 (dq, J = 6.9, 6.9, 3.3 Hz, 1H), 1.77–1.06 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃: 100 MHz) δ 167.9, 167.7, 103.3, 81.8, 72.1, 61.4, 61.3, 56.1, 32.2, 31.7, 30.9, 22.4, 21.5, 19.2, 16.7, 14.1, 13.9.

2-[1-(6-Methyl-tetrahydro-pyran-2-yloxy)-heptyl]-malonic acid diethyl ester (17): ¹H NMR (CDCl₃: 600 MHz) δ 4.43 (dd, J = 9.5, 2.0 Hz, 1H), 4.25 (m, 1H), 4.14 (dq, J = 7.1, 3.5 Hz,

4H), 3.54 (d, $J = 8.6$ Hz, 1H), 3.44 (ddq, $J = 12.3, 6.2, 1.8$ Hz, 1H), 1.75–1.05 (m, 16H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H), 0.83 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 167.8, 167.5, 103.1, 77.6, 72.0, 61.3, 57.4, 34.1, 32.2, 31.7, 30.9, 22.6, 22.3, 21.5, 16.7, 14.1, 14.0.

2-(Hydroxy-thiophen-2-yl-methyl)-malonic acid dimethyl ester (20). To a stirred solution of 5 (23mg, 0.067mmol) in MeOH (2ml) was added MP-TsOH II (23mg, 0.098mmol, 4.2 mmol/g) and stirred for 2 h 30 mins at r.t., filtered and concentrated in vacuo to get the title compound 20 (16mg, 100%) as an oil: $[\alpha]_{\text{D}}^{25} = +9.3$ (c 0.77, CHCl_3); IR (film) ν_{max} 3473, 1732, 1435, 1256, 1196, 1149, 1015, 752, 704 cm^{-1} ; ^1H NMR (CDCl_3 : 500 MHz) δ 7.27 (dd, $J = 5.0, 1.2$ Hz, 1H), 6.98 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.95 (dd, $J = 5.0, 3.6$ Hz, 1H), 5.57 (d, $J = 6.9$ Hz, 1H), 3.86 (d, $J = 6.9$ Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 168.9, 167.1, 143.8, 126.7, 125.5, 124.6, 69.3, 59.2, 52.9, 52.8; MS-EI m/z (rel int) 262 ($[\text{M}+\text{NH}_4]^+$, 14), 227 (100), 192 (16), 133 (12); HRMS-EI (calcd for $[\text{M}+\text{Na}]^+$) 267.0303, found 267.0303.

2-(Hydroxy-phenyl-methyl)-malonic acid dimethyl ester (21): ^1H NMR (CDCl_3 : 500 MHz) δ 7.37-7.26 (m, 5H), 5.32 (d, $J = 7.2$ Hz, 1H), 3.80 (d, $J = 7.2$ Hz, 1H), 3.74 (s, 3H), 3.63 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 169.0, 167.4, 139.9, 128.5, 128.3, 126.2, 72.8, 59.1, 52.7, 52.6.

2-(Hydroxy-phenyl-methyl)-malonic acid dibenzyl ester (22): ^1H NMR (CDCl_3 : 400 MHz) δ 7.36-7.21 (m, 13H), 7.12 (m, 2H), 5.36 (d, $J = 7.3$ Hz, 1H), 5.19 (d, $J = 12.3$ Hz, 1H), 5.14 (d, $J = 12.4$ Hz, 1H), 5.04 (d, $J = 12.3$ Hz, 1H), 4.99 (d, $J = 12.3$ Hz, 1H), 3.91 (d, $J = 7.4$ Hz, 1H), 3.48 (s, 1H); ^{13}C NMR (CDCl_3 : 100 MHz) δ 168.4, 166.8, 139.8, 135.0, 128.5, 128.2, 126.4, 72.9, 67.5, 67.3, 59.4.

2-(Furan-2-yl-hydroxy-methyl)-malonic acid diethyl ester (23): ^1H NMR (CDCl_3 : 500 MHz) δ 7.36 (s, 1H), 6.31 (s, 2H), 5.31 (d, $J = 6.7$ Hz, 1H), 4.23 (m, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.92 (d, $J = 6.7$ Hz, 1H), 3.77 (s, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3H), ; ^{13}C NMR (CDCl_3 : 100 MHz) δ 168.5, 166.8, 152.9, 142.4, 110.3, 107.5, 66.9, 61.9, 61.8, 56.4, 13.9.