

Cyclodextrin tetraplexes: first syntheses and potential as cross-linking agent

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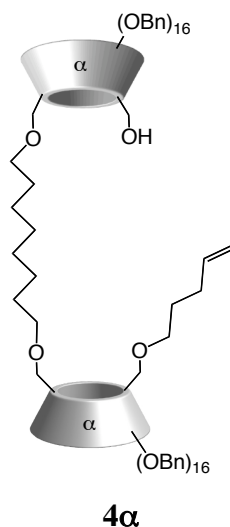
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General remarks:

Optical rotations were measured at 20±2 °C with a Perkin-Elmer Model 241 digital polarimeter, in a 10 cm, 1 mL cell. MALDI mass spectra were recorded on a PerSeptive Biosystems Voyager Elite (Framingham, MA, USA) time-of-flight mass spectrometer. This instrument was equipped with a nitrogen laser (337 nm), a delayed extraction and a reflector. PEG standards were used to calibrate the mass scale by use of the two points calibration software 3.07.1 from PerSeptive Biosystems. The matrix, 2,5-dihydroxybenzoic acid (2,5-DHB), was from Sigma (France) and was used without further purification. Elemental analyses were performed by the Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. ¹H NMR spectra were recorded with a Bruker DRX 400 spectrometer for solutions in CDCl₃, D₂O or *d*₆-DMSO at ambient temperature. Assignments were aided by COSY experiments. ¹³C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer for solutions in CDCl₃, D₂O or *d*₆-DMSO, with adoption of 77.00 ppm for the central line of CDCl₃. Assignments were aided by the J-mod technique and HMQC experiments. Reactions were monitored by thin-layer chromatography (TLC) on a precoated silica gel 60 F254 plate (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh, E. Merck). For reactions, Tetrahydrofurane (THF) was distilled over sodium/benzophenone and dichloromethane (CH₂Cl₂) was distilled over phosphorous pentoxide. All reactions were conducted under an argon atmosphere.

Dimer- α -cyclodextrin-monopentenyl **4 α** :



KH 30 % m/m (42mg, 316 μ mol), 18-Crown-6 (6mg, 24 μ mol) and 5-bromo-pent-1-ene (37 μ L, 316 μ mol) were added to a stirred solution of diol **3 α** ¹ (1.2g, 243 μ mol) in dry THF (20mL), under argon at r.t. More KH and 5-bromo-pent-1-ene (0.6 eq. each) were added twice. The reaction mixture was quenched by MeOH (10mL) and concentrated. A solution of the residue in dichloromethane (100mL) was washed with aq. sat. NH₄Cl (2 \times 50mL), dried (MgSO₄), filtered and concentrated. Column chromatography (cyclohexane/EtOAc 5:1 then 3:1) on silica gel gave the dimer monopentenyl **4 α** (620 mg, 51%) as a white foam.

$[\alpha]_D^{20} = + 33$ (*c* 1.0, CHCl₃).

TLC analysis: *R_f* 0.28 (Cyclohexane/EtOAc 3:1).

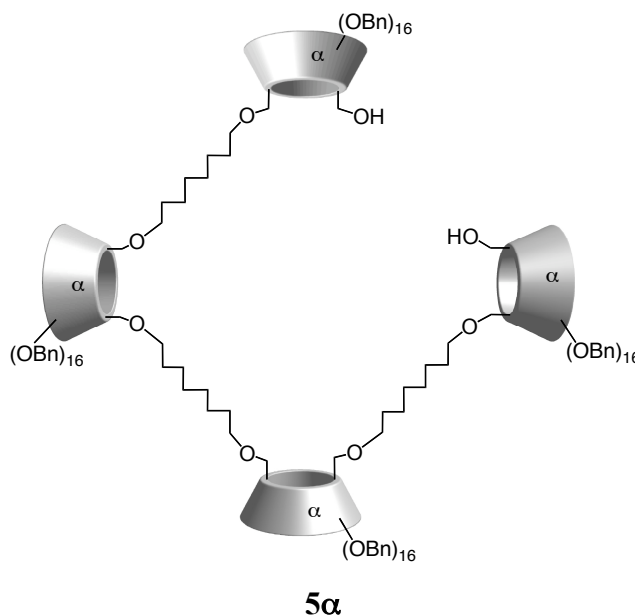
¹H NMR (400MHz, CDCl₃): δ 7.32-7.20 (m, 160H, arom-H), 5.83 (dddd, ³*J*_{b,a'} = 16.8Hz, ³*J*_{b,a} = 10.3Hz, ³*J*_{b,c'} = ³*J*_{b,c} = 5.6Hz, 1H, b-H), 5.38-5.10 (m, 24H, 12 \times 1-H, 12 \times CHPh), 5.09-5.00 (m, 2H, 2 \times a-H), 4.99-4.89 (m, 12H, 12 \times CHPh), 4.67-4.36 (m, 40H, 40 \times CHPh), 4.31-3.95 (m, 42H, 12 \times 3-H, 12 \times 4-H, 8 \times 5-H, 10 \times 6-H), 3.66 (m, 2H, 2 \times 6-H), 3.91 (br d, ³*J*_{5,4} = 9.3Hz, 3H, 3 \times 5-H), 3.82 (br d, ³*J*_{5,4} = 9.0Hz, 1H, 5-H), 3.70-3.51 (m, 20H, 12 \times 2-H, 8 \times 6-H), 3.49-3.38 (m, 7H, 3 \times OCH₂, 4 \times 6-H), 3.33-3.25 (m, 3H, 3 \times OCH₂), 2.76 (br s, 1H, OH), 2.16-2.02 (m, 2H, c-H), 1.55-1.82 (m, 14H, CH₂).

^{13}C NMR (100MHz, CDCl_3): δ 139.3-139.2 (arom. quat.-C), 138.35-138.2 (arom. quat.-C), 138.15-138.1 (arom. quat.-C), 138.0-137.9 (arom. quat.-C), 138.0 (C-b), 126.6-128.3 (arom-CH), 114.7 (C-a), 98.6 (2 \times C-1), 95.5 (4 \times C-1), 98.4, 98.3 (2 \times C-1), 98.2 (3 \times C-1), 97.9 (C-1), 81.2-80.9 (CH), 80.7 (CH), 79.6-78.6 (CH), 78.4 (CH), 78.1, 77.9 (2 \times CH), 75.8-75.2 (OCH_2Ph), 73.4-73.2 (OCH_2Ph), 72.9-72.4 (OCH_2Ph), 72.3 (OCH_2Ph), 71.8, 71.7 (2 \times OCH_2), 71.6-71.4 (C-5), 71.25, 71.2 (2 \times C-5), 70.9 (OCH_2), 69.2-68.8 (C-6), 30.2, 30.1, 29.7, 28.7, 26.8 (CH_2).

MS (MALDI-TOF): 5027.3 m/z ($\text{M}+\text{Na}$) $^+$.

Elemental analysis calcd. for $\text{C}_{309}\text{H}_{334}\text{O}_{60}$: C 74.11 H 6.72, found C 73.98 H 6.81.

Tetramer- α -cyclodextrin-diol 5α :



Grubbs catalyst (5mg, 6 μmol) was added to a solution of 4α (570mg, 114 μmol) in degassed dichloromethane (1mL), under argon at r.t.. The reaction mixture was heated under reflux for 6 h. $\text{Pb}(\text{OAc})_4$ (4mg, 1.5eq/Ru) was added to the cooled (r.t.) solution and the reaction mixture was stirred overnight, and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc 2:1) to give the unsaturated tetramer: MS (MALDI-TOF): 10010.2 m/z ($\text{M}+\text{Na}$) $^+$. A mixture of this product and PtO_2 (140mg) in EtOAc (20mL) was stirred under H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite $^{\text{®}}$ and

concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc 2:1), to give the tetramer-diol **5α** (421mg, 74% over two steps) as a white foam.

$[\alpha]_D^{20} = +34$ (c 1.0, CHCl_3).

TLC analysis: R_f 0.32 (Cyclohexane/EtOAc 2:1).

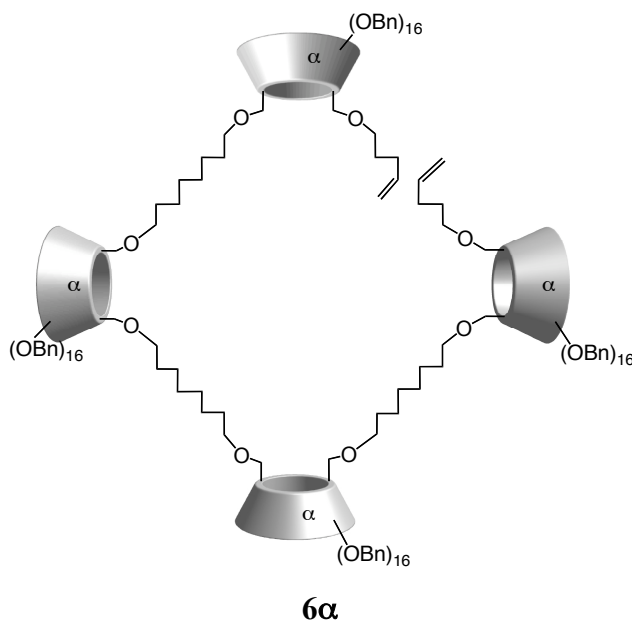
^1H NMR (400MHz, CDCl_3): δ 7.20-7.32 (m, 320H, arom-H.), 5.51 (d, $^3J_{1,2} = 3.6\text{Hz}$, 2H, 2 \times 1-H), 5.48 (d, $^3J_{1,2} = 3.5\text{Hz}$, 2H, 2 \times 1-H), 5.41-5.31 (m, 12H, 4 \times 1-H, 8 \times CHPh), 5.28-5.07 (m, 18H, 2 \times 1-H, 16 \times CHPh), 5.05-4.82 (m, 38H, 14 \times 1-H, 24 \times CHPh), 4.74-4.33 (m, 80H, 80 \times CHPh), 4.27-3.79 (m, 90H, 24 \times 3-H, 24 \times 4-H, 18 \times 5-H, 24 \times 6-H), 3.76-3.72 (m, 4H, 4 \times 5-H), 3.70-3.62 (m, 4H, 2 \times 5-H, 2 \times 6-H), 3.62-3.40 (m, 42H, 24 \times 2-H, 18 \times 6-H), 3.40-3.31 (m, 10H, 3 \times OCH₂, 4 \times 6-H), 3.29-3.19 (m, 6H, 3 \times OCH₂), 2.74 (t, $^3J_{\text{OH},6} = ^3J_{\text{OH},6'} = 5.8\text{Hz}$, 2H, 2 \times OH), 1.62-1.45 (m, 12H, CH₂), 1.35-1.25 (m, 24H, CH₂).

^{13}C NMR (100MHz, CDCl_3): δ 139.5-139.1 (arom. quat.-C), 138.5-137.9 (arom. quat.-C), 128.3-127.3 (arom-CH), 98.8-97.9 (C-1), 81.3-80.7 (CH), 80.4-79.7 (CH), 79.4-79.1 (CH), 78.9 (CH), 78.6-78.4 (CH), 78.0, 77.5, 76.6 (CH), 76.1-75.6 (OCH₂Ph), 73.4-72.3 (OCH₂Ph), 72.1 (OCH₂Ph), 71.4 (OCH₂), 71.7-71.1 (C-5), 70.7 (OCH₂), 69.4-68.8 (C-6), 30.1, 29.9-29.7, 26.9-26.7 (CH₂).

MS (MALDI-TOF): 10012.1 m/z (M+Na)⁺.

Elemental analysis calcd. for C₆₁₆H₆₆₆O₁₂₀: C 74.06 H 6.72, found C 73.81 H 6.95

Tetramer- α -cyclodextrin-bis-pentenyl **6 α** :



KH 30 % m/m (21mg, 152 μ mol), 18-Crown-6 (1mg, 4 μ mol) and 5-bromo-pent-1-ene (18 μ L, 152 μ mol) were added to a stirred solution of diol **5 α** (380mg, 38 μ mol) in dry THF (10mL), under argon at r.t. More KH and 5-bromo-pent-1-ene (3 equiv.) were added twice. Stirring was continued until complete disappearance of the starting material (ca 24 h). The reaction was quenched with MeOH (1mL), and concentrated. A solution of the residue in dichloromethane (50mL) was washed with aq. sat. NH_4Cl (2 \times 25mL), dried (MgSO_4), filtered and concentrated. Chromatography of the residue (cyclohexane/EtOAc 4:1) on silica gel gave **6 α** (325mg, 86%) as a white foam.

$[\alpha]_D^{20} = +34$ (c 1.0, CHCl_3).

TLC analysis: R_f 0.37 (Cyclohexane/EtOAc 4:1).

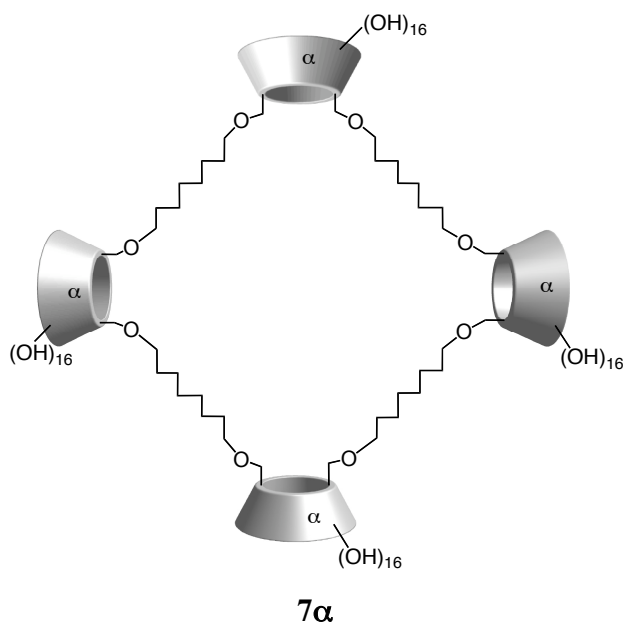
^1H NMR (400MHz, CDCl_3): δ 7.32-7.20 (m, 320H, arom-H), 5.85 (dddd, $^3J_{b,a'} = 16.8\text{Hz}$, $^3J_{b,a} = 10.3\text{Hz}$, $^3J_{b,c'} = ^3J_{b,c} = 5.6\text{Hz}$, 2H, 2 \times b-H), 5.32 (d, $^2J = 10.6\text{Hz}$, 4H, 4 \times CHPh), 5.36 (d, $^3J_{1,2} = 3.4\text{Hz}$, 4H, 4 \times 1-H), 5.32 (d, $^2J = 10.8\text{Hz}$, 4H, 4 \times CHPh), 5.28-5.06 (m, 34H, 16 \times 1-H, 2 \times a-H 16 \times CHPh), 5.04-4.88 (m, 30H, 4 \times 1-H, 2 \times a-H, 24 \times CHPh), 4.78-4.38 (m, 80H, 80 \times CHPh), 4.29-3.95 (m, 88H, 24 \times 3-H, 24 \times 4-H, 16 \times 5-H, 24 \times 6-H), 3.93-3.85 (m, 8H, 8 \times 5-H), 3.68-3.51 (m, 40H, 24 \times 2-H, 16 \times 6-H), 3.48-3.35 (m, 16H, 4 \times OCH₂, 8 \times 6-H), 3.32-3.22 (m, 8H, 4 \times OCH₂), 2.15-2.01 (m, 4H, 4 \times c-H), 1.62-1.45 (m, 16H, CH₂), 1.35-1.25 (m, 24H, CH₂).

^{13}C NMR (100MHz, CDCl_3): δ 139.4-139.2 (arom. quat.-C), 138.4-137.9 (arom. quat.-C), 138.0 (C-b), 128.3-127.3 (arom-CH), 114.7 (C-a), 98.6-98.4 (C-1), 81.2-80.9 (CH), 80.1 (CH), 79.6-78.4 (CH), 77.6 (CH), 75.9-74.9 (OCH_2Ph), 73.4-73.3 (OCH_2Ph), 72.9-72.5 (OCH_2Ph), 71.7 (OCH_2), 71.6 (OCH_2), 71.5-71.3 (C-5), 70.9 (OCH_2), 69.2-68.9 (C-6), 30.2, 30.1, 29.6-29.8, 28.7, 26.9 (CH_2).

MS (MALDI-TOF): 10149.1 m/z ($\text{M}+\text{Na}$) $^+$.

Elemental analysis calcd. for $\text{C}_{626}\text{H}_{682}\text{O}_{120}$: C 74.25 H 6.79, found C 74.09 H 6.83.

Tetraplex- α -cyclodextrin **7 α** :



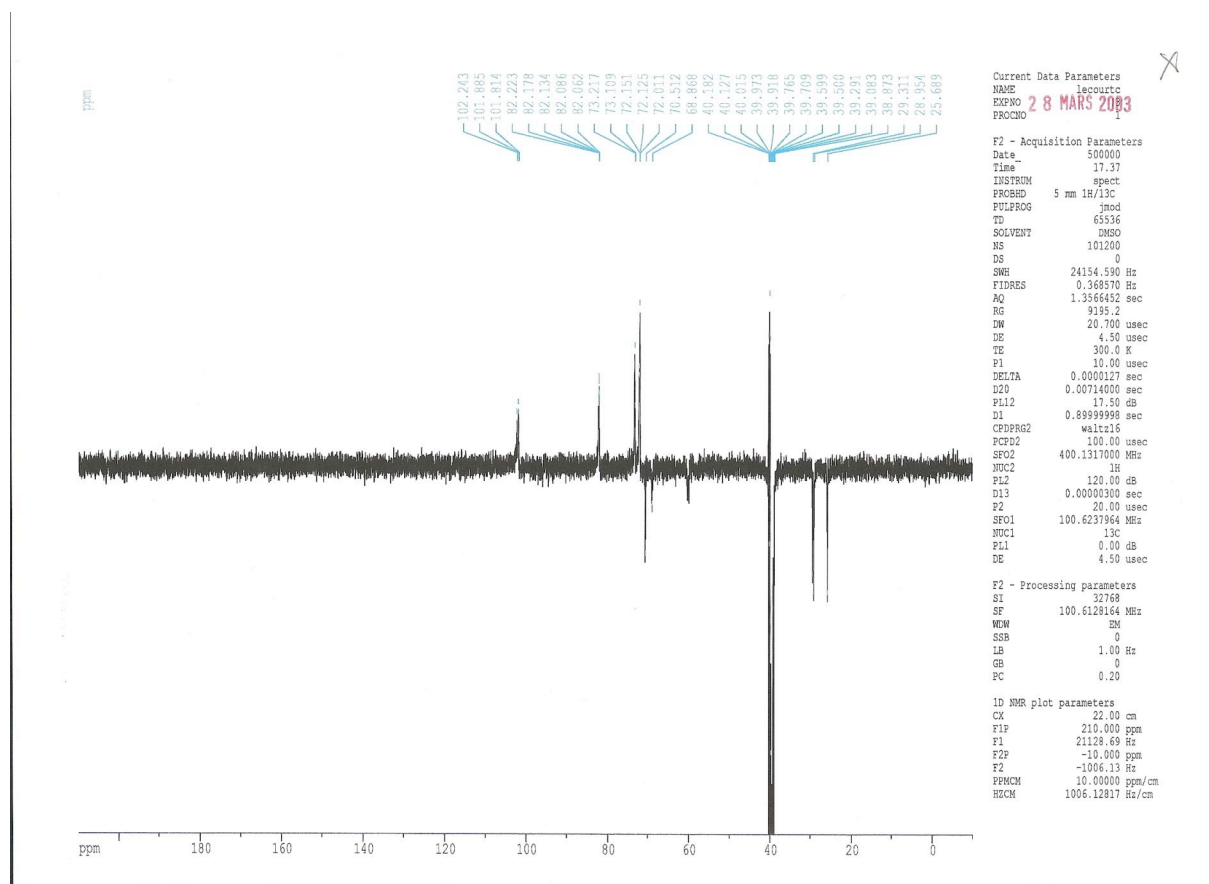
Grubbs catalyst (1,6mg, $2\mu\text{mol}$) was added to a stirred solution of **6 α** (200mg, $20\mu\text{mol}$) in degassed dichloromethane (20mL), under argon at r.t., The reaction mixture was heated under reflux for 24 h, and more Grubbs catalyst (1,6mg, $2\mu\text{mol}$) was added. After heating under reflux for 24 h, $\text{Pb}(\text{OAc})_4$ (2,6mg, 1.5eq/Ru) was added to the cooled solution (r.t.). The reaction mixture was stirred overnight at r.t., and concentrated. Chromatography of the residue (cyclohexane/EtOAc 4:1) on silica gel afforded the macrocycle (94 mg, 47%) as a white foam: MS (MALDI-TOF): 10121.3 m/z ($\text{M}+\text{Na}$) $^+$. The macrocycle (70 mg, $7\mu\text{mol}$) was dissolved in a mixture of THF/ NH_3 1:1 (10mL) at -78°C . Small pieces of Na (excess) were

added. The blue solution was refluxed for 1 h (-33°C), carefully quenched by iPrOH (10mL) and concentrated. A solution of the residue in water (15mL) was neutralized with IR-120 H⁺ resin, diluted with EtOAc (15mL), stirred vigorously for 30 minutes and filtrated. The organic layer was separated, extracted with water (3×10mL) and the combined aqueous layers were concentrated. A mixture of this residue and Pd/C 10 % (20mg) in MeOH/water 1:1 (5 mL) was stirred under H₂ atmosphere for 12 h, filtered trough Celite® and concentrated. The residue was purified by chromatography on Sephadex G25 column (water) and lyophilized to give the tetraplexe **7α** (19mg, 64% over two steps) as a white powder.

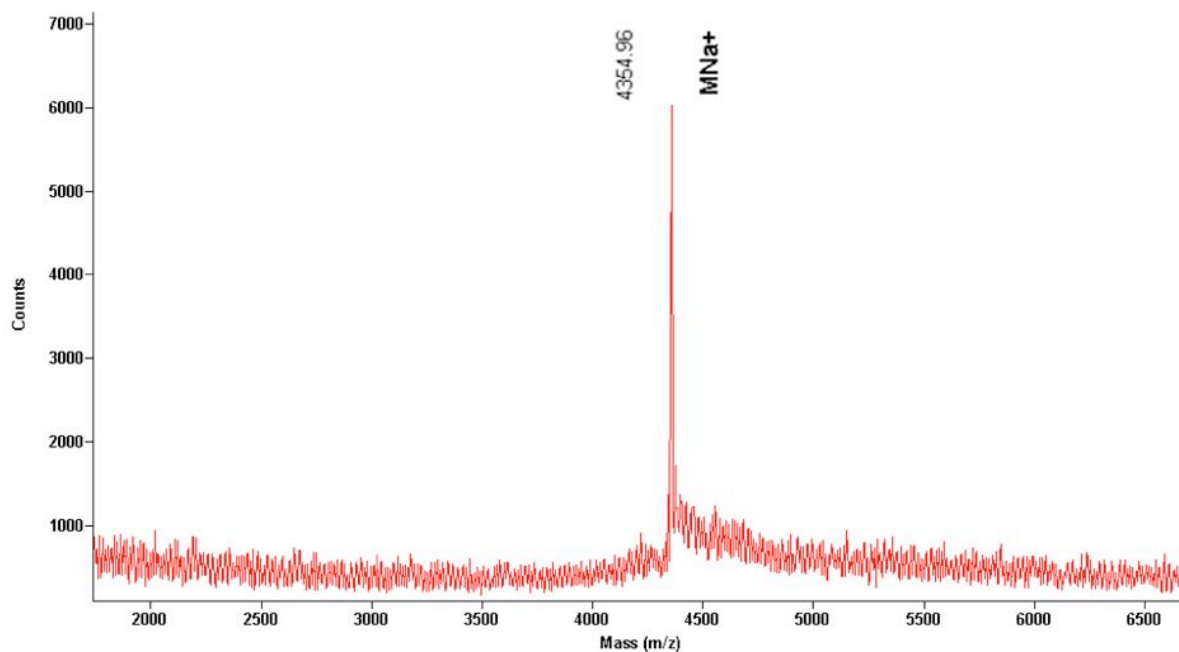
$[\alpha]_D^{20} = + 121$ (*c* 0.5, MeOH).

¹H NMR (400MHz, *d*₆-DMSO): δ 5.02 (d, ³*J*_{1,2} = 1.6Hz, 16H, 2×1-H), 4.95 (d, ³*J*_{1,2} = 3.5Hz, 8H, 1-H), 4.12-3.71 (m, 96H), 3.65-3.48 (m, 64H), 1.75-1.65 (m, 16H, CH₂), 1.52-1.43 (m, 32H, CH₂).

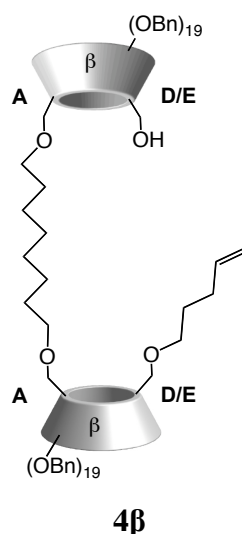
¹³C NMR (100MHz, *d*₆-DMSO): δ = 102.2, 101.9, 101.8 (C-1), 82.2-82.1 (CH), 73.4-73.2 (CH), 72.4-72.0 (CH), 70.5 (OCH₂), 68.9-68.7 (OCH₂), 60.2-59.7 (OCH₂), 29.3, 28.9, 25.7 (-CH₂-).



MS (MALDI-TOF): 4354.9 m/z ($M+Na$)⁺.



Dimer- β -cyclodextrin-monopentenyl **4 β** :



KH 30 % m/m (54mg, 403 μ mol), 18-Crown-6 (8mg, 31 μ mol) and 5-bromo-pent-1-ene (37 μ L, 316 μ mol) were added to a stirred solution of diol **3 β** ¹ (1.8g, 310 μ mol) in dry THF (25mL), under argon at r.t. More KH and 5-bromo-pent-1-ene (0.6 eq. each) were added twice. The reaction mixture was quenched by MeOH (10mL) and concentrated. A solution of the residue in dichloromethane (120mL) was washed with aq. sat. NH₄Cl (2 \times 60mL), dried (MgSO₄), filtered and concentrated. Column chromatography (cyclohexane/EtOAc 5:1 then 3:1) on silica gel gave the dimer monopentenyl **4 β** (965 mg, 53%) and the starting material (342 mg, 19%) as white foams.

$[\alpha]_D^{20} = +33$ (*c* 1.0, CHCl₃).

TLC analysis: *R_f* 0.29 (Cyclohexane/ EtOAc 3:1).

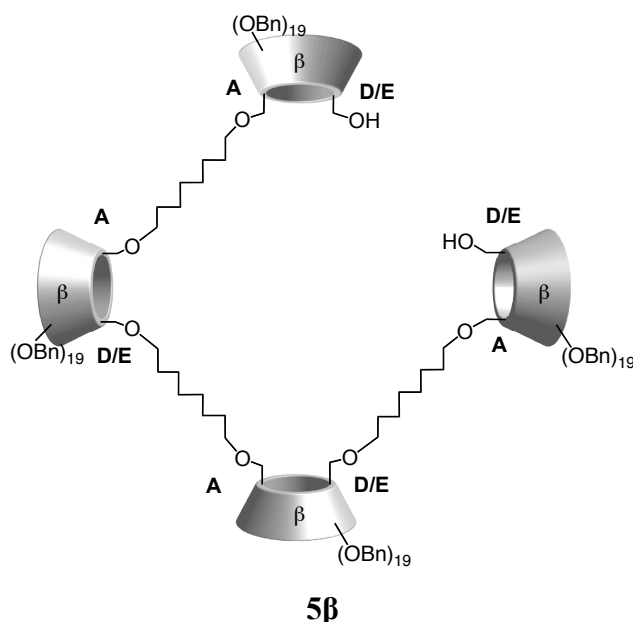
¹H NMR (400MHz, CDCl₃): δ 7.31-7.18 (m, 190H, arom-H), 5.81 (dddd, ³*J*_{b,a'} = 16.8Hz, ³*J*_{b,a} = 10.3Hz, ³*J*_{b,c'} = ³*J*_{b,c} = 5.6Hz, 1H, b-H), 5.37 (d, ³*J*_{1,2} = 3.42Hz, 1H, H-1), 5.40-5.48 (m, 2H, 2 \times H-1), 5.35-4.93 (m, 27H, 11 \times 1-H, 2 \times a-H, 14 \times CHPh), 4.89-4.67 (m, 14H, 14 \times CHPh), 4.63-4.35 (m, 48H, 48 \times CHPh), 4.15-3.81 (m, 56H, 14 \times 3-H, 14 \times 4-H, 14 \times 5-H, 14 \times 6-H), 3.77-3.42 (m, 28H, 14 \times 2-H, 14 \times 6-H), 3.41-3.22 (m, 6H, 3 \times OCH₂), 2.53 (br s, 1H, OH), 2.17-2.01 (m, 2H, c-H), 1.79-1.48 (m, 14H, CH₂).

^{13}C NMR (100MHz, CDCl_3): δ 139.4-138.7 (arom. quat.-C), 138.4-137.6 (arom. quat.-C), 138.0 (C-b), 128.7-126.4 (arom-CH), 114.8 (C-a), 98.9-97.9 (C-1), 80.9-80.7 (CH), 79.5-78.3 (CH), 75.9-74.6 (OCH_2Ph), 73.4-73.1 (OCH_2Ph), 72.9-72.1 (OCH_2Ph), 71.8, 71.7 ($2\times\text{OCH}_2$), 71.3 (OCH_2), 71.8-71.1 (C-5), 70.9-70.7 (OCH_2), 69.4-68.9 (C-6), 30.2, 30.1, 29.7-29.6, 28.7, 26.8 (CH_2).

MS (MALDI-TOF): 5896.4 m/z ($\text{M}+\text{Na}$) $^+$.

Elemental analysis calcd. for $\text{C}_{363}\text{H}_{390}\text{O}_{70}$: C 74.24 H 6.69; found C 73.88 H 6.85.

Tetramer- β -cyclodextrin-diol **5 β** :



Grubbs catalyst (6mg, $8\mu\text{mol}$) was added to a solution of **4 β** (900mg, $153\mu\text{mol}$) in degassed dichloromethane (1.5mL), under argon at r.t.. The reaction mixture was heated under reflux for 6 h. $\text{Pb}(\text{OAc})_4$ (5mg, 1.5eq/Ru) was added to the cooled (r.t.) solution and the reaction mixture was stirred overnight, and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc 2:1) to give the unsaturated tetramer: MS (MALDI-TOF): 11740.6 m/z ($\text{M}+\text{Na}$) $^+$. A mixture of this product and PtO_2 (225mg) in EtOAc (30mL) was stirred under H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite® and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc 2:1), to give the tetramer-diol **5 β** (673mg, 75% over two steps) as a white foam.

TLC analysis: R_f 0.30 (Cyclohexane/EtOAc 2:1).

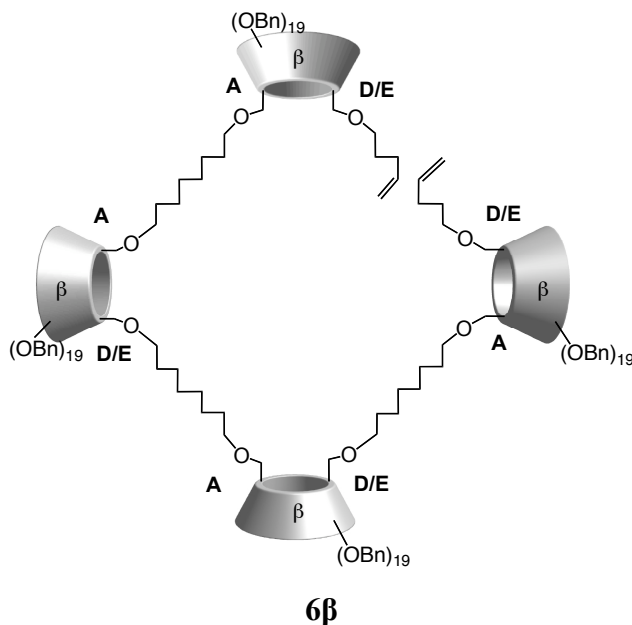
^1H NMR (400MHz, CDCl_3): δ 7.32-7.07 (m, 380H, arom-H), 5.48-4.93 (m, 56H, $28\times 1\text{-H}$, $28\times \text{CHPh}$), 4.88-4.35 (m, 124H, $124\times \text{CHPh}$), 4.18-3.82 (m, 112H, $28\times 3\text{-H}$, $28\times 4\text{-H}$, $28\times 5\text{-H}$, $28\times 6\text{-H}$), 3.79-3.24 (m, 68H, $28\times 2\text{-H}$, $28\times 6\text{-H}$, $12\times \text{OCH}_2$), 2.74-2.02 (br s, 2H, $2\times \text{OH}$), 1.58-1.46 (m, 12H, CH_2), 1.35-1.20 (m, 24H, CH_2).

^{13}C NMR (100MHz, CDCl_3): δ 139.4-138.8 (arom. quat.-C), 138.4-137.7 (arom. quat.-C), 128.6-127.1 (arom-CH), 98.9-97.8 (C-1), 80.9-80.6 (CH), 80.5-78.4 (CH), 76.0-74.9 (OCH_2Ph), 73.6-73.2 (OCH_2Ph), 72.9-72.4 (OCH_2Ph), 71.7 (OCH_2), 71.8-71.1 (C-5), 69.5-68.9 (C-6), 30.1, 29.9-29.7, 26.2 (CH_2).

MS (MALDI-TOF): 11742.7 m/z ($\text{M}+\text{Na}$) $^+$.

Elemental analysis calcd. for $\text{C}_{724}\text{H}_{778}\text{O}_{140}$: C 74.20 H 6.69; found C 73.97 H 7.05.

Tetramer- β -cyclodextrin-bis-pentenyl 6β :



KH 30 % m/m (28mg, 212 μmol), 18-Crown-6 (1.3mg, 5 μmol) and 5-bromo-pent-1-ene (25 μL , 212 μmol) were added to a stirred solution of diol 5β (620mg, 53 μmol) in dry THF

(15mL), under argon at r.t. More KH and 5-bromo-pent-1-ene (3 equiv.) were added twice. Stirring was continued until complete disappearance of the starting material (ca 24 h). The reaction was quenched with MeOH (1mL), and concentrated. A solution of the residue in dichloromethane (50mL) was washed with aq. sat. NH_4Cl (2×25mL), dried (MgSO_4), filtered and concentrated. Chromatography of the residue (cyclohexane/EtOAc 4:1) on silica gel gave **6 β** (514mg, 82%) as a white foam.

TLC analysis: R_f 0.35 (Cyclohexane/EtOAc 4:1).

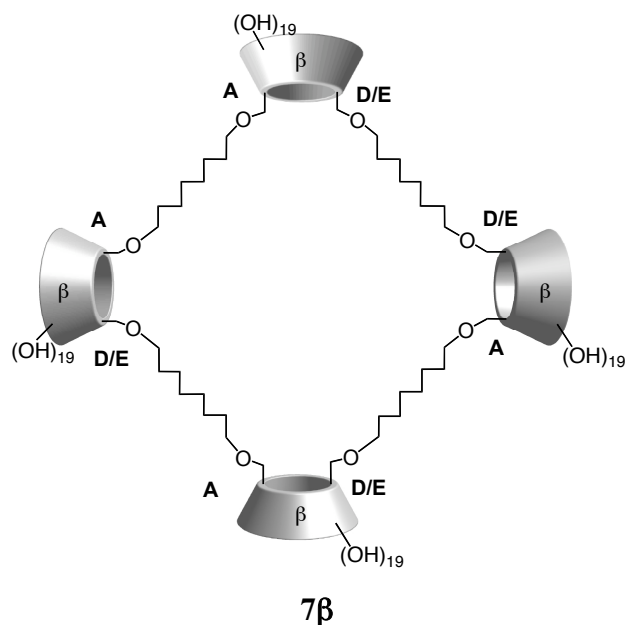
^1H NMR (400MHz, CDCl_3): δ 7.34-7.10 (m, 380H, H-aromatique), 5.85 (dddd, $^3J_{b,a'} = 16.8\text{Hz}$, $^3J_{b,a} = 10.3\text{Hz}$, $^3J_{b,c'} = ^3J_{b,c} = 5.6\text{Hz}$, 2H, 2×b-H), 5.45-5.38 (m, 3H, 3×1-H), 5.33-4.91 (m, 57H, 25×1-H, 4×a-H, 28×CHPh), 4.83-4.73 (m, 28H, 28×CHPh), 4.61-4.36 (m, 98H, 98×CHPh), 4.12-3.81 (m, 112H, 28×3-H, 28×4-H, 28×5-H, 28×6-H), 3.68-3.22 (m, 72H, 28×2-H, 28×6-H, 16× OCH_2), 2.09-1.96 (m, 4H, 4×c-H), 1.61-1.44 (m, 16H, CH_2), 1.29-1.21 (m, 24H, CH_2).

^{13}C NMR (100MHz, CDCl_3): δ 138.7-139.4 (C-arom. quat.), 138.5-138.0 (C-arom. quat.), 138.0 (C-b), 128.3-126.9 (CH-aromatique), 114.8 (C-a), 98.5-97.8 (C-1), 80.9-80.7 (CH), 79.4-78.3 (CH), 75.9-74.7 (OCH_2Ph), 73.3-73.1 (OCH_2Ph), 72.8-72.4 (OCH_2Ph), 71.7 (OCH_2), 71.6-71.3 (C-5), 70.8-70.7 (OCH_2), 69.6-68.8 (C-6), 30.2, 29.8-29.7, 28.7, 26.2 (CH_2).

MS (MALDI-TOF): 11879.4 m/z ($\text{M}+\text{Na}$)⁺.

Elemental analysis calcd. for $\text{C}_{734}\text{H}_{794}\text{O}_{140}$: C 74.36 H 6.75, found C 74.12 H 7.01.

Tetraplex- β -cyclodextrin **7 β** :

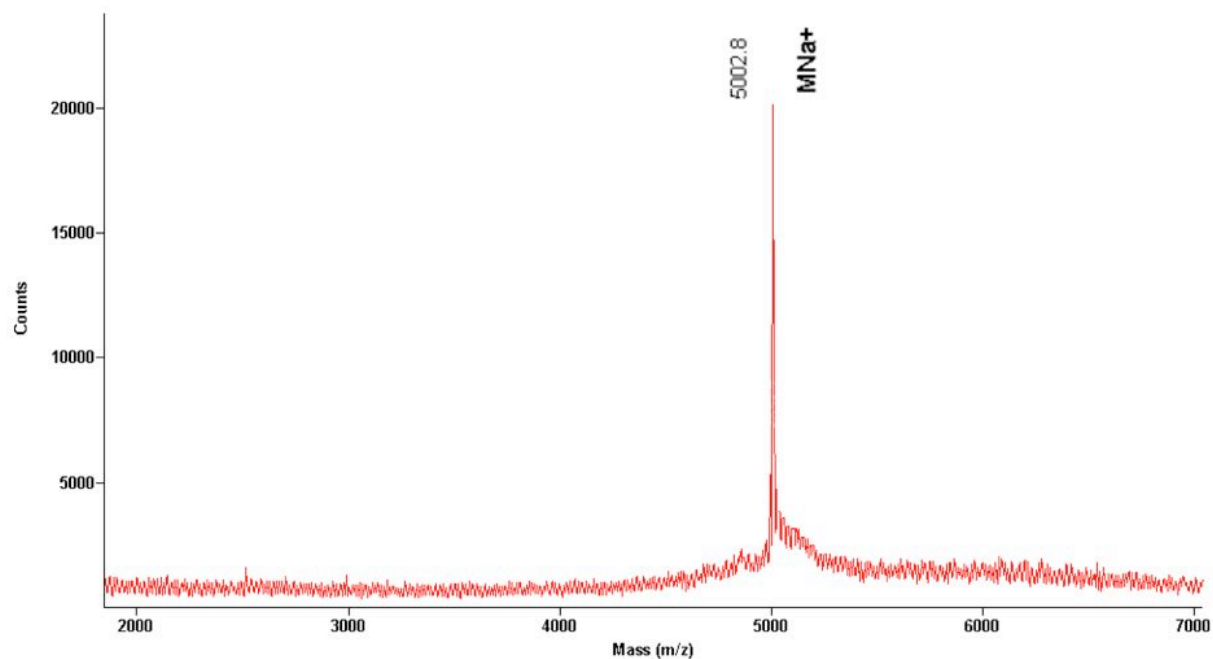


Grubbs catalyst (1,7mg, 2.1 μ mol) was added to a stirred solution of **6 β** (250mg, 21 μ mol) in degassed dichloromethane (21mL), under argon at r.t., The reaction mixture was heated under reflux for 24 h, and more Grubbs catalyst (1,7mg, 2.1 μ mol) was added. After heating under reflux for 24 h, Pb(OAc)₄ (2,8mg, 1.5eq/Ru) was added to the cooled solution (r.t.). The reaction mixture was stirred overnight at r.t., and concentrated. Chromatography of the residue (cyclohexane/EtOAc 4:1) on silica gel afforded the macrocycle (117 mg, 47%) as a white foam: MS (MALDI-TOF): 11851.2 *m/z* (M+Na)⁺. The macrocycle (100 mg, 8.5 μ mol) was dissolved in a mixture of THF/NH₃ 1:1 (10mL) at -78°C. Small pieces of Na (excess) were added. The blue solution was refluxed for 1 h (-33°C), carefully quenched by iPrOH (10mL) and concentrated. A solution of the residue in water (15mL) was neutralized with IR-120 H⁺ resin, diluted with EtOAc (15mL), stirred vigorously for 30 minutes and filtrated. The organic layer was separated, extracted with water (3 \times 10mL) and the combined aqueous layers were concentrated. A mixture of this residue and Pd/C 10 % (30mg) in MeOH/water 1:1 (5 mL) was stirred under H₂ atmosphere for 12 h, filtered trough Celite® and concentrated. The residue was purified by chromatography on Sephadex G25 column (water) and lyophilized to give the tetraplexe **7 β** (29mg, 69% over two steps) as a white powder.

¹H NMR (400MHz, D₂O): δ 5.12-4.96 (m, 28H, 1-H), 4.05-3.55 (m, 184H, 2-H, 3-H, 4-H, 5-H, 6-H, OCH₂), 1.55-1.35 (m, 48H, CH₂).

^{13}C NMR (100MHz, D_2O): δ 102.7-102.4 (C-1), 81.7-81.3 (CH), 74.2-71.4 (CH), 60.1-59.6 (OCH₂).

MS (MALDI-TOF): 5002.8 m/z (M+Na)⁺.



¹ Lecourt, T.; Mallet, J.-M.; Sinaÿ, P. *Eur. J. Org. Chem.* **2003**, 4553.