Elettronic Supplementary Information

Designing nanomolar antagonists of DC-SIGN-mediated HIV infection: ligand presentation using molecular rods

Stefania Ordanini,a Norbert Varga,a Vanessa Porkolab,b,c,d Michel Thépaut,c,b,d Laura Belvisi,a,h Andrea Bertaglia,a Alessandro Palmioli,a Angela Berzi,e Daria Trabattoni,e Mario Clerici,f,g Franck Fieschi,b,c,d Anna Bernardia,h

a Università degli Studi di Milano, Dipartimento di Chimica, via Golgi 19, 20133 - Milano, Italy
b Univ. Grenoble Alpes, Institut de Biologie Structurale, F-38044 Grenoble, France.
c CNRS, IBS, F-38044 Grenoble, France.
d CEA, IBS, F-38044 Grenoble, France.
e Università degli Studi di Milano, Dipartimento di Scienze Biomediche e Cliniche “L. Sacco”, Via GB Grassi 74, 20157, Milano, Italy.
f Università degli Studi di Milano, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Via F.lli Cervi 93, 20090, Segrate, Italy.
g Fondazione Don Carlo Gnocchi IRCCS, Via Capecelatro 66, 20147, Milano, Italy.
h CNR-ISTM, Institute of Molecular Science and Technologies, Milano, Italy

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**Synthesis**

**General procedures**

Chemicals were purchased from commercial sources and used without further purification, unless otherwise indicated. When anhydrous conditions were required, the reactions were performed in oven-dried glassware under nitrogen atmosphere. Anhydrous solvents were purchased from Sigma-Aldrich® with a content of water ≤0.005 % v/v. THF was dried over Na/benzophenone and freshly distilled prior to use. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F254 plates (Merck) with UV detection (254 nm and 365 nm) or using appropriate developing solutions. Flash column chromatography was performed on silica gel 230-400 mesh (Merck), according with the procedure described in literature.1 Automated flash chromatography was performed on a Biotage® Isolera™ Prime system. Final compounds were purified by size-exclusion chromatography using Sephadex LH-20 from GE Helthcare Life Science® and through reverse phase automated flash chromatography (C18) when required. NMR experiments were recorded on a Bruker AVANCE 400 MHz instrument at 298 K. Chemical shifts (δ) are reported in ppm downfield from TMS as internal standard, coupling constants (J) in Hz. The 1H and 13C-NMR resonances of compounds were assigned with the assistance of COSY and HSQC experiments. HSQC experiments were also used to assign the chemical shift of protons overlapping with the solvent signals. Mass spectra were recorded on ThermoFischer LCQ apparatus (ESI ionization), Apex II ICR FTMS (ESI ionization-HRMS), Waters Micromass Q-Tof (ESI ionization-HRMS), or Bruker Daltonics Microflex MALDI-TOF apparatus. Specific optical rotation values were measured using a Perkin-Elmer 241, at 589 nm in a 1 mL cell.

The monovalent ligands 6<sup>2</sup> and 4<sup>4</sup>, the dialkyne 1<sup>4</sup> and the trivalent dendrons 5<sup>5</sup> were prepared according to the established procedures. Rods 2 and 3 were prepared immediately before performing the azide-alkyne cycloaddition by in situ desilylation of the corresponding tri-isopropyl-alkynysilane TIPS-2 and TIPS-3<sup>4</sup>, according to the general Scheme SI-3 (p. 9).
**Electronic Supplementary Information**

**Synthetic sequences leading to compounds 7.4 and 7.6**

The long-linker conjugates 7 were synthesised coupling 4 and 6 with linker 9, prepared from commercially available 3,7-dioxa-1,9-nonanediol 10 as shown in Scheme SI-1.

![Scheme SI-1](image)

Scheme SI-1: Synthesis of 7.4 and 7.6. 

- **a)** Propargyl-Br, NaH, DMF, 0 °C to rt, overnight, 50%; 
- **b)** TsCl, Pyridine, CH₂Cl₂, 0 °C to rt, overnight, 69%; 
- **c)** CuSO₄∙5H₂O, Na Ascorbate, TBTA, THF:H₂O 1:1 rt, 95%; 
- **d)** NaN₃, DMF, 60 °C, 97%.

**Compound 11**

A stirred solution of 3,7-dioxa-1,9-nonanediol 10 (130.9 mg, 0.8 mmol, 1 eq.) in dry DMF (3.5 mL) was slowly treated with NaH (60% in oil, 35.0 mg, 0.9 mmol, 1.1 eq.) at 0 °C under nitrogen atmosphere. After 30 min propargyl bromide (80% in toluene, 94.5 µL, 0.9 mmol, 1.1 eq.) was added. The reaction mixture was left to warm to room temperature and stirred under nitrogen overnight. The reaction was quenched by slow addition of iced water and then concentrated under reduced pressure. The crude was purified by flash chromatography (Hex:AcOEt 3:7) affording 81 mg of pure 11 as a yellow oil (yield 50%). Also 26 mg of the bis-propargyl ether byproduct was isolated as yellow oil (yield 13 %).

- **¹H NMR** (400 MHz, CD₂OD) δ 4.19 (d, J = 2.4 Hz, 2H, H₁); 3.68 – 3.63 (m, 4H, H₂, H₃); 3.61 – 3.60 (m, 2H, H₄); 3.59 – 3.54 (m, 4H, H₅, H₆); 3.52 – 3.50 (m, 2H, H₂); 2.85 (t, J = 2.4 Hz, 1H, H₁₀); 1.84 (tt, J = 6.4 Hz, 1H, H₉).
- **¹³C NMR** (100 MHz, CD₂OD) δ 75.97 (C₁₀, C₅); 73.31 (C₁); 71.02 (C₆); 70.06 (C₇); 69.11 (C₈, C₉); 62.22 (C₄); 59.08 (C₃); 31.05 (C₂). 

MS (ESI-HRMS): m/z calculated for [C₁₀H₁₆O₄Na⁺]: 225.10973; found = 225.10959.
Compound 9

To a stirred solution of 11 (72.4 mg, 0.4 mmol, 1 eq.) in dry CH₂Cl₂ (500 µL), TsCl was added (102.4 mg, 0.5 mmol, 1.5 eq.), then pyridine (57.7 µL, 0.7 mmol, 2 eq.) was added at 0 °C under nitrogen atmosphere. The reaction mixture was left to warm to room temperature and stirred under nitrogen overnight. CH₂Cl₂ (10 mL) was added and the mixture was washed with water (10 mL), HCl 1 M (10 mL), water (10 mL), NaHCO₃ sat. sol. (10 mL) and water again (10 mL). The organic phase was finally dried on Na₂SO₄ and concentrated under reduced pressure. The crude was purified by flash chromatography (Hex:AcOEt 65:35) affording 88 mg of pure compound 9 as a yellow oil (yield 69 %). ¹H NMR (400 MHz, CD₃OD): δ 7.80 (d, J = 8.3 Hz, 2H, H₁₂); 7.45 (d, J = 8.3 Hz, 2H, H₁₁); 4.18 (d, J = 2.4 Hz, 2H, H₈); 4.15 – 4.13 (m, 2H, H₁); 3.66 – 3.64 (m, 2H, H₇); 3.60 – 3.56 (m, 4H, H₄, H₅); 3.51 – 3.43 (m, 4H, H₃, H₆); 2.85 (t, J = 2.4 Hz, 1H, H₁₀); 2.46 (s, 3H, H₁₃); 1.74 (tt, J = 6.3 Hz, 1H, H₉).¹³C NMR (100 MHz, CD₃OD): δ 146.4 (C₁₁); 134.4 (C₁₄); 131.0 (C₁₃); 129.0 (C₁₂); 80.3 (C₁₀); 75.7 (C₉); 71.0 (C₈); 70.0 (C₇); 68.9 (C₆); 68.7 (C₅); 59.1 (C₄, C₁₀); 30.6 (C₁); 21.5 (C₁₅). MS (ESI-HRMS): m/z calculated for [C₁₇H₂₄O₆S₁Na]+: 379.11858; found: 379.11815.

Compound 12.6

Reagents were added in the reaction vessel as solids or solutions in the following order: linker 9 as a solid (60.7 mg, 170 µmol, 1 eq.), TBTA in THF (18.0 mg, 34 µmol, 0.2 eq., 960 µL of THF), CuSO₄·5H₂O in H₂O (4.2 mg, 17 µmol, 0.1 eq., 226 µL of H₂O) and sodium ascorbate in H₂O (13.5 mg, 68 µmol, 0.4 eq., 530 µL of H₂O). The reaction mixture was stirred at room temperature, under nitrogen atmosphere and in the dark for 10 minutes. Then 6 (87.1 mg, 190 µmol, 1.1 eq.) was added as a solid. THF and H₂O volumes were adjusted to 4 mL each. The reaction was stirred at room temperature, under nitrogen atmosphere and in the dark. TLC analysis (Hex:AcOEt 7:3) showed total conversion of linker 9; TLC (AcOEt:MeOH:H₂O 85:15:2.5) showed the formation of a single new product. Quadrasil™-MP (S/Pd 2:1, 20 mg) was added to
the reaction mixture, which was stirred for 10 minutes, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 126 mg of pure 12.6 as a colourless oil (yield 91 %). 1H NMR (400 MHz, CD3OD): δ 8.80 (s, 1H, H12); 7.79 (d, J = 8.3 Hz, 2H, H22); 7.44 (d, J = 8.3 Hz, 2H, H23); 4.89 (br s, 1H, H1); 4.65 (s, 2H, H13); 4.60 (t, J = 5.0 Hz, 2H, H8); 4.16 – 4.11 (m, 2H, H20); 3.98 – 3.85 (m, 4H, H6a, H6b, H27, H28); 3.82 – 3.80 (m, 1H, H2); 3.70 – 3.61 (m, 11H, H3, H6b, H27, H28, H9, H10); 3.61 – 3.44 (m, 10H, H4, H14, H15, H16, H18, H5); 2.82 – 2.62 (m, 1H, H44, H55); 2.02 – 1.94 (m, 2H, H33eq, H66eq); 1.79 – 1.66 (m, 3H, H17, H33ax or H66ax); 1.61 – 1.49 (m, 1H, H33ax or H66ax). 13C NMR (100 MHz, CD3OD): δ 176.7 (C9); 146.5 (C21); 145.9 (C12); 134.5 (C26); 131.1 (C23); 128.8 (C22); 126.1 (H11); 100.5 (C1); 75.7 (C3); 75.6 (C4); 72.5 (C20); 72.4 (C3); 72.1 (C2); 71.2 (C14, C15); 71.0 (C20); 70.7 (C19); 69.4, 68.94, 68.91 (C16, C18); 68.6 (C4); 68.4 (C7); 65.0 (C13); 63.1 (C6); 52.5 (C10); 51.7 (C8); 40.1 (C44, C55); 31.0 (C17); 28.8 (C33 or C66); 28.4 (C33 or C66); 21.6 (C25). MS (ESI-HRMS): m/z calculated for [C35H33N3O3]Na+: 842.29879; found: 842.29713. [α]025: 26.5 (c 0.34, MeOH).

**Compound 7.6**

To a solution of 12.6 (117 mg, 140 µmol, 1 eq.) in DMF dry (1.5 mL), NaN₃ (37 mg, 570 µmol, 4 eq.) and Bu₄Nl (6.0 mg, 16 µmol, 0.1 eq.) were added. The reaction mixture was stirred at 65 °C under nitrogen for 20 h. ESI-MS analysis showed total conversion of the starting material. The solvent was removed under reduced pressure and the resulting crude was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 89 mg of 7.6 as a white foam (yield 88 %), still containing 3 % (w/w, as measured by NMR integration) of a tosylate salt. Compound 7.6 was used for conjugation to the rods without further purifications. 1H NMR (400 MHz, CD3OD): δ 8.80 (s, 1H, H11); 4.89 (br s, 1H, H1); 4.65 (s, 2H, H13); 4.60 (t, J = 5.1 Hz, 2H, H8); 3.99 – 3.82 (m, 4H, H6a, H6b, H1); 3.81 (dd, J = 3.2, 1.7 Hz, 1H, H1); 3.70 – 3.60 (m, 15H, H3, H6b, H10, H14, H15, H19); 3.60 – 3.54 (m, 5H, H4, H16, H18); 3.54 – 3.45 (m, 1H, H5); 3.37 – 3.32 (m, 2H, H20); 2.82 – 2.64 (m, 2H, H44, H55); 2.02 – 1.95 (m, 2H, H33eq, H66eq); 1.84 (tt, J = 6.3 Hz, 2H, H17); 1.77 – 1.49 (m, 2H, H33ax, H66ax). 13C NMR (100 MHz, CD3OD): δ 176.8; 176.7 (C9); 146.0 (C11); 100.5 (C1); 75.7 (C3); 75.6 (C4); 72.5 (C21); 72.4 (C2); 72.1 (C20); 71.2, 70.9, 70.7 (C14, C15, C19); 68.96, 68.90 (C16, C18); 68.6 (C4); 68.4 (C3); 65.0 (C13); 63.1 (C8); 52.4 (C10); 51.8 (C9); 51.6 (C20); 40.2, 40.1
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(C_{64}, C_{65}); 31.1 (C_{17}); 28.9 (C_{63}, or C_{66}); 28.2 (C_{63}, or C_{66}). MS (ESI): m/z calculated for [C_{68}H_{46}N_{6}O_{4}Na]^+: 713.7; found: 713.4.

**Compound 12.4**

Reagents were added in the reaction vessel as solids or solutions in the following order: linker 9 as solid (55.8 mg, 160 µmol, 1 eq.), TBTA in THF (16.7 mg, 31 µmol, 0.2 eq., 960 µL of THF), CuSO_{4}·5H_{2}O in H_{2}O (3.9 mg, 16 µmol, 0.1 eq., 710 µL of H_{2}O) and sodium ascorbate in H_{2}O (12.4 mg, 63 µmol, 0.4 eq, 880 µL of H_{2}O). The reaction mixture was stirred at room temperature, under nitrogen atmosphere and in dark for 10 minutes. Then 4 (115.9 mg, 170 µmol, 1.1 eq.) was added as solid. THF and H_{2}O volumes were adjusted to 4 mL each. The reaction continued overnight, stirring at room temperature, under nitrogen atmosphere and in dark. TLC analysis (Hex:AcOE 7:3) showed total conversion of linker 9; TLC (CHCl_{3}:MeOH:H_{2}O 85:25:2.5) showed the formation of a single new product. Quadrasil™-MP (S/Pd 2:1, 20 mg) was added to the reaction mixture, which was stirred for 10 minutes, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 155 mg of pure 12.4 as a colourless oil (yield 96%).

^1H NMR (400 MHz, CD_{3}OD): δ 8.04 (s, 1H, H_{16}); 7.78 (d, J = 8.3 Hz, 2H, H_{27}); 7.42 (d, J = 8.3 Hz, 2H, H_{28}); 7.28 – 7.19 (m, 8H, H_{12}, H_{13}); 4.90 (br s, 1H, H_{1}); 4.64 – 4.52 (m, 8H, H_{18}, H_{15}, H_{8}); 4.30 – 4.28 (m, 4H, H_{10}); 4.14 – 4.07 (m, 2H, H_{22}); 4.02 – 3.81 (m, 5H, H_{2}, H_{02}, H_{6a}, H_{1}); 3.72 – 3.65 (m, 3H, H_{03}, H_{3}, H_{6a}); 3.62 – 3.59 (m, 2H, H_{24}); 3.58 – 3.49 (m, 6H, H_{5}, H_{4}, H_{19}, H_{30}); 3.46 – 3.41 (m, 4H, H_{21}, H_{22}); 2.89 – 2.74 (m, 2H, H_{04}, H_{05}); 2.44 (s, 3H, H_{30}); 1.97 – 1.74 (m, 4H, H_{03}, H_{06}); 1.70 (tt, J = 6.3 Hz, 2H, H_{22}). ^13C NMR (100 MHz, CD_{3}OD): δ 176.9, 176.7 (C_{6}); 146.5 (C_{26}); 146.0 (C_{17}); 141.5 (C_{29}); 139.1 (C_{11}, C_{14}); 134.4 (C_{28}); 131.1 (C_{27}); 128.4, 128.3, 128.2, 128.1 (C_{12}, C_{13}); 128.1, 126.1 (C_{27}); 100.3 (C_{1}); 76.2 (C_{5}); 75.54 (C_{6}); 72.53 (C_{01}); 72.3 (C_{2}); 72.1 (C_{02}); 71.1, 71.0, 70.7 (C_{19}, C_{20}, C_{25}); 69.3, 68.9 (C_{21}, C_{23}, C_{24}); 68.8 (C_{6}); 68.4 (C_{7}); 64.9 (C_{15}, C_{18}); 63.1 (C_{0}); 51.6 (C_{8}); 43.6 (C_{16}); 41.8 (C_{4}, C_{5}); 30.8 (C_{21}); 29.7 (C_{03} or C_{06}); 28.9 (C_{03} or C_{06}); 21.6 (C_{30}). MS (ESI): m/z calculated for [C_{68}H_{46}N_{6}O_{4}Na]^+: 1053.0; found: 1052.6. [α]_{D}^{25}: 3.9 (c 0.42, MeOH).
To a solution of **12.4** (147.8 mg, 140 µmol, 1 eq.) in DMF dry (1.5 mL), NaN₃ (37.3 mg, 570 µmol, 4 eq.) and NaI (3.5 mg, 23 µmol, 0.16 eq.) were added. The reaction mixture was stirred at 65 °C under nitrogen for 20 h. ESI-MS analysis showed total conversion of the starting material. The solvent was evaporated under reduced pressure and the resulting crude was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 121 mg of **7.4** as a white foam (yield 93 %), still containing the 0.4 % (w/w, as measured by NMR integration) of a tosylate salt. Compound **7.4** was used for conjugation with the rods without further purifications.

**1H NMR** (400 MHz, CD₃OD): δ 8.05 (s, 1H, H₁₆); 7.29 – 7.21 (m, 8H, H₁₂, H₁₃); 4.9 (br s, 1H, H₁); 4.63 – 4.53 (m, 8H, H₁₈, H₁₅, H₈); 4.29 (d, J = 5.5 Hz, 4H, H₁₀); 4.01 – 3.82 (m, 5H, H₇, H₂₂, H₆₉, H₉₂); 3.71 – 3.64 (m, 3H, H₂₀, H₆₈, H₆₉); 3.63 – 3.55 (m, 6H, H₁₉, H₂₀, H₂₄); 3.55 – 3.52 (m, 6H, H₆₆, H₂₁, H₂₃); 3.35 – 3.32 (m, 2H, H₂₃); 2.92 – 2.71 (m, 2H, H₁₈, H₂₈); 1.99 – 1.69 (m, 6H, H₁₃, H₁₄, H₁₅, H₁₆, H₁₇, H₁₈).

**13C NMR** (100 MHz, CD₃OD): δ 176.9, 176.7 (C₉); 146.0 (C₁₀); 141.5 (C₁₁); 128.36, 128.34, 128.15, 128.13 (C₁₂, C₁₃); 126.1 (C₁₆); 100.2 (C₁); 76.1 (C₅); 75.6 (C₆); 72.5 (C₁₆); 72.3, 72.2, (C₂, C₃); 71.1, 70.9, 70.7 (C₁₅, C₂₀, C₂₄); 68.94, 68.87 (C₂₃, C₂₂); 68.78 (C₄); 68.4 (C₇); 64.9 (C₁₅, C₁₈); 63.1 (C₆₈, C₆₉); 50.35 (C₂₃); 50.25 (C₆); 42.27 (C₁₀); 40.36, 40.32 (C₆₄, C₆₅); 29.63 (C₂₂); 28.34 (C₆₉ or C₆₈); 27.54 (C₆₄ or C₆₅). MS (ESI): m/z calculated for [C₄₂H₆₀N₈O₁₄]⁺: 923.9; found: 923.4.
Synthesis of the rod-dendrimers

Scheme SI-2 Strategy for the design of the rod-based dendrimers

Scheme SI-3 Synthesis of the rod-dendrimers.
**General procedure for the CuAAC reaction.** In the optimized Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) procedure, starting materials and reagents were added to the reaction mixture as solids or as solutions in water or THF. Water was degassed by bubbling with nitrogen and THF was freshly distilled. The reagents were added to the reaction vessel in the following order: alkyne (1 eq., solid or THF), TBTA (0.2 eq., THF), CuSO₄·5H₂O (0.1 eq., H₂O), sodium ascorbate (0.4 eq., H₂O) and finally the azide monovalent ligand (1.1 eq. per each triple bond, solid or water solution). The final concentration of multivalent scaffold was 3-15 mM in a 1:1 THF:H₂O mixture, depending on the solubility of the components and the products in water. When a concentration ≥ 10 mM in 1:1 THF:H₂O could be obtained, the reaction was stirred at room temperature for 12-24 hours, under nitrogen atmosphere and protected from light. For less soluble mixtures, the reaction was performed at lower concentrations (typically 3 mM) under microwave assisted conditions for 1-2 h at 60 °C. In both cases, the reaction was monitored by TLC and/or MALDI mass spectrometry (DHB or sinapinic acid matrix) until completion. In general, the formation of divalent compounds could be monitored by TLC (eluent: CH₂Cl₂:MeOH:H₂O 75:25:2.5) while hexavalent compounds were best analysed by MALDI mass. When intermediates were observed but the azide monovalent ligand was totally consumed, the latter was added together with additional 0.4 eq. of sodium ascorbate. The crude was purified by size exclusion chromatography on a Sephadex LH20 column (Ø 3 cm, H 55 cm; eluent: MeOH) as MeOH solution and by reverse phase chromatography (C18; eluent: water with a gradient of MeOH from 0 % to 100 %), when required. The metal scavenger Quadrasil™-MP was used to remove copper salts either from the reaction mixtures before purification, or from a solution of the isolated final compound. In either case, the suspension was stirred for 10 min and the resin filtered off.

**Compound 1.5.6**

The reaction between 1⁻ (3.7 mg, 11.1 μmol, 1 eq.) and 5.6⁻ (42.7 mg, 24.3 μmol, 2.2 eq.) was performed in 1:1 THF:H₂O ([1] 15 mM), according to the general procedure for 18 h at room temperature, under nitrogen atmosphere and in the dark. The crude mixture was directly purified by size exclusion chromatography onto a Sephadex LH-20 column (MeOH), obtaining 38 mg of pure 1.5.6 as a white solid (yield 90%). Copper salts were removed by adding Quadrasil™-MP (S/Pd 7:1, 5 mg) to a solution of the product in MeOH; the
mixture was stirred for 10 min, then the resin was filtered off and the solvent evaporated. \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta\) 8.59 (s, 2H, H2); 7.92 (s, 6H, H11); 7.86 (s, 2H, H8); 4.89 (br s, 6H, H3); 4.70 – 4.61 (m, 4H, H20); 4.57 (t, \(J = 4.8\) Hz, 12H, H6); 4.47 (s, 12H, H13); 4.31 (s, 4H, H21); 4.02 – 3.80 (m, 38H, H7, H6a, H2, H52, H19, H22); 3.79 – 3.73 (m, 4H, H13); 3.72 – 3.63 (m, 22H, H6a, H13, H1, H46); 3.62 (s, 36H, H14); 3.60 – 3.54 (m, 10H, H1, H11); 3.53 – 3.45 (m, 10H, H5, H12); 3.38 (s, 12H, H14); 3.35 (s, 4H, H16); 2.77 (td, \(J = 12.5, 3.5\) Hz, 6H, H64); 2.66 (td, \(J = 12.2, 3.4\) Hz, 6H, H65); 2.05 – 1.88 (m, 12H, H32eq, H66eq); 1.70 (t, \(J = 13.3\) Hz, 6H, H66ax or H33ax); 1.54 (t, \(J = 12.7\) Hz, 6H, H66ax or H33ax). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 176.8, 176.6 (C3); 150.9 (C83); 146.2 (C12); 143.7 (C22); 127.6 (C21); 125.7 (C11); 121.0 (C61); 112.26 (C82); 100.5 (C4); 75.7 (C5); 75.6 (C3); 73.7 (C63); 72.5 (C61); 72.4 (C3); 72.2 (C22); 72.0 (C14a); 71.5 (C17); 70.8 (C16); 70.6 (C62); 69.9 (C14, C16); 68.6 (C4); 68.4 (C7); 65.4 (C13); 63.1 (C9); 62.3 (C64); 52.5, 52.5 (C10); 51.5 (C8, C20); 46.55 (C15); 40.21 (C84); 40.08 (C63); 28.86 (C63 or C66); 28.32 (C63 or C66). MS (ESI–HRMS): m/z calculated for [C\(_{162}H_{247}N_{2}O_{82}]+^+: 3841.5929; found: 3841.5871 (after deconvolution). [\(\alpha\)]\(D\)\(^{25}\): +29.5 (c 0.65, MeOH).

**Compound 2.5.6**

To a stirred solution of TIPS-2\(^4\) (5 mg, 5.2 \(\mu\)mol, 1 eq.) in THF (120 \(\mu\)L), TBAF (1 M in THF, 10.5 \(\mu\)L, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH\(_3\)Cl\(_2\)/MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 5.6\(^\circ\) (20 mg, 11.4 \(\mu\)mol, 2.2 eq.) was added as a solid; the final concentration of 2 was 15 mM. The reaction was stirred overnight in the dark, Quadrasil\(^{TM}\)-MP (S/Pd 14:1, 5 mg) was added, stirred for 10 min, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 13 mg of pure 2.5.6 as a yellow solid (yield 62%).\(^{1}\)H NMR (400 MHz, CD\(_3\)OD): \(\delta\) 8.60 (s, 2H, H21); 7.92 (s, 6H, H11); 7.85 (s, 2H, H6); 7.22 (s, 2H, H6); 4.87 (br s, 6H, H3); 4.69 – 4.63 (m, 4H, H20); 4.59 (t, \(J = 4.7\) Hz, 12H, H6); 4.46 (s, 12H, H13); 4.34 – 4.24 (m, 8H, H6a, H22); 4.00 – 3.90 (m, 24H, H62, H66, H7, H19); 3.90 – 3.79 (m, 18H, H62, H6, H6a); 3.79 – 3.71 (m, 8H, H6a, H66); 3.71 – 3.63 (m, 26H, H63, H67, H3, H6b, H12); 3.62 (s, 36H, H14); 3.60 – 3.53 (m, 10H, H4, H17, or H18); 3.53 – 3.46 (m, 10H, H6, H12, or H18); 3.35 (s, 16H, H6a, H16); 2.77 (td, \(J = 12.6, 3.4\) Hz, 6H, H64); 2.66 (td, \(J = 12.3, 3.5\) Hz, 6H, H65); 2.03 – 1.91 (m, 12H, H32eq, H66eq); 1.75 – 1.49 (m, 12H, H33ax, H66ax). \(^{13}\)C
NMR (100 MHz, CD3OD): δ 176.8, 176.6 (C8); 155.3 (C80); 150.5 (C83); 146.2 (C22); 143.5 (C12); 125.7 (C22); 125.6 (C11); 122.3 (C81); 118.4 (C83); 114.5 (C82); 100.6 (C1); 75.70 (C3); 75.6 (C7); 74.1; 73.8 (C62, C67); 72.5 (C61); 72.4 (C2); 72.2 (C62); 72.0, 71.5 (C17, C18); 70.9, 70.7, 70.5 (C62, C66, C61); 69.9 (C14, C16); 69.5 (C63); 68.6 (C4); 68.4 (C7, C19); 65.4 (C13); 63.1 (C6); 62.4, 62.3 (C64, C68); 52.5, 52.5 (C10); 51.6 (C6, C26); 40.2, 40.1 (C64, C65); 28.9 (C63 or C66); 28.3 (C63 or C66). MS (MALDI, matrix: sinapinic acid, solvent: MeOH): m/z calculated for [C178H267N24O88]+: 4151.22; found: 4150.0. MS (ESI-HRMS): calculated for [C178H266N24O88]: 4147.70772; found: 4147.71526 (after deconvolution). [α]D25: +24.1 (c 0.24, MeOH).

**Compound 3.5.6**

To a stirred solution of TIPS-3 (12.4 mg, 9.8 μmol, 1 eq.) in THF (400 μL), TBAF (1 M in THF, 22.0 μL, 2 eq.) was added at room temperature under nitrogen. After 1 h, TLC analysis (CH3Cl2:MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 5.6 (42.7 mg, 24.3 μmol, 2.2 eq.) was added as a solid; the final concentration of 2 was 10 mM. The crude mixture was directly purified by size exclusion chromatography onto a Sephadex LH-20 column (MeOH), obtaining 37 mg of pure 3.5.6 as yellow solid (yield 85%). Copper salts were removed by adding Quadrasil™-MP (S/Pd 7:1, 5 mg) to a 3.5.6 solution in MeOH; the mixture was stirred for 10 min, then the resin was filtered off and the solvent evaporated. 1H NMR (400 MHz, CD3OD): δ 8.58 (s, 2H, H12); 7.92 (s, 6H, H11); 7.84 (s, 2H, H610); 7.20 (s, 4H, H62, H63); 4.89 (br s, 6H, H11); 4.65 (s, 4H, H20); 4.58 (t, J = 4.7 Hz, 12H, H3); 4.46 (s, 12H, H12); 4.35 – 4.21 (m, 12H, H62, H63, H69); 4.00 – 3.89 (m, 28H, H3, H19, H52, H66, H10); 3.89 – 3.83 (m, 12H, H62, H66); 3.82 (dd, J = 3.1, 1.6 Hz, 6H, H2); 3.78 – 3.71 (m, 12H, H63, H67, H1111); 3.71 – 3.64 (m, 30H, H3, H6b, H62, H66, H12); 3.62 (s, 36H, H10); 3.60 – 3.53 (m, 10H, H62, H11); 3.53 – 3.45 (m, 10H, H5a, H5b); 3.35 (s, 12H, H12); 3.33 (s, 4H, H16); 2.77 (td, J = 12.4, 3.5 Hz, 6H, H2a); 2.66 (td, J = 12.4, 3.5 Hz, 6H, H2a); 2.06 – 1.86 (m, 12H, H66a, H13a); 1.70 (t, J = 13.4 Hz, 6H, H66a or H13a); 1.54 (t, J = 12.6 Hz, 6H, H66a or H13a). 13C NMR (100 MHz, CD3OD): δ 176.8, 176.6 (C8); 155.3, 155.0, 150.5, 146.2 (C12); 143.5 (C22); 127.06 (C12); 125.7 (C11); 122.4, 119.1 (C62); 118.3 (C80); 115.9, 114.3, 112.9 (C610); 103.2, 101.4, 100.5 (C1); 92.8, 91.7, 91.1, 75.7 (C8); 75.6 (C3); 74.1, 73.7, 72.5 (C61); 72.4 (C2); 72.2 (C62); 72.0 (C13); 71.5 (C12); 71.0, 70.9, 70.8, 70.7, 70.5, 69.8 (C13, C18); 69.5 (C6a); 68.6 (C4a); 68.4 (C4); 65.4 (C13); 63.1 (C6); 62.4, 62.4, 62.3, 52.5, 52.5 (C10); 51.5 (C6, C26); 46.6 (C15); 40.2 (C64); 40.1 (C65); 28.9 (C63 or C66); 28.3 (C63 or C66). MS (ESI-HRMS): m/z calculated
for \([\text{C}_{194}\text{H}_{287}\text{N}_{36}\text{O}_{94}]^+\): 5103.4; found: 5102.6. MS (ESI-HRMS): \(m/z\) calculated for \([\text{C}_{246}\text{H}_{330}\text{N}_{36}\text{O}_{92}]^+\): 5100.27592; found: 5100.29384 (after deconvolution). \([\alpha]_D^25^\circ\) -18.9 (c 0.1, MeOH).

**Compound 1.5.4**

The reaction between 1\(^4\) (1.2 mg, 3.4 µmol, 1 eq.) and 5.4\(^5\) (18 mg, 7.4 µmol, 2.2 eq.) was performed in 1:1 THF:H\(_2\)O ([\(\text{I}\)] 3.4 mM), according to the general procedure at 60 °C under microwave irradiation for 90 min. Quadrasil™-MP (S/Pd 22:1, 5 mg) was added to the reaction mixture, stirred for 10 min and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 9 mg of pure 1.5.4 as a white solid (yield 50 %). \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta\) 8.55 (s, 2H, H\(_{26}\)); 7.90 (s, 6H, H\(_{16}\)); 7.82 (s, 2H, H\(_{62}\)); 7.27 – 7.12 (m, 48H, H\(_{12}, H_{13}\)); 4.88 (br s, 6H, H\(_{1}\)); 4.61 – 4.56 (m, 4H, H\(_{23}\)); 4.53 (s, 24H, H\(_{13}\)); 4.50 – 4.44 (m, 12H, H\(_{6}\)); 4.40 (s, 12H, H\(_{18}\)); 4.26 – 4.24 (m, 28H, H\(_{10}, H_{21}\)); 3.93 - 3.85 (m, 32H, H\(_{2}, H_{92}, H_{7}, H_{24}, H_{62}\)); 3.82 (bs, 6H, H\(_{16}\)); 3.72 - 3.67 (m, 14H, H\(_{6b}, H_{63}, H_{64}\)); 3.65 – 3.62 (m, 12H, H\(_{9}, H_{91}\)); 3.60 - 3.52 (m, 16H, H\(_{4}, H_{39}, H_{23}\)); 3.45 – 3.44 (m, 4H, H\(_{22}\)); 3.33 – 3.27 (m, 16H, H\(_{19}, H_{21}\)); 2.91 – 2.74 (m, 12H, H\(_{44}, H_{93}\)); 1.96 – 1.66 (m, 24H, H\(_{db}, H_{66}\)). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 177.1, 176.8 (C\(_6\)); 146.3 (C\(_{17}\)); 141.7, 141.7 (C\(_{14}\)); 139.2, 139.2 (C\(_{11}\)); 128.6, 128.5, 128.3, 128.3 (C\(_{13}, C_{12}\)); 126.4 (C\(_{26}\)); 126.1 (C\(_{16}\)); 112.6 (C\(_{22}\)); 100.6 (C\(_1\)); 76.3 (C\(_3\)); 75.7 (C\(_2\)); 73.9 (C\(_{43}\)); 72.6, 72.4, 72.3 (C\(_{21}, C_{22}, C_{23}\)); 71.9, 71.2 (C\(_{22}, C_{23}\)); 70.50 (C\(_{22}\)); 69.83 (C\(_{19}, C_{21}\)); 68.7 (C\(_4\)); 69.0 (C\(_{61}\)); 68.5 (C\(_7, C_{24}\)); 65.5 (C\(_{18}\)); 65.1 (C\(_{15}\)); 63.3 (C\(_8\)); 62.5 (C\(_{64}\)); 51.7 (C\(_{25}, C_{6}\)); 43.9 (C\(_{10}\)); 41.9 (C\(_{24}, C_{95}\)); 29.7 (C\(_{30}\) or C\(_{66}\)); 29.1 (C\(_{93}\) or C\(_{66}\)). MS (MALDI, matrix: sinapinic acid, solvent: MeOH): \(m/z\) calculated for \([\text{C}_{246}\text{H}_{330}\text{N}_{36}\text{O}_{92}]^+\): 5103.4; found: 5102.6. MS (ESI-HRMS): \(m/z\) calculated for \([\text{C}_{246}\text{H}_{330}\text{N}_{36}\text{O}_{92}]^+\): 5100.27592; found: 5100.29384 (after deconvolution). \([\alpha]_D^25^\circ\) +24.1 (c 0.65, MeOH).

**Compound 2.5.4**
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To a stirred solution of TIPS-2\(^4\) (4.1 mg, 4.4 μmol, 1 eq.) in THF (200 μL), TBAF (1 M in THF, 8.8 μL) was added under nitrogen. After 1 h, TLC analysis (CH\(_2\)Cl\(_2\):MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 5.4\(^4\) (23 mg, 9.6 μmol, 2.2 eq.) was added as a solid; the final concentration of 2 was 4 mM. The reaction mixture was heated at 60 °C under microwave irradiation for 60 min and then left stirring at room temperature overnight in the dark. Quadrasil™-MP (S/Pd 17:1, 5 mg) was added to the reaction mixture, which was stirred for 10 minutes, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 12 mg of pure 2.5.4 as a yellow solid (yield 52%). \(^1\)H NMR (400 MHz, CD\(_3\)OD): δ 8.56 (s, 2H, H\(_{26}\)); 7.93 (s, 6H, H\(_{16}\)); 7.80 (s, 2H, H\(_{62}\)); 7.25 – 7.16 (m, 50H, H\(_{12r}\), H\(_{13r}\), H\(_{8r}\)); 4.88 (br s, 6H, H\(_1\)); 4.65 – 4.60 (m, 4H, H\(_{10}\)); 4.55 – 4.48 (m, 36H, H\(_{15}\), H\(_8\)); 4.40 (s, 12H, H\(_{18}\)); 4.29 – 4.16 (m, 32H, H\(_{10r}\), H\(_{6}G_{1r}\), H\(_{6}G_{5r}\)); 3.95 - 3.80 (m, 42H, H\(_2\), H\(_{4a}\), H\(_{2D}\), H\(_7\), H\(_{2A}\), H\(_{6G_{2r}}\), H\(_{6G_{6r}}\)); 3.71 - 3.62 (m, 34H, H\(_{8b}\), H\(_{D1r}\), H\(_3\), H\(_{G3r}\), H\(_{67}\), H\(_{6A}\), H\(_{G8}\)); 3.59 - 3.50 (m, 16H, H\(_4\), H\(_5\), H\(_{22}\)); 3.45 - 3.42 (m, 4H, H\(_{23}\)); 3.33 – 3.27 (m, 16H, H\(_{22r}\), H\(_{19}\)); 2.85 – 2.80 (m, 12H, H\(_{D4}\), H\(_{D3}\)); 1.92 – 1.65 (m, 24H, H\(_{D3}\), H\(_{D6}\)). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): δ 179.0, 176.7 (C\(_6\)); 146.1 (C\(_{21}\)); 143.5 (C\(_{27}\)); 141.6 – 141.53 (C\(_{14}\)); 139.1, 139.0 (C\(_{11}\)); 128.4, 128.2 (C\(_{13}\), C\(_{12}\)); 126.3 (C\(_{26}\)); 125.7 (C\(_{10}\)); 118.3 (C\(_{8}\)); 112.7 (C\(_{82}\)); 100.5 (C\(_1\)); 76.1 (C\(_6\)); 75.6 (C\(_10\)); 74.0 (C\(_{G3r}\), C\(_{G7}\)); 72.6 (C\(_{D1}\)); 72.3 (C\(_2\), C\(_{D2}\)); 71.99, 71.49 (C\(_{D2}\), C\(_{D3}\)); 70.8 - 69.5 (C\(_{G1}\), C\(_{G5r}\), C\(_{G2r}\), C\(_{G6r}\), C\(_{19}\), C\(_{21}\)); 68.8 (C\(_4\)); 68.3 (C\(_7\), C\(_{24}\)); 65.3 (C\(_{14a}\)); 64.9 (C\(_{13}\)); 63.0 (C\(_4\)); 62.3 (C\(_{G4}\), C\(_{G8}\)); 51.5 (C\(_{25}\), C\(_8\)); 43.6 (C\(_{10}\)); 41.7 (C\(_{D4}\), C\(_{D5}\)); 29.7 (C\(_{D3}\) or C\(_{D6}\)); 29.0 (C\(_{D3}\) or C\(_{D6}\)). MS (MALDI, matrix: sinapinic acid, solvent: MeOH): m/z calculated for [C\(_{262}H_{353}N_{36}O_{88}\]^+: 5412.3; found: 5413.2. MS (ESI-HRMS): calculated for [C\(_{262}H_{350}N_{36}O_{88}\]):5411.41100; found: 5411.42469 (after deconvolution). [\(\alpha\)]\(_D\)\(^{25}\): -1.7 (c 0.51, MeOH).

Compound 3.5.4

To a stirred solution of TIPS-3\(^4\) (3.2 mg, 2.5 μmol, 1 eq.) in THF (200 μL), TBAF (1 M in THF, 5.1 μL) was added under nitrogen atmosphere. After 1 h, TLC analysis (CH\(_2\)Cl\(_2\):MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 5.4\(^4\) (13.3 mg, 5.6 μmol, 2.2 eq.) was added as a solid; the final concentration of 3 was 3 mM. The reaction mixture was heated at 60 °C under microwave irradiation for 90 min. Quadrasil™-MP (S/Pd 30:1, 5 mg) was added to the reaction mixture, which was stirred for 10 min, and then filtered off. The solvent was removed under
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Reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 12 mg of pure 3.5.4 as a yellowish solid (yield 85 %).

$^1$H NMR (400 MHz, CD$_3$OD): δ 8.56 (s, 2H, H$_{26}$); 7.92 (s, 6H, H$_{16}$); 7.82 (s, 2H, H$_{12}$); 7.28 – 7.13 (m, 52H, H$_{12}$, H$_{13}$, H$_{85}$, H$_{810}$); 4.88 (br s, 6H, H$_3$); 4.62 – 4.57 (m, 4H, H$_{23}$); 4.56 – 4.48 (m, 36H, H$_{15}$, H$_4$); 4.39 (s, 12H, H$_{18}$); 4.32 – 4.17 (m, 36H, H$_{10}$, H$_{61}$, H$_{65}$, H$_{69}$); 3.95 – 3.79 (m, 46H, H$_2$, H$_{69}$, H$_{62}$, H$_7$, H$_{24}$, H$_{62}$, H$_{66}$, H$_{610}$); 3.75 - 3.61 (m, 42H, H$_{69}$, H$_{63}$, H$_3$, H$_{63}$, H$_{67}$, H$_{611}$, H$_{64}$, H$_{68}$, H$_{612}$); 3.60 - 3.39 (m, 16H, H$_4$, H$_5$, H$_{22}$); 3.45 – 3.44 (m, 4H, H$_{23}$); 3.33 – 3.27 (m, 16H, H$_{19}$, H$_{21}$); 2.89 – 2.75 (m, 12H, H$_{64}$, H$_{63}$); 1.96 – 1.66 (m, 24H, H$_{63}$, H$_{66}$). $^{13}$C NMR (100 MHz, CD$_3$OD): δ 177.1, 176.8 (C$_8$); 146.3 (C$_{15}$); 143.7 (C$_{27}$); 141.7(C$_{14}$); 139.2, 139.2 (C$_{11}$); 128.6, 128.5, 128.3 (C$_{12}$, C$_{12}$); 126.3 (C$_{26}$); 126.0 (C$_{16}$); 119.3 (C$_{510}$, C$_{85}$); 113.5 (C$_{82}$); 100.6 (C$_1$); 76.3 (C$_4$); 75.7 (C$_3$); 74.3, 74.3, 73.9 (C$_{63}$, C$_{67}$, C$_{611}$); 72.6, 72.4, 72.3 (C$_{62}$, C$_{2}$, C$_{2}$); 72.3 – 69.0 (C$_{22}$, C$_{23}$, C$_{18}$, C$_{21}$, C$_{62}$, C$_{66}$, C$_{610}$, C$_{61}$, C$_{65}$, C$_{69}$); 69.0 (C$_4$); 68.5 (C$_7$, C$_{24}$); 65.5 (C$_{18}$); 65.1 (C$_{61}$); 63.3 (C$_8$); 62.6, 62.5, 62.5 (C$_{64}$, C$_{68}$, C$_{612}$); 51.7 (C$_{25}$, C$_9$); 43.9 (C$_{20}$); 42.0, 41.9 (C$_{64}$, C$_{65}$); 29.9 (C$_{63}$ or C$_{66}$); 29.2 (C$_{63}$ or C$_{66}$). MS (MALDI, matrix: sinapinic acid, solvent: MeOH): m/z calculated for [C$_{278}$H$_{370}$N$_{36}$O$_{94}$Na$^+$]: 5743.1; found = 5744.6; calculated for [C$_{278}$H$_{370}$N$_{36}$O$_{94}$]: 5720.1; found = 5719.9. MS (ESI-HRMS): m/z calculated for [C$_{278}$H$_{370}$N$_{36}$O$_{94}$Na$^+$$^+$]: 5716.52790; found = 5719.52543 (after deconvolution). [α]$_D^{25}$: -8.1 (c 0.22, MeOH).

**Compound 1.7.6**

![](image)

The reaction between 1$^+$ (4.0 mg, 12.0 µmol, 1 eq.) and 7.6 (19.1 mg 97 % w/w, 26.8 µmol, 2.2 eq.) was performed in 1:1 THF:H$_2$O ([I] 20 mM), according to the general procedure at room temperature under nitrogen in the dark overnight. Quadrasili™-MP (S/Pd 6:1, 5 mg) was added to the reaction mixture, stirred for 10 min and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 15 mg of pure 1.7.6 as a white solid (yield 73 %). $^1$H NMR (400 MHz, CD$_3$OD): δ 8.60 (s, 2H, H$_{21}$); 7.93 (s, 2H, H$_{11}$); 7.90 (s, 2H, H$_{62}$); 4.88 (br s, 2H, H$_3$); 4.65 (t, J = 4.9 Hz, 4H, H$_{20}$); 4.57 – 4.53 (m, 8H, H$_8$, H$_{13}$); 4.36 – 4.31 (m, 4H, H$_{61}$); 3.98 – 3.94 (m, 4H, H$_{62}$); 3.94 – 3.84 (m, 10H, H$_{15}$, H$_7$, H$_{22}$); 3.83 – 3.80 (m, 4H, H$_{68}$, H$_3$); 3.78 – 3.73 (m, 4H, H$_{64}$); 3.71 – 3.68 (m, 4H, H$_{63}$); 3.65 – 3.61 (m, 18H, H$_6$, H$_{68}$, H$_{610}$, H$_{10}$); 3.59 – 3.50 (m, 10H, H$_{65}$, H$_{14}$ or H$_{15}$, H$_{16}$ or H$_{18}$); 3.50 – 3.39 (m, 10H, H$_4$, H$_{14}$ or H$_{15}$, H$_{16}$ or H$_{18}$); 2.76 (td, J = 12.6, 3.5 Hz, 2H,
**Elettronic Supplementary Information**

Compound 2.7.6

To a stirred solution of TIPS-2^4 (13.4 mg, 14.0 µmol, 1 eq.) in THF (300 µL), TBAF (1 M in THF, 28.0 µL, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH\textsubscript{2}Cl\textsubscript{2}:MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 7.6 (22.3 mg 97 % w/w, 31.3 µmol, 2.2 eq.) was added as a solid; the final concentration of 2 was 15 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil\textsuperscript{TM}-MP (S/Pd 5:1, 5 mg) was added to the reaction mixture, stirred for 10 min and then filtered. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 23 mg of **2.7.6** not pure. The remaining tetrabutylammonium salt was removed by automated reverse phase flash chromatography (C18, water with gradient of MeOH from 0 % to 100 %), obtaining 17 mg of pure **2.7.6** as a yellow solid (yield 60 %). \(^1\)H NMR (400 MHz, CD\textsubscript{3}OD): \(\delta\ 8.58\ (s, 2H, H_{212}); 7.94\ (s, 2H, H_{111}); 7.87\ (s, 2H, H_{82}); 7.22\ (s, 2H, H_{83}); 4.87\ (br s, 2H, H_{21}); 4.64\ (t, J = 4.8 Hz, 4H, H_{220}); 4.62 \textendash 4.52\ (m, 8H, H_{68}, H_{13}); 4.37 \textendash 4.30\ (m, 4H, H_{G1}); 4.30 \textendash 4.22\ (m, 4H, G_{G2}); 3.98 \textendash 3.92\ (m, 8H, H_{G2}, H_{G6}); 3.92 \textendash 3.88\ (m, 4H, H_{7} or H_{19}); 3.88 \textendash 3.83\ (m, 6H, H_{7} or H_{19}, H_{102}); 3.83 \textendash 3.78\ (m, 4H, H_{69}, H_{72}); 3.78 \textendash 3.70\ (m, 8H, H_{G3}, H_{G4}); 3.70 \textendash 3.59\ (m, 26H, H_{G7}, H_{G8}, H_{G6}, H_{O1}, H_{3}, H_{10}); 3.59 \textendash 3.47\ (m, 12H, H_{16} or H_{18}, H_{14} or H_{15}, H_{4}, H_{3}); 3.47 \textendash 3.37\ (m, 8H, H_{16} or H_{18}, H_{14} or H_{15}); 2.76\ (td, J = 12.6, 3.6 Hz, 2H, H_{DA} or H_{DB}); 2.64\ (td, J = 12.6, 3.6 Hz, 2H, H_{DA} or H_{DB}); 1.95\ (t, J = 14.2 Hz, 4H, H_{D3eq}; H_{D6eq}); 1.77\ (tt, J = 6.4 Hz, 4H, H_{17}); 1.72 \textendash 1.64\ (m, 2H, H_{D3ax} or H_{D6ax}); 1.56 \textendash 1.48\ (m, 2H, H_{D3ax} or H_{D6ax}). \(^{13}\)C NMR (100 MHz,
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CD$_3$OD): $\delta$ 176.8, 176.6 (C$_6$); 155.3 (C$_{86}$); 150.5 (C$_{83}$); 145.84 (C$_{22}$); 143.5 (C$_{12}$); 127.1 (C$_{41}$); 125.9 (C$_{13}$); 122.2 (C$_{40}$); 118.8, 118.3 (C$_{85}$); 114.6 (C$_{44}$); 112.9 (C$_{62}$); 100.5 (C$_{1}$); 91.8 (C$_{77}$); 75.7 (C$_{3}$); 75.6 (C$_{8}$); 74.1, 73.7 (C$_{83}$, C$_{74}$); 72.5, 72.4 (C$_{3}$, C$_{51}$); 72.1 (C$_{3}$, C$_{52}$); 71.1 (C$_{14}$ or C$_{15}$); 71.0, 70.9 (C$_{62}$, C$_{66}$); 70.7 (C$_{61}$); 70.6 (C$_{14}$ or C$_{15}$); 70.2 (C$_{7}$ or C$_{29}$); 69.5 (C$_{53}$); 68.9 (C$_{16}$, C$_{18}$); 68.6 (C$_{4}$); 68.4 (C$_{7}$ or C$_{19}$); 64.9 (C$_{13}$); 63.1 (C$_{1}$); 62.4, 62.3 (C$_{44}$, C$_{46}$); 52.4 (C$_{10}$); 51.6 (C$_{6}$, C$_{8}$); 40.2, 40.1 (C$_{44}$, C$_{45}$); 30.9 (C$_{1}$); 28.8 (C$_{63}$ or C$_{66}$); 28.3 (C$_{63}$ or C$_{66}$). MS (MALDI, matrix: sinapinic acid, solvent: MeOH): $m/z$ calculated for [C$_{90}$H$_{134}$N$_{12}$O$_{66}$Na]$^+$: 2047.0; found: 2046.4. MS (ESI-HRMS): calculated for [C$_{90}$H$_{134}$N$_{12}$O$_{66}$]: 2022.88203; found: 2022.88641 (after deconvolution). [$\alpha$]$_D$$^{25}$: +16.1 (c 0.50 MeOH).

**Compound 3.7.6**

To a stirred solution of TIPS-3-4 (13.0 mg, 10.5 µmol, 1 eq.) in THF (280 µL), TBAF (1 M in THF, 21.0 µL, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH$_2$Cl$_2$:MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 7.6 (16.8 mg 97 % w/w, 23.6 µmol, 2.2 eq.) was added as a solid; the final concentration of 3 was 15 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil™-MP (S/Pd 7:1, 5 mg) was added to the reaction mixture, which was stirred for 10 min, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 23 mg of pure 3.7.6 as a yellow solid (yield 92 %). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 8.56 (s, 2H, H$_{22}$); 7.93 (s, 2H, H$_{11}$); 7.86 (s, 2H, H$_{41}$); 7.20 (s, 2H, H$_{83}$); 7.17 (s, 2H, H$_{810}$); 4.87 (br s, 2H, H$_2$); 4.64 (t, $J = 4.7$ Hz, 4H, H$_{20}$); 4.61 – 4.52 (m, 8H, H$_{68}$, H$_{13}$); 4.34 – 4.24 (m, 12H, H$_{63}$, H$_{65}$, H$_{69}$); 3.98 – 3.88 (m, 16H, H$_{62}$, H$_{66}$, H$_{610}$, H$_7$ or H$_{19}$); 3.88 – 3.84 (m, 8H, H$_{7}$ or H$_{19}$, H$_{62}$, H$_{66}$); 3.84 – 3.78 (m, 4H, H$_2$, H$_{66}$); 3.77 – 3.74 (m, 4H, H$_{44}$); 3.74 – 3.70 (m, 8H, H$_{63}$, H$_{77}$); 3.70 – 3.66 (m, 12H, H$_{68}$, H$_{612}$, H$_{811}$); 3.65 – 3.63 (m, 4H, H$_3$, H$_{10}$); 3.62 (s, 12H, H$_{10}$); 3.59 – 3.47 (m, 12H, H$_{16}$ or H$_{18}$, H$_{14}$ or H$_{15}$, H$_8$, H$_9$); 3.46 – 3.39 (m, 8H, H$_{14}$ or H$_{15}$, H$_{16}$ or H$_{18}$); 2.76 (td, $J = 12.7$, 3.6 Hz, 2H, H$_{20}$ or H$_{53}$); 2.65 (td, $J = 12.7$, 3.6 Hz, 2H, H$_{40}$ or H$_{55}$); 1.83 – 1.73 (m, 4H, H$_{117}$); 1.73 – 1.64 (m, 2H, H$_{33}$ or H$_{34}$); 1.57 – 1.47 (m, 2H, H$_{33}$ or H$_{34}$); 1.33 (m, 4H, H$_{33}$ or H$_{34}$); 1.33 (m, 4H, H$_{33}$ or H$_{34}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 176.77, 176.62 (C$_6$); 155.32, 154.92 (C$_{86}$, C$_{811}$); 150.46 (C$_{83}$); 145.81 (C$_{22}$); 143.43 (C$_{12}$); 127.09 (C$_{21}$); 125.87 (C$_{11}$); 122.30 (C$_{81}$); 119.00 (C$_{10}$); 118.20 (C$_{83}$); 115.86 (C$_{44}$); 114.34 (C$_{85}$); 112.79 (C$_{42}$); 100.48 (C$_{1}$); 92.81, 91.70 (C$_{77}$, C$_{8}$); 75.68 (C$_{5}$); 75.57 (C$_{3}$);
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74.12, 73.74 (C_{63}, C_{67}, C_{611}); 72.47, 72.39 (C_{61}, C_{2}); 72.09 (C_{20}); 71.12 (C_{14} or C_{15}); 70.93, 70.83 (C_{61}, C_{63}); 70.67 (C_{62}, C_{66}, C_{610}); 70.55 (C_{14} or C_{15}); 70.19 (C_7 or C_{19}); 69.40 (C_{69}); 68.84 (C_{16}, C_{18}); 68.61 (C_4); 68.34 (C_7 or C_{19}); 64.86 (C_{13}); 63.08 (C_6); 62.38, 62.36, 62.27 (C_{64}, C_{68}, C_{12}); 54.83, 52.45 (C_{10}); 51.58, 51.53 (C_{20}, C_{8}); 40.19, 40.05 (C_{24}, C_{25}); 30.85 (C_{13}); 28.81 (C_{63} or C_{66}); 28.26 (C_{63} or C_{66}). MS (ESI-HRMS): calculated for [C_{106}H_{154}N_{12}O_{46}]^{+}: 2331.0082; found: 2331.00805 (after deconvolution). [α]_{D}^{25}: +8.5 (c 0.29, MeOH).

**Compound 1.7.4**

![1.7.4](image)

The reaction between 1 (4.0 mg, 12.0 µmol, 1 eq.) and 7.4 (19.1 mg 99.6 % w/w, 26.6 µmol, 2.2 eq.) was performed in 1:1 THF:H2O ([1] 20 mM), according to the general procedure at room temperature under nitrogen in the dark overnight. Quadrasil™-MP (S/Pd 6:1, 5 mg) was added to the reaction mixture, stirred for 10 min and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 20 mg of 1.7.4 not pure. The remaining tetrabutylammonium salt was removed through automated reverse phase flash chromatography (C18, water with gradient of MeOH from 0 % to 100 %), obtaining 17 mg of pure 1.7.4 as a white solid (yield 65 %). 1H NMR (400 MHz, CD3OD): δ 8.58 (s, 2H, H_{2a}); 7.96 (s, 2H, H_{16}); 7.88 (s, 2H, H_{2a}); 7.30 – 7.15 (m, 16H, H_{12}, H_{13}); 4.89 (br s, 2H, H_{1}); 4.62 (t, J = 4.9 Hz, 4H, H_{2b}); 4.58 – 4.47 (m, 16H, H_{6b}, H_{15}, H_{18}); 4.29 (dd, J = 13.2, 4.8 Hz, 12H, H_{10}, H_{5}); 3.96 – 3.85 (m, 16H, H_{62}, H_{7}, H_{2a}, H_2, H_{2d}); 3.83 (d, J = 5.0 Hz, 2H, H_{6a}); 3.74 (t, J = 3.6 Hz, 4H, H_{64}); 3.72 – 3.60 (m, 10H, H_{63}, H_{6}, H_{6b}, H_{61}); 3.58 – 3.48 (m, 12H, H_{5}, H_{21}, H_{19}, H_{4}); 3.45 – 3.36 (m, 8H, H_{23}, H_{20}); 2.89 – 2.71 (m, 4H, H_{64}, H_{65}); 1.97 – 1.78 (m, 8H, H_{69}, H_{66}); 1.78 – 1.71 (m, 4H, H_{22}). 13C NMR (100 MHz, CD3OD): δ 176.9, 176.7 (C_{9}); 150.9 (C_{63}); 145.8 (C_{23}); 143.7 (C_{17}); 141.6, 141.5 (C_{61}); 139.1, 139.0 (C_{14}); 128.3, 128.2 (C_{12}, C_{13}); 126.9 (C_{69}); 126.1 (C_{16}); 121.0 (C_{64}); 112.2 (C_{62}); 100.4 (C_{7}); 76.2 (C_{6}); 75.6 (C_{3}); 73.7 (C_{61}); 72.6, 72.3, 72.1 (C_{61}, C_{2}, C_{62}); 71.1 – 70.2 (C_{19}, C_{20}, C_{61}, C_{62}); 69.3 (C_{61}); 68.88, 68.86 (C_{21}, C_{23}); 68.81(C_{4}); 68.4 (C_{7}, C_{24}); 64.9, 64.9 (C_{15}, C_{18}); 63.1 (C_{6}); 62.3 (C_{64}); 51.6, 51.5 (C_{8}, C_{25}); 43.7, 43.6 (C_{10}); 41.8, 41.7 (C_{64}, C_{65}); 30.9 (C_{22}); 29.7 (C_{63} or C_{66}); 29.0 (C_{63} or C_{64}). MS (ESI-HRMS): m/z calculated for [C_{106}H_{154}N_{12}O_{46}Na]^+: 2157.97666; found: 2157.98424. [α]_{D}^{25}: -3.2 (c 0.39, MeOH).
**Compound 2.7.4**

To a stirred solution of TIPS-2\(^{1}\) (12.0 mg, 12.6 \(\mu\)mol, 1 eq.) in THF (300 \(\mu\)L), TBAF (1 M in THF, 25.1 \(\mu\)L, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH\(_2\)Cl\(_2\):MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 7.4 (25.3 mg 99.6 % w/w, 28.0 \(\mu\)mol, 2.2 eq.) was added as a solid; the final concentration of 2 was 15 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil\textsuperscript{TM}-MP (S/Pd 6:1, 5 mg) was added to the reaction mixture, which was stirred for 10 min, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 19 mg of 2.7.4 not pure. The remaining tetrabutylammonium salt was removed through automated reverse phase flash chromatography (C18, water with gradient of MeOH from 0 % to 100 %), obtaining 17 mg of pure 2.7.4 as a yellow solid (yield 57 %). \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta\) 8.57 (s, 2H, H\(_{26}\)); 7.98 (s, 2H, H\(_{16}\)); 7.86 (s, 2H, H\(_{62}\)); 7.26 – 7.17 (m, 18H, H\(_{12}\), H\(_{13}\), H\(_{63}\)); 4.87 (br s, 2H, H\(_2\)); 4.66 – 4.59 (m, 4H, H\(_{123}\)); 4.59 – 4.52 (m, 16H, H\(_8\), H\(_{15}\), H\(_{18}\)); 4.35 – 4.29 (m, 4H, H\(_{61}\)); 4.27 (d, \(J = 4.8\) Hz, 8H, H\(_{10}\)); 4.26 – 4.21 (m, 4H, H\(_{63}\)); 3.95 – 3.82 (m, 24H, H\(_{62}\), H\(_{66}\), H\(_7\), H\(_{24}\), H\(_{62}\), H\(_2\), H\(_6\)); 3.78 – 3.73 (m, 4H, H\(_{64}\)); 3.73 – 3.69 (m, 4H, H\(_{63}\) or H\(_{67}\)); 3.67 – 3.63 (m, 12H, H\(_{68}\), H\(_{63}\) or H\(_{67}\), H\(_{65}\), H\(_3\)); 3.57 – 3.51 (m, 4H, H\(_{6}\), H\(_2\)); 3.50 – 3.48 (m, 4H, H\(_{19}\) or H\(_{20}\), H\(_{12}\) or H\(_{23}\)); 3.44 – 3.34 (m, 4H, H\(_{19}\) or H\(_{20}\), H\(_{12}\) or H\(_{23}\)); 2.86 – 2.71 (m, 4H, H\(_{24}\), H\(_{65}\)); 1.95 – 1.78 (m, 8H, H\(_{63}\), H\(_{66}\)); 1.77 – 1.73 (m, 4H, H\(_{22}\)). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 176.9, 176.7 (C\(_9\)); 155.4 (C\(_{66}\)); 150.5 (C\(_{83}\)); 145.8 (C\(_{27}\)); 143.5 (C\(_{17}\)); 141.6, 141.5 (C\(_{13}\)); 139.1, 139.0 (C\(_{14}\)); 128.4, 128.2 (C\(_{12}\), C\(_{13}\)); 127.1 (C\(_{25}\)); 126.1 (C\(_{16}\)); 122.2 (C\(_{41}\)); 118.3 (C\(_{65}\)); 114.6 (C\(_{64}\)); 112.9 (C\(_{82}\)); 100.3 (C\(_1\)); 91.8 (C\(_{67}\)); 76.2 (C\(_9\)); 75.6 (C\(_8\)); 74.1, 73.7 (C\(_{63}\), C\(_{67}\)); 72.6, 72.3, 72.11 (C\(_{61}\), C\(_2\), C\(_{62}\)); 71.1 – 70.2 (C\(_{19}\), C\(_{20}\), C\(_{61}\), C\(_{62}\), C\(_{66}\)); 69.5 (C\(_{65}\)); 68.9 (C\(_{21}\), C\(_{23}\)); 68.8 (C\(_4\)); 68.4 (C\(_7\), C\(_{24}\)); 64.92, 64.87 (C\(_{15}\), C\(_{18}\)); 63.1 (C\(_4\)); 62.4, 62.3 (C\(_{69}\), C\(_{64}\)); 51.7, 51.5 (C\(_{25}\), C\(_8\)); 43.7, 43.6 (C\(_{10}\)); 41.8 (C\(_{D4}\), C\(_{D3}\)); 30.9 (C\(_{22}\)); 29.7 (C\(_{D3}\) or C\(_{DK}\)); 29.0 (C\(_{D3}\) or C\(_{DK}\)).
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MS (ESI-HRMS): calculated for [C118H162N16O40]: 2443.11342; found: 2443.11450 (after deconvolution). [α]_D^25: +3.9 (c 0.95, MeOH).

**Compound 3.7.4**

To a stirred solution of TIPS-3 (12.4 mg, 10.0 µmol, 1 eq.) in THF (250 µL), TBAF (1 M in THF, 20.0 µL, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH₂Cl₂:MeOH 9:1) showed that the reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 7.4 (20.2 mg 99.6 % w/w, 22.3 µmol, 2.2 eq.) was added as a solid; the final concentration of 3 was 16 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil™-MP (S/Pd 8:1, 5 mg) was added to the reaction mixture, which was stirred for 10 min, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 20 mg of 3.7.4 not pure. The remaining tetrabutylammonium salt was removed through automated reverse phase flash chromatography (C18, water with gradient of MeOH from 0 % to 100 %), obtaining 17 mg of pure 3.7.4 as a yellow solid (yield 60 %). ^1H NMR (400 MHz, CD₂OD): δ 8.56 (s, 2H, H₁₀); 7.98 (s, 2H, H₁₆); 7.85 (s, 2H, H₁₂); 7.28 – 7.15 (m, 20H, H₁₃, H₁₉, H₁₅, H₁₈); 4.87 (br s, 2H, H₁); 4.62 (t, J = 4.8 Hz, 4H, H₁₅); 4.57 – 4.51 (m, 16H, H₉, H₁₅, H₁₈); 4.34 – 4.29 (m, 4H, H₁₁); 4.29 – 4.20 (m, 16H, H₉, H₁₃, H₁₉, H₁₁₀); 3.98 – 3.88 (m, 16H, H₇ or H₂₄, H₂₀, H₁₆, H₁₈); 3.88 – 3.80 (m, 10H, H₇ or H₂₄, H₁₂, H₂, H₁₆a); 3.77 – 3.61 (m, 30H, H₁₆a, H₁₆b, H₁₆c, H₁₆d, H₁₆e); 3.59 – 3.51 (m, 4H, H₁₂, H₁₃); 3.50 – 3.47 (m, 8H, H₁₂₀ or H₁₂₁ or H₁₂₂); 3.43 – 3.33 (m, 8H, H₁₉ or H₂₀₀, H₁₉₁ or H₁₉₂); 2.89 – 2.70 (m, 4H, H₁₆₄, H₁₆₅); 1.93 – 1.80 (m, 8H, H₁₉₃, H₁₉₄); 1.78 – 1.69 (m, 4H, H₁₂₂). ^13C NMR (100 MHz, CD₂OD): δ 176.9, 176.7 (C₉); 155.4, 154.9 (C₁₆, C₁₁₁); 150.5 (C₁₁₁); 145.8 (C₁₇); 143.5 (C₁₇); 141.6, 141.5 (C₁₁₄); 139.1, 139.0 (C₈₅); 128.4, 128.4, 128.15 (C₁₂, C₁₃); 127.1 (C₁₆); 126.1 (C₁₆); 122.3 (C₁₁); 119.0 (C₁₆ or C₈₁₀); 118.2 (C₈₅ or C₈₁₀); 115.9 (C₁₆a); 114.4 (C₁₆₃); 112.8 (C₁₂); 100.3 (C₁); 92.8, 91.7 (C₁₁₇, C₁₁₈); 76.2 (C₉); 75.6 (C₉); 74.1, 73.7 (C₁₆₃, C₁₆₇, C₁₁₁); 72.5, 72.3, 72.1 (C₁₂₁, C₂, C₁₂₂); 71.1 (C₁₉ or C₂₀); 71.1 – 70.6 (C₂₀, C₁₆₆, C₁₁₀, C₁₆₅, C₁₆₇, C₁₆₉, C₁₁₂, C₁₆₁, C₁₆₄, C₁₆₈).
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C₁₉ or C₂₀; 70.2 (C₂₀); 69.4 (C₆₉); 68.9 (C₂₁, C₂₃); 68.8 (C₆); 68.4 (C₇, C₂₄); 64.9, 64.9 (C₁₅, C₁₈); 63.1 (C₆); 62.4, 62.3 (C₉₄, C₉₈, C₉₁₂); 51.7, 51.5 (C₂₅, C₉); 43.7, 43.6 (C₁₀₈); 41.8 (C₇₄ or C₇₅); 41.7 (C₇₄ or C₇₅); 30.9 (C₇₂); 29.7 (C₀₃ or C₀₆); MS (MALDI, matrix: sinapinic acid, solvent: MeOH): m/z calculated for [C₁₃₄H₁₈₃N₁₆O₄₆]⁺: 2754.0; found: 2752.3. MS (ESI-HRMS): calculated for [C₁₃₄H₁₈₂N₁₆O₄₆]: 2751.23941; found: 2751.23567 (after deconvolution). [α]₀⁺²⁵: −4.6 (c 0.33, MeOH).

**Compound 3.6**

![Compound 3.6 Image]

To a stirred solution of TIPS-3⁻ (16.2 mg, 12.8 μmol, 1 eq.) in THF (300 μL), TBAF (1 M in THF, 26.0 μL, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH₂Cl₂:MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 6⁻ (13.1 mg, 28.2 μmol, 2.2 eq.) was added as a solid; the final concentration of 3 was 16 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil™-MP (S/Pd 6:1, 5 mg) was added to the reaction mixture, which was stirred for 10 min, and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redisolved in MeOH and purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 22 mg of 3.6 not pure. The remaining tetrabutylammonium salt was removed through automated reverse phase flash chromatography (C₁₈, water with gradient of MeOH from 0 % to 100 %), obtaining 18 mg of pure 3.6 as a yellow solid (yield 75 %).

¹H NMR (400 MHz, CD₂OD): δ 8.61 (s, 2H, H₁₁₁); 7.88 (s, 2H, Hₑ₂); 7.22 (s, 2H, H₈₅); 7.17 (s, 2H, H₉₁₀); 4.88 (br s, 2H, H₁); 4.67 (t, J = 4.6 Hz, 4H, H₆); 4.39 – 4.31 (m, 4H, H₉₉); 4.30 – 4.21 (m, 8H, H₉₁, H₉₂); 4.00 – 3.91 (m, 16H, H₇, H₆₂, H₆₆, H₆₁₀); 3.90 – 3.81 (m, 4H, H₂₂₂, H₆₆); 3.80 – 3.74 (m, 6H, H₂, H₆₁₂); 3.74 – 3.63 (m, 26H, H₀₁, H₃, H₆₆, H₆₄, H₆₈, H₆₉, H₆₁₁, H₆₇, H₆₂); 3.62 – 3.45 (m, 16H, H₁₀, H₄, H₉); 2.81 – 2.57 (m, 4H, H₄₄, H₉₅); 2.04 – 1.85 (m, 4H, H₀₃₈₉, H₀₆₆₆); 1.73 – 1.62 (m, 2H, H₀₃₉₈₉ or H₀₆₆₆₆); 1.52 – 1.44 (m, 2H, H₀₃₉₈₉ or H₀₆₆₆₆). ¹³C NMR (100 MHz, CD₂OD): δ 176.9, 176.4 (C₆); 155.4, 154.9 (C₆₆, C₁₁₁); 150.6 (C₆₁); 143.5 (C₁₂); 127.3 (C₁₁₁); 122.5 (C₆₁); 119.1 (C₁₁₀); 118.4 (C₅₂); 116.0, 114.3 (C₆₄, C₅₈); 113.0 (C₂₂); 100.4 (C₁); 92.7, 91.7 (C₉₇, C₉₉); 75.6 (C₆); 75.5 (C₆); 74.1, 73.7 (C₉₃, C₉₇, C₁₁₁); 72.5 (C₁₂₁); 72.4 (C₁₂); 71.9 (C₁₂₂); 70.9 (C₁₂₁ or C₉₃); 70.9 (C₉₃); 70.6 (C₉₂, C₆₆, C₁₁₀); 69.4 (C₁₂₁ or C₉₃); 68.6 (C₆); 68.5 (C₁₁); 63.1 (C₆); 62.4, 62.3 (C₆₄, C₆₈, C₁₁₂); 52.4 (C₁₁₀); 51.6 (C₆); 40.1 (C₄₄, C₄₈, C₄₉, C₄₁₀, C₆₈, C₆₁₁, C₆₁₂).
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C₉₀; 29.1 (C₀₃ or C₀₆); 28.1 (C₀₃ or C₀₆). MS (ESI): m/z calculated for [C₈₆H_{12₀}N₈O₄₀Na₂]²⁺: 961.8; found: 961.9. MS (ESI-HRMS): m/z calculated for [C₈₆H_{12₀}N₈O₄₀]⁺: 1876.75403; found: 1876.76014. [α]D²⁵: +27.5 (c 0.59, MeOH).

**Compound 3.4**

![Image of compound 3.4]

To a stirred solution of TIPS-3⁴ (11.5 mg, 9.1 µmol, 1 eq.) in THF (200 µL), TBAF (1 M in THF, 18.0 µL, 2 eq.) was added under nitrogen. After 1 h, TLC analysis (CH₂Cl₂:MeOH 9:1) showed that the desilylation reaction was complete. The CuAAC reaction was performed in situ, according to the general procedure. 4⁷ (13.5 mg, 20.0 µmol, 2.2 eq.) was added as a solid; the final concentration of 3 was 15 mM. The reaction was stirred at room temperature under nitrogen in the dark overnight. Quadrasil™-MP (S/Pd 8:1, 5 mg) was added to the reaction mixture, stirred for 10 minutes and then filtered off. The solvent was removed under reduced pressure and the resulting mixture was redissolved in MeOH purified by size exclusion chromatography (Sephadex LH-20, MeOH), obtaining 15 mg of 3.4 not pure. The remaining tetrabutylammonium salt was removed through automated reverse phase chromatography (C18, water with gradient of MeOH from 0 % to 100 %), obtaining 11 mg of pure 3.4 as a yellow solid (yield 54 %). ¹H NMR (400 MHz, CD₃OD): δ 8.61 (s, 2H, H₁₆); 7.84 (s, 2H, H₁₁); 7.28 – 7.13 (m, 20H, H₁₂, H₁₃, H₈₅, H₁₁₀); 4.90 (br s, 2H, H₁); 4.68 – 4.61 (m, 4H, H₈); 4.56 (d, J = 6.2 Hz, 8H, H₁₅); 4.32 – 4.13 (m, 20H, H₁₀, H₁₉, H₁₆, H₁₇, H₁₈); 4.01 (t, J = 4.8 Hz, 4H, H₁₁); 3.96 – 3.80 (m, 20H, H₁₂, H₁₆, H₁₁₀, H₁₀, H₁₈, H₁₁₂); 3.78 – 3.61 (m, 28H, H₁₆, H₁₉, H₁₄, H₁₇, H₁₈, H₁₁₂, H₁₁₅, H₁₁₆); 3.60 – 3.48 (m, 4H, H₈, H₉); 2.88 – 2.75 (m, 4H, H₁₄, H₁₅); 1.94 – 1.60 (m, 8H, H₁₉, H₁₂). ¹³C NMR (100 MHz, CD₃OD): δ 177.0, 176.7 (C₀); 155.4, 155.0 (C₈₅, C₁₁₁); 150.4 (C₁₀); 143.5 (C₁₂); 141.6 (C₁₄); 139.1, 139.0 (C₁₁); 128.4, 128.3, 128.19, 128.15 (C₁₂, C₁₃); 127.0 (C₁₄); 122.4 (C₁₅); 119.1, 118.5 (C₈₅, C₈₆); 116.0, 114.4 (C₈₄, C₈₉); 112.8 (C₀₁); 100.3 (C₁); 92.8, 91.7 (C₈₇, C₈₈); 76.5 (C₁); 75.5 (C₁₁); 74.1 (C₈₃, C₆₇, C₁₁₁); 72.5, 72.2 (C₁, C₁₂, C₁₃); 71.0 - 70.7 (C₈₂, C₆₆, C₁₁₀); 69.5, 68.9 (C₆₁, C₆₅, C₆₉, C₁); 68.7 (C₄); 65.0 (C₁₃); 63.0 (C₁₁₂); 62.4, 62.4 (C₈₄, C₈₉); 62.3 (C₁₀); 51.7 (C₈); 43.6 (C₁₀); 41.8 (C₄₄, C₅₉); 30.0 (C₉₃ or C₉₆); 29.0 (C₉₃ or C₉₆). MS (ESI-HRMS): m/z calculated for [C₁₄₄H₁₄₈N₁₉O₄₀Na₂]²⁺: 1171.48194; found: 1171.47672. [α]D²⁵: 1.7 (c 0.75, MeOH).
Elettronic Supplementary Information

Modeling

Computational methods and details
All calculations were run by using the Schrödinger Suite 2012 through the Maestro molecular modeling environment.

Conformational analysis of glycodendrimers. The conformational analysis of glycodendrimers 1.7.6, 3.7.6, 3.6, 3.5.6 and 8.6 was obtained by consecutive cycles of Simulated Annealing (SA) followed by Stochastic Dynamics (SD) simulations using MacroModel version 9.9. The input structure was generated manually through Maestro’s graphical interface and was minimized using the TNCG method (convergence threshold 0.05 on the gradient), the OPLS-2005 force field and the GB/SA water solvation model, using extended cut-off of 25 Å for the H-bond and 35 Å for the Van der Waals and electrostatic interactions. The minimized structure was used as the starting point for both experiments: a SD run to analyze the structure along the simulation, and a SA run to obtain a new starting point for the following SD cycle, as shown by the flow chart in Scheme SI-4. In total 6 SD and 5 SA runs were performed for ligands 1.7.6, 3.7.6 and 3.5.6, whereas 5 SD and 4 SA runs were carried out for compounds 3.6 and 8.6, using the same parameters described for the minimization step.

![Scheme SI-4 Flow chart of the simulation protocol.](image)

Simulated annealing (SA) protocol. Starting from a minimized structure, the glycodendrimer was equilibrated for 100 ps at 300 K with a time step of 1 fs. After equilibration, each ligand was simulated for 10 ns with SHAKE treatment (bonds to H constrained) and with a time step of 1.0 fs, starting from an initial temperature of 1000 K and linearly reaching the final one of 50 K with default setting. Extended cut-off of 25 Å for the H-bond and 35 Å for the Van der Waals and electrostatic interactions were applied. Torsional constraints were applied to the cyclohexane ring of 6 to avoid chair inversion that was found to occur at high simulation temperature.
Electronic Supplementary Information

**Stochastic dynamics (SD) protocol.** The SD simulations were started with a 100 ps equilibration phase with the same settings described above for SA. For each dendrimer, five or six SD simulations were run for 25 ns with SHAKE protocol at 300 K with a time step of 1.0 fs, storing the structures each 5 ps.

The stored structures were analysed to gauge the average dimension of the glycodendrimers. For the divalent rods 1.7.6, 3.7.6 and 3.6 the interatomic distance between Man-O3 atoms of two distal sugar residues was plotted against the simulation time in Figures SI-1 to SI-3. Average distance values are reported in Table SI-1. For the hexavalent dendrimer 3.5.6 the time course of the distance between 9 pairs of distal Man-O3 atoms is shown in Figure SI-1A and the variation of the gyration radius during the same simulations is shown in Figure SI-1B.

The gyration radius $R_g$ of each stored structure was calculated as

$$R_g^2 = \left( \frac{1}{M} \right) \left( \sum_{i=1}^{N} m_i |r_i - R|^2 \right)$$

Where $M$ is the total mass of the molecule, $m_i$ the mass of atom $i$, $r_i$ the position of atom $i$, $N$ the total number of atoms in the molecule and $R$ the center of mass. The values were averaged over all the stored structures to get the average gyration radius value $<\text{gyr radius}>$ collected in Table SI-1.

**Explicit solvent molecular dynamics simulation.**

To check that the results were not determined by the implicit water solvation model employed, which may overestimate intramolecular hydrogen bonding interactions, extended simulations (2 x 50 ns) of 1.7.6 were also performed using an explicit water model (Figure SI-5). Compared to the GB/SA simulation, larger fluctuations were observed and, as expected, more extended conformations were sampled with higher frequency. However, the average Man-O3/Man-O3 distance $<\text{dO3-O3}>$ was actually found to be shorter than the value found by the simulation in implicit water solvent (15.1 Å vs. 18.8 Å).

Two 50 ns Molecular Dynamics (MD) simulations of dendrimer 1.7.6 were performed at 300 K using Desmond\(^9\) version 3.1 with the explicit TIP3P\(^{10}\) water model and the OPLS-2005 force field, under periodic boundary conditions. The system was solvated in a cubic box adding 8713/9192 TIP3P water molecules and equilibrated using the Desmond standard relaxation protocol. Finally, the 50 ns simulation L\(_{\text{NPT}}\) (Langevin constant pressure and temperature) processes were performed with a time step of 2.0 fs. Particle Mesh Ewald method\(^{11}\) was used for treating long range electrostatics, using a cut-off of 9 Å. The time course of the Man-O3/Man-O3 distance is shown in Figure SI-5.
Results of the Dynamics simulations

The potential of multivalent compounds to simultaneously coordinate two sites was evaluated by monitoring the distance between Man-O3 of two distal sugar residues (d_{O3-O3}) during the simulations. Table SI-1 shows the average values of the distance <d_{O3-O3}> and the values at maximum extension Max d_{O3-O3} of each simulated dendrimer. The dendrimer gyration radius (Gyradius), which is correlated to the ligand separation d_{O3-O3}, affords a simpler representation of the size of the hexavalent constructs 3.5.6 and 8.6.

Table SI-1. Average values of ManO3-ManO3 and Gyration radius

<table>
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<tr>
<th>Cmpd</th>
<th>Rod length (Å)</th>
<th>Max d_{O3-O3} b</th>
<th>&lt;d_{O3-O3}&gt; c (Å)</th>
<th>Max Gyradius b,d (Å)</th>
<th>&lt;Gyradius&gt;e (Å)</th>
<th>% extendedf</th>
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</tr>
</tbody>
</table>

Table SI-1 a See compound structures in Table 1: R= Me, active ligand 6. b Most extended conformations sampled during the simulations. c Average value of the distance, as monitored during the simulations (every 10 time steps). d Gyration radius calculated as defined in the Experimental section. e Average value of the radius, as calculated from the coordinates of the sampled snapshots. f % of conformations with d_{O3-O3} larger than 35 Å. g From ref 5.

The simulations confirms that the hexavalent dendrimer 8.6 cannot chelate between two DC-SIGN binding sites, even at its maximum extension (Max d_{O3-O3} 35.4 Å, Table SI-1). Insertion of even the shortest rod 1 at the dendrimer core affords structures that, in their extended conformations, can simultaneously reach two binding sites of DC-SIGN (Max d_{O3-O3} > 50 Å, Table SI-1). However, folded conformations of the type shown in Figure 4 are much more populated. The % of sampled conformations that feature d_{O3-O3} larger than 35 Å and can be considered productive as protein chelating agents is shown in Table SI-1, %extended column. 3.6 (Max d_{O3-O3} 43.3 Å and < d_{O3-O3} > 31.7 Å), with %extended=30 is the best preorganized of the ligands, followed by 3.5.6 (Max d_{O3-O3} 64.7 Å and < d_{O3-O3} > 20 Å) whih features %extended=5.
Time course of the interatomic distances (Man-O3 vs. Man-O3, Y axes) during the SD simulations. The yellow bar on the plots marks the 35-40 Å distance range. Six simulations of 25 ns each are shown for each molecule. The corresponding course of the gyration radius is also shown for 1.7.6 and 3.5.6.

Figure SI-1A. Time course of the Man-O3/Man-O3 distance for 1.7.6

Figure SI-1B. Time course of the gyration radius of 1.7.6 during the same simulations
Figure SI-2. Time course of the Man-O3/Man-O3 distance for 3.7.6
**Figure SI-3.** Time course of the Man-O3/Man-O3 distance for 3.6
Figure SI-4A. Time course of the 9 pairs of Man-O3/Man-O3 distance of 3.5.6

Figure SI-4B. Time course of the gyration radius of 3.5.6 during the same simulations
**Figure SI-5.** Time course of the Man-O3/Man-O3 distance (Y axes) during the simulation of 1.7.6 using an explicit model for the water solvent. The yellow bar on the plots marks the 35-40 Å distance range.
Modeling of the DC-SIGN complexes.

Docking of dimeric ligands within DC-SIGN and MD simulation of the complexes. The starting structures for the MD simulations of the dimeric ligands 1.7.6, 3.7.6 and 3.6 with two adjacent carbohydrate-recognition domains (CRD) of the DC-SIGN tetramer were built using the X-ray structure of the monovalent ligand 6 in the DC-SIGN CRD structure (PDB code 2xr5) and a model of the CRDs tetramer derived from the fitting of four copies of a CRD monomer (PDB code 1k9i) into the SAXS envelope of DC-SIGN extracellular domain. In particular, two copies of the 2xr5 X-ray complex were positioned in two adjacent binding sites of the tetramer, by aligning the three CRD calcium ions. The system formed by the two 2xr5 X-ray complexes constrained to the tetramer spatial arrangement was completed by connecting the two monovalent ligands with the proper linker to generate the divalent ligand (1.7.6, 3.7.6 and 3.6) in complex with two CRDs. The resulting systems were then prepared using the Protein Preparation Wizard of the Maestro graphical interface followed by a restrained minimization of the whole system (0.30 Å of RMSD on heavy atoms) using the OPLSAA force field. The final refined structures were used as input for 25 ns SD simulations with the OPLS-2005 force field and the GB/SA water solvation model using MacroModel version 9.9. The SD simulations were run with equilibration and production phases with the same settings used for glycodendrimers, freezing the protein CRDs to their crystallographic coordinates.

The simulation of 3.6 showed a complex stably bound for all the 25 ns (Figure SI-6A). Similar complexes generated for the long linker dimers 3.7.6 (Figure SI-6B) and 1.7.6 (Figure SI-6C) also showed stable chelation over the course of 25 ns simulations, accompanied by extensive dynamics of the flexible linkers.
FIGURE SI-6 Docked complexes of divalent ligands A) 3.6, B) 3.7.6 and C) 1.7.6 on DC-SIGN tetramer show that all these compounds can potentially bridge to adjacent binding sites.
Elettronic Supplementary Information

SPR

Material and methods

SPR competition experiments were performed on a Biacore 3000 instrument. Flow cells (Fc) 1 and 2 of a CM4 sensor chip were functionalized at 5µL/min with mannosylated bovine serum albumine (Man α1-3[Manα1-6]Man BSA (Man-BSA), Dextra Laboratories - average number of 15 tri-mannoses) or prepared as control surface respectively, as described previously. After blocking with 30 µL of 1M ethanolamine, both Fcs were treated with 10µL of 10 mM HCl and 20µL of 50 mM EDTA to remove unspecifically bound protein and to condition the surface to the regeneration protocol. On Fc2, the final response of immobilized level of Man-BSA was 1500 RU.

The competition experiment was performed using 25 mM Tris-HCl pH 8, 150 mM NaCl, 4 mM CaCl2, 0.005% v/v P20 as the running buffer at 5 µL/min flow rate. The binding of soluble tetrameric DC-SIGN ECD to immobilized Man-BSA was inhibited by the compounds at increasing concentrations (up to 2 mM or 0.9 mM for divalent and hexavalent compounds, respectively). For this reason, 13 µL of each DC-SIGN ECD (20 µM)/compound mixture was injected over the surfaces. The bound lectin was washed off injecting 5 µL of 50 mM EDTA pH 8. DC-SIGN ECD equilibrium binding responses (R_{eq}) for each sample were obtained from the reference surface corrected sensorgrams 150 s after the start of the injection.

\[
y = R_{hi} - \frac{R_{hi} - R_{lo}}{1 + \left(\frac{Conc}{A_1}\right)^{A_2}}
\]

(1)

\[
IC_{50} = A_1 \left(\frac{R_{hi} - R_{lo}}{R_{hi} - 50} - 1\right)^{\frac{1}{A_2}}
\]

(2)

Where \(R_{hi}\) and \(R_{lo}\) are maximum and minimum asymptotes, \(A_1\) is the inflection point, \(A_2\) is a slope of the curve and \(Conc\) is the compound concentration.

The obtained \(R_{eq}\) values were converted to DC-SIGN residual activity values (y, %) with respect to \(R_{eq}\) of DC-SIGN alone, which was assigned a 100 % activity value. After plotting residual activity against corresponding compound concentration, the 4-parameter logistic model (eq. 1) was fitted to the plots, and finally the IC_{50} values were calculated using equation 2.
Elettronic Supplementary Information

Figure SI-7 - SENSOGRAMS

a) Psdi-Man derivatives (Dendrimers based on 6):

![Graphs showing sensograms for different compounds and concentrations.](image-url)
b) Man030 derivatives (dendrimers based on 4):
**Figure SI-8** - Inhibition of DC-SIGN interaction with BSA-Mannotriose surface. DC-SIGN (20 μM) and compounds were co-injected over the surface. The responses were extracted from the sensorgrams (of Figure SI-6), converted to DC-SIGN activity and plotted against corresponding concentrations of compound 6 derivatives (in blue, Figure SI-8b) and compound 4 derivatives (in green, Figure SI-8a).

a)

![Graph a)](image1)

b)

![Graph b)](image2)
Infection studies: materials and methods

Trans-Infection assay in vitro.

PBMCs were isolated from buffy coats of healthy donors upon written consent by centrifugation on a Ficoll gradient (Cederlane Laboratories, Burlington, Canada). CD4+ T-lymphocytes were purified from PBMCs using anti-human CD4 microbeads (Miltenyi Biotech, Caldara di Reno, Italy). CD4+ T cells were activated by culturing them with PHA (Sigma Aldrich, St Louis, USA) and IL-2 (R&D Systems, Minneapolis, USA) for 2 days.

B-THP1/DC-SIGN and B-THP1 cells (both from NIBSC, Potter Bar, UK) were incubated with increasing concentrations of the compounds, or medium culture alone at 37°C for 30 minutes. Then cells were pulsed with 40 TCID₅₀ HIV-1 BaL (NIBSC, Potter Bar, UK), without removing the inhibitors, at 37°C for 3 hours. After extensive washing, B-THP1/DC-SIGN and B-THP1 cells were cultured with the pre-activated CD4+ T-lymphocytes in culture medium containing IL-2. At day 3 post infection, p24 concentration in the culture supernatants was assessed by ELISA (Express Bio, Thurmont, MD, USA). Non-transfected B-THP-1 cells were used as a negative control and, as expected, did not transmit the virus (not shown).

Flow cytometry. BTHP1-DC-SIGN cell were incubated with the compounds for 3h and 30 min or 24 h and then were with 7-AAD (Beckman Coulter, Milan, Italy). Samples were acquired by using a Cytomics FC-500 flow cytometer and data were analysed with CXP 21 software (both Beckman Coulter).

Cytotoxicity.

The compounds were found to be not cytotoxic, as evaluated by 7AAD assay. The B-THP-1/DC-SIGN cells were exposed to the indicated concentrations of the compounds 1.5.4, 3.5.4, 3.7.4, 3.4, or to medium culture without inhibitors (Medium) for 3 h and 30 min. The percentage of 7-AAD positive B-THP1/DC-SIGN (not-viable cells) was shown.

Figure SI-9. Toxicity of compounds 1.5.4, 3.5.4, 3.7.4, 3.4 on B-THP-1/DC-SIGN cells.
References