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Experimental procedures for the synthesis of 3-O-benzyl-α,β-D-xylopyranose (15) from diacetone-D-glucose and analytical data

![Scheme S1. Synthesis of 3-O-benzyl-α-D-xylopyranose 15.](image)

(a) BnBr, NaH, DMF, r.t., 4 h, 99%; (b) AcOH, H₂O, 45 °C, 19 h, 85%; (c) 1) NaIO₄, MeOH, H₂O, r.t., 1.5 h; 2) NaBH₄, MeOH, 0 °C, 40 min, 99%; (d) 1M H₂SO₄, THF, 60 °C, 16 h, 98%.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (S1)

To a solution of diacetone-D-glucose (20.0 g, 76.84 mmol) in dry DMF (240 mL) at 0 °C was added portionwise NaH (2.5 eq., 7.80 g, 195.02 mmol, 60% on mineral oil) and the reaction mixture was stirred at room temperature for 1 h. BnBr (1.5 eq., 13.8 mL, 115.36 mmol) was added and the mixture was kept stirring at room temperature for 4 h. For quenching, MeOH (30 mL) was slowly added. The solvent was then evaporated under reduced pressure. The residue was diluted with Et₂O (150 mL) and water (100 mL), the organic layer was separated and the aqueous layer was extracted with Et₂O (2×150 mL). The combined organic layers were washed successively with sat. aqueous NaHCO₃ and water, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 5:95 to 20:80) to afford S1 (26.55 g, 99%) as a yellow oil. The analytical data of S1 are in accordance with literature data.¹ ¹H-NMR (CDCl₃, 300 MHz) δ 1.31 (s, 3H; CH₃), 1.38 (s, 3H; CH₃), 1.43 (s, 3H; CH₃), 1.49 (s, 3H; CH₃), 4.00 (dd, J = 8.7, 5.9 Hz, 1H; H₆-β), 4.02 (d, J = 2.9 Hz, 1H; H-3), 4.12 (dd, J = 8.7, 6.2 Hz, 1H; H₆-β), 4.15 (dd, J = 7.7, 3.1 Hz, 1H; H-4), 4.37 (ddd, J = 7.7, 6.2, 5.9 Hz, 1H; H-5), 4.59 (d, J = 3.7 Hz, 1H; H-β), 4.63 (d, J = 11.9 Hz, 1H; OCH₂Ph), 4.69 (d, J = 11.9 Hz, 1H; OCH₂Ph), 5.90 (d, J = 3.7 Hz, 1H; H-1), 7.27-7.35 (m, 5H; H₆Ar). ¹³C-NMR (CDCl₃, 100 MHz) δ 25.6, 26.4, 26.9, 27.0 (4×CH₃), 67.5 (C-6), 72.5 (OCH₂Ph), 72.7 (C-5), 81.5 (C-4), 81.9 (C-3), 82.8 (C-2), 105.4 (C-1), 109.1 (C-7), 111.9 (C-8), 127.8, 128.0, 128.5 (5×CH₆Ar), 137.8 (C₆Ar).
3-0-Benzyl-1,2-0-isopropylidene-α-D-glucofuranose (S2)

Compound S1 (13.46 g, 38.41 mmol) was dissolved in a mixture of AcOH and water (1:1, 40 mL) and the solution was heated at 45 °C for 19 h. The solvent was removed under reduced pressure and the residue was dissolved in AcOEt and washed with sat. aqueous NaHCO₃ until neutral. The aqueous layers were extracted with AcOEt and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 40:60 to 60:40) to afford S2 (10.18 g, 85%) as a colorless oil. The analytical data of S2 are in accordance with literature data.

1H-NMR (CDCl₃, 300 MHz) δ 1.32 (s, 3H; CH₃), 1.49 (s, 3H; CH₃), 2.12 (dd, J = 6.5, 5.7 Hz, 1H; OH), 2.52 (d, J = 6.2 Hz, 1H; OH), 3.69 (ddd, J = 11.5, 5.7, 5.6 Hz, 1H; H₆-6), 3.81 (ddd, J = 11.5, 6.5, 3.4 Hz, 1H; H₈-8), 4.03 (dd, J = 7.4, 6.0, 5.6, 3.4 Hz, 1H; H-5), 4.10 (d, J = 3.3 Hz, 1H; H-3), 4.13 (dd, J = 7.4, 3.3 Hz, 1H; H-4), 4.54 (d, J = 11.9 Hz, 1H; OCH₂Ph), 4.63 (d, J = 3.7 Hz, 1H; H-2), 4.74 (d, J = 11.9 Hz, 1H; OCH₂Ph), 5.94 (d, J = 3.7 Hz, 1H; H-1), 7.28-7.41 (m, 5H; H Ar). 13C-NMR (CDCl₃, 100 MHz) δ 26.4, 26.9 (2×CH₃), 64.6 (C-6), 69.5 (C-5), 72.3 (OCH₂Ph), 80.2 (C-4), 82.2 (C-3), 82.3 (C-2), 105.3 (C-1), 112.0 (C-7), 128.0, 128.4, 128.9 (5×CH Ar), 137.3 (CAr).

3-0-Benzyl-1,2-0-isopropylidene-α-D-xylofuranose (S3)

Compound S2 (16.81 g, 54.17 mmol) was dissolved in a mixture of H₂O and MeOH (1:1, 230 mL) then NaIO₄ (1.2 eq., 13.44 g, 62.83 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 1 h 30, then ethylene glycol (1 eq., 3 mL, 53.80 mmol) was added, followed by additional stirring for 20 min. The mixture was diluted with cold MeOH (300 mL), the resulting white precipitate was filtered off and the filtrate was concentrated under reduced pressure. This step was repeated once. The residue was dissolved in CH₂Cl₂ and washed with sat. aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to afford S3 (15.15 g, 99%) as a colorless oil. The analytical data of S3 are in accordance with literature data.

1H-NMR (CDCl₃, 400 MHz) δ 1.33 (s, 3H; CH₃), 1.49 (s, 3H; CH₃), 2.08 (br s, 1H; OH), 3.86 (dd, J = 12.0, 4.7 Hz, 1H; H₆-6), 3.95 (dd, J = 12.0, 5.2 Hz, 1H; H₈-8), 4.02 (d, J = 3.5 Hz, 1H; H-3), 4.28 (ddd, J = 5.2, 4.7, 3.5 Hz, 1H; H-4), 4.49 (d, J = 11.9 Hz, 1H; OCH₂Ph), 4.64 (d, J = 3.9 Hz, 1H; H-2), 4.72 (d, J = 11.9 Hz, 1H; OCH₂Ph), 5.99 (d, J = 3.8 Hz, 1H; H-1), 7.29-7.39
(m, 5H; H$_{Ar}$). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 26.5, 27.0 (2×CH$_3$), 61.2 (C-5), 72.1 (OCH$_2$Ph), 80.2 (C-4), 82.6 (C-2), 82.9 (C-3), 105.2 (C-1), 111.9 (C(CH$_3$)$_2$), 127.9, 128.4, 128.8 (5×CH$_{Ar}$), 137.2 (C$_{Ar}$).

3-O-Benzyl-α,β-D-xylopyranose (15)

![Structure of 3-O-Benzyl-α,β-D-xylopyranose (15)](image)

A solution of S3 (1.34 g, 4.78 mmol) in 1M H$_2$SO$_4$ aqueous solution (2.1 eq., 10 mL, 10 mmol) and THF (16 mL) was heated at 60 °C for 16 h. The reaction mixture was neutralized by addition of 30% NH$_4$OH aqueous solution and the solvents were evaporated under reduced pressure. The residue was dissolved in MeOH and the insoluble material was filtered and washed with MeOH. The filtrate was concentrated under reduced pressure to afford 15 (1.13 g, 98%) as an anomic mixture (α/β 1:2.5) and as a white solid. $^1$H-NMR (CD$_3$OD, 300 MHz) $\delta$ 3.19-3.37 (m, 10H; H$_{\beta}$-2, H$_{\beta}$-3, H$_{\beta}$-4, H$_{\beta}$A-5), 3.49 (dd, $J = 8.6, 3.4$ Hz, 1H; H$_{\alpha}$-2), 3.52-3.77 (m, 6.5H; H$_{\alpha}$-3, H$_{\alpha}$-4, H$_{\beta}$-4, C(H$_\alpha$)$_2$-5), 3.84 (dd, $J = 11.4, 5.5$ Hz, 2.5H; H$_{\beta}$B-5), 4.44 (d, $J = 7.1$ Hz, 2.5H; H$_{\beta}$-1), 4.88-4.91 (m, 7H; OC(H$_{\alpha}$)$_2$Ph, OC(H$_{\beta}$)$_2$Ph), 5.03 (d, $J = 3.5$ Hz, 1H; H$_{\alpha}$-1), 7.22-7.48 (m, 17.5H; H$_{Ar}$). $^{13}$C-NMR (CD$_3$OD, 100 MHz) $\delta$ 63.1 (C$_{\beta}$-5), 67.1 (C$_{\alpha}$-5), 71.18, 71.24 (C$_{\alpha}$-4, C$_{\beta}$-4), 73.7 (C$_{\beta}$-2), 75.8, 75.9 (OC(H$_{\alpha}$)$_2$Ph, OC(H$_{\beta}$)$_2$Ph), 76.1 (C$_{\alpha}$-2), 83.2 (C$_{\alpha}$-3), 86.1 (C$_{\beta}$-3), 94.3 (C$_{\alpha}$-1), 99.0 (C$_{\beta}$-1), 128.5, 129.1, 129.2 (CH$_{Ar}$), 140.4, 140.5 (C$_{Ar}$). IR (neat) 3340 cm$^{-1}$ (O-H). HRMS (ESI) m/z calculated for C$_{12}$H$_{16}$O$_5$Na : 263.089 [M+Na]$^+$; found 263.088.
Experimental procedures for the synthesis of arms and linkers and analytical data

Scheme S2. Synthesis of all arms and linkers for the synthesis of heterodimers, dimers and monomers.

(a) NaN₃, DMF, 50 °C, 18 h, 93%; (b) TsCl, Et₃N, CH₂Cl₂, r.t., 48 h, 86%; (c) NaN₃, DMF, 60 °C, 17 h, 94%; (d) TsCl, Et₃N, CH₂Cl₂, r.t., 43 h, 72%; (e) TsCl, Et₃N, DMAP, CH₂Cl₂, r.t., 18 h, 87%; (f) 27, NaH, DMF, 0 °C to r.t., 2 h, 20%; (g) NaN₃, DMF, 100 °C (µw), 45 min, 91%; (h) TsCl, KOH, CH₂Cl₂, 0 °C, 4 h, 95%; (i) 27, NaH, DMF, r.t., 6 h, 38%; (j) TsCl, KOH, CH₂Cl₂, 0 °C, 4 h, 96%; (k) 28, NaH, DMF, r.t., 22 h, 39%; (l) TsCl, NaOH, THF, 0 °C, 3.5 h, 86%; (m) NaN₃, EtOH, 70 °C, 18 h, 61%; (n) MeI, NaH, THF, r.t., 18 h, 47%.

1-Azidononane (26)

A mixture of 1-bromononane (540 mg, 2.607 mmol) and NaN₃ (1.1 eq., 190 mg, 2.923 mmol) in dry DMF (3 mL) was heated under microwave irradiation at 100 °C for 15 min. Additional NaN₃ (0.9 eq., 152 mg, 2.34 mmol) was added and the reaction mixture was heated under microwave irradiation at 100 °C for another 30 min. The reaction mixture was diluted with Et₂O and washed with water (3×) and brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (CH₂Cl₂) to afford 26 (401 mg, 91%) as a colorless oil. The analytical data of 26 are in accordance with literature data.⁴ ¹H-NMR (CDCl₃, 400 MHz) δ 0.88 (t, J = 7.0 Hz,
3H; CH$_3$-9), 1.24-1.40 (m, 12H; CH$_2$-3, CH$_2$-4, CH$_2$-5, CH$_2$-6, CH$_2$-7, CH$_2$-8), 1.60 (tt, $J = 7.3$, 7.0 Hz, 2H; CH$_2$-2), 3.25 (t, $J = 7.0$ Hz, 2H; CH$_2$-1).

**6-Azidohexan-1-ol (27)**

![Structural formula of 6-Azidohexan-1-ol (27)]

A mixture of 6-chlorohexan-1-ol (2.0 g, 14.64 mmol) and NaN$_3$ (1.5 eq., 1.43 g, 22.00 mmol) in dry DMF (30 mL) was stirred at 50 °C for 18 h. The solvent was evaporated under reduced pressure and the residue was partitioned between Et$_2$O and water. The organic layer was separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water (3×), dried over MgSO$_4$, filtered and concentrated under reduced pressure to afford 27 (1.95 g, 93%) as a colorless oil. The analytical data of 27 are in accordance with literature data.$^5$ $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 1.34-1.44 (m, 4H; CH$_2$-3, CH$_2$-4), 1.53-1.65 (m, 5H; CH$_2$-2, CH$_2$-5, OH), 3.25 (t, $J = 6.9$ Hz, 2H; CH$_2$-6), 3.62 (t, $J = 6.6$ Hz, 2H; CH$_2$-1).

**10-Azidodecan-1-ol (28)**

![Structural formula of 10-Azidodecan-1-ol (28)]

A mixture of 10-bromodecanol (1.28 g, 5.40 mmol) and NaN$_3$ (2.5 eq., 0.875 g, 13.46 mmol) in dry DMF (13 mL) was stirred at 60 °C for 17 h. The solvent was evaporated under reduced pressure and the residue was partitioned between Et$_2$O and water. The organic layer was separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water (3×), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether 10:90) to afford 28 (1.01 g, 94%) as a pale yellow oil. The analytical data of 28 are in accordance with literature data.$^6$ $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.26-1.39 (m, 12H; CH$_2$-3, CH$_2$-4, CH$_2$-5, CH$_2$-6, CH$_2$-7, CH$_2$-8), 1.44 (br s, 1H; OH), 1.52-1.62 (m, 4H; CH$_2$-2, CH$_2$-9), 3.24 (t, $J = 6.9$ Hz, 2H; CH$_2$-10), 3.62 (t, $J = 6.6$ Hz, 2H; CH$_2$-1).

**6-Azido-1-(4-methylbenzenesulfonate)hexan-1-ol (29)**

![Structural formula of 6-Azido-1-(4-methylbenzenesulfonate)hexan-1-ol (29)]

To a solution of 27 (208 mg, 1.453 mmol) and dry Et$_3$N (1.2 eq., 0.24 mL, 1.727 mmol) in dry CH$_2$Cl$_2$ (10 mL) at 0 °C was added TsCl (1.2 eq., 333 mg, 1.747 mmol) and the reaction mixture was stirred at room temperature for 25 h. Additional dry Et$_3$N (0.5 eq., 0.1 mL, 0.719 mmol) and TsCl (0.5 eq., 139 mg, 0.729 mmol) were added and the reaction mixture was stirred at room temperature for another 23 h. The reaction mixture was washed with water and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude
residue was purified by flash column chromatography (AcOEt/Petroleum ether, 5:95) to afford 29 (372 mg, 86%) as a colorless oil. The analytical data of 29 are in accordance with literature data.\(^7\) \(^{1}\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta 1.28-1.38\) (m, 4H; CH\(_2\)-3, CH\(_2\)-4), 1.51-1.58 (m, 2H; CH\(_2\)-5), 1.62-1.68 (m, 2H; CH\(_2\)-2), 2.45 (s, 3H; CH\(_3\)-9), 3.23 (t, \(J = 6.9 \text{ Hz}\), 2H; CH\(_2\)-6), 4.02 (t, \(J = 6.4 \text{ Hz}\), 2H; CH\(_2\)-1), 7.35 (d, \(J = 8.2 \text{ Hz}\), 2H; H-8), 7.79 (d, \(J = 8.2 \text{ Hz}\), 2H; H-7).

10-Azido-1-(4-methylbenzenesulfonate)decan-1-ol (30)

To a solution of 28 (177 mg, 0.888 mmol) and dry Et\(_3\)N (1.7 eq., 0.21 mL, 1.511 mmol) in dry CH\(_2\)Cl\(_2\) (7 mL) at 0 °C was added TsCl (1.7 eq., 289 mg, 1.516 mmol) and the reaction mixture was stirred at room temperature for 18 h. Additional dry Et\(_3\)N (0.5 eq., 0.06 mL, 0.432 mmol) and TsCl (0.5 eq., 85 mg, 0.446 mmol) were added and the reaction mixture was stirred at room temperature for another 25 h. The reaction mixture was washed with water and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2×). The combined organic layers were washed with brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 2:98) to afford 30 (225 mg, 72%) as a colorless oil. The analytical data of 30 are in accordance with literature data.\(^8\) \(^{1}\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta 1.18-1.39\) (m, 12H; CH\(_2\)-3, CH\(_2\)-4, CH\(_2\)-5, CH\(_2\)-6, CH\(_2\)-7, CH\(_2\)-8), 1.55-1.67 (m, 4H; CH\(_2\)-2, CH\(_2\)-9), 2.45 (s, 3H; CH\(_3\)-13), 3.25 (t, \(J = 7.0 \text{ Hz}\), 2H; CH\(_2\)-10), 4.02 (t, \(J = 6.5 \text{ Hz}\), 2H; CH\(_2\)-1), 7.34 (d, \(J = 8.2 \text{ Hz}\), 2H; H-12), 7.79 (d, \(J = 8.2 \text{ Hz}\), 2H; H-11).

1,6-Bis(4-methylbenzenesulfonate)hexan-1,6-diol (S4)

Hexan-1,6-diol (2.0 g, 16.92 mmol), DMAP (0.01 eq., 17 mg, 0.1392 mmol) and dry Et\(_3\)N (5 eq., 11.8 mL, 84.89 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (34 mL). A solution of TsCl (2.5 eq., 8.07 g, 42.33 mmol) in dry CH\(_2\)Cl\(_2\) (34 mL) was then slowly added over a period of 30 min under vigorously stirring. The reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (CH\(_2\)Cl\(_2\)/Petroleum ether, 40:60 to 100:0) to afford S4 (6.27 g, 87%) as a white solid. The analytical data of S4 are in accordance with literature data.\(^9\) \(^{1}\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta 1.23-1.30\) (m, 4H; CH\(_2\)-3, CH\(_2\)-3’), 1.55-1.63 (m, 4H; CH\(_2\)-2, CH\(_2\)-2’), 2.45 (s, 6H; CH\(_3\)-6, CH\(_3\)-6’), 3.98 (t, \(J = 6.4 \text{ Hz}\), 4H; CH\(_2\)-1, CH\(_2\)-1’), 7.34 (d, \(J = 8.2 \text{ Hz}\), 4H; H-5, H-5’), 7.77 (d, \(J = 8.2 \text{ Hz}\), 4H; H-4, H-4’).
To a stirred solution of 27 (250 mg, 1.746 mmol) in dry DMF (20 mL) at 0 °C was added NaH (4 eq., 279 mg, 6.976 mmol, 60% on mineral oil) portionwise under argon atmosphere. After 30 min stirring at 0 °C, a solution of S4 (2 eq., 1.49 g, 3.493 mmol) in dry DMF (10 mL) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 1 h 30. For quenching, water was added and the solvents were evaporated under reduced pressure. The residue was diluted with AcOEt and washed with water. The aqueous layer was extracted with AcOEt (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 10:90) to afford 31 (138 mg, 20%) as a colorless oil.

**1H-NMR (CDCl₃, 400 MHz) δ** 1.20-1.38 (m, 8H; CH₂-3, CH₂-4, CH₂-9, CH₂-10), 1.43-1.63 (m, 8H; CH₂-2, CH₂-5, CH₂-8, CH₂-11), 2.40 (s, 3H; CH₃-15), 3.21 (t, J = 6.9 Hz, 2H; CH₂-1), 3.30 (t, J = 6.5 Hz, 2H; CH₂-6 or CH₂-7), 3.33 (t, J = 6.5 Hz, 2H; CH₂-6 or CH₂-7), 3.97 (t, J = 6.5 Hz, 2H; CH₂-12), 7.30 (d, J = 8.2 Hz, 2H; H-14), 7.73 (d, J = 8.2 Hz, 2H; H-13).

**13C-NMR (CDCl₃, 100 MHz) δ** 21.7 (C-15), 25.3, 25.7, 25.9, 26.7 (C-3, C-4, C-9, C-10), 28.9 (C-2, C-11), 29.6, 29.7 (C-5, C-8), 51.5 (C-1), 70.66 (C-12), 70.71, 70.77 (C-6, C-7), 127.9, 129.9 (4×CH₃Ar), 133.3 (SO₂-C₆H₅), 144.7 (C₆H₅-CH₃). IR (neat) 2093 (N₃), 1359 (SO₂), 1175 cm⁻¹ (SO₂). HRMS (ESI) m/z calculated for C₁₉H₃₁N₃O₄SNa : 420.193 [M+Na]⁺; found 420.193.

**Triethylene glycol di(4-methylbenzenesulfonate) (S5)**

To a solution of triethylene glycol (2.0 g, 13.32 mmol) in CH₂Cl₂ (15 mL) was added TsCl (2 eq., 5.08 g, 26.65 mmol) and the mixture was cooled to 0 °C. KOH (8 eq., 5.98 g, 106.58 mmol) was carefully added portionwise maintaining the temperature below 5 °C and the reaction mixture was stirred at 0 °C for 4 h. A mixture of ice and water was added, followed by CH₂Cl₂. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2×). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford S5 (5.81 g, 95%) as a white solid. The analytical data of S5 are in accordance with literature data. **1H-NMR (CDCl₃, 400 MHz) δ** 2.44 (s, 6H; CH₃-6, CH₃-6′), 3.52 (s, 4H; CH₂-3, CH₂-3′), 3.63-3.66 (m, 4H; CH₂-2, CH₂-2′), 4.12-4.14 (m, 4H; CH₂-1, CH₂-1′), 7.33 (d, J = 8.2 Hz, 4H; H-5, H-5′), 7.78 (d, J = 8.2 Hz, 4H; H-4, H-4′).
Compound 32

To a stirred solution of 27 (250 mg, 1.746 mmol) and S5 (2 eq., 1.60 g, 3.489 mmol) in dry DMF (30 mL) was added NaH (4 eq., 279 mg, 6.976 mmol, 60% on mineral oil) portionwise under argon atmosphere. The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure and the residue was diluted with CH$_2$Cl$_2$ and washed with water. The aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 30:70) to afford 32 (287 mg, 38%) as a colorless oil. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.31-1.40 (m, 4H; CH$_2$-3, CH$_2$-4), 1.53-1.61 (m, 4H; CH$_2$-2, CH$_2$-5), 2.42 (s, 3H; CH$_3$-15), 3.23 (t, $J = 7.0$ Hz, 2H; CH$_2$-1), 3.42 (t, $J = 6.7$ Hz, 2H; CH$_2$-6), 3.52-3.59 (m, 8H; CH$_2$-7, CH$_2$-8, CH$_2$-9, CH$_2$-10), 3.66 (t, $J = 4.8$ Hz, 2H; CH$_2$-11), 4.13 (t, $J = 4.8$ Hz, 2H; CH$_2$-12), 7.32 (d, $J = 8.2$ Hz, 2H; H-14), 7.77 (d, $J = 8.2$ Hz, 2H; H-13). $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 21.7 (C-15), 25.7, 26.6, 28.8, 29.5 (C-2, C-3, C-4, C-5), 51.4 (C-1), 68.7 (C-11), 69.3 (C-12), 70.1, 70.6, 70.7, 70.8 (C-7, C-8, C-9, C-10), 71.3 (C-6), 128.0, 129.9 (4×CH$_3$Ar), 133.1 (SO$_2$-C$_6$H$_4$), 144.8 (C$_6$H$_5$-CH$_3$). IR (neat) 2094 (N$_3$), 1354 (SO$_2$), 1176 cm$^{-1}$ (SO$_2$). HRMS (ESI) m/z calculated for C$_{19}$H$_{31}$N$_3$O$_6$SNa: 452.183 [M+Na]$^+$; found 452.185.

Tetraethylene glycol di(4-methylbenzenesulfonate) (S6)

To a solution of tetraethylene glycol (2.0 g, 10.30 mmol) in CH$_2$Cl$_2$ (10 mL) was added TsCl (2 eq., 3.92 g, 20.56 mmol) and the mixture was cooled to 0 °C. KOH (8 eq., 4.62 g, 82.34 mmol) was carefully added portionwise maintaining the temperature below 5 °C and the reaction mixture was stirred at 0 °C for 4 h. A mixture of ice and water was added, followed by CH$_2$Cl$_2$. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford S6 (4.99 g, 96%) as a colorless oil. The analytical data of S6 are in accordance with literature data.$^{11}$ $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.43 (s, 6H; CH$_3$-7, CH$_3$-7’), 3.52-3.57 (m, 8H; CH$_2$-3, CH$_2$-3’, CH$_2$-4, CH$_2$-4’), 3.65-3.67 (m, 4H; CH$_2$-2, CH$_2$-2’), 4.12-4.15 (m, 4H; CH$_2$-1, CH$_2$-1’), 7.32 (d, $J = 8.2$ Hz, 4H; H-6, H-6’), 7.77 (d, $J = 8.2$ Hz, 4H; H-5, H-5’).
Compound 33

To a stirred solution of 28 (367 mg, 1.842 mmol) and S6 (2 eq., 1.83 g, 3.641 mmol) in dry DMF (30 mL) was added NaH (4 eq., 295 mg, 7.376 mmol, 60% on mineral oil) portionwise under argon atmosphere. The reaction mixture was stirred at room temperature for 22 h. The solvent was evaporated under reduced pressure and the residue was diluted with CH₂Cl₂ and washed with water. The aqueous layer was extracted with CH₂Cl₂ (2×). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 40:60) to afford 33 (379 mg, 39%) as a colorless oil.

1H-NMR (CDCl₃, 400 MHz) δ 1.24-1.38 (m, 12H; CH₂-3, CH₂-4, CH₂-5, CH₂-6, CH₂-7, CH₂-8), 1.52-1.61 (m, 4H; CH₂-2, CH₂-9), 2.43 (s, 3H; CH₃-21), 3.24 (t, J = 7.0 Hz, 2H; CH₂-1), 3.42 (t, J = 6.8 Hz, 2H; CH₂-10), 3.54-3.64 (m, 12H; CH₂-11, CH₂-12, CH₂-13, CH₂-14, CH₂-15, CH₂-16), 3.67 (t, J = 4.8 Hz, 2H; CH₂-17), 4.14 (t, J = 4.8 Hz, 2H; CH₂-18), 7.33 (d, J = 8.2 Hz, 2H; H-20), 7.78 (d, J = 8.2 Hz, 2H; H-19). 13C-NMR (CDCl₃, 100 MHz) δ 21.7 (C-21), 26.2, 26.8, 28.9, 29.2, 29.52, 29.56, 29.7 (C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9), 51.6 (C-1), 68.8 (C-17), 69.3 (C-18), 70.1, 70.6, 70.65, 70.70, 70.8 (C-11, C-12, C-13, C-14, C-15, C-16), 71.6 (C-10), 128.1, 129.9 (4×CHAr), 133.0 (SO₂-C₆Ar), 144.9 (C₆Ar-CH₃). IR (neat) 2094 (N₃), 1355 (SO₂), 1176 cm⁻¹ (SO₂). HRMS (ESI) m/z calculated for C₂₅H₄₃N₃O₇SNa : 552.271 [M+Na]⁺; found 552.268.

Tetraethylene glycol mono(4-methylbenzenesulfonate) (S7)

NaOH (1.5 eq., 29 mg, 0.725 mmol) was added to a solution of tetraethylene glycol (10 eq., 1.0 g, 4.802 mmol) in THF (0.3 mL) at 0 °C, followed by slow addition of a solution of TsCl (92 mg, 0.483 mmol) in THF (0.9 mL). The reaction mixture was stirred at 0 °C for 3 h 30. The reaction mixture was poured into a mixture of ice and water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3×). The combined organic layers were washed with water (2×), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt/Petroleum ether, 90:10) to afford S7 (144 mg, 86%) as a colorless oil. The analytical data of S7 are in accordance with literature data. ¹H-NMR (CDCl₃, 400 MHz) δ 2.27 (br s, 1H; OH), 2.44 (s, 3H; CH₃-11), 3.58-3.72 (m, 14H; CH₂-1, CH₂-2, CH₂-3, CH₂-4, CH₂-5, CH₂-6, CH₂-7), 4.15-4.17 (m, 2H; CH₂-8), 7.34 (d, J = 8.2 Hz, 2H; H-10), 7.80 (d, J = 8.2 Hz, 2H; H-9).
2-[2-[2-(2-Azidoethoxy)ethoxy]ethoxy]ethanol (S8)

A mixture of S7 (136 mg, 0.390 mmol) and NaN₃ (5 eq., 127 mg, 1.952 mmol) in EtOH (3 mL) was stirred at 70 °C for 18 h. The reaction was quenched by addition of water (2 mL). The solvents were evaporated under reduced pressure and the residue was partitioned between water and AcOEt. The organic layer was separated and the aqueous layer was extracted with AcOEt (3×). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (AcOEt) to afford S8 (52 mg, 61%) as a colorless oil. The analytical data of S8 are in accordance with literature data.¹² ¹H-NMR (CDCl₃, 400 MHz) δ 2.68 (br s, 1H; OH), 3.36 (t, J = 5.1 Hz, 2H; CH₂-8), 3.56-3.58 (m, 2H; CH₂-7), 3.62-3.65 (m, 10H; CH₂-2, CH₂-3, CH₂-4, CH₂-5, CH₂-6), 3.67-3.70 (m, 2H; CH₂-1).

1-Azido-2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethane (34)

To a stirred suspension of NaH (2 eq., 37 mg, 0.925 mmol, 60% on mineral oil) in dry THF (3.6 mL) was added a solution of S8 (100 mg, 0.456 mmol) in dry THF (1.2 mL). After 30 min stirring at room temperature, MeI (10.6 eq., 0.30 mL, 4.819 mmol) was added and stirring was prolonged for 18 h. The reaction mixture was diluted with Et₂O and washed with water and brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (CH₂Cl₂/MeOH, 100:0 to 98:2) to afford 34 (50 mg, 47%) as a colorless oil. The analytical data of 34 are in accordance with literature data.¹³ ¹H-NMR (CDCl₃, 400 MHz) δ 3.33-3.37 (m, 5H; CH₂-1, OCH₃), 3.50-3.52 (m, 2H; CH₂-2), 3.60-3.66 (m, 12H; CH₂-3, CH₂-4, CH₂-5, CH₂-6, CH₂-7, CH₂-8).
Fig S1. $^1$H NMR (300 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound 15.
Fig S2. $^1$H NMR (300 MHz, Acetone-$d_6$) and $^{13}$C (100 MHz, Acetone-$d_6$) spectra of compound 16.
Fig S3. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 17.
Fig S4. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 18.
Fig S5. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 19.
Fig S6. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 20.
Fig S7. $^1$H NMR (400 MHz, CDCl₃) and $^{13}$C (100 MHz, CDCl₃) spectra of compound 21.
Fig S8. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 22.
Fig S9. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 23.
Fig S10. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 24.
Fig S11. $^1$H NMR (300 MHz, CDCl$_3$) and $^{13}$C (75.5MHz, CDCl$_3$) spectra of compound 25.
Fig S12. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound (+)-14.
Fig S13. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 31.
Fig S14. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 32.
Fig S15. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 33.
Fig S16. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 35a.
Fig S17. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 35b.
Fig S18. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 35c.
Fig S19. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 35d.
Fig S20. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 35e.
Fig S21. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 36a.
Fig S22. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 36b.
Fig S23. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 36c.
Fig S24. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 36d.
Fig S25. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 36e.
Fig S26. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 37a.
Fig S27. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 37b.
Fig S28. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 37c.
Fig S29. $^1$H NMR (300 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 37d.
Fig S30. $^1$H NMR (300 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 37e.
Fig S31. $^1$H NMR (400 MHz, D$_2$O) and $^{13}$C (75.5 MHz, D$_2$O) spectra of compound 9a.
Fig S32. $^1$H NMR (400 MHz, D$_2$O) and $^{13}$C (100 MHz, D$_2$O) spectra of compound 9b.
Fig S33. $^1$H NMR (400 MHz, D$_2$O) and $^{13}$C (100 MHz, D$_2$O) spectra of compound 9c.
Fig S34. $^1$H NMR (400 MHz, D$_2$O) and $^{13}$C (100 MHz, D$_2$O) spectra of compound 9d.
Fig S35. $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound 9e.
Fig S36. $^1$H NMR (300 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 38.
Fig S37. $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound (+)-10.
Fig S38. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 39.
Fig S39. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 40.
Fig S40. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 41.
Fig S41. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 42a.
Fig S42. $^1$H NMR (300 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 42b.
Fig S43. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 42c.
**Fig S44.** $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound (+)-11a.

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Fig S45. $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound (+)-11b.
Fig S46. $^1$H NMR (400 MHz, CD$_2$OD) and $^{13}$C (100 MHz, CD$_2$OD) spectra of compound (+)-11c.
Fig S47. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (75.5 MHz, CDCl$_3$) spectra of compound 43a.
Fig S48. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 43b.
Fig S49. $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound (-)-12.
Fig S50. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 44.
**Fig S51.** $^1$H NMR (400 MHz, CD$_3$OD) and $^{13}$C (100 MHz, CD$_3$OD) spectra of compound (+)-13.
Fig S52. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 45.
Fig S53. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) spectra of compound 46.
**Biological evaluation**

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<td>96.01 ± 4.92</td>
<td>86.86 ± 2.25*</td>
<td>80.41 ± 1.22*</td>
<td>77.06 ± 1.66*</td>
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<td>93.66 ± 10.38</td>
<td>93.36 ± 2.84</td>
<td>71.43 ± 14.37*</td>
<td>78.34 ± 6.22*</td>
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<td>77.94 ± 3.26</td>
<td>73.01 ± 9.44*</td>
<td>82.17 ± 3.89*</td>
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<td>81.30 ± 4.58*</td>
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<td>66.00 ± 4.29*</td>
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<td>89.79 ± 6.66*</td>
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<td>42.57 ± 13.54</td>
<td>98.93 ± 13.39</td>
<td>91.03 ± 1.30</td>
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**Table S1 Activity towards glycosidases.**

Wild-type fibroblasts were treated for 6 days with selected compounds. Activity is normalized against untreated cells (0.1 % DMSO). Values are the median ± confidence interval of 3 experiments. Statistically significant data (p <0.05) are denoted by an asterisk and are marked in color (yellow: inhibition; green: activation)
Figure S54 GBA1 activity enhancement. Normalized GBA1 activity of human fibroblast cell lines after treatment with compounds at the indicated concentrations, for 6 days. The normalized enzyme activity was calculated by the percentage between treated cells and untreated (0.1% DMSO) cells. Values are the Median ± confidence interval of 3-6 separate experiments performed by triplicates. * Values higher than 100 statistically different from values of fibroblast treated with vehicle (p ≤0.05)
**Figure S55 Synergistic effect evaluation.** Normalised GBA1 activity of human fibroblast bearing the G202R/G202R mutation after treatment with compounds (±)-11c and (±)-13 at the indicated concentrations, for 6 days. The normalised enzyme activity was calculated by the percentage between treated cells and untreated (0.1% DMSO) cells.
Figure S56  Inhibition of imiglucerase by 9a. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S57 Inhibition of imiglucerase by 9b. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S58 Inhibition of imiglucerase by 9c. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S59 Inhibition of imiglucerase by 9d. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S60 Inhibition of imiglucerase by 9e. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S61 Inhibition of imiglucerase by (+)-10. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S62 Inhibition of imiglucerase by (-)-10. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S63 Inhibition of imiglucerase by (+)-11a. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S64 Inhibition of imiglucerase by (+)-11b. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S65 Inhibition of imiglucerase by (+)-11c. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S66 Inhibition of imiglucerase by (+)-13. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
**Figure S67** Inhibition of imiglucerase by (-)-11c. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S68  Inhibition of imiglucerase by (-)-12. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
Figure S69 Inhibition of imiglucerase by (-)-13. Double reciprocal plot of imiglucerase incubated at different concentrations of substrate and compound at pH 5.2 (A) or pH 7.4 (B). Regression lines arise from data obtained in two different experiments with triplicates.
References


