An Accessible Bicyclic Architecture for Synthetic Lectins

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Supporting Information

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1. **General**

All **commercially available compounds** were purchased from Sigma Aldrich Ltd, Acros Organics or Alfa Aesar. Metal catalysts were purchased from Strem Chemicals Inc. Bis(pinacolato) diboron was purchased from Apollo Scientific. N-Acetyl neuraminic acid was purchased Carbosynth Ltd. Gentiobiose was purchased from Megazyme Ltd.

**Solvents** were used as supplied unless otherwise stated. Anhydrous THF, CH$_2$Cl$_2$, CH$_3$CN, Et$_2$O, toluene or hexanes were dried by passing through a modified Grubbs system$^1$ manufactured by Anhydrous Engineering. Anhydrous methanol and Et$_3$N were dried by distillation from CaH$_2$.$^2$

Anhydrous methanol saturated with ammonia was obtained by bubbling ammonia through previously distilled methanol under a nitrogen atmosphere until a constant volume was reached.

$^1$H and $^{13}$C NMR spectra were recorded on Varian 400-MR, Jeol Eclipse (400 MHz), Varian System 500A or Varian VNMRS600 Cryo spectrometers. All spectra were referenced either to their residual internal solvent peak or to TMS and were recorded at 298 K unless otherwise stated.

Electron impact mass spectra, were recorded on a VG Analytical Autospec. Electrospray ionisation mass spectra were recorded on VG Analytical Quattro or Applied Biosystems 4700 spectrometers.

Routine monitoring of reactions was performed by means of TLC using precoated silica gel plates (Merck silica gel 60 F254). Spots were visualised by either UV light (254 or 365 nm), ethanolic solution of phosphomolybdic acid, potassium permanganate, or ninhydrin.

**Flash column chromatography** was performed using silica gel (Fisher brand silica 60 Å particle size 35-70 micron) as the absorbent.

**HPLC purification** was performed using a Waters 600 multi-solvent delivery system and 2998 photodiode array detector. Either an analytical column (Waters Symmetry, C18, 3.5 µm particle size, 4.6 x 75 mm) or a semi-preparative column (Hichrom Kromasil, C18, 5 µm particle size, 21.2 x 250 nm) was used. The chromatogram was recorded at 254 nm detection wavelength as standard and at other wavelengths where stated.

![Image of receptor 8](image_url)

**Tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (10).** Tert-butyl 4-bromobenzylcarbamate\(^3\) (2.18 g, 7.62 mmol) was dissolved in DMF (20 mL) along with bis(pinacolato)diboron (2.12 g, 8.38 mmol) and potassium acetate (2.24 g, 22.85 mmol). This mixture was degassed under vacuum for 15 minutes. A headspace of nitrogen was then applied, and Pd(dpdpf)Cl\(_2\) (312 mg, 382 µmol) was added to give a deep red suspension. This was stirred at 80 °C for 12 hours then cooled to room temperature. The crude reaction mixture was filtered directly through a pad of celite, then diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). After removal of the EtOAc under reduced pressure, the crude material was purified by flash column chromatography (7:3, EtOAc-hexanes) to furnish the product 10 as clear colourless crystals (2.07 g, 82%); \(R_f = 0.22\) (1:4, EtOAc-hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 1.34\) (s, 12H, -C\(_\text{H}_3\)), 1.47 (s, 9 H, -C(C\(_\text{H}_3\)\(_3\))\(_3\)), 4.34 (d, 2H, \(J = 5.6\) Hz, -CH\(_2\)NHBoc), 4.84 (bs, 1H, -NH), 7.29 (d, 2H, \(J = 8.1\) Hz, aryl -CH), 7.78 (d, 2H, \(J = 8.1\) Hz, aryl -CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 24.84\) (-CH\(_3\)), 25.02 (-C(CH\(_3\)_3)), 28.39 (-C\(_\text{H}_2\)NH-), 44.74 (-C(CH\(_3\)_2)\(_2\)), 83.77 (-C(CH\(_3\)_3)), 126.74 (aryl \_CH), 129.20 (aryl \_C\(_6\)), 135.09 (aryl \_CH), 142.05 (aryl \_C\(_6\)), 155.84 (CO); HRMS (ESI): \(m/z\) calculated for C\(_{18}\)H\(_{28}\)BN\(_2\)O\(_4\)Na\(^+\) [M+Na\(^+\)]: 356.2009. Found: 356.2011.
$^1$H NMR of 10, 400 MHz, CDCl$_3$.

$^{13}$C NMR of 10, 100 MHz, CDCl$_3$. 
**Tert-butyl (3',5'-bis(azidomethyl)biphenyl-4-yl)methylcarbamate (A)**

Borinate ester 10 (1.13 g, 3.39 m.mol) was placed in a Schlenk tube from which light had been excluded (by wrapping in foil) and DMF (20 mL) was added. The solution formed was degassed, then under a positive pressure of nitrogen, 1,3-bis(azidomethyl)-5-iodobenzene was added as a 60% solution in DMF (2.11 g, containing 1.27 g azide, 4.09 mmol). Pd(PPh₃)₄ (391 mg, 339 µmol) and K₂PO₄ (2.15 g, 10.27 m.mol) were also added. The resulting suspension was heated to 80 °C for 4 hours, then allowed to cool. Water (70 mL) was added and the mixture extracted with EtOAc (2 x 100 mL). The organic extract was dried over MgSO₄, filtered, and concentrated to a black oil. Flash column chromatography (2:8, EtOAc-hexanes) then yielded the product A as a clear colourless oil (1.02 g, 77%). R_f = 0.32 (4:6, EtOAc-hexanes); FTIR (ATR): ν_max = 3356, 2978, 2093 (N₃), 1704, 1603, 1506 and 1454 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.44 (s, 9H, -C(CH₃)₃), 4.33 (d, 2H, J = 5.6 Hz, CH₃NBoc), 4.40 (s, 4H, CH₂N₃), 5.01 (bs, 1H, NHBoc), 7.22 (s, 1H, aryl -CH), 7.34 (d, 2H, J = 8.1 Hz, aryl -CH), 7.45 (s, 2H, aryl -CH), 7.52 (d, 2H, J = 8.1 Hz, aryl -CH); ¹³C NMR (100 MHz, CDCl₃) δ = 28.4 (C(CH₃)₃), 44.3 (CH₃NH-), 54.5 (CH₂N₃), 77.2 (-C(CH₃)₃), 126.5 (aryl CH), 126.6 (aryl CH), 127.4 (aryl CH), 128.0 (aryl C₆), 136.7 (aryl CH), 138.7 (aryl C₆), 139.1 (aryl C₆), 142.2 (aryl C₆), 155.9 (CO); HRMS (ESI): m/z calculated for C₂₀H₂₃N₇O₂Na⁺ [M+Na⁺]: 416.1811. Found: 416.1790.
$^1$H NMR of A, 400 MHz, CDCl$_3$.

$^{13}$C NMR of A, 100 MHz, CDCl$_3$. 
To a stirred solution of biaryl A (418 mg, 1.06 mmol) at 0 °C in CH$_2$Cl$_2$ (20 mL) was added trifluoroacetic acid (4 mL). The solution was stirred at 0 °C for 2 hours after which time TLC analysis indicated the starting material had been consumed. The solvent was then removed under reduced pressure and the residue obtained redissolved in EtOAc (50 mL) and washed with an aqueous solution of 2M NaOH (2 x 20 mL). The organic portion was then dried over sodium sulfate, filtered and concentrated to yield an oil. Flash column chromatography (95:5, CH$_2$Cl$_2$-MeOH saturated with ammonia) then yielded the product B as a clear colourless oil which solidified to a white solid (237 mg, 76%) on standing. $R_f$ = 0.29 (95:5, CH$_2$Cl$_2$-MeOH saturated with ammonia); FTIR (ATR): $\nu_{max}$ = 3027, 2914, 2861, 2090 (N$_3$), 1661, 1602, 1515 and 1456 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.96 (s, 2H, -CH$_2$NH$_2$), 4.46 (s, 4H, CH$_2$N$_3$), 7.26 (t, 1H, $J$ = 1.6 Hz, aryl -CH), 7.42 (d, 2H, $J$ = 8.3 Hz, aryl -CH), 7.51 (d, 2H, $J$ = 1.6 Hz, aryl -CH), 7.58 (d, 2H, $J$ = 8.3 Hz, aryl -CH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 46.1 (CH$_2$NH$_2$), 54.6 (CH$_2$N$_3$), 126.4 (aryl $\equiv$CH), 126.7 (aryl $\equiv$CH), 127.6 (aryl $\equiv$CH), 127.7 aryl $\equiv$CH), 136.7 (aryl $\equiv$CH), 138.6 (aryl $\equiv$CH), 142.3 (aryl $\equiv$CH), 143.0 (aryl $\equiv$CH); HRMS (ESI): $m/z$ calculated for C$_{15}$H$_{16}$N$_6$ [M - NH$_2$]: 277.1202. Found: 277.1200; $m/z$ calculated for C$_{15}$H$_{16}$N$_7$ $^+$ [M+H]$^+$: 294.1467. Found: 294.1465.
$^1$H NMR of B, CDCl$_3$, 400 MHz.
Tetra-azide C

Amine B (100 mg, 0.34 mmol) was dissolved in anhydrous THF (1 mL) under a nitrogen environment. Anhydrous DIPEA (100 µL) was added followed by a solution of pentafluorophenyl ester 11 (159 mg, 0.156 mmol) in anhydrous THF (2.5 mL). The resulting clear, pale yellow solution was stirred for 3 hours before the THF was removed under reduced pressure. The residue obtained was redissolved in CHCl₃ (50 mL) and washed with saturated aqueous NH₄Cl (30 mL), brine (30 mL) and saturated aqueous NaHCO₃ (30 mL). The aqueous washings were back-extracted with CHCl₃. The organic portions were combined, dried over magnesium sulfate, filtered and concentrated. The oil obtained was purified by flash column chromatography (6:4, EtOAc-hexanes) to furnish the product C as a colourless solid (174 mg, 90%). Rᵢ = 0.38 (6:4, EtOAc-hexanes); FTIR (ATR): νₑₓₐₓ = 2929, 2854, 2117 (N₃), 1729, 1668, 1605, 1516 and 1450 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 1.33 (s, 27H, C(CH₃)₃), 2.40 (t, 6H, J = 6.1 Hz, -CH₂CH₂CO), 3.67 (t, 6H, J = 6.1 Hz, OCH₂CH₂⁻), 3.82 (s, 6H, -CH₂-O), 4.44 (s, 8H, CH₂N₃), 4.70 (d, 4H, J = 5.6 Hz, CH₂NH⁻), 6.72 (s, 2H, aryl CH), 7.46 (d, 4H, J = 8.3 Hz, aryl CH), 7.48 (d, 4H, J = 1.7 Hz, aryl CH), 7.57 (d, 4H, J = 8.3 Hz, aryl CH); ¹³C NMR (100 MHz, CDCl₃) δ = 28.0 (C(CH₃)₃), 36.4 (CH₂CO²⁻), 44.0 (CH₂NH⁻), 54.6 (CH₃N₃), 60.4 (CCH₂O⁻), 67.1 (OCH₂CH₂⁻), 69.0 (CCH₂O⁻), 80.7 (CO₂C(CH₃)₃), 126.4 (aryl CH), 126.7 (aryl CH), 127.5 (aryl CH), 128.3 (aryl CH), 128.7 (aryl CH), 129.6 (aryl CH), 135.2 (aryl C₆), 136.0 (aryl C₆), 136.8 (aryl C₆), 137.7 (aryl C₆), 139.5 (aryl C₆), 142.2 (aryl C₆), 165.9 (CO), 166.1 (CO), 171.3 (CO); HRMS (ESI): m/z calculated for C₆₄H₇₇N₁₅O₁₂Na⁺ [M+Na]⁺: 1270.5774. Found: 1270.5786.
$^1$H NMR of C, 500 MHz, CDCl$_3$.

$^{13}$C NMR of C, 125 MHz, CDCl$_3$. 
Protected receptor D

Triphenylphosphine (359 mg, 1.37 mmol, 10 eq.) was added to a solution of tetra-azide C (171 mg, 137 µmol) in THF (25 mL). The resulting clear colourless solution was heated at 60 °C for 14 hours. Water (4 mL) was then added and the temperature maintained at 60 °C for a further 4 hours. After this time the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (1:3, EtO-MeCN then 1:9, aqueous NH4OH-MeCN) to yield the corresponding tetra-amine as a white solid (0.134 g, 86%). The compound was then used directly in the next step.

A solution of pentafluorophenyl-activated ester 11e (760 mg, 74 µmol) in anhydrous THF (50 mL) was added to a solution of the foregoing tetra-amine (421 mg, 369 µmol) and DIPEA (370 µL, 2.22 mmol) in THF (1.8 L) slowly over a period of 30 hours using a gas-tight syringe and syringe pump. After the addition had completed, the reaction was allowed to stir for a further 5 days. The solvent was then removed under reduced pressure and the residue obtained redissolved in CH2Cl2 (50 mL). This was washed with saturated aqueous NH4Cl (50 mL) and then brine (50 mL). The organic portion was dried over sodium sulfate, filtered and concentrated to a colourless oil. The crude product was first purified by means of flash column chromatography (CH2Cl2 to 1:4, CH2Cl2-EtOAc). The white solid obtained was further purified by preparative high performance liquid chromatography (Hichrom Kromasil column, 21.2 x 250 mm, 5µm, C18, eluent: H2O-MeOH 1:1 then after 7 minutes H2O-MeOH 1:19, flow rate 21 mL.min−1) to yield the product D as a white solid (52 mg, 19%). Rf = 16.2 minutes; Rf = 0.38 (EtOAc); 1H NMR (CDCl3 + 6% MeOD, 500 MHz) δ = 1.34 (s, 81H, C(CH3)3), 2.46 (m, 18H, J = 6.1 Hz, CH2CH2CO-), 3.66 (m, 18H, J = 5.6 Hz, OCH2CH2-), 3.78 (s, 6H, C(CH3O)-), 3.79 (s, 12H, C(CH3O)-), 4.35 (d, 4H, J = 13.9 Hz, CH2NH-), 4.50 (s, 4H, CH2NH-), 4.62 (d, 4H, J = 13.8 Hz, CH2NH-), 5.84 (s, 1H, CH2NH-), 6.88 (s, 2H, CH2NH-), 7.25 (d, 4H, J = 9.2 Hz, aryl CH), 7.30 (s, 2H, aryl CH), 7.38 (d, 4H, J = 8.3 Hz, aryl CH), 7.40 (s, 4H, aryl CH), 7.98 (s, 1H, aryl CH), 8.03 (s, 2H, aryl CH), 8.26 (s, 2H, aryl CH), 8.32 (s, 4H, aryl CH); 13C NMR (CDCl3, 125 MHz) δ = 28.0 (C(CH3)3), 36.5 (-C2H2O2), 36.7 (-C2H2CO2Bu), 43.7 (-CH2NH-), 44.4 (-CH2NH-), 60.3 (-COCH2-), 60.4 (-COCH2-), 67.1 (-OCH2CH2-), 67.2 (-OCH2CH2-), 69.0 (-CH2OCH2-), 69.1 (-CH2OCH2-), 80.7 (-C(CH3)3), 80.8 (-C(CH3)3), 126.5 (aryl -CH), 127.2 (aryl -CH), 127.6 (aryl C6), 128.3 (aryl -CH), 128.3 (aryl C6), 128.4 (aryl C6), 128.9 (aryl -CH), 129.3 (aryl C6), 134.7 (aryl -CH), 134.9 (aryl C6), 135.1 (aryl C6), 135.2 (aryl C6), 137.5 (aryl C6), 138.9 (aryl -CH), 139.0 (aryl -CH), 141.6 (aryl -CH), 165.7 (-CONH-), 165.8 (-CONH-), 165.9 (-CONH-), 166.7
(-CONH-), 171.3 (-CO₂Bu), 171.4 (-CO₂²Bu); HRMS (ESI): m/z calculated for C₁₃₂H₁₇₉N₉O₃₆Na [M+Na]⁺: 2489.2350. Found: 2489.2249.

¹H NMR of D, 500 MHz, CDCl₃.
$^{13}$C NMR of D, 125 MHz, CDCl$_3$. 
Receptor 8

To bicycle D (56 mg, 23 µmol) dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C under a nitrogen atmosphere was added trifluoroacetic acid (3 mL). The solution was stirred for 2 hours. The solvent was then completely removed (via repeated evaporation) under reduced pressure and the white solid obtained immediately suspended in MeOH–H₂O, 6:4 (10 mL). The suspension was neutralised using aqueous NaOH (5%), such that the pH = 7 as measured with a pH meter, whereupon it formed a clear colourless solution. Removal of the solvent then furnished the receptor 8 as a white solid (49 mg, 100%); ¹H NMR (500 MHz, D₂O) δ = 2.50 (t, 18H, J = 6.1 Hz, -CH₂CO₂Na), 3.79 (t, 18H, J = 6.1 Hz, -OC₂H₂CH₂-), 3.89 (s, 18H, -C₂H₂O(CH₂)₂-), 4.52 (app. d, 4H, J = 14.5, benzyl -CH₂-NH-), 4.59-4.64 (m, 8H, benzyl -CH₂NH-), 7.44 (app. d, 4H, J = 8.2 Hz, aryl -CH), 7.47 (s, 2H, aryl -CH), 7.62 (app. d, 4H, J = 8.4 Hz, aryl -CH), 7.65 (s, 4H, aryl -CH), 7.93 (s, 2H, linker aryl -CH), 8.07 (s, 1H, linker aryl -CH), 8.28 (s, 2H, linker aryl -CH), 8.29 (s, 4H, linker aryl -CH); ¹³C NMR (125 MHz, D₂O) δ = 37.52 (-CH₂CO₂Na), 43.33 (benzyl -CH₂NH-), 44.13 (benzyl -CH₂NH-), 60.93 (-C(=O)CH₂-), 68.56 (-CH₂OCH₂), 68.67 (-OCH₂CH₂-), 117.28 (aryl C), 126.68 (aryl -CH), 127.03 (aryl -CH), 128.21 (aryl -CH), 128.51 (aryl C), 128.77 (aryl C), 129.02 (aryl C), 129.22 (aryl C), 134.45 (aryl -CH), 134.82 (aryl -CH), 135.65 (aryl C), 135.83 (aryl C), 137.33 (aryl -CH), 138.79 (aryl -CH), 139.01 (aryl -CH), 140.81 (aryl C), 168.43 (-CONH), 169.02 (-CONH), 169.31 (-CONH), 173.03 (-CONH), 180.11 (-CO₂Na); HRMS (ESI): m/z calculated for C₉₆H₁₀₇N₉O₃₆Na₂⁺ [M+2Na]²⁺: 1003.8301. Found: 1003.8301. ⁵

(See later sections for ¹³C NMR and ¹H NMR spectra, and assignments).

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\text{Cl-NHBoc}
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*Tert*-butyl ((6-chloropyridin-3-yl)methyl)carbamate (E)*

5-aminomethyl-2-chloropyridine 18 (1.87 g, 13.1 mmol) was dissolved in anhydrous CH₂Cl₂ (15 mL) and to this was added DIPEA (3.4 mL, 26.2 mmol) and Boc₂O (5.74 g, 26.2 mmol). The clear solution formed was allowed to stir overnight. Water (40 mL) was added followed by further CH₂Cl₂ (60 mL). The organic portion was separated, dried over sodium sulfate, filtered and then concentrated to under reduced pressure to yield E as an oil which solidified to a colourless solid (3.02 g, 95%) on standing. Mp. 42-45 °C (Lit.,⁴ 43-44 °C); FTIR (ATR): \( \nu_{\text{max}} = 3037, 3002, 2880, 1677, 1586, 1509, 1457, 1389, 1250 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta = 1.45 \text{ (s, 9H, -C(CH₃)}₃)\), 4.31 (d, 2H, \( J = 6.1 \text{ Hz, -CH}_2\)), 4.97 (bs, 1H, -NH), 7.29 (d, \( J = 8.0 \text{ Hz, aryl-CCH} \)), 7.61 (dd, \( J = 8.1, 2.4 \text{ Hz, aryl-CH} \)), 8.30 (dd, \( J = 2.2, 0.7 \text{ Hz, aryl-CH} \)). (Lit.,⁴ (CDCl₃, 300 MHz) \( \delta = 1.37, 4.22, 5.40, 7.20, 7.54 \text{ and } 8.22 \)). Elemental analysis: Calculated for C₁₁H₁₅ClN₂O₂: C 54.44, H 6.23, N 11.54. Found: C 54.70, H 6.21, N 11.42.

\(^1\)H NMR of E, 400 MHz, CDCl₃.
Dimethyl 5-((tert-butoxycarbonylamino)methyl)pyridin-2-yl)isophthalate (F)

Dimethyl 5-iodoisophthalate (17) (478 mg, 1.49 mmol) was dissolved in DMF (10 mL), then bis(pinacolato)diboron (417 mg, 1.64 mmol, 1.1 eq) and potassium acetate (439 mmol, 4.49 mmol, 3 eq) were added. The suspension was degassed and backfilled with nitrogen three times. Then under a positive pressure of nitrogen Pd(dppf)Cl\(_2\) (121 mg, 149 µmol, 10 mol%) was added. The resulting suspension was heated to 80 °C for 5 hours. The mixture was allowed to cool to ambient temperature, then chloropyridine (397 mg, 1.64 mmol), a 2M aqueous solution of sodium carbonate (4 mL, 8 mmol) and further Pd(dppf)Cl\(_2\) (121 mg) were added. The resultant mixture was again heated to 80 °C overnight. After cooling the mixture was diluted with EtOAc (150 mL) and water (100 mL). The organic fraction was separated and further washed with brine (2 x 30 mL), then dried over magnesium sulfate, filtered and concentrated to a crude brown oil. Purification via flash column chromatography (3:7, EtOAc-hexanes) then yielded the product F as a yellow solid (357 mg, 60%); \(R_f = 0.28\) (4:6, EtOAc-hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 1.46\) (s, 9H, -CH\(_3\)\(_3\)), \(3.97\) (s, 6H, -CO\(_2\)C\(_6\)H\(_5\)), \(4.38\) (d, 2H, \(J = 5.8\) Hz, -CH\(_2\)NH-), \(4.96\) (bs, 1H, -NH-), \(7.75\) (app. d, 2H, \(J = 8.8\) Hz, aryl CH), \(7.82\) (app. d, 2H, \(J = 7.9\) Hz, aryl CH), \(8.64\) (d, 1H, \(J = 2.1\) Hz, aryl CH), \(8.72\) (t, 1H, \(J = 1.7\) Hz, aryl CH), \(8.85\) (d, 2H, \(J = 1.6\) Hz, aryl CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 28.55\) (-CH\(_3\)\(_3\)), \(42.37\) (-CH\(_2\)NH-), \(52.59\) (-CO\(_2\)C\(_6\)H\(_5\)), \(83.05\) (-CH\(_6\)), \(120.64\) (aryl CH), \(126.95\) (aryl C\(_6\)), \(131.02\) (aryl C\(_6\)), \(131.35\) (aryl CH), \(132.12\) (aryl C\(_6\)), \(134.20\) (aryl CH), \(140.03\) (aryl C\(_6\)), \(145.18\) (aryl C\(_6\)), \(149.21\) (aryl N=CH-), \(154.50\) (-NHCO-), \(166.30\) (-CO\(_2\)C\(_6\)H\(_5\))); HRMS (ESI): \(m/z\) calculated for C\(_{21}\)H\(_{24}\)N\(_2\)O\(_6\)Na\(^+\) \([M+Na]^+\): 423.1532. Found: 423.1530
$^1$H NMR of F, 400 MHz, CDCl$_3$.

$^{13}$C NMR of F, 100 MHz, CDCl$_3$. 
Tert-butyl (6-(3,5-bis(hydroxymethyl)phenyl)pyridin-3-yl)methylcarbamate (G)

Diester F (605 mg, 1.51 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0 °C. Anhydrous MeOH (735 µL, 12 eq.) was added, followed by LiBH₄ (4M in THF, 4.53 mL, 12 eq.) whereupon the solution turned deep red. The reaction was then heated to 50 °C overnight. The mixture was then cooled on an ice bath and quenched with saturated aqueous NH₄Cl (10 mL) and water (50 mL). The THF was removed under reduced pressure and the resultant mixture extracted with CH₂Cl₂ (60 mL) and EtOAc (60 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated to yield the product G as a white solid (381 mg, 73%); Rᶠ = 0.12 (1:4, CH₂Cl₂-EtOAc); ³¹H NMR (400 MHz, CDCl₃) δ = 1.46 (s, 9H, -C(CH₃)₃), 4.33 (d, 2H, J = 4.5 Hz, -CH₂NHBOc), 4.70 (s, 4H, -CH₂OH), 5.08 (bs, 1H, -NH), 7.35 (s, 1H, aryl CH), 7.60-7.89 (m, 4H, aryl CH), 7.77 (s, 2H, aryl CH), 8.52 (s, 1H, aryl CH); ¹³C NMR (100 MHz, CDCl₃) δ = 28.36 (C(CH₃)₃), 64.82 (-C₂H₂OH), 79.90 (-C(CH₃)₃), 120.75 (aryl CH), 124.44 (aryl CH), 126.01 (aryl CH), 133.26 (aryl C≈), 136.26 (aryl CH), 139.04 (aryl C≈), 141.98 (aryl C≈), 148.40 (aryl CH), 156.21 (aryl C≈), 156.19 (CO); HRMS (ESI): m/z calculated for C₁₉H₂₅N₂O₄ [M+H]+: 345.1814. Found: 345.1802. Calculated for C₁₉H₂₄N₂O₄Na [M+Na]+: 367.1634. Found: 367.1620. Elemental analysis: Calculated for C₁₉H₂₄N₂O₄: C 66.26, H 7.02, N 8.13. Found: C 66.20, H 7.22, N 7.55.
**Tert-butyl (6-{3,5-bis(azidomethyl)phenyl}pyridin-3-yl)methyl)carbamate (H)**

Diol G (339 mg, 984 μmol) was dissolved in CH₂Cl₂ (10 mL) with Et₃N (824 μL, 5.90 mmol, 6 eq.) and methanesulfonyl chloride (456 μL, 5.90 mmol, 6 eq.) was added. The reaction was stirred at room temperature for 5 hours, then diluted with CH₂Cl₂ (50 mL) and saturated aqueous sodium hydrogen carbonate (50 mL). The organic portion was extracted, and the aqueous layer further washed with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to an oil. This crude dimesylate was directly dissolved in DMF (10 mL) with sodium azide (640 mg, 9.84 mmol, 10 eq.) and the resultant suspension heated to 80 °C overnight. The resulting orange suspension was partitioned between EtOAc (50 mL) and water (50 mL). The organic portion was separated, dried over magnesium sulfate, filtered and concentrated to an oil. Purification of this crude material via flash column chromatography (1:4, EtOAc-hexanes) then furnished diazide H as a white solid (206 mg, 53%); Rf = 0.27 (1:4, EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ = 1.45 (s, 9H, -C(CH₃)₃), 4.34 (d, 2H, J = 5.6 Hz, -CH₂NH-), 4.43 (s, 4H, -CH₂N₃), 5.12 (bs, 1H, -NH-), 7.30 (s, 1H, J = 1.8 Hz, aryl -CH), 7.68-7.70 (m, 2H, 2 x aryl -CH), 8.58 (s, 1H, aryl -CH); ¹³C NMR (100 MHz, CDCl₃) δ = 28.44 (-C(CH₃)₃), 41.99 (-CH₂NH-), 54.56 (-CH₂N₃), 74.95 (-C(CH₃)₃), 120.54 (aryl -CH), 126.43 (aryl -CH), 128.09 (aryl -CH), 133.79 (aryl Cq), 136.28 (aryl Cq), 136.84 (aryl -CH), 140.37 (aryl Cq), 148.98 (aryl -CH), 155.35 (aryl Cq), 155.99 (CO); HRMS (ESI): m/z calculated for C₁₉H₂₂N₈O₂ [M+H]+: 395.1944. Found: 395.1931. Calculated for C₂₀H₂₂N₈O₂Na⁺ [M+Na]+: 417.1763. Found: 417.1748.
$^1$H NMR of H, 400 MHz, CDCl$_3$.

$^{13}$C NMR of H, 100 MHz, CDCl$_3$. 
Tetra-azide I

Tert-butylcarbamate protected biaryl H (206 mg, 522 µmol) was dissolved in CH₂Cl₂ (5 mL) and cooled to 0 °C. Trifluoroacetic acid (2 mL) was added slowly and the mixture stirred at 0 °C for 20 minutes and then at room temperature for 5 hours. After this time the reaction mixture was concentrated under reduced pressure and purified via flash column chromatography (1:9, NH₃ saturated MeOH-CH₂Cl₂) to yield the corresponding amine as a colourless oil.

The amine (152 mg, 522 µmol) was used directly in the next step. It was dissolved in anhydrous THF (5 mL) under an atmosphere of nitrogen and DIPEA (273 µL, 1.56 mmol) was added. A solution of activated linker 1 (258 mg, 261 µmol) in anhydrous THF (10 mL) was then added and the reaction stirred at room temperature overnight. After concentration under reduced pressure and purification via flash column chromatography (1:1 to 9:1, EtOAc-hexanes) the product I was obtained as a clear colourless oil (157 mg, 48%); Rf = 0.17 (7:3, EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ = 1.31 (s, 27H, -C(CH₃)₃), 2.39 (t, 6H, J = 6.1 Hz, -CH₂CO₂tBu), 3.65 (t, 6H, J = 6.1 Hz, -OC₂H₅), 3.79 (s, 6H, -CC₂H₂O-), 4.44 (s, 8H, -C₄H₂N₃), 4.68 (d, 4H, J = 5.7 Hz, -CH₂NH-), 6.71 (s, 1H, -NH), 7.32 (s, 2H, aryl –C₆H₄), 7.57 (t, 2H, J = 5.8 Hz, -CH₂NH-), 7.67-7.71 (dd, 2H, J = 8.1 Hz, J = 0.7 Hz, aryl -CH), 7.78-7.82 (dd, 2H, J = 8.2, 2.2 Hz, aryl CH), 7.87 (2, 4H, aryl –CH), 8.30 (d, 2H, J = 1.7 Hz, linker aryl –CH), 8.55 (t, 1H, J = 1.7 Hz, linker aryl –CH), 8.64 (d, 2H, J = 1.7 Hz, aryl –CH); ¹³C NMR (400 MHz, CDCl₃) δ = 28.00 (-C(CH₃)₃), 36.35 (-CH₂CO₂tBu), 41.47 (-CH₂NH-), 54.47 (-C₆H₄N₃), 60.54 (-C₂H₅O-), 67.26 (-OCH₂-), 69.16 (-C₂H₂O-), 80.94 (-C(CH₃)₃), 120.70 (aryl –CH), 126.50 (aryl –CH), 128.23 (aryl Cq), 128.46 (linker aryl –CH), 129.88 (linker aryl –CH), 132.97 (aryl Cq), 135.05 (aryl Cq), 136.29 (aryl Cq), 136.83 (aryl –CH), 137.04 (aryl Cq), 140.27 (aryl Cq), 142.33 (aryl –CH), 155.63 (aryl Cq), 166.17 (CO), 166.20 (CO), 171.51 (-CO₂tBu); HRMS (ESI): m/z calculated for C₆₂H₇₅N₁₇O₁₂Na [M+Na]⁺: 1272.5679. Found: 1272.5672.
$^1$H NMR of I, 400 MHz, CDCl$_3$.

$^{13}$C NMR of I, 100 MHz, CDCl$_3$. 
**Protected receptor J**

Tetra(azide) I (131 mg, 104 µmol) was dissolved in THF (10 mL) and PPh₃ (274 mg, 1.04 mmol) was added. The resulting solution was heated to 60 °C overnight, then water (2 mL) was added and the temperature maintained for a further 5 hours. After this time the water and THF were removed under reduced pressure to give a white solid. This was loaded onto a short silica column and first washed with 1:1, EtOAc-CH₂Cl₂ to remove the P(Ph)₃ and OP(Ph)₃ and secondly with 1:9, NH₂OH (aq.)-MeCN. The product-containing fractions were then azeotropically distilled with toluene to furnish the tetra(amine) as a clear colourless solid (105 mg, 87%). This material was used directly in the next step.

The crude tetra(amine) (105 mg, 92 µmol) was placed in an oven-dried 2-neck round bottomed flask and evacuated for 30 minutes. It was then placed under an atmosphere of nitrogen and dissolved in anhydrous THF (200 mL) before DIPEA (95 µL, 550 µmol, 6 eq.) was added. A solution of activated linker 11² (188 mg, 183 µmol) in anhydrous THF (50 mL) was then added via a gas-tight syringe and septum over a period of 25 hours using a syringe pump. Once addition was complete the reaction was stirred at room temperature for a further 5 days. The solvent was then removed under reduced pressure and the crude material obtained dissolved in EtOAc (50 mL) and washed with saturated aqueous NH₄Cl (30 mL), water (30 mL) and brine (30 mL). The organic portion was then dried over MgSO₄, filtered and concentrated once again. The material was then subjected to flash column chromatography (eluting first with 4:1, EtOAc-CH₂Cl₂ then 3:47, MeOH-CH₂Cl₂). The material obtained after flash chromatography was finally purified via HPLC (Hichrom Kromasil column, 21.2 x 250 mm, 5µm, C18; Eluent: 1:1, MeOH-H₂O graduated to 100% MeOH over 10 minutes, flow rate = 20 mL min⁻¹, Rₜ = 14 minutes) to furnish the product J as a white solid (48 mg, 21%) after drying. Rₜ = 0.29 (3:47 MeOH-CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ = 1.37 (s, 27H, -CO₂C(CH₃)₃), 1.38 (s, 54H, -CO₂C(CH₃)₃), 2.45-2.50 (m, 18H, -CH₂CO₂Bu), 3.67-3.73 (m, 18H, -OCH₂CH₂), 3.84 (s, 6H, -CH₂O⁻), 3.85 (s, 12H, -CH₂O⁻), 4.45 (d, 4H, J = 12.3 Hz, -CH₂NH⁻), 4.56 (d, 4H, J = 12.7 Hz, -CH₂NH⁻), 4.65 (d, 4H, J = 12.3 Hz, -CH₂NH⁻), 6.59 (s, 3H, -NH⁻), 7.31 (s, 2H, -NH⁻), 7.40 (s, 6H, -NH⁻), 7.41 (s, 2H, aryl -CH), 7.53 (d, 2H, J = 8.3 Hz, aryl -CH), 7.54 (s, 4H, -NH⁻), 7.68 (d, 2H, J = 8.3 Hz, aryl -CH), 7.84 (s, 4H, aryl -CH), 8.01 (s, 1H, linker aryl -CH), 8.06 (s, 2H, linker aryl -CH), 8.31 (s, 2H, linker aryl -CH), 8.37 (s, 4H, linker aryl -CH), 8.53 (s, 2H, aryl -CH); ¹³C NMR (100 MHz, CDCl₃) δ = 28.20 (-C(CH₃)₃), 28.21 (-C(CH₃)₃).
$J$, 36.72 (–$\text{CH}_2\text{CO}_2^-$Bu), 36.76 (–$\text{CH}_2\text{CO}_2^-$Bu), 41.40 (–$\text{CH}_2\text{NH}^-$), 44.84 ((–$\text{CH}_2\text{NH}^-$), 67.34 (–OCH$_2^-$), 69.25 (–CCH$_2$O–), 80.73 (–$\text{C}(\text{CH}_3)_3$), 80.77 (–$\text{C}(\text{CH}_3)_3$), 120.5 (aryl –$\text{C}$H), 126.5 (aryl –$\text{C}$H), 128.2 (aryl $\text{C}_3$), 128.7 (aryl $\text{C}_3$), 129.0 (aryl –$\text{C}$H), 134.6 (aryl –$\text{C}$H), 130.9 (aryl $\text{C}_3$), 132.6 (aryl $\text{C}_3$), 134.7 (aryl –$\text{C}$H), 134.9 (aryl $\text{C}_q$), 136.5 (aryl $\text{C}_q$), 136.8 (aryl –$\text{C}$H), 136.9 (aryl –$\text{C}$H), 139.0 (aryl –$\text{C}$H), 139.8 (aryl $\text{C}_2$), 149.4 (aryl –$\text{C}$H), 155.64 (aryl $\text{C}_q$), 165.79 (–$\text{CONH}$), 165.83 (–$\text{CONH}$), 166.38 (–$\text{CONH}$), 166.51 (–$\text{CONH}$), 171.33 (–$\text{CO}_2^-$Bu), 171.36 (–$\text{CO}_2^-$Bu); HRMS (ESI): $m/z$ calculated for $\text{C}_{130}\text{H}_{177}\text{N}_{11}\text{O}_{36}\text{Na}^+$ [M+Na]$^+$: 1257.1256 Found: 1257.1083.

$^1$H NMR of $J$, 400 MHz, CDCl$_3$. 
\(^{13}\)C NMR of J, 100 MHz, CDCl\(_3\).
Bicycle J (48 mg, 19 µmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. TFA (1.5 mL) was added slowly and after 10 minutes the solution was allowed to warm to room temperature at which it was stirred for 4 hours. The solvent and residual TFA were completely removed under reduced pressure to yield a white solid. This was dissolved in MeOH-H₂O (8:2) and neutralised with a dilute aqueous solution of NaOH, such that the pH = 7 as measured with a pH meter. After removal of the MeOH under reduced pressure and freeze-drying overnight receptor 9 was obtained as a fluffy white solid (42 mg, 100%). ¹H NMR (500 MHz, D₂O) δ = 2.48-2.53 (m, 18H, -C₆H₂CO₂Na), 3.78-3.82 (m, 18H, -OC₆H₄CH₂-), 3.90 (s, 18H, -CC₆H₂O-), 4.54 (d, 4H, J = 13.4 Hz, -CH₃NH-), 4.64 (s, 4H, -CH₃NH-), 4.67 (d, 4H, J = 13.3 Hz, -CH₃NH-), 7.58 (s, 2H, aryl-CH), 7.76 (s, 2H, aryl-CH), 7.85 (s, 4H, aryl-CH₂), 7.90 (d, 2H, J = 8.4 Hz, aryl-CH), 7.94 (s, 2H, aryl-CH), 8.05 (s, 1H, aryl-CH), 8.29-8.31 (bs, 6H, 2x aryl-CH), 8.55 (s, 2H, aryl-CH); ¹³C (125 MHz, D₂O) δ = 37.6 (-CH₂CO₂tBu), 41.0 (benzyl-CH₂NH₂), 44.0 (benzyl-CH₂NH₂), 61.0 (aliphatic C₂), 68.5 (-C(CH₂O-)), 68.7 (-OC₆H₄CH₂-), 115.3 (aryl C₆), 117.2 (aryl C₆), 121.9 (aryl C₆), 126.8 (aryl-CH), 128.6 (aryl C₆), 129.1 (aryl-CH), 129.2 (aryl-CH), 130.5 (aryl C₆), 132.9 (aryl C₆), 134.4 (aryl-CH), 134.6 (aryl-CH), 135.7 (aryl-CH), 138.0 (aryl-CH), 139.0 (aryl-CH), 148.1 (aryl-CH), 155.2 (aryl C₆), 162.7 (aryl- C₆), 168.2 (-CONH-), 168.9 (-CONH-), 169.1 (-CONH-), 169.2 (-CONH-), 180.01 (-CO₂tBu), 180.09 (-CO₂tBu); HRMS (ESI): m/z calculated for C₉₄H₁₀₇N₁₁O₃₆ [M+2H]²⁺: 982.8440 Found: 982.8416. ²
$^1$H NMR (water peak pre-saturated) of receptor 9, 500 MHz, D$_2$O.

Detail of receptor 9 $^1$H NMR, showing proton assignment.

4.1 Procedure for preparing N-acetylneuraminic acid or glucuronic acid sodium salts

N-acetyl neuraminic acid (Neu5Ac) 16 was purchased from Carbosynth Ltd. Neu5Ac (1 g) was dissolved in distilled water (50 mL) and a solution of sodium hydroxide (2 mg mL\(^{-1}\)) was added until the solution was neutralised (pH = 7, as monitored by pH probe). The resulting solution was freeze dried to yield a white solid which could be diluted to give standard solutions of Neu5Ac sodium salt. The same procedure was used for preparing the sodium salt of glucuronic acid.

4.2 \(^1\)H NMR titrations

Solutions of carbohydrates were made up in D\(_2\)O (99.9%). Solutions of reducing sugars were allowed to equilibrate for 12 hours before use. Aliquots of the carbohydrate solutions were then added to 500 \(\mu\)L of a receptor solution, also in D\(_2\)O ([Host]\(_{\text{initial}}\) = 0.5 mM) with a DSS standard ((CH\(_3\))\(_3\)Si(CH\(_2\))\(_3\)SO\(_3\)Na; 4,4-dimethyl-4-silapentane-1-sulfonic acid sodium salt). The resulting solutions were shaken vigorously after each addition and \(^1\)H NMR spectra were then recorded at 298 K (unless otherwise stated) on a Varian Systems 500 MHz spectrometer. Variations in chemical shifts were entered into a specifically written non-linear least squares curve-fitting program implemented within Excel. Assuming 1:1 stoichiometry, the programme calculates \(K_a\) and the limiting change in chemical shift \(\Delta\delta\). Errors are calculated as standard deviations for \(K_a\) values computed from individual data points employing the limiting \(\Delta\delta\). In the present work the errors for \(^1\)H NMR titrations were estimated at \(\leq 10\%\) for most cases where \(K_a \geq 10\) M\(^{-1}\).

For each receptor a dilution study was carried out to check for aggregation. A receptor solution was prepared as described above (500 \(\mu\)L, 0.5 mM) and successive aliquots of pure D\(_2\)O (5 x 20 \(\mu\)L, then 4 x 50 \(\mu\)L) were added in (giving a final [receptor] = 0.31 mM). This represented the concentration range experienced by the receptor in most NMR titration experiments. The same procedure was performed for both receptors 8 and 9. In both cases no change in peak positions was observed, suggesting that the receptors are monomeric at these concentrations.

4.3 Induced circular dichroism titrations

A solution of receptor was first prepared in distilled water such that [receptor] = 1.6 x10\(^{-4}\) M. A solution of the sugar guest molecule (typically 1 – 3 mM) was then prepared using the receptor solution as the diluent. The two solutions were then mixed in various ratios such that in each sample the [receptor] was the same, but the [guest] varied. The CD spectrum of each of these solutions was recorded sequentially on a Jasco J-815 CD spectrometer. 16 scans were recorded of at each concentration using the interval data analysis mode with time interval set to zero. The mean of these 16 scans was calculated using Microsoft Excel and the mean absorbance at 265 nm (unless otherwise stated) was then plotted against [guest] for each sample. A binding constant was calculated from the data as described for the \(^1\)H NMR titrations.
4.4 $^{13}$C NMR titrations

The $^{13}$C titrations were performed analogously to the $^1$H NMR titrations. This technique was only used to study the interaction between receptor 8 and Neu5Ac 16. 2 mg of 8 was dissolved in D$_2$O (500 µL) to give the initial host solution ([host]$_{initial} = 2$ mM) including a DSS internal standard. Aliquots of Neu5Ac were added sequentially. The $^{13}$C spectrum was recorded for 8 hours after each addition using a Varian VNMRS600 spectrometer equipped with a triple-resonance H{C,N} cryogenically cooled probe. The binding constants, limiting $\Delta$δ and errors were calculated in the same way as described for the $^1$H NMR titrations.
5. $^1$H NMR assignments for receptor 8.

The assignment of the $^1$H spectrum of receptor 8 was possible on the basis of chemical shift and integration except in the case of protons i and h, where a 1D ROESY experiment was performed to assign the peaks.

**Figure S1** – $^1$H NMR spectrum of receptor 8 in D$_2$O, 500 MHz
Figure S2 – Partial $^1$H NMR spectra of receptor 8 (aromatic region) showing proton assignments.
6. $^1$H NMR titration binding isotherms for receptor 8.

Receptor 8 + Me-β-D-glucoside

\[ \Delta \delta \text{ calculated} \]
\[ \Delta \delta \text{ observed} \]

**Figure S3** – Plot of experimental and calculated $\Delta \delta$ (peak f) against concentration of Me-β-D-glucoside in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 1 M. $K_a$ = 6 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

**Figure S4** – Plot of experimental and calculated $\Delta \delta$ (peak m) against concentration of Me-β-D-glucoside in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 1 M. $K_a$ = 4 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Receptor 8 + N-acetyl-D-glucosamine 3

Figure S5 – Plot of experimental and calculated $\Delta \delta$ (peak j) against concentration of N-acetyl-D-glucosamine 3 in D$_2$O at 298 K. [Host]$_{initial} = 2.3$ mM. [Guest]$_{titrant} = 0.8$ M. $K_a = 15$ M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

Figure S6 – Plot of experimental and calculated $\Delta \delta$ (peak f) against concentration of N-acetyl-D-glucosamine 3 in D$_2$O at 298 K. [Host]$_{initial} = 2.3$ mM. [Guest]$_{titrant} = 0.8$ M. $K_a = 23$ M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Receptor 8 + D-xylose

Figure S7 – Plot of experimental and calculated $\Delta\delta$ (peak j) against concentration of D-xylose in D$_2$O at 298 K. $[\text{Host}]_{\text{initial}} = 1 \text{ mM}$. $[\text{Guest}]_{\text{titrant}} = 1 \text{ M}$. $K_a = 8 \text{ M}^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

Figure S8 – Plot of experimental and calculated $\Delta\delta$ (peak n) against concentration of D-xylose in D$_2$O at 298 K. $[\text{Host}]_{\text{initial}} = 1 \text{ mM}$. $[\text{Guest}]_{\text{titrant}} = 1 \text{ M}$. $K_a = 8 \text{ M}^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Figure S9 – Plot of experimental and calculated ∆δ (peak n) against concentration of 2-deoxy-D-glucose in D₂O at 298 K. [Host]_{initial} = 1 mM. [Guest]_{titrant} = 1 M. $K_a = 6 \text{ M}^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Receptor 8 + D-ribose

Figure S10 – Plot of experimental and calculated $\Delta \delta$ (peak m) against concentration of D-ribose in D$_2$O at 298 K. [Host]$_{initial}$ = 1 mM. [Guest]$_{titrant}$ = 0.7 M. $K_a = 7$ M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

Figure S11 – Plot of experimental and calculated $\Delta \delta$ (peak n) against concentration of D-ribose in D$_2$O at 298 K. [Host]$_{initial}$ = 1 mM. [Guest]$_{titrant}$ = 0.7 M. $K_a = 7$ M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Receptor 8 + cellobiose 6

**Figure S12** – Plot of experimental and calculated $\Delta\delta$ (peak j) against concentration of $\beta$-cellobiose 6 in $D_2O$ at 298 K. $[\text{Host}]_{\text{initial}} = 1$ mM. $[\text{Guest}]_{\text{trant}} = 0.2$ M. $K_a = 50 \text{ M}^{-1}$. See Figs. S1/2 for the assigned $^1\text{H}$ NMR spectrum of 8.

**Figure S13** – Plot of experimental and calculated $\Delta\delta$ (peak m) against concentration of $\beta$-cellobiose 6 in $D_2O$ at 298 K. $[\text{Host}]_{\text{initial}} = 1$ mM. $[\text{Guest}]_{\text{trant}} = 0.2$ M. $K_a = 54 \text{ M}^{-1}$. See Figs. S1/2 for the assigned $^1\text{H}$ NMR spectrum of 8.
**Figure S14** – Plot of experimental and calculated $\Delta \delta$ (peak j) against concentration of d-lactose 12 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.33 M. $K_a$ = 32 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

**Figure S15** – Plot of experimental and calculated $\Delta \delta$ (peak f) against concentration of d-lactose 12 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.33 M. $K_a$ = 42 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
**Receptor 8 + D-maltose 13**

![Graph showing experimental and calculated Δδ (peak m) against concentration of D-maltose 13 in D₂O at 298 K.](image1)

**Figure S16** – Plot of experimental and calculated Δδ (peak m) against concentration of D-maltose 13 in D₂O at 298 K. [Host]ₜₐᵢₜᵢₜ = 1 mM. [Guest]ₜᵢᵢᵢᵢₜ = 0.5 M. Kₐ = 14 M⁻¹. See Figs. S1/2 for the assigned ¹H NMR spectrum of 8.

![Graph showing experimental and calculated Δδ (peak j) against concentration of D-maltose 13 in D₂O at 298 K.](image2)

**Figure S17** – Plot of experimental and calculated Δδ (peak j) against concentration of D-maltose 13 in D₂O at 298 K. [Host]ₜₐᵢₜᵢₜᵢ = 1 mM. [Guest]ₜᵢᵢᵢᵢₜ = 0.5 M. Kₐ = 14 M⁻¹. See Figs. S1/2 for the assigned ¹H NMR spectrum of 8.
**Figure S18** – Plot of experimental and calculated $\Delta \delta$ (peak m) against concentration of *gentiobiose* 14 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.5 M. $K_a$ = 25 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.

**Figure S19** – Plot of experimental and calculated $\Delta \delta$ (peak m) against concentration of *gentiobiose* 14 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.5 M. $K_a$ = 20 M$^{-1}$. See Figs. S1/2 for the assigned $^1$H NMR spectrum of 8.
Receptor 8 + Neu5Ac salt

![Graph](image)

Figure S20 – Plot of experimental and calculated $\Delta \delta$ (peak f) against concentration of Neu5Ac sodium salt in D$_2$O at 298 K. $[\text{Host}]_{\text{initial}} =$ 1 mM. $[\text{Guest}]_{\text{tirant}} =$ 1 M. $K_a = 7 \text{ M}^{-1}$.
7. $^1$H NMR titration results and binding isotherms for receptor 9.

Table S1. Association constants ($K_a$) for receptor 9 binding carbohydrate substrates.

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<th>Carbohydrate</th>
<th>$K_a$ (M$^{-1}$)$^a$</th>
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<td>N-acetylneuraminic acid (Neu5Ac) 16</td>
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</tr>
</tbody>
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$^a$All values determined by $^1$H NMR titration. Values denoted ~0 were too small for analysis.
Receptor 9 + cellobiose 6

Figure S21 – Plot of experimental and calculated $\Delta \delta$ (peak n) against concentration of cellobiose 6 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.25 M. $K_a$ = 14 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.

Figure S22 – Plot of experimental and calculated $\Delta \delta$ (peak k) against concentration of cellobiose 6 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.25 M. $K_a$ = 14 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.
Figure S23 – Plot of experimental and calculated $\Delta \delta$ (peak k) against concentration of N-acetyl glucosamine 3 in D$_2$O at 298 K. $[\text{Host}]_{\text{initial}} = 1 \text{ mM}$. $[\text{Guest}]_{\text{strant}} = 0.5 \text{ M}$. $K_a = 5 \text{ M}^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.
Receptor 9 + maltose 13

Figure S24 – Plot of experimental and calculated $\Delta \delta$ (peak n) against concentration of maltose 13 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.4 M. $K_a$ = 1 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.

Figure S25 – Plot of experimental and calculated $\Delta \delta$ (peak o) against concentration of maltose 13 in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.4 M. $K_a$ = 10 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.
Figure S26 – Plot of experimental and calculated $\Delta\delta$ (peak f) against concentration of lactose 12 in $\text{D}_2\text{O}$ at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.3 M. $K_a$ = 10 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.

Figure S27 – Plot of experimental and calculated $\Delta\delta$ (peak f) against concentration of lactose 12 in $\text{D}_2\text{O}$ at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.3 M. $K_a$ = 8 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.
Figure S28 – Plot of experimental and calculated \( \Delta \delta \) (peak k) against concentration of \textit{D-xylose} in \( \text{D}_2\text{O} \) at 298 K. \([\text{Host}]_{\text{initial}} = 1 \text{ mM.} \ [\text{Guest}]_{\text{final}} = 0.4 \text{ M.} \ K_a = 3 \text{ M}^{-1}. \) See page S26 for the assigned \( ^{1}H \) NMR spectrum of \textit{9}.

Figure S29 – Plot of experimental and calculated \( \Delta \delta \) (peak n) against concentration of \textit{D-xylose} in \( \text{D}_2\text{O} \) at 298 K. \([\text{Host}]_{\text{initial}} = 1 \text{ mM.} \ [\text{Guest}]_{\text{final}} = 0.4 \text{ M.} \ K_a = 3 \text{ M}^{-1}. \) See page S26 for the assigned \( ^{1}H \) NMR spectrum of \textit{9}.
Figure S30 – Plot of experimental and calculated $\Delta \delta$ (peak n) against concentration of $\text{Me-\text{\textbeta-D-glucoside}}$ in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.5 M. $K_a$ = 5 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.

Figure S31 – Plot of experimental and calculated $\Delta \delta$ (peak n) against concentration of $\text{Me-\text{\textbeta-D-glucoside}}$ in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 1 mM. [Guest]$_{\text{titrant}}$ = 0.5 M. $K_a$ = 6 M$^{-1}$. See page S26 for the assigned $^1$H NMR spectrum of 9.
8. $^{13}$C NMR titration spectra and binding isotherms for receptor 8 + Neu5Ac 16.

Figure S32 – Partial $^{13}$C NMR spectra (D$_2$O) from the titration of 8 with Neu5Ac sodium salt
Figure S33 – Plot of experimental and calculated $\Delta \delta$ (peak at 140.83 p.p.m.) against concentration of Neu5Ac sodium salt in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 2 mM. [Guest]$_{\text{titrant}}$ = 1 M. $K_a$ = 5.2 M$^{-1}$. Estimated error ± 11 %

Figure S34 – Plot of experimental and calculated $\Delta \delta$ (peak at 134.45 p.p.m.) against concentration of Neu5Ac sodium salt in D$_2$O at 298 K. [Host]$_{\text{initial}}$ = 2 mM. [Guest]$_{\text{titrant}}$ = 1 M. $K_a$ = 5.4 M$^{-1}$. Estimated error ± 10 %
9. ICD spectra and associated binding curves.

Receptor 8 + cellobiose 6:

Figure S35 – Successive ICD spectra for mixtures of [8] = 1.6 x10^{-4} M and various [cellobiose] in H_{2}O.

Figure S36 – Plot of experimental and calculated ΔAbs (at 263 nm) against concentration of cellobiose 6 in H_{2}O at 298 K. [Host]_{init} = 0.16 mM. \( K_s = 30 \text{ M}^{-1} \).
Receptor 8 + maltose 13:

Figure S37 – Successive ICD spectra for [8] = 1.6 x 10^{-4} M and various [maltose] in H2O.

Figure S38 – Plot of experimental and calculated ΔAbs (at 263 nm) against concentration of maltose 13 in H2O at 298 K. [Host]_{initial} = 0.16 mM. K_a = 16 M^{-1}. 

Molecular modelling was performed using MacroModel 9.9 (MMFFs force field, water GB/SA solvation) accessed via the Maestro 9.2 interface. In the case of uncomplexed 8, Monte Carlo Molecular Mechanics (MCMM) searches were employed, in which the macrocyclic rings were allowed to break and all single bonds within the bicyclic framework were given freedom to rotate. For complexes with disaccharides, starting conformations for minimisation were based on the NMR structure previously obtained for 1 + GlcNAc-β-OMe.8

Figure S39 – Ground state conformation found for uncomplexed bicyclic receptor 8 in water, using MCMM. Side chains are omitted for clarity, and the biphenyls are shown with transparent CPK surfaces.
Figure S40 – Model of tricyclic receptor 1 binding β-D-cellobiose 6 (magenta). Side chains are omitted for clarity, and the biphenyls are shown with transparent CPK surfaces. The glucosyl residue protruding from the cavity (towards the viewer) is twisted at an angle to the bound glucosyl due to interference from the isophthalamide spacers. This distortion is not observed in the corresponding complex of bicyclic 8 + 6 (see Fig. 1).

Figure S41 – Model of bicyclic receptor 8 binding β-D-maltose 13 (magenta). It is assumed that the β-glucosyl residue occupies the cavity while the α-glucosyl residue protrudes. Although the isophthalamide spacers are angled towards the α-glucosyl in this conformation, there is no enforced distortion of the substrate.
Figure S42 – Model of tricyclic receptor 1 binding β-D-maltose 13 (magenta). It is assumed that the β-glucosyl residue occupies the cavity while the α-glucosyl residue protrudes. Steric interaction with the spacer causes the α-glucosyl to rotate away from its preferred orientation. Experimentally, no binding is observed in this case.

References

5. The dodeca(anion) was not visible by mass spectrometry. Formic acid was added to a sample to furnish the acid form which was analysed by MS.
7. Formic acid was added to the receptor sample prior to running the MS experiment.