Highly Stereoselective Michael Addition Reactions of camTHP* Desymmetrised Glycinamide for the Synthesis of Functionally Dense Amino Acid Derivatives

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Supporting Information

Experimental (P S1-S5)

General procedure for the Michael reaction of 1

To a stirred solution of **1** (133 mg, 0.3 mmol) in degassed THF (3 ml) at -78 °C under argon was added LiHMDS (1.0 M in THF, 0.6 ml, 0.6 mmol) and the pale yellow solution stirred for 1 hour before the addition of Michael acceptor (0.36 mmol, 1.2 eq). The reaction was stirred at -78 °C for 1 hour and at -20 °C for a further 1 hour before being quenched at -20 °C by the rapid addition of AcOH (0.08 ml, 1.2 mmol). After warming to room temperature the reaction mixture was filtered through a plug of silica (10 mm x 10 mm dia.) eluting with EtOAc (50 ml) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, neat petroleum ether (40-60 °C) gradient to neat Et₂O) to give the products **5-17**.

Data for **5** (R=Ph, EWG=NO₂)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.36-7.30 (m, 5H), 7.25-7.20 (m, 5H), 5.36 (d, *J* = 9.6 Hz, 1H), 5.20 (dd, *J* = 11.5, 2.1 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.96 (dd, *J* = 13.1, 9.5 Hz, 1H), 4.81 (d, *J* = 12.3 Hz, 1H), 4.77 (dd, *J* = 13.1, 4.0 Hz, 1H), 4.33 (ddd, *J* = 9.6, 9.5, 4.0 Hz, 1H), 2.92 (s, 6H), 2.23 (ddt, *J* = 12.6, 11.8, 4.1 Hz, 1H), 2.08 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.87-1.82 (m, 1H), 1.67-1.26 (m, 8H), 1.15 (d, *J* = 12.8, 1H), 0.96-0.91 (m, 1H), 0.91 (s, 3H), 0.82 (s, 3H), 0.76 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 592.3386, C₃₄H₄₆N₃O₆⁺ requires 592.3381.

Data for 6 (R=2-Nap, EWG=NO₂)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.87-7.80 (m, 3H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.51-7.47 (m, 2H), 7.28-7.19 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.18 (dd, *J* = 11.5, 2.0 Hz, 1H), 5.08 (dd, *J* = 13.1, 9.5 Hz, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.87 (dd, *J* = 13.1, 4.0 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.53 (ddd, *J* = 9.7, 9.5, 4.0 Hz, 1H), 2.95 (s, 6H), 2.29 (ddt, *J* = 12.4, 11.9, 4.0 Hz, 1H), 2.06 (dt, *J* = 12.7, 3.3 Hz, 1H), 1.89-1.85 (m, 1H), 1.73-1.23 (m, 8H), 1.13 (d, *J* = 12.7, 1H), 0.95-0.90 (m, 1H), 0.90 (s, 3H), 0.82 (s, 3H), 0.77 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 642.3533, C₃₈H₄₈N₃O₆⁺ requires 642.3538.

Data for 7 (R=PMP, EWG=NO₂)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.36-7.31 (m, 3H), 7.25-7.22 (m, 4H), 6.80-6.77 (m, 2H), 5.30 (d, *J* = 9.7 Hz, 1H), 5.19 (dd, *J* = 11.4, 2.1 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.89 (dd, *J* = 13.0, 9.5 Hz, 1H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.72 (dd, *J* = 13.0, 4.0 Hz, 1H), 4.26 (ddd, *J* = 9.7, 9.5, 4.0 Hz, 1H), 3.75 (s, 3H), 2.91 (s, 6H), 2.20 (ddt, *J* = 12.6, 11.8, 4.0 Hz, 1H), 2.08 (dt, *J* = 13.2, 4.0 Hz, 1H), 1.86-1.82 (m, 1H), 1.64-1.25 (m, 8H), 1.15 (d, *J* = 12.8, 1H), 0.96-0.91 (m, 1H), 0.91 (s, 3H), 0.82 (s, 3H), 0.75 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 622.3490, C₃₅H₄₈N₃O₇⁺ requires 622.3487.

Data for 8 (R=ⁿHexyl, EWG=NO₂)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.39-7.33 (m, 5H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.14 (dd, *J* = 11.3, 2.2 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 9.8 Hz, 1H), 4.57 (dd, *J* = 13.3, 5.4 Hz, 1H), 4.54 (dd, *J* = 13.3, 4.3 Hz, 1H), 2.88 (s, 6H), 2.85-2.79 (m, 1H), 2.12 (dt, *J* = 12.5, 3.5 Hz, 1H), 2.04 (ddt, *J* = 12.4, 12.0, 4.1 Hz, 1H), 1.82-1.76 (m, 1H), 1.68-1.20 (m, 19H), 0.98 (s, 3H), 0.97-0.93 (m, 1H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.84 (s, 3H), 0.74 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 600.4009, C₃₄H₅₄N₃O₆⁺ requires 600.4007.

Data for 9 (R=ⁱPr, EWG=NO₂)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.42-7.31 (m, 5H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.08 (dd, *J* = 11.3, 2.1 Hz, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 4.53 (dd, *J* = 14.5, 5.0 Hz, 1H), 4.29 (dd, *J* = 14.5, 4.3 Hz, 1H), 2.96-2.91 (m, 1H), 2.89 (s, 6H), 2.10 (dt, *J* = 12.8, 3.7 Hz, 1H), 2.05 (ddt, *J* = 12.4, 12.0, 4.1 Hz, 1H), 1.95 (double septet, *J* = 6.9, 10.1 Hz, 1H), 1.80-1.76 (m, 1H), 1.68-1.26 (m, 8H), 1.24 (d, *J* = 12.8 Hz, 1H), 0.99 (s, 3H), 0.98-0.95 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.72 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 558.3541, C₃₁H₄₈N₃O₆⁺ requires 558.3538.

Data for 10 (R=Me, EWG=CO₂^tBu)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.40-7.31 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.04 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 2.89 (s, 6H), 2.63-2.54 (m, 1H), 2.25 (dd, *J* = 14.6, 3.7 Hz, 1H), 2.17-2.09 (m, 2H), 1.99 (dd, *J* = 14.6, 8.4 Hz, 1H), 1.78-1.72 (m, 1H), 1.68-1.24 (m, 8H), 1.42 (s, 9H), 1.24 (d, *J* = 12.8 Hz, 1H), 1.00 (s, 3H), 0.98-0.94 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 3H), 0.73 (s, 3H); HRMS (ESI+) *m/z* Found [M+H]⁺ 585.3893, C₃₄H₅₃N₂O₆⁺ requires 585.3898.

Data for 11 (R=ⁿPr, EWG=CO₂^tBu)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.39-7.30 (m, 5H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.10-5.09 (m, 1H), 5.08 (d, *J* = 10.9 Hz, 1H), 2.90 (s, 6H), 2.54-2.46 (m, 1H), 2.24 (dd, *J* = 15.1, 4.2 Hz, 1H), 2.19 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.16-2.09 (m, 2H), 1.77-1.73 (m, 1H), 1.68-1.62 (m, 2H), 1.55-1.13 (m, 11H), 1.42 (s, 9H), 1.01 (s, 3H), 0.98-0.93 (m, 1H), 0.84 (s, 3H), 0.82 (t, *J* = 7.0 Hz, 3H), 0.73 (s, 3H); HRMS (ESI+) *m/z* Found

$[M+H]^+$ 613.4207, $C_{36}H_{57}N_2O_6^+$ requires 613.4211.

Data for 12 (R=ⁱPr, EWG=CO₂^tBu)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.39-7.30 (m, 5H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 11.0 Hz, 1H), 5.08-5.06 (m, 1H), 2.90 (s, 6H), 2.61-2.56 (m, 1H), 2.19 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.14-2.05 (m, 2H), 1.91 (double septet, *J* = 9.4, 6.8 Hz, 1H), 1.86 (dd, *J* = 16.1, 4.3 Hz, 1H), 1.77-1.60 (m, 3H), 1.54-1.23 (m, 7H), 1.42 (s, 9H), 1.02 (s, 3H), 0.98-0.93 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.72 (s, 3H); HRMS (ESI+) *m/z* Found $[M+NH_4]^+$ 630.4470, $C_{36}H_{60}N_3O_6^+$ requires 630.4477.

Data for 13 (R=Me, EWG=CO₂Et)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.40-7.30 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.06 (dd, *J* = 11.3, 2.2 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.07 (dq, *J* = 7.1, 1.6 Hz, 2H), 2.89 (s, 6H), 2.68-2.59 (m, 1H), 2.32 (dd, *J* = 14.9, 3.7 Hz, 1H), 2.17-2.09 (m, 2H), 2.09 (dd, *J* = 14.9, 8.3 Hz, 1H), 1.78-1.72 (m, 1H), 1.68-1.60 (m, 2H), 1.54-1.26 (m, 6H), 1.23 (d, *J* = 12.8 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 3H), 0.98-0.93 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 3H), 0.73 (s, 3H); HRMS (ESI+) *m/z* Found $[M+H]^+$ 557.3586, $C_{32}H_{49}N_2O_6^+$ requires 557.3585.

Data for 14 (R=ⁿPr, EWG=CO₂Et)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.40-7.31 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.10 (dd, *J* = 11.2, 2.2 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.05 (dq, *J* = 7.1, 3.1 Hz, 2H), 2.89 (s, 6H), 2.58-2.52 (m, 1H), 2.29 (dd, *J* = 15.3, 4.4 Hz, 1H), 2.25 (dd, *J* = 15.3, 6.1 Hz, 1H), 2.15-2.07 (m, 2H), 1.78-1.73 (m, 1H), 1.68-1.60 (m, 2H), 1.54-1.12 (m, 10H), 1.23 (d, *J* = 12.8 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 3H), 0.98-0.93 (m, 1H), 0.84 (s, 3H), 0.81 (t, *J* = 7.1 Hz, 3H), 0.73 (s, 3H); HRMS (ESI+) *m/z* Found $[M+H]^+$ 585.3895, $C_{34}H_{53}N_2O_6^+$ requires 585.3898.

Data for 15 (R=ⁱPr, EWG=CO₂Et)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.39-7.31 (m, 5H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 10.9 Hz, 1H), 5.06 (dd, *J* = 11.3, 2.2 Hz, 1H), 4.04 (dq, *J* = 7.1, 2.0 Hz, 2H), 2.90 (s, 6H), 2.63-2.59 (m, 1H), 2.26 (dd, *J* = 15.9, 5.9 Hz, 1H), 2.12-2.04 (m, 2H), 1.94 (dd, *J* = 15.9, 4.7 Hz, 1H), 1.94-1.88 (m, 1H), 1.76-1.72 (m, 1H), 1.69-1.60 (m, 2H), 1.53-1.24 (m, 6H), 1.24 (d, *J* = 12.8 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 3H), 0.98-0.93 (m, 1H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.71 (s, 3H); HRMS (ESI+) *m/z* Found $[M+NH_4]^+$ 602.4164, $C_{34}H_{56}N_3O_6^+$ requires 602.4164.

Data for 16 (R,EWG=-(*o*-C₄H₆)OC(O)-)

¹H-NMR (d₆-DMSO, 120 °C, 500 MHz): 7.36-7.20 (m, 7H), 7.05 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.39 (dd, *J* = 11.5, 2.1 Hz, 1H), 4.91 (d, *J* = 12.3 Hz, 1H), 4.87 (d, *J* = 9.3 Hz, 1H), 4.66 (d, *J* = 12.3 Hz, 1H), 3.79 (ddd, *J* = 9.3, 6.7, 2.6 Hz, 1H), 2.92 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.83 (s, 6H), 2.82 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.22 (ddt, *J* = 12.5, 11.9, 4.0 Hz, 1H), 2.16 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.91-1.86 (m, 1H), 1.81-1.78 (m, 1H), 1.66-1.59 (m, 2H), 1.45-1.27 (m, 4H), 1.23 (d, *J* = 12.8 Hz, 1H), 1.10-0.94 (m, 1H), 0.93 (s, 3H), 0.83 (s, 3H), 0.73 (s, 3H); HRMS (ESI+) *m/z* Found $[M+Na]^+$ 611.3118, $C_{35}H_{44}N_2O_6Na^+$ requires 611.3092.

Data for 17 (R=Ph, EWG=COPh)

$^1\text{H-NMR}$ (d_6 -DMSO, 120 °C, 500 MHz): 7.81 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.34-7.19 (m, 7H), 7.16-7.07 (m, 3H), 5.50 (d, J = 10.6 Hz, 1H), 5.16 (dd, J = 11.6, 1.9 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.77 (d, J = 12.3 Hz, 1H), 4.21 (ddd, J = 10.6, 9.5, 3.6 Hz, 1H), 3.32 (dd, J = 15.9, 9.5 Hz, 1H), 3.22 (dd, J = 15.9, 3.6 Hz, 1H), 2.97 (s, 6H), 2.37 (ddt, J = 12.2, 11.9, 4.1 Hz, 1H), 2.06 (dt, J = 12.8, 3.3 Hz, 1H), 1.83-1.58 (m, 4H), 1.50-1.21 (m, 5H), 1.33 (d, J = 12.8 Hz, 1H), 0.96-0.90 (m, 1H), 0.88 (s, 3H), 0.81 (s, 3H), 0.73 (s, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{H}]^+$ 651.3797, $\text{C}_{41}\text{H}_{51}\text{N}_2\text{O}_5^+$ requires 651.3792.

Acid hydrolysis of 13

18

A solution of **13** (105 mg, 0.19 mmol) in TFA/ H_2O (9:1, 3 ml) was stirred at ambient temperature for 6 hours before being quenched with saturated aqueous NaHCO_3 (15 ml) and extracted with DCM (3x15 ml) and EtOAc (3x50 ml). The combined organics were concentrated *in vacuo* to give an orange oil/solid which was purified by column chromatography (silica, petroleum ether (40-60 °C): Et_2O , 1:1 gradient to neat Et_2O) to give **18** as a pale yellow oil (40.4 mg, 0.12 mmol, 61 %). $^1\text{H-NMR}$ (CDCl_3 , 27 °C, 500 MHz): 7.39-7.30 (m, 5H), 5.78 (d, J = 8.4 Hz, 1H), 5.11 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.89 (dd, J = 8.4, 3.0 Hz, 1H), 4.22-4.15 (m, 2H), 3.22 (s, 3H), 2.98 (s, 3H), 2.50 (dd, J = 16.9, 8.8 Hz, 1H), 2.41-2.33 (m, 1H), 2.21 (dd, J = 16.9, 5.2 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{H}]^+$ 351.1911, $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_5^+$ requires 351.1914.

Preparation of the pyroglutamic acid derivative 19

18

19

To a solution of **18** (25 mg, 0.07 mmol) in EtOAc (2.5 ml) was added Pd/C (10 % by mass, 2.5 mg) and the mixture stirred under an atmosphere of hydrogen (approx. 1 bar) for 16 hours. The reaction mixture was filtered through celite and concentrated *in vacuo* to give a yellow oil which was re-dissolved in MeOH (2.5 ml) and heated at reflux under argon for 2 days. The solution was concentrated *in vacuo* to give essentially clean **19** as a pale yellow oil (10.2 mg, 0.06 mmol, 86%). A small sample was purified for analysis by column chromatography (silica, MeOH in DCM, 1% gradient to 10 %). $^1\text{H-NMR}$ (CDCl_3 , 27 °C, 500 MHz): 5.93 (bs, 1H), 4.61 (d, J = 6.9 Hz, 1H), 3.06 (s, 3H), 3.02 (s, 3H), 2.86 (dddq, J = 8.0, 7.1, 6.9, 3.7 Hz, 1H), 2.62 (dd, J = 16.5, 8.0 Hz, 1H), 2.10 (dd, J = 16.5, 3.7 Hz, 1H), 1.00 (d, J = 7.1 Hz, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{H}]^+$ 171.1131, $\text{C}_8\text{H}_{15}\text{N}_2\text{O}_3^+$ requires 171.1128.

General procedure for the reductive *N*-Boc protection of 5-7

To a stirred solution of the nitro compound (**5-7**, 0.05 mmol) in THF (0.5 ml) and MeOH (0.3 ml) at ambient temperature under argon was added $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (24 mg, 0.1 mmol). After 10 minutes the yellow solution was cooled to 0 °C and NaBH_4 (12 mg, 0.3 mmol) added and the resultant dark green solution stirred for 3 hours at 0 °C before the addition of Boc_2O (33 mg, 0.15 mmol). The reaction was allowed to warm to room temperature and stirred under argon for a further 16 hours before being filtered through silica (10 mm x 10 mm dia.) eluting with Et_2O (20 ml) and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by column chromatography (silica, petroleum ether (40-60 °C): Et_2O , 3:1 gradient to 1:3).

Data for 20 (R=Ph)

$^1\text{H-NMR}$ (d_6 -DMSO, 120 °C, 500 MHz): 7.35-7.14 (m, 10H), 5.49 (bs, 1H), 5.34 (d, $J = 10.5$ Hz, 1H), 5.07 (dd, $J = 11.5, 1.9$ Hz, 1H), 5.06 (d, $J = 12.3$ Hz, 1H), 4.84 (d, $J = 12.3$ Hz, 1H), 3.81 (dt, $J = 10.5, 6.1$ Hz, 1H), 3.19 (t, $J = 6.1$ Hz, 2H), 2.95 (s, 6H), 2.30 (ddt, $J = 12.3, 11.9, 4.0$ Hz, 1H), 2.03 (dt, $J = 9.4, 3.6$ Hz, 1H), 1.78-1.74 (m, 1H), 1.63-1.56 (m, 1H), 1.50-1.47 (m, 1H), 1.44-1.19 (m, 6H), 1.32 (s, 9H), 1.09 (d, $J = 12.7$, 1H), 0.93-0.88 (m, 1H), 0.87 (s, 3H), 0.80 (s, 3H), 0.71 (s, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{H}]^+$ 662.4163, $\text{C}_{39}\text{H}_{56}\text{N}_3\text{O}_6^+$ requires 662.4164.

Data for 21 (R=2-Nap)

$^1\text{H-NMR}$ (d_6 -DMSO, 120 °C, 500 MHz): 7.82 (dt, $J = 9.4, 3.3$ Hz, 1H), 7.76-7.73 (m, 2H), 7.70 (d, $J = 8.5$ Hz, 1H), 7.46-7.43 (m, 3H), 7.28-7.2 (m, 3H), 7.12 (d, $J = 7.1$ Hz, 2H), 5.62 (bs, 1H), 5.49 (d, $J = 10.7$ Hz, 1H), 5.03 (dd, $J = 11.6, 2.0$ Hz, 1H), 5.01 (d, $J = 12.2$ Hz, 1H), 4.79 (d, $J = 12.2$ Hz, 1H), 4.01 (dt, $J = 10.7, 6.0$ Hz, 1H), 3.29-3.26 (m, 2H), 2.98 (s, 6H), 2.35 (ddt, $J = 12.2, 11.9, 4.0$ Hz, 1H), 1.98 (dt, $J = 12.5, 3.0$ Hz, 1H), 1.79-1.75 (m, 1H), 1.61-1.51 (m, 3H), 1.42-1.19 (m, 5H), 1.26 (s, 9H), 1.06 (d, $J = 12.7$, 1H), 0.91-0.85 (m, 1H), 0.82 (s, 3H), 0.78 (s, 3H), 0.71 (s, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{NH}_4]^+$ 729.4592, $\text{C}_{43}\text{H}_{61}\text{N}_4\text{O}_6^+$ requires 729.4586.

Data for 22 (R=PMP)

$^1\text{H-NMR}$ (d_6 -DMSO, 120 °C, 500 MHz): 7.35-7.31 (m, 3H), 7.25-7.23 (m, 2H), 7.17-7.14 (m, 2H), 6.76-6.73 (m, 2H), 5.44 (bs, 1H), 5.29 (d, $J = 10.7$ Hz, 1H), 5.09 (d, $J = 12.3$ Hz, 1H), 5.08 (dd, $J = 11.4, 2.0$ Hz, 1H), 4.86 (d, $J = 12.3$ Hz, 1H), 3.75 (dt, $J = 10.6, 6.3$ Hz, 1H), 3.74 (s, 3H), 3.16-3.13 (m, 2H), 2.95 (s, 6H), 2.29 (ddt, $J = 12.3, 11.9, 4.1$ Hz, 1H), 2.03 (dt, $J = 12.7, 3.2$ Hz, 1H), 1.78-1.74 (m, 1H), 1.62-1.57 (m, 2H), 1.49-1.20 (m, 6H), 1.33 (s, 9H), 1.09 (d, $J = 12.7$, 1H), 0.93-0.88 (m, 1H), 0.88 (s, 3H), 0.80 (s, 3H), 0.71 (s, 3H); HRMS (ESI+) m/z Found $[\text{M}+\text{H}]^+$ 692.4283, $\text{C}_{40}\text{H}_{58}\text{N}_3\text{O}_7^+$ requires 692.4275.