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Sialyl*exo*enitols as Precursor for New Analogues of Sialidase Inhibitors

Barbara Richichi,[1] Carlotta Lunghi,[1] Athanasios Papakyriakou,[3] Oscar Francesconi[1] and Cristina Nativi[1,2]*

[1]*Dipartimento di Chimica "Ugo Schiff", Universita' degli Studi di Firenze, via della Lastruccia, 13 50019 Sesto F.no (FI) Italy*

[2]*CNR, Istituto di Metodologie Chimiche IMC, Area di Ricerca di Roma 1, via Salaria Km 29, 300- 00015 Monterotondo Roma, Italy.*

[3]*Chemical Biology and Designed Molecules Laboratory, NCSR "Demokritos", 15310 Ag. Paraskevi, Athens, Greece*

E-mail: cristina.nativi@unifi.it

Supporting Information

Synthesis of compound 14. To a stirred suspension of N-acetyl neuraminic acid methyl ester **7** (1.00 g, 3.093 mmol) in dry CH_2Cl_2 (6.0 mL) Pyridine (1.3 mL) was added. The reaction mixture was cooled at 0°C and TBDMSOTf (2.56 mL, 11.13 mmol) was slowly added. After 10' the mixture was warmed to RT, stirred for 30 min, then diluted with CH_2Cl_2 (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/ AcOEt 6/1) to give **14** (1.66 g, 81%) as white solid.

M.p.:171-173 °C; $[\alpha]_D^{25}$= + 25.3 (c 1.25, $CHCl_3$); ^{1}H NMR (400MHz, C_6D_6): δ 4.83 (d, 1H, J_{OH-7} = 4.8 Hz, OH), 4.47 (d, 1H, J_{NH-5} = 4.0 Hz, NH), 4.29-4.23 (m, 3H, H_5 , H_6, OH), 4.17-4.08 (m, 3H, H_4, H_8, H_{9a}), 3.94 (add, 1H, J_{7-OH} = 4.8 Hz, J = 9.2 Hz, H_7), 3.85 (ad, 1H, J_{9b-9a} = 8.8 Hz, H_{9b}), 3.19 (s, 3H, CO_2CH_3), 2.33 (atd, 1H, J = 12.4 Hz, J = 1.6 Hz, H_{3a}), 2.21-2.17 (B part of an ABX system, 1H, J_{BA} = 12.6 Hz, J_{BX} = 5.2 Hz, H_{3b}), 1.55 (s, 3H, CH_3CONH), 1.08 (s, 9H, (CH_3)$_3$C)), 1.03 (s, 9H, (CH_3)$_3$C)), 0.84 (s, 9H, (CH_3)$_3$C)), 0.31 (s, 3H, CH_3Si), 0.23 (s, 3H, CH_3Si), 0.14 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), -0.03 (s, 3H, CH_3Si), -0.09 (s, 3H, CH_3Si); ^{13}C NMR (100MHz, C_6D_6): δ 171.5 (Cq), 170.9 (Cq), 95.3 (Cq), 72.6 (C_5 o C_6), 72.4 (C_8 o C_4), 68.3 (C_4 o C_8), 68.1 (C_7), 64.5 (C_9), 54.2 (C_6 o C_5), 52.8 (CO_2CH_3), 40.5 (C_3), 26.3 ((CH_3)$_3$C), 26.2 ((CH_3)$_3$C), 25.6 ((CH_3)$_3$C), 22.7 (CH_3CONH) 18.6 (Cq), 18.5 (Cq), 17.9 (Cq), -3.89 (CH_3Si), -3.91 (CH_3Si), -4.1 (CH_3Si), -4.65 (CH_3Si), -5.2 (CH_3Si), -5.3 (CH_3Si); ESI-MS: 666.34 $[M+H]^+$; 688.67 $[M+Na]^+$.

Synthesis of compound 16. To an ice-cooled suspension of **14** (0.165 g, 0.248 mmol) in *i*-PrOH (2.5 mL), $NaBH_4$ (0.009 g, 0.248 mmol) was added. The reaction mixture was stirred for 30 min at 0°C, then AcOH (0.015 mL, 0.248 mmol) was added dropwise. The mixture was warmed to RT, diluted with AcOEt (50 mL) and washed with a saturated solution of $NaHCO_3$ (1 x 10 mL) and with brine (1 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness to give 155 mg of crude **15**. The crude **15** (155 mg) was dissolved in MeOH (1.2 mL), and 240 uL of a 1M suspension of $NaIO_4$ (0.052 g, 0.243 mmol) in H_2O were added. The mixture was warmed to 40°C and stirred for 20 h, then it was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 x 5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (CH_2Cl_2/AcOEt/Tol 30/1/1) to give **16** (0.070 g, 0.116 mmol, 40% over two steps) as a white solid.

M.p.: 153-155°C; $[\alpha]_D^{25}$: + 38.3 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 4.69 (d, 1H, J_{NH-4} = 8.0 Hz, NH), 4.48 (dd, 1H, J_{5-4} = 10.0 Hz, J_{5-6} = 1.2 Hz, H_5), 4.27 (d, 1H, J_{OH-6} = 5.6 Hz, OH), 4.12-4.08 (m, 1H, H_7), 4.01-3.94 (m, 2H, H_4 ,H_{8a}), 3.88-3.81 (m, 3H, H_3, H_{8a}, H_6), 2.84-2.79 (A part of an ABX system, J_{AB} = 16.8 Hz, J_{AX} = 6.0 Hz, H_{2a}), 2.36-2.30 (B part of an ABX system,

1H, J_{BA} = 16.8 Hz, J_{BX} = 7.2 Hz, H_{2b}), 1.50 (s, 3H, NHCOCH_3), 1.02 (s, 9H, (CH_3)$_3$C)), 0.98 (s, 9H, (CH_3)$_3$C)), 0.80 (s, 9H, (CH_3)$_3$C)), 0.29 (s, 3H, CH_3Si), 0.20 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si), -0.16 (s, 3H, CH_3Si); ^{13}C NMR (50 MHz, C_6D_6): δ 170.9, 169.1, 76.6, 72.2, 69.3, 68.5, 65.5, 53.6, 39.6, 26.29, 26.25, 25.7, 22.7, 18.6, 18.5, 17.9, -4.1, -4.2, -4.3, -4.7, -5.1, -5.2; ESI-MS: 606.42 $[M+H]^+$; 628.60 $[M+Na]^+$.

Synthesis of compound 17. A solution of **16** (0.180 g, 0.297mmol) in dry pyridine (0.7 mL) was cooled to –78°C and 1.48 mL of Tebbe's reagent (0.5M in toluene) were slowly added. The reaction mixture was then warmed to rt and stirred for 30 min. After this time, the mixture was cooled to –40°C and 3.5 mL of a 0.1 M NaOH were added dropwise. The mixture was stirred for 10 min, diluted with Et_2O (30 mL), warmed to RT and filtered through a pad of Celite. The filtrate was concentrated to dryness to give a crude which was purified by flash column chromatography on silica gel (petroleum ether/AcOEt/NEt_3 8/1/0.1) to afford **17** (0.123 g, 67%) as a white glassy solid.

$[\alpha]_D^{25}$: -36.73 (*c* 0.325, Hexane); ^{1}H NMR (400MHz, C_6D_6): δ 4.90 (d, 1H, J_{NH-5} = 8.8 Hz, NH), 4.64-4.63 (m, 2H, H_{1a}, OH), 4.22 (ddd, 1H, J_{8-9a} = 3.2 Hz, J_{8-9b} = 2.4 Hz, J_{8-7} = 9.2 Hz, H_8), 4.15-4.14 (m, 1H, H_{1b}), 4.11-4.09 (m, 1H, H_5), 4.07-4.03 (A part of an ABX system, 1H, J_{AB} = 10.8 Hz, J_{AX} = 3.2 Hz, H_{9a}), 3.93-3.89 (B part of an ABX system, 1H, J_{BA} = 10.8 Hz, J_{BX} = 2.4 Hz, H_{9b}), 3.80-3.76 (m, 1H, H_7), 3.75 (dd, 1H, J_{6-5} = 10.8 Hz, J_{6-7} = 1.2 Hz, H_6), 3.60 (td, *J* = 10.4 Hz, *J* = 4.8 Hz, 1H, H_4), 2.45-2.40 (A part of an ABX system, 1H, J_{AB} = 13.6 Hz, J_{AX} = 5.2 Hz, H_{3a}), 2.21-2.14 (m, 1H, H_{3b}), 1.53 (s, 3H, NHCOCH_3), 1.02 (s, 9H, (CH_3)$_3$C)), 0.99 (s, 9H, (CH_3)$_3$C)), 0.81 (s, 9H, (CH_3)$_3$C)), 0.25 (s, 3H, CH_3Si), 0.22 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), -0.11 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si); ^{13}C NMR (50 MHz, C_6D_6): δ 170.9, 156.4, 94.2, 77.6, 725., 70.5, 68.3, 64.9, 53.8, 39.1, 26.2, 26.0, 25.4, 22.5, 18.4, 17.7, -4.0, -4.1, -4.3, -4.7, -5.2, -5.3; ESI-MS: 604.34 $[M+H]^+$; 626.4 $[M+Na]^+$.

Synthesis of compound 8. To a stirred solution of N-acetyl neuraminic acid methyl ester **7** (0.500 g, 1.546 mmol) in dry DMF (3 mL), Imidazole (0.210 g, 3.092 mmol) and TBDPSiCl (0.80 mL, 3.092 mL), were added. The reaction mixture was stirred for 20 h at RT then diluted with CH_2Cl_2 (30 mL) and washed with a saturated solution of NH_4Cl (2 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/AcOEt 2/1) to afford **8** (0.900 g, 73%) as a white solid.

M.p.: 108-109 °C; $[\alpha]_D^{25}$: -5.3 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ 7.72-7.68 (m, 8H, Ph), 7.61-7.39 (m, 12H, Ph), 6.23 (d, 1H, J_{NH-5} = 9.2 Hz, NH), 4.54 (bs, 1H, OH), 4.27 (d,

1H, J = 4.4 Hz, OH), 4.24-4.18 (m, 1H, H_4), 3.95 (m, 1H, H_5), 3.84 (dd, 1H, $J_{6\text{-}7}$ = 10.8 Hz, $J_{6\text{-}5}$ = 0.8 Hz, H_6), 3.81-3.80 (m, 2H, H_{9a}, H_{9b}), 3.70 (s, 1H, CO_2CH_3), 3.65-3.58 (m, 2H, H_7, H_8), 2.88 (d, 1H, J = 6.4 Hz, OH), 2.05-2.00 (m, 2H, H_{3a}, H_{3b}), 1.74 (s, 3H, $NHCOCH_3$), 1.04 (s, 9H, $(CH_3)_3C$)), 1.03 (s, 9H, $(CH_3)_3C$)); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.1, 169.8, 135.7, 135.6, 135.4, 135.2, 133.1, 133.0, 132.9, 132.6, 130.1, 129.9, 129.6, 127.9, 127.8, 127.5, 95.0, 71.2, 69.5, 68.5, 67.9, 64.9, 53.8, 53.1, 39.6, 26.9, 26.8, 22.9, 19.4, 19.3; ESI-MS: 800.32 $[M+H]^+$; 822.70 $[M+Na]^+$; 1621.96 $[2M+Na]^+$.

Synthesis of compound 9. To a stirred solution of **8** (0.850 g, 1.06 mmol) in acetone (10 mL), 2,2-dimethoxypropane (10 mL) and (±)-camphor-10-sulfonic acid (0.050 g, 0.212 mmol) were added. The reaction mixture was stirred at RT for 1 h, then neutralized with Et_3N and diluted with CH_2Cl_2 (50 mL). The organic phase was washed with H_2O (3 x 10 mL), then dried over Na_2SO_4, filtered and concentrated to dryness to give 895 mg of crude **9** which was used without any further purification for the following reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.56 (m, 8H, Ph), 7.46-7.33 (m, 12H, Ph), 4.41 (d, 1H, $J_{NH\text{-}5}$ = 8.8 Hz, NH), 4.31-4.24 (m, 1H, H_8), 4.13-4.02 (m, 2H, H_5, H_6), 4.0 (td, 1H, J = 4.8 Hz, J = 10.4 Hz, H_4), 3.88-3.84 (A part of an ABX system, 1H, J_{AB} = 10.0 Hz, J_{AX} = 5.6 Hz, H_{9a}), 3.71 (s, 3H, CO_2CH_3), 3.71-3.62 (m, 2H, $H_{9b,}$ H_7), 3.23 (bs, 1H, OH), 2.20-2.15 (m, 1H, H_{3a}), 2.05-2.00 (B part of an ABX system, 1H, J_{BA} = 12.4 Hz, J_{BX} = 4.4 Hz, H_{3b}), 1.55 (s, 1H, CH_3CONH), 1.37 (s, 6H, $(CH_3)_2C$), 1.32 (s, 6H, $(CH_3)_2C$), 1.03 (s, 9H, $(CH_3)_3C$), 0.96 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.9 (Cq), 169.5 (Cq), 135.7 (CH, Ph), 135.4 (CH, Ph), 133.5 (Cq), 133.2 (Cq), 133.1 (Cq), 132.8 (Cq), 129.9 (CH, Ph), 129.7 (CH, Ph), 129.6 (CH, Ph), 127.7 (CH, Ph), 127.5 (CH, Ph), 109.4 (Cq), 94.4 (Cq), 76.4 (C_8), 70.9 (C_6 o C_5), 70.9 (C_7), 68.6 (C_4), 62.9 (C_9), 53.2 (C_5 o C_6), 53.1 (CO_2CH_3), 39.3 (C_3), 26.9 (CH_3), 26.1 (CH_3), 25.9 (CH_3), 23.5 (Cq), 19.3 (Cq), 19.2 (Cq); ESI-MS: 840.19 $[M+H]^+$; 862.72 $[M+Na]^+$; 1702.08 $[2M+Na]^+$.

Synthesis of compound 11. To an ice-cooled suspension of crude 5 (895 mg) in *i*-PrOH (8.0 mL), $NaBH_4$ (0.040 g, 1.06 mmol) was added. The reaction mixture was stirred for 1 h at 0°C, then AcOH (0.020 mL, 0.337 mmol) was added dropwise. The mixture was warmed to RT, diluted with CH_2Cl_2 (50 mL) and washed with a saturated solution of $NaHCO_3$ (1 x 10 mL) and with brine (2 x 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness to give 780 mg of crude **10**. The crude **10** (780 mg) was dissolved in MeOH (16.0 mL) then H_2O (1.6 mL) and $NaIO_4$ (234 mg, 1.10 mmol) were added. The mixture was warmed to 40°C and stirred for 20 h, then it was diluted with CH_2Cl_2 (60 mL) and washed with H_2O (2 x 10 mL). The organic phase was

dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/ AcOEt 3/1) to give **11** (0.114 g, 14% over three steps) as a white solid.

M.p.: 74-76 °C; $[\alpha]_D^{25}$: + 3.7 (c 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 7.69-7.57 (m, 8H, Ph), 7.16-7.10 (m, 12H, Ph), 4.51 (d, 1H, J_{NH-4} = 8.8 Hz, NH), 4.48-4.44 (m, 2H, H_5, H_7), 4.36 (ad, 1H, J = 7.6 Hz, H_6), 4.28-4.23 (A part of an ABX system, 1H, J_{AB} = 10.0 Hz , J_{AX} = 8.0 Hz, H_{8a}), 4.23-4.20 (B part of an ABX system, 1H, J_{BA} = 10.0 Hz, J_{BX} = 5.6 Hz, H_{8b}), 4.17-4.13 (m, 1H, H_3), 3.96-3.90 (m, 1H, H_4), 2.90-2.85 (A part of an ABX system, 1H, J_{AB} = 15.6 Hz, J_{AX} = 4.8 Hz, H_{2a}), 2.66-2.61 (B part of an ABX system, 1H, J_{BA} = 15.6 Hz, J_{BX} = 6.4 Hz, H_{2b}), 1.56 (s, 3H, C*H*$_3$CONH), 1.29 (s, 6H, (C*H*$_3$)$_2$C), 1.22 (s, 6H, (C*H*$_3$)$_2$C), 1.08 (s, 9H, (C*H*$_3$)$_3$C), 1.04 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.8, 169.2, 135.7, 135.6, 135.3, 133.1, 132.8, 132.7, 130.2, 130.0, 129.7, 127.9, 127.8, 127.6, 109.6, 76.6 , 76.0, 75.7, 68.4, 62.3, 54.6, 38.7, 26.9, 26.8, 26.2, 25.3, 23.2, 19.2; ESI-MS: 780.25 $[M+H]^+$; 802.68 $[M+Na]^+$.

Synthesis of compound 12. To a stirred solution of **11** (0.114 g, 0.146 mmol) in glacial AcOH (2.0 mL), H_2O (0.50 mL), was slowly added. The reaction mixture was warmed to 60°C and stirred for 3 h. After this time, the solvent was co-evaporated with toluene under reduced pressure to give crude **12** (0.096 g, 90%) as a white solid, which was used without any further purification for the following reaction.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72-7.61 (m, 6H, Ph), 7.51-7.34 (m, 14H, Ph), 5.08 (d, 1H, J = 4.6 Hz, NH), 4.19-4.06 (m, 3H), 3.96-3.87 (m, 2H), 3.81-3.73 (m, 2H), 3.44 (d, 1H, J = 9.2 Hz, OH), 3.11-3.00 (A part of an ABX system, 1H, J_{AB} = 17.6 Hz, J_{AX} = 5.4 Hz), 2.81-2.69 (B part of an ABX system, 1H, J_{BA} = 18.0 Hz, J_{BX} = 7.2 Hz), 2.37 (s, 1H, OH), 1.63 (s, 3H, C*H*$_3$CONH), 1.07 (s, 9H, (C*H*$_3$)$_3$C), 1.03 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.1, 168.7, 135.5, 135.4, 135.3, 132.8, 132.7, 132.5, 132.2, 130.4, 130.2, 129.6, 129.4, 128.1, 128.0, 127.6, 77.0, 69.4 , 68.2, 68.1, 65.3, 52.3, 39.2, 26.9, 26.8, 22.9, 19.4, 19.2.

Synthesis of compound 13. A solution of **12** (0.096 g, 0.136 mmol) in dry pyridine (0.3 mL) was cooled to –78°C and 680 uL of Tebbe's reagent (0.5 M in Toluene) were slowly added. The reaction mixture was then warmed to rt and stirred for 45 min. After this time, the mixture was cooled to –40°C and 2.0 mL of a 0.1 M NaOH were added dropwise. The mixture was stirred for 10 min, diluted with Et_2O (20 mL), warmed to rt and filtered through a pad of Celite. The filtrate was concentrated to dryness to give a crude which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc/NEt_3 3/1/0.1) to afford **13** (0.022 g, 23%) as a yellow oil.

Selected data: ^{1}H NMR (200 MHz, C_6D_6): δ 7.76-7.69 (m, 3H, Ph), 7.62-7.52 (m, 3H, Ph), 7.21-7.08 (m, 14H, Ph), 4.92 (d, 1H, *J* = 4.6 Hz), 4.63 (bs, 1H), 4.39-4.29 (m, 2H), 4.12-4.10 (m, 2H), 4.04 (bs, 1H), 3.72-3.62 (m, 2H), 3.48-3.44 (m, 1H), 2.59-2.50 (A part of an ABX system, 1H, J_{AB} = 13.2 Hz, J_{AX} = 5.0 Hz), 2.42-2.30 (m, 1H, H_{2b}), 1.25 (s, 3H, C*H*$_3$CONH), 1.06 (s, 9H, (C*H*$_3$)$_3$C), 1.00 (s, 9H, (C*H*$_3$)$_3$C).

Synthesis of compound 25. A solution of **21** (1.5 g, 7.04 mmol) in ethylacetoacetate (18 mL) was stirred for 1 h at rt, then the reaction mixture was cooled at 0°C and 100 mL of hexane were added. The suspension was filtered to give 1.2 g (57%) of **25** as mixture of keto-enol tautomers.

^{1}H NMR (200 MHz, $CDCl_3$): δ 13.9 (s, 1H, OH), 7.98-7.72 (m, 4H, PhtN keto + PhtN enol), 4.25 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$ keto), 4.21-4.16 (m, 4H, C*H*$_2$CH$_3$ enol), 2.77 (s, 3H, C*H*PhtNS), 1.32 (t, *J* = 7.0 Hz, 3H, CH$_2$C*H*$_3$ keto), 1.28 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$ enol); ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.6, 172.3, 167.6, 134.9, 134.4, 132.2, 124.3, 123.6, 96.72, 62.0, 21.6, 14.0.

Synthesis of compounds 28 and 28a. To a stirred solution of **17** (0.196 g, 0.324 mmol) in $CHCl_3$ (1.0 mL), pyridine (1.0 mL) and **22** (0.122 g, 0.454 mmol) were added. The mixture was warmed at 50°C for 20 h then it was diluted with $CHCl_3$ (30 mL) and washed with a saturated solution of NH_4Cl (1 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/ AcOEt 6/1) to give a diastereomeric mixture of **28** and **28a** (0.170 g, 69%) in ratio 7:1. The mixture **28** and **28a** was used without any further purification for the following reaction.

Selected data: ^{1}H NMR (400 MHz, C_6D_6): δ 4.45 (d, J_{NH-5} = 8.0 Hz, 1H, NH, **28**), 3.11-3.07 (A part of an AB system, J_{AB} = 13.2 Hz, 1H, H_{1a}, **28a**), 2.70-2.67 (A part of an AB system, J_{AB} = 12.8 Hz, 1H, H_{1a}, **28**), 2.65 (s, 3H, C*H*$_3$C=), 2.58-2.55 (B part of an AB system, J_{BA} = 13.2 Hz, 1H, H_{1b}, **28a**), 2.39 (dd, J_{3a-3b} = 12.8 Hz, J_{3a-4} = 4.4 Hz, 1H, H_{3a}, **28**), 2.33-2.30 (B part of an AB system, J_{BA} = 12.8 Hz, 1H, H_{1b}, **28**), 2.19-2.14 (A part of an ABX system, J_{AB} = 13.6 Hz, J_{AX} = 6.0 Hz, 1H, H_{3a}, **28a**), 2.06-2.00 (B part of an ABX system, J_{BA} = 13.2 Hz, J_{BX} = 9.2 Hz, 1H, H_{3b}, **28a**), 1.56 (s, 3H, NHCOC*H*$_3$, **28**), 1.37 (dd, J_{3b-3a} = 12.8 Hz, J_{3b-4} = 11.2 Hz, 1H, H_{3b}, **28**), 1.07 (s, 9H, (C*H*$_3$)$_3$C, **28**), 1.06 (s, 9H, (C*H*$_3$)$_3$C, **28**), 1.01 (t *J* = 4.0 Hz, CH$_2$C*H*$_3$) 0.85 (s, 9H, (C*H*$_3$)$_3$C, **28**), 0.23 (s, 3H, C*H*$_3$Si, **28**), 0.22 (s, 3H, C*H*$_3$Si, **28**), 0.19 (s, 3H, C*H*$_3$Si, **28**), 0.14 (s, 3H, C*H*$_3$Si, **28**), -0.02 (s, 3H, C*H*$_3$Si, **28**), -0.07 (s, 3H, C*H*$_3$Si, **28**); ^{13}C NMR (100 MHz, C_6D_6): δ 171.4 (Cq), 165.0 (Cq), 157.6 (Cq), 98.3 (Cq), 98.2 (Cq), 73.1, 72.4, 68.7, 67.8, 64.8, 60.8, 54.1, 41.8 (C_3), 33.2 (C_1), 26.4 ((*C*H$_3$)$_3$C), 26.24 ((*C*H$_3$)$_3$C), 26.21 ((*C*H$_3$)$_3$C), 25.85 ((*C*H$_3$)$_3$C), 25.80 ((*C*H$_3$)$_3$C), 25.6 ((*C*H$_3$)$_3$C),

22.7 (*C*H_3CONH), 21.7(CH_2*C*H_3), 18.6 (Cq), 18.5 (Cq), 17.9 (Cq), 14.1 (*C*H_3C=), -3.9 (CH_3Si), -4.0 (CH_3Si), -4.1 (CH_3Si), -4.6 (CH_3Si), -5.1 (CH_3Si), -5.3 (CH_3Si); ESI-MS: 764.19 $[M+H]^+$; 786.41 $[M+Na]^+$; 1549.87 $[2M+Na]^+$.

Synthesis of compound 29. To a stirred solution of mixture of **28** and **28a** (0.149 g, 0.195 mmol) in AcOH (3.0 mL), 2.0 mL of H_2O were added. The reaction mixture was warmed at 60°C for 4 h, then the solvent was co-evaporated with toluene under reduced pressure. The crude was purified by flash column chromatography on silica gel (AcOEt/MeOH 10/1) to give **29** (0.065 g, 48% over two steps) as a white glassy solid.

$[\alpha]_D^{25}$: -30.42 (*c* 0.94, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.38-4.22 (m, 3H, H_4, C*H*$_2$$CH_3$), 4.03-4.01 (m, 2H, H_5, H_6), 3.89-3.81 (m, 2H, H_8, H_{9a}), 3.74-3.69 (m, 1H, H_{9b}), 3.65 (ad, *J* = 8.0 Hz, 1H, H_7), 3.09-3.06 (A part of an AB system, J_{AB} = 13.2 Hz, 1H, H_{1a}), 3.03-3.00 (B part of an AB system, J_{BA} = 13.2 Hz, 1H, H_{1b}), 2.49-2.04 (m, 1H, H_{3a}), 2.45 (s, 3H, C*H*$_3$C=), 2.16 (s, 3H, NHCOC*H*$_3$), 1.82 (dd, $J_{3b\text{-}4}$ = 11.2 Hz, $J_{3b\text{-}3a}$ = 13.2 Hz, 1H, H_{3b}), 1.42 (t, *J* = 7.2 Hz, 3H, CH_2C*H*$_3$); ^{13}C NMR (100 MHz, CD_3OD): δ 170.9 (Cq), 162.8 (Cq), 154.0 (Cq), 95.3 (Cq), 92.5 (Cq), 69.2 (C_6 o C_5), 68.2 (C_8), 65.8 (C_7), 63.6 (C_4), 61.0 (C_9), 58.0 (*C*$H_2$$CH_3$), 50.1 ($C_5$ o C_6), 39.0 (C_3), 29.6 (C_1), 18.7 (*C*H_3CONH), 17.4 (*C*H_3C=), 10.5 (CH_2*C*H_3); ESI-MS: 444.27 $[M+Na]^+$.

Synthesis of compound 34. To a stirred solution of **29** (0.045 g, 0.107 mmol) in THF (3.0 mL), 534 uL of 1M solution of LiOH (0.534 mmol) in H_2O were added. The reaction mixture was warmed at 50°C for 14 h then 1M solution of H_3PO_4 was added to reach pH 5. The solvent was co-evaporated with toluene under reduced pressure to give a crude which was suspended in dry MeOH and filtered through a PTFE membrane (pore size 0.20 uM). The filtrate was concentrated to dryness to give 38 mg of **34** (88%) as white glassy solid.

$[\alpha]_D^{25}$: -28.25 (*c* 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.29-4.23 (m, 1H, H_4), 4.01-3.90 (m, 3H, H_5, H_6, H_8,), 3.88-3.85 (A part of an ABX system, J_{AB} = 11.6 Hz, J_{AX} = 3.2 Hz, 2H, H_{9a}), 3.59-3.55 (B part of an ABX system, J_{BA} = 11.2 Hz, J_{BX} = 5.6 Hz, 1H, H_{9b}), 3.63 (dd, *J* = 8.4 Hz, *J* = 0.8 Hz, 1H, H_7), 3.06-3.02 (A part of an AB system, J_{AB} = 12.8 Hz, 1H, H_{1a}), 3.02-2.99 (B part of an AB system, J_{BA} = 12.8 Hz, 1H, H_{1b}), 2.40 (dd, $J_{3a\text{-}3b}$ = 12.8 Hz, $J_{3a\text{-}4}$ = 4.8 Hz, 1H, H_{3a}), 2.31 (s, 3H, C*H*$_3$C=), 2.16 (s, 3H, C*H*$_3$CONH), 1.80 (dd, $J_{3b\text{-}3a}$ = 13.2 Hz, $J_{3b\text{-}4}$ = 11.6 Hz, 1H, H_{3b}); ^{13}C NMR (50 MHz, CD_3OD): δ 170.9 (Cq), 144.2 (Cq), 103.1 (Cq), 90.4 (Cq), 68.6 (C_6), 67.6 (C_8), 66.1 (C_7), 64.2 (C_4), 61.3 (C_9), 50.2 (C_5), 39.3 (C_3), 30.3 (C_1), 18.6 (*C*H_3CONH), 16.3 (*C*H_3C=); ESI-MS: 416.27 $[M+Na]^+$; 432.18 $[M+K]^+$.

Synthesis of compound 27. To an ice-cooled solution of **20** (0.900 g, 4.05 mmol) in $CHCl_3$ (3 mL), **21** (0.776 g, 3.65 mmol) was added. The reaction mixture was stirred for 1 h at this temperature then concentrated to dryness to give 1.53 g of crude **27** as mixture of keto-enol tautomers which was used without any further purification for the following reaction.

Selected data:^{1}H NMR (200 MHz, $CDCl_3$): δ 13.9 (s, 1H, OH enol), 7.49-7.90 (m, 2H, PhtN keto + PhtN enol), 7.81-7.76 (m, 2H, PhtN keto), 7.44-7.41 (m, 2H, Ha, Hd keto), 7.32 (at, J = 8.0 Hz, 1H, Hc keto), 7.14-7.08 (m, 1H, Hb keto), 5.5 (s, 1H, PhtNSC*H* keto), 4.23-4.06 (m, 2H, C*H*$_2$CH$_3$ keto + C*H*$_2$CH$_3$ enol), 3.83 (s, 3H, OCH_3 keto), 1.13 (t, J = 7.2 Hz, 3H, CH_2CH_3 keto), 1.12 (t, J = 7.2 Hz, 3H, CH_2CH_3 enol); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.0, 167.5, 166.2, 159.8, 135.8, 134.6, 134.2, 131.9, 129.8, 129.6, 123.9, 123.5, 121.1, 121.0, 112.3, 62.9, 59.4, 55.4, 53.4, 13.6.

Synthesis of compound 32. To a stirred solution of **17** (0.200 g, 0.331 mmol) in pyridine (1.0 mL) a solution of crude **24** (0.159 g, 0.397 mmol) in $CHCl_3$ (1.0 mL) was added. The mixture was warmed at 50°C for 20 h then it was diluted with $CHCl_3$ (30 mL) and washed with a saturated solution of NH_4Cl (1 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/ AcOEt 6/1) to give 254 mg of **32** as impure compound containing phtalimide. The crude **32** was used without any further purification for the following reaction.

^{1}H NMR (400 MHz, C_6D_6): δ 7-18-7.17 (m, 1H, *m*-OMe-C$_6$*H*$_4$), 7.13-7.07 (m, 2H, *m*-OMe-C$_6$*H*$_4$), 6.68-6.65 (m, 1H, *m*-OMe-C$_6$*H*$_4$), 4.51 (d, $J_{NH\text{-}5}$ = 8.8 Hz, 1H, NH), 4.35-4.27 (m, 2H, H_6, H_4), 4.18 (A part of an ABX system, J_{AB} = 10.8 Hz, J_{AX} = 2.8 Hz, 1H, H_{9a}), 4.14-4.06 (m, 2H, H_5, H_7), 3.90-3.75 (m, 5H, OH, H_{9b}, H_8, C*H*$_2$CH$_3$), 3.36 (s, 3H, OC*H*$_3$), 2.86-2.83 (A part of an AB system, J_{AB} = 13.2 Hz, 1H, H_{1a}), 2.66 (dd, $J_{3a\text{-}3b}$ = 13.6 Hz, $J_{3a\text{-}4}$ = 4.8 Hz, 1H, H_{3a}), 2.45-2.42 (B part of an AB system, J_{BA} = 12.8 Hz, 1H, H_{1b}), 1.48 (s, 3H, NHCOC*H*$_3$), 1.46-1.41 (dd, $J_{3b\text{-}3a}$ = 13.2 Hz, $J_{3b\text{-}4}$ = 10.8 Hz, 1H, H_{3b}), 1.01 (s, 9H, (C*H*$_3$)$_3$C), 0.87 (s, 9H, (C*H*$_3$)$_3$C), 0.84 (s, 9H, (C*H*$_3$)$_3$C), 0.70 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.14 (s, 3H, C*H*$_3$Si), 0.11 (s, 3H, C*H*$_3$Si), 0.10 (s, 3H, C*H*$_3$Si), 0.03 (s, 3H, C*H*$_3$Si), 0.02 (s, 3H, C*H*$_3$Si), 0.00 (s, 3H, C*H*$_3$Si); ^{13}C NMR (100 MHz, C_6D_6): δ 171.3 (Cq), 165.0 (Cq), 159.8 (Cq), 156.0 (Cq), 139.0 (Cq), 128.9 (CH, *m*-OMe-*C*$_6$H$_4$), 121.9 (CH, *m*-OMe-*C*$_6$H$_4$), 115.6 (CH, *m*-OMe-*C*$_6$H$_4$), 114.2 (CH, *m*-OMe-*C*$_6$H$_4$), 101.6 (Cq), 99.5 (Cq), 73.1 (C_6), 72.2 (C_7), 69.0 (C_8), 67.7 (C_4), 64.9 (C_9), 60.8 (*C*H$_2$CH$_3$), 55.0 (OCH_3), 54.3 (C_5), 41.0 (C_3), 32.7 (C_1), 26.24 ((*C*H$_3$)$_3$C), 26.21 ((*C*H$_3$)$_3$C), 25.7 ((*C*H$_3$)$_3$C), 22.8 (*C*H$_3$CONH), 18.6 (Cq), 18.3 (Cq), 18.9 (Cq), 13.6 (CH$_2$*C*H$_3$), -4.00 (CH_3Si), -4.04 (CH_3Si), -4.5 (CH_3Si), -5.21 (CH_3Si), -5.29 (CH_3Si); ESI-MS: 878.51 $[M+Na]^+$; 894.41 $[M+K]^+$.

Synthesis of compound 33. To a stirred solution of crude **32** (0.254 g) in CH_2Cl_2 (1.0 mL), AcOH (6.5 mL) and H_2O (1.5 mL) were added. The reaction mixture was warmed at 60°C for 16 h, then the solvent was co-evaporated with toluene under reduced pressure. The crude was purified by flash column chromatography on silica gel (AcOEt/MeOH 10/1) to give **33** (0.101 g, 60% over two step) as a white glassy solid.

$[\alpha]_D^{25}$: +33.10 (*c* 0.435, CH_3OH);^{1}H NMR (400 MHz, CD_3OD): δ 7.45-7.41 (m, 1H, *m*-OMe-C_6H_4), 7.16-7.10 (m, 3H, *m*-OMe-C_6H_4), 4.30 (td, *J* = 11.2 Hz, *J* = 4.8 Hz, 1H, H_4), 4.23 (dd, $J_{6\text{-}5}$ = 10.8 Hz, $J_{6\text{-}7}$ = 1.6 Hz, H_6), 4.13 (q, *J* = 6.4 Hz, 1H, CH_2CH_3), 4.08 (at, *J* = 7.2 Hz, 1H, H_5), 4.01-3.97 (m, 1H, H_8), 3.97 (s, 3H, OCH_3), 3.94-3.91 (A part of an ABX system, J_{AB} = 11.2 Hz, J_{AX} = 3.2 Hz, 1H, H_{9a}), 3.79-3.75 (B part of an ABX system, J_{BA} = 11.2 Hz, J_{BX} = 5.6 Hz, 1H, H_{9b}), 3.74 (dd, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H, H_7), 3.30-3.26 (A part of an AB system, J_{AB} = 13.2 Hz, 1H, H_{1a}), 3.23-3.19 (B part of an AB system, J_{BA} = 13.2 Hz, 1H, H_{1b}), 2.57 (dd, $J_{3a\text{-}3b}$ = 13.2 Hz, $J_{3a\text{-}4}$ = 5.2 Hz, 1H, H_{3a}), 2.19 (s, 3H, $NHCOCH_3$), 1.95 (dd, $J_{3b\text{-}3a}$ = 13.2 Hz, $J_{3b\text{-}4}$ = 11.2 Hz, 1H, H_{3b}), 1.12 (t, *J* = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (50 MHz, CD_3OD): δ 175.2 (Cq), 167.6 (Cq), 160.7 (Cq), 156.0 (Cq), 139.6 (Cq), 129.9 (CH, *m*-OMe-C_6H_4), 122.1 (CH, *m*-OMe-C_6H_4), 115.6 (CH, *m*-OMe-C_6H_4), 115.3 (CH, *m*-OMe-C_6H_4), 102.8 (Cq), 96.7 (Cq), 73.4 (C_6), 72.0 (C_8), 70.0 (C_7), 67.5 (C_4), 65.2 (C_9), 62.3 (CH_2CH_3), 55.8 (OCH_3), 54.2 (C_5), 43.1 (C_3), 33.9 (C_1), 22.6 ($NHCOCH_3$), 13.9 (CH_3C=); ESI-MS: 536.14 $[M+Na]^+$.

Synthesis of compound 26. To an ice-cooled solution of **19** (0.910 g, 4.33 mmol) in $CHCl_3$ (2 mL), **21** (0.830 g, 3.90 mmol) was added. The reaction mixture was stirred for 1 h at this temperature then concentrated to dryness to give 1.09 g of crude **26** which was used without any further purification for the following reaction.

Selected data: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89-7.74 (m, 6H), 7.78-7.09 (m, 2H), 5.48 (s, 1H, CHPhtNS), 4.24-4.08 (m, 2H, CH_2CH_3) , 1.13 (t, *J* = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.6, 168.8, 167.5, 166.1, 134.9, 134.7, 134.2, 132.0, 131.4, 131.2, 124.3, 124.0, 116.4, 115.9, 63.0, 59.3, 13.6.

Synthesis of compound 30. To a stirred solution of **17** (0.200 g, 0.331 mmol) in $CHCl_3$ (1.0 mL), Pyridine (1.0 mL) and crude **23** (0.180 g, 0.463 mmol) were added. The mixture was warmed at 50°C for 22 h then it was diluted with $CHCl_3$ (30 mL) and washed with a saturated solution of NH_4Cl (1 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on silica gel (petroleum ether/AcOEt 8/1)

to give **30** (0.242 g) as impure compound containing phtalimide. The crude **30** was used without any further purification for the following reaction.

^{1}H NMR (400 MHz, C_6D_6): δ 7.47-7.43 (m, 2H, *p*-F-C_6H_4), 6.93-6.89 (m, 2H, *p*-F-C_6H_4), 4.62 (d, J_{NH-5} = 8.0 Hz, 1H, NH), 4.42-4.35 (m, 2H, H_6, H_4), 4.22-4.18 (A part of an ABX system, J_{AB} = 10.8 Hz, J_{AX} = 2.8 Hz, 1H, H_{9a}), 4.11-3.99 (m, 2H, H_5, H_7), 3.93-3.77 (m, 5H, H_8, H_{9b}, O*H*, C*H*$_2$CH$_3$), 2.82-2.79 (A part of an AB system, J_{AB} = 12.8 Hz, 1H, H_{1a}), 2.58 (dd, J_{3a-3b} = 13.6 Hz, J_{3a-4} = 4.8 Hz, 1H, H_{3a}), 2.47-2.44 (B part of an AB system, J_{BA} = 12.8 Hz, 1H, H_{1b}), 1.53 (s, 3H, C*H*$_3$CONH), 1.49-1.43 (m, 1H, H_{3b}), 0.91 (s, 9H, (C*H*$_3$)$_3$C), 0.89 (s, 9H, (C*H*$_3$)$_3$C), 0.88 (s, 9H, (C*H*$_3$)$_3$C), 0.74 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 0.17 (s, 6H, C*H*$_3$Si), 0.14 (s, 6H, C*H*$_3$Si), 0.13(s, 6H, C*H*$_3$Si); ^{13}C NMR (100 MHz, C_6D_6): δ 171.2 (Cq), 164.9 (Cq), 163.66 (d, *J* = 248.0 Hz, Cq, *p*-F-C_6H_4), 155.1 (Cq), 133.65 (d, *J* = 3.0 Hz, Cq, *p*-F-C_6H_4), 131.41 (d, *J* = 7.6 Hz, CH, *p*-F-C_6H_4), 115.01 (d, *J* = 22.1 Hz, CH, *p*-F-C_6H_4), 102.0 (Cq), 99.4 (Cq), 72.9 (C_6), 72.3 (C_7), 69.5 (C_8), 67.3 (C_4), 65.1 (C_9), 60.9 (*C*H$_2$CH$_3$), 54.7 (C_5), 41.2 (C_3), 33.8 (C_1), 26.1 ((*C*H$_3$)$_3$C), 26.0 ((*C*H$_3$)$_3$C), 25.8 ((*C*H$_3$)$_3$C), 25.7 ((*C*H$_3$)$_3$C), 22.8 (*C*H$_3$CONH), 18.5 (Cq), 18.2 (Cq), 18.1 (Cq), 13.7 (CH$_2$*C*H$_3$), -3.4 (CH$_3$Si), -4.03 (CH$_3$Si), -4.09 (CH$_3$Si), -4.1 (CH$_3$Si), -4.5 (CH$_3$Si), -5.2 (CH$_3$Si); ESI-MS: 866.51 [M+Na]$^+$.

Synthesis of compound 31. To a stirred solution of **30** (0.242 g, 0.286 mmol) in CH_2Cl_2 (1.0 mL), AcOH (5.7 mL) and H_2O (1.4 mL) were added. The reaction mixture was warmed at 60°C for 24 h, then the solvent was co-evaporated with toluene under reduced pressure. The crude was purified by flash column chromatography on silica gel (AcOEt/MeOH 10/1) to give **31** (0.101 g, 61% over two step) as a white glassy solid.

$[\alpha]_D^{25}$: +23.03 (*c* 0.66, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 7.44-7.40 (m, 2H, *p*-F-C_6H_4), 7.10-7.04 (m, 2H, *p*-F-C_6H_4), 4.13 (td, J = 11.2 Hz, J = 5.2 Hz, 1H, H_4), 4.06 (dd, J_{6-5} = 10.4 Hz, J_{6-7} = 1.2 Hz, 1H, H_6), 3.96 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 3.89 (at, *J* = 10.4 Hz, 1H, H_5), 3.82-3.77 (m, 1H, H_8), 3.76-3.72 (A part of an ABX system, J_{AB} = 11.2 Hz, J_{AX} = 3.2 Hz, 1H, H_{9a}), 3.61-3.54 (m, 2H, H_{9b}, H_7), 3.12-3.08 (A part of an AB system, J_{AB} = 13.6 Hz, 1H, H_{1a}), 2.40-2.35 (dd, J_{3a-3b} = 13.2 Hz, J_{3a-4} = 5.2 Hz, 1H, H_{3a}), 2.02 (s, 3H, C*H*$_3$CONH), 1.77 (dd, J_{3b-3a} = 12.8 Hz, J_{3b-4} = 11.2 Hz, 1H, H3b), 0.98 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (50 MHz, CD_3OD): δ 175.1 (Cq), 167.4 (Cq), 164.54 (d, *J* = 245.8 Hz, Cq, *p*-F-C_6H_4), 155.4 (Cq), 134.75 (d, *J* = 3.0 Hz, Cq, *p*-F-C_6H_4), 132.06 (d, *J* = 8.3 Hz, CH, *p*-F-C_6H_4), 115.67 (d, *J* = 22.0 Hz, CH, *p*-F-C_6H_4), 103.1 (Cq), 96.8 (Cq), 73.3 (C_6), 72.0 (C_8), 70.0 (C_7), 67.5 (C_4), 65.1 (C_9), 62.3 (*C*H$_2$CH$_3$), 54.2 (C_5), 43.0 (C_3), 33.9 (C_1), 22.6 (*C*H$_3$CONH), 13.9 (CH$_2$*C*H$_3$); ESI-MS: 524.15 [M+Na]$^+$; 1024.81 [2M+Na]$^+$.