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Use of the olefin metathesis reaction for highly efficient β-cyclodextrin modification

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Abstract—A series of novel primary face mono-substituted β-cyclodextrin derivatives have been synthesised using the olefin metathesis reaction. Mono-6-allylamino-6-deoxy-β-cyclodextrin easily synthesised by nucleophilic substitution of mono-6-tosyl-β-cyclodextrin is the key synthon in the preparation of cyclodextrin derivatives mono-functionalised at the primary face by alkyl, aryl or perfluoroalkyl groups using Grubbs catalyst. In the cases of vinylbenzene and 1H,1H,2H-perfluoro-1-octene, the metathesis reactions yield with 95% stereoselectivity of the *E*-isomer.

1. Introduction

Olefin metathesis is one of the most powerful synthetic tools in organic chemistry, with a large scope of applications from natural product to polymer synthesis.[1–4] More specifically, this reaction has been applied with success to carbohydrate chemistry.[5,6] In the particular case of cyclodextrins (CDs) or cyclomaltoheptaoses, only a few examples have been reported so far. Thus, in 2000, Stoddart et al.[7] described the use of olefin metathesis to generate face-to-face 2-2′ and 3-3′ dimers of β-cyclodextrin. This was achieved by a homodimerisation reaction between mono-substituted cyclodextrins having ethylene oxy-alkene groups present at either the O-2 or the O-3 positions.

Following this, in 2002, Sinaÿ et al. synthesised 'head-to-head' dimers of α- and β-cyclodextrin using mono-substitution at the O-6 position with alkylidene chains.[8–10] More recently, the same authors described the synthesis of a heteroduplex system containing both α- and β-cyclodextrin disubstituted units using the metathesis reaction.[11]

Generally, the introduction of bioactive substituents onto the cyclodextrins has been treated in a case by case manner, with each coupling specific to the introduced recognition antenna. This has been achieved using esters,[12] amides[13] or thioalkyl[14] linkages with success. However, linkages using ether or amine functions are much more difficult. In order to make the introduction of antenna more efficient and allow rapid generation of libraries of such molecules, a 'base unit' consisting of a mono-substituted cyclodextrin capable of accepting a wide range of antennae under a standard coupling condition would seen to be highly attractive.

In this work, we describe an efficient synthesis by olefin metathesis reaction of new β-cyclodextrin derivatives mono-substituted at the primary face by different hydrophilic or hydrophobic chains linked by a nitrogen atom at the C-6 position. This reaction opens up the facile synthesis of a wide range of CDs derivatives using one simple building block.

2. Results and discussion

2.1. Synthesis and characterisation

The synthetic procedure for the synthesis of the new β-cyclodextrin derivatives **9**, **10**, **11**, **12** mono-functionalised at the primary face by different groups (oct-1-ene, vinylbenzene, 3-(2-methoxyethoxy)-prop-1-ene, 1H,1H,2H-perfluoro-1-octene) and the homodimer **13** was based on an olefin metathesis reaction in four steps from mono-6-allylamino-6-deoxy-β-cyclodextrin **1** (Scheme 1).[15]

The use of the Grubbs catalyst requires protection of the nitrogen atom and the lack of solubility of **1** in organic solvents

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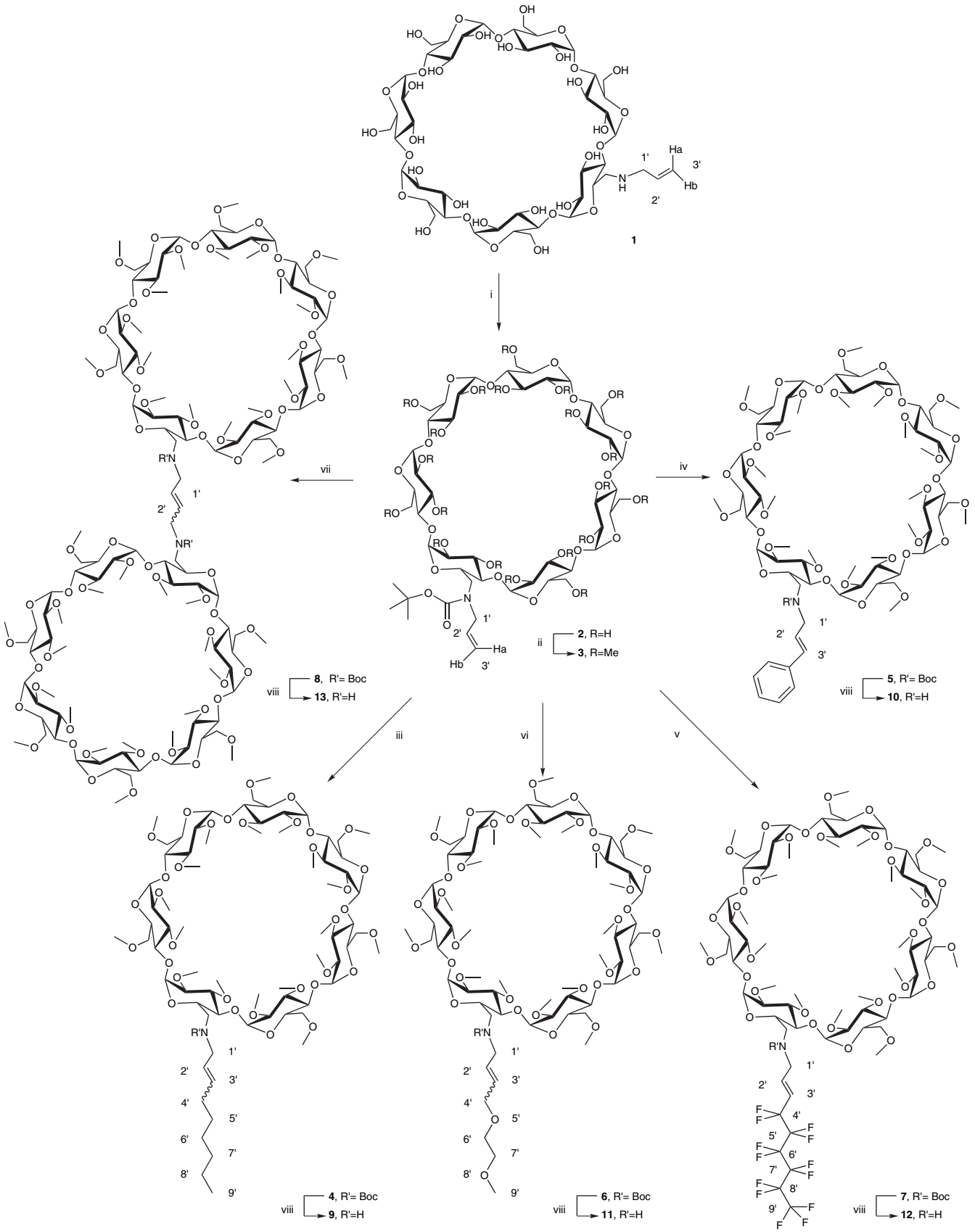

Scheme 1. Reagents and conditions: (i) Boc_2O, $NaHCO_3$, MeOH, ultrasonication; (ii) NaH, CH_3I, DMF, 20 °C; (iii) oct-1-ene, Grubbs catalyst [$Cl_2(PCy_3)2Ru{=}CHPh$], CH_2Cl_2, 55 °C; (iv) vinylbenzene, [$Cl_2(PCy_3)2Ru{=}CHPh$], CH_2Cl_2, 55 °C; (v) 3-(2-methoxyethoxy)-prop-1-ene, [$Cl_2(PCy_3)2Ru{=}CHPh$], CH_2Cl_2, 55 °C; (vi) 1H,1H,2H-perfluoro-1-octene, Grubbs–Hoveyda catalyst ($C_{31}H_{38}Cl_2N_2ORu$), CH_2Cl_2, 55 °C; (vii) [$Cl_2(PCy_3)2Ru{=}CHPh$], CH_2Cl_2, 55 °C; (viii) TFA, 20 °C.

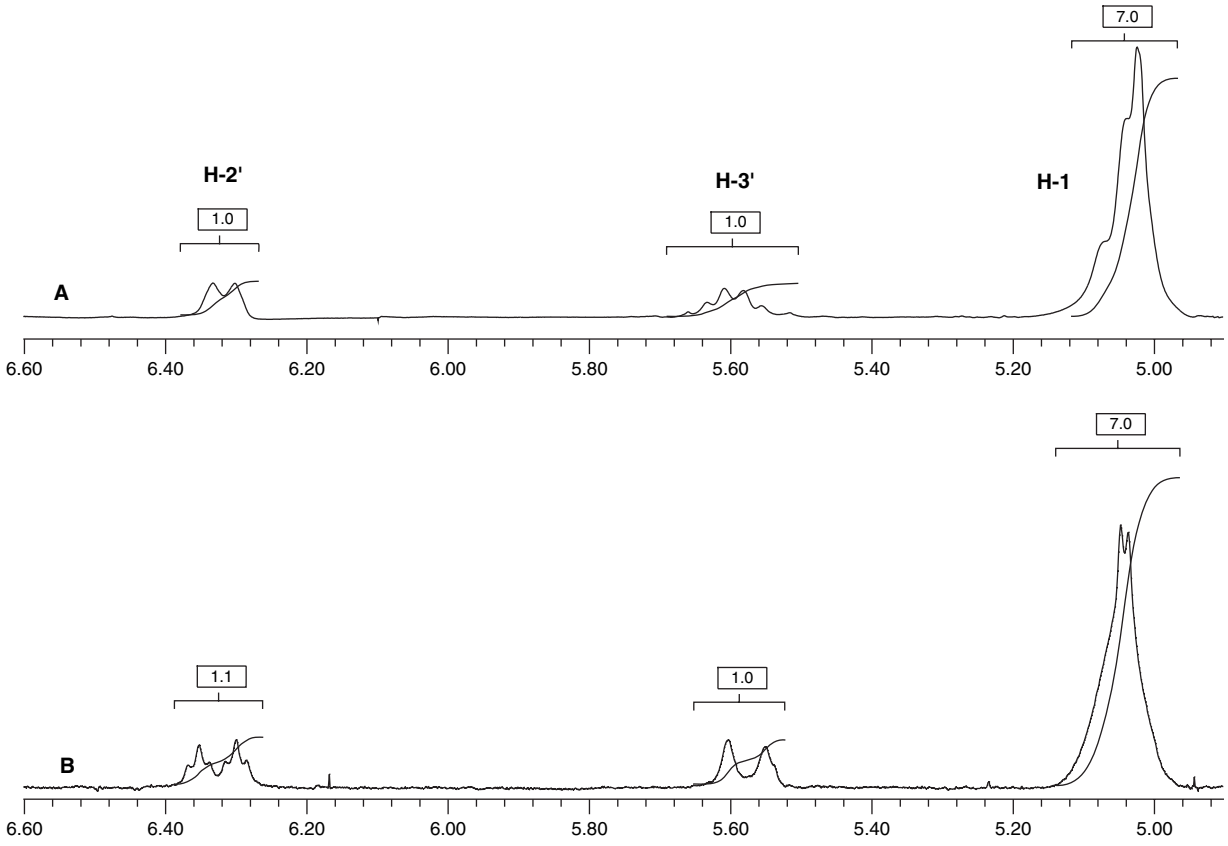

Figure 1. (A) ^{1}H NMR spectrum of **7**; (B) ^{1}H with ^{19}F decoupled NMR spectrum of **7**.

necessitates modification of the free hydroxyl groups at the O-2, O-3 and O-6 positions. N-protection was carried out using di-*tert*-butyl dicarbonate (Boc_2O) according to the conditions of peptide synthesis[16] to give **2** in 67% isolated yield. O-methylation at the six primary hydroxyl groups and the fourteen secondary hydroxyl groups of the β-CD **2** was realised using of 50 equiv of methyl iodide in dry DMF with 60 equiv of sodium hydride. The new cyclodextrin derivative **3** was purified by flash chromatography (eluent gradient $CHCl_3$/acetone, 100/0 to 60/40) in 67% isolated yield. The degree of the substitution was assessed by MALDI mass spectrometry (*m*/*z* 1576.7 $[M+Na]^+$ 1592.7 $[M+K]^+$) and the structure confirmed by ^{1}H, ^{13}C and HMBC NMR spectroscopy.

Mono(6^{A}-*N*-allyl-*N*-*tert*-butoxycarbonylamino,6^{A}-deoxy)-hexakis(6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-*O*-methyl)-heptakis(2,3-di-*O*-methyl)-β-cyclodextrin **3** (0.25 M in CH_2Cl_2) in the presence of the Grubbs catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (15% mol/mol for **4** and **5**, 20% mol/mol for **6**) was reacted at 55 °C, under argon, with oct-1-ene, vinylbenzene or 3-(2-methoxyethoxy)-prop-1-ene[17] (2.5 equiv) during 18 h for **4** and **5**, 46 h for **6**. The cyclodextrins derivatives **4**, **5** and **6** were isolated by flash chromatography on silica gel with eluent gradient Et_2O/MeOH 100/0 to 96/4 for **4** and **5**, 100/0 to 95/5 for **6**, in 70, 73 and 53% yields, respectively. The coupling of the olefins was confirmed via ^{1}H NMR spectroscopy (500 MHz, solvent $CDCl_3$) by the changes in the chemical shifts of the vinylic protons situated at C-2′ and C-3′. The signal for the proton H-3′ shows the largest perturbation, being shifted downfield (5.46–6.38 ppm) in the new compounds **4**, **5** and **6** with respect to initial values (m, 4.95–5.07 ppm) in *N*-Boc-allyl-amino β-cyclodextrin **3**. Mono-substitution of β-cyclodextrin by a long chain, which may be hydrophobic or hydrophilic, is known to reduce the geometry of the cavity. This leads to a separation in the peaks for H-1 (m, 4.94–5.11 ppm) into three signals; a broad singlet at 4.94 ppm, integration 1, a multiplet around 5.03 ppm, integration 5 and a broad singlet at 5.11 ppm, integration 1. In the case of coupling with vinylbenzene there is less perturbation, one signal at 5.12 ppm, integration 1 and a second at 5.03 ppm, integration 6.

Determination of the *E*, *Z* selectivity of this reaction is not trivial as the signals of the vinylic protons of compounds **4** and **6** are present as multiplets. However for β-cyclodextrin derivative **5**, the coupling constant H-2′/H-3′ at 15.0 Hz confirms *E* geometry. The metathesis reaction yields stereoselectively (95%) the *E*-isomer,[†] in 73% yield, which is interesting when compared to the generally measured ratio *E*/*Z* isomer (7/3). It should be noted that in the case of the ether-linked 3-3′-β-CD dimer described by Stoddart, the authors concluded after much work, that the isomers were present in the 9:1 ratio.[7]

Given the facile nature of the above synthesis, we applied the reaction to the introduction of perfluoroalkyl chains, leading to the synthesis of the β-CD derivative **7**. Only few examples of metathesis have been published so far with fluorinated

[†] The actual ratio, as determined, is within the experimental limits of incertitude for ^{1}H NMR spectroscopy.

olefins with one or two fluorine atoms[18,19] or with longer fluorous chains.[20,21] In previous studies, we have synthesised mono-fluorinated amphiphilic cyclodextrin from mono-6-tosyl-β-cyclodextrin with 3-perfluorohexylpropanethiol by nucleophilic attack at the tosyl group.[22] Introduction of perfluoroalkyl chains in carbohydrates has been carried out using radical reactions from allylic compounds.[23] This method is not available for the cyclodextrins.[24] The novel derivative **7** was synthesised by a metathesis reaction between the olefinic cyclodextrin derivative **3** and 13 equiv of the 1H,1H,2H-perfluoro-1-octene in presence of the Grubbs–Hoveyda catalyst[25] ($C_{31}H_{38}Cl_2N_2ORu$) in CH_2Cl_2 at 55 °C for 9 days. Purification by flash chromatography yields **7** and the cyclodextrin dimer **8**. However, we have directly isolated **8** by the homodimerisation of the cyclodextrin derivative **3** in presence of the first generation Grubbs catalyst (14% mol/mol) at 50 °C for 21 h in 60% yield. Comparing the above results we propose that **8** is first synthesised as the kinetic product, which then reacts with the fluorous olefin to give **7**. Stereoselectivity of the metathesis reaction is again confirmed by NMR in $CDCl_3$ of **7**. In the ^1H decoupled ^{19}F spectrum (Fig. 1B) the appearance of a multiplet for H-2′ at 6.32 ppm and a doublet for H-3′ at 5.58 ppm with the coupling constant H-2′/H-3′=16 Hz is characteristic of the *E*-isomer. The anomeric signal H-1 was converted from a multiplet to a doublet ($^3J_{H\text{-}1/H\text{-}2}$=3.5 Hz). In the ^{13}C NMR C-2′ and C-3′ were observed at 139.4 and 117.5 ppm, respectively. Analysis by electrospray mass spectrometry (ESMS) confirms the structure of **7** (*m/z* 1894.9 $[M+Na]^+$ 959.0 $[M+2+Na]^{2+}$).

Selective removal of the *N*-Boc protecting group by trifluoroacetolysis (TFA, 20 °C) to gives the secondary amino cyclodextrin derivatives **9**, **10**, **11**, **12** and **13** in 94, 82, 94, 89 and 91% yields, respectively.

3. Conclusion

We have synthesised a variety of primary face mono-substituted β-cyclodextrin derivatives by the use of the metathesis reaction. This reaction gives direct access to β-cyclodextrin derivatives via a single synthon mono-6-allyl-6-deoxy-β-cyclodextrin **1** and various olefins presenting hydrophobic or hydrophilic nature. We also show the feasibility of this synthesis for the coupling of perfluoroalkyl-olefin. In the cases of vinylbenzene and 1H,1H,2H-perfluoro-1-octene, we obtained the *E*-isomer in 95% whereas the previous best stereoselectivities observed in the chemistry of cyclodextrins were 9:1. This metathesis reaction presents a highly promising route to novel mono-functionalised cyclodextrin derivatives.

4. Experimental

4.1. General

Ruthenium catalysts were purchased from Aldrich. β-Cyclodextrin was generously provided by Roquette (France). ^1H, ^{13}C, COSY, HSQC and HMBC NMR experiments were performed at 300 and 75 MHz, respectively, or 500 and 125 MHz, respectively, using a Bruker DRX 300 spectrometer or a Bruker AM 500 spectrometer. ^{19}F NMR experiments were obtained at 280 MHz with a Bruker ALS 300 spectrometer. It should be noted that mono-substitution of any cyclodextrin totally removes the axial symmetry of the molecule leading to considerable overlap in closely related chemical shifts of every proton or carbon and rendering spectral analysis extremely complex. ES mass spectra were measured using a Perkin–Elmer Sciex spectrometer and MALDI-TOF mass spectra were measured using Applied Biosystems Voyager-DE Pro. IR spectra were recorded on a Perkin–Elmer instrument. The optical rotations were tested on a Perkin–Elmer 241 Polarimeter.

4.1.1. Mono-(6^A-*N*-allylamino-6^A-deoxy)-cyclomaltoheptaose 1. The mono-(6^A-deoxy-6^A-(*p*-toluenesulfonyl))-cyclomaltoheptaose[26] was converted into **1** by the procedure described by Lai and Ng.[15] Yield: 81%; R_f (*n*-BuOH/EtOH/H_2O, 5/4/3)=0.06; mp: >250 °C; $[\alpha]_D$ +138 (*c* 1.000, MeOH); IR (cm^{-1}, KBr): 3395 (O–H), 2927 (C–H), 1657 (C=C), 1158 (C–O–C), 1033 (C–N); ^1H NMR (DMSO-d_6, 300 MHz, assignments by HSQC): δ (ppm): 2.69 (m, 1H, H-6aA), 2.92 (m, 1H, H-6bA), 3.18 (m, 2H, H-1′), 3.32–3.40 (m, 14H, H-4, H-5), 3.53–3.63 (m, 26H, H-2, H-3, H-6a, H-6b), 4.44 (br s, 6H, OH-6), 4.83 (br s, 7H, H-1), 5.03 (d, 1H, H-3′b, $^3J_{H\text{-}3'b/H\text{-}2'}$=10.1 Hz), 5.14 (d, 1H, H-3′a, $^3J_{H\text{-}3'a/H\text{-}2'}$=17.7 Hz), 5.67–5.81 (m, 15H, OH-2, OH-3, H-2′); ^{13}C NMR (DMSO-d_6, 75 MHz, assignments by HSQC): δ (ppm): 49.8 (C-6A), 52.5 (C-1′), 60.8 (C-6), 72.8 (C-2), 73.3 (C-5), 73.9 (C-3), 82.1–82.4 (C-4), 84.7 (C-4A), 102.8–103.1 (C-1), 116.1 (C-3′), 138.3 (C-2′); ESMS (+) *m/z*: $[M+Na]^+$ 1197.2; $C_{45}H_{75}NO_{34}$.

4.1.2. Mono-(6^A-*N*-allyl-*N*-*tert*-butoxycarbonylamino-6^A-deoxy)-cyclomaltoheptaose 2. To a solution of **1** (2.00 g, 1.70 mmol) in MeOH (50 mL) at room temperature were added Boc_2O (0.45 g, 2.05 mmol, 1.2 equiv) and $NaHCO_3$ (0.43 g, 5.11 mmol, 3 equiv). The reaction mixture was placed for 12 h in an ultrasonic bath and monitored by TLC. The solvent was evaporated and the white solid was purified by column chromatography (Silica gel 100 C_{18}-reversed phase, H_2O/MeOH, step gradient: 100/0 to 50/50) to afford **2** as a white powder. Yield: 67%; R_f (*n*-BuOH/EtOH/H_2O, 5/4/3)=0.44; mp: 206 °C; $[\alpha]_D$ +132 (*c* 1.015, MeOH); IR (cm^{-1}, KBr): 3395 (O–H), 2918 (C–H), 1676 (C=O), 1155 (C–N), 1028 (C–O–C); ^1H NMR (MeOD-d_4, 500 MHz, assignments by COSY and HSQC): δ (ppm): 1.51 (s, 9H, CH_3 Boc), 2.84 (dd, 1H, H-6aA, $^2J_{H\text{-}6aA/H\text{-}6bA}$= 14.5 Hz and $^3J_{H\text{-}6aA/H\text{-}5A}$=10.5 Hz), 3.18 (t, 1H, H-4A, $^3J_{H\text{-}4A/H\text{-}3A}$=$^3J_{H\text{-}4A/H\text{-}5A}$=9.5 Hz), 3.50–3.74 (m, 20H, H-2, H-4, H-5, H-1′b), 3.79–4.03 (m, 21H, H-3, H-6a, H-6b), 4.26 (t, 1H, H-5A, $^3J_{H\text{-}5A/H\text{-}4A}$=$^3J_{H\text{-}5A/H\text{-}6bA}$=10.3 Hz), 4.46 (d, 1H, H-1′a, $^2J_{H\text{-}1'a/H\text{-}1'b}$=14.5 Hz), 4.97–5.03 (m, 7H, H-1), 5.15 (m, 2H, H-3′), 5.80 (m, 1H, H-2′); ^{13}C NMR (MeOD-d_4 and 10% of Pyridine-d_5, 125 MHz, assignments by DEPT and HSQC): δ (ppm): 27.9, 28.6 (*C*H_3 Boc), 48.3 (C-6A), 51.8 (C-1′), 60.8 (C-6), 70.6 (C-5A), 72.4–74.1 (C-2, C-3, C-5), 80.1 (O–*C* Boc), 82.1–82.5 (C-4), 85.3 (C-4A), 101.7 (C-1A), 102.8–103.4 (C-1), 115.1 (C-3′), 134.1 (C-2′), 155.8 (–*C*=O Boc); ESMS (+) *m/z*: $[M+Na]^+$ 1296.4, $[M+H]^+$ 1275.4; $C_{50}H_{83}NO_{36}$.

4.1.3. Mono-(6^A-*N*-allyl-*N*-*tert*-butoxycarbonylamino-6^A-deoxy)-hexakis-6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 3. NaH 60% (4.70 g, 117.6 mmol, 60 equiv, 3 equiv/OH) was added to

a solution of **2** (2.50 g, 1.9 mmol) in DMF (40 mL). The mixture was stirred for 3 h, then ICH_3 (6.10 mL, 98 mmol, 50 equiv, 2.5 equiv/OH) was added dropwise to the suspension (the temperature must be kept below 35 °C). After stirring for 18 h at room temperature, excess NaH was destroyed carefully by addition of methanol (10 mL) and the solution was diluted with water (50 mL). The organic layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with water, dried over Na_2SO_4. The solvent was evaporated and the yellow solid was subjected to column chromatography (SiO_2, $CHCl_3$/acetone, step gradient: 100/0 to 60/40) to afford **3**. Yield: 65%; R_f (Et_2O/MeOH, 90/10)=0.26; mp: 80 °C; $[\alpha]_D$ +140 (*c* 1.025, $CHCl_3$); IR (cm^{-1}, KBr): 2930 (C–H), 1700 (C=O), 1164 (C–O–C), 1037 (C–N); ^1H NMR ($CDCl_3$, 300 MHz, assignments by COSY and HSQC): δ (ppm): 1.43 (s, 9H, CH_3 Boc), 2.86 (m, 1H, H-6aA), 3.10–3.13 (m, 8H, H-2, H-4A), 3.31–3.81 (m, 93H, H-3, H-4, H-5, H-6a, H-6b, 2-OC*H*$_3$, 3-OC*H*$_3$, 6-OC*H*$_3$, H-1′b), 4.01 (m, 1H, H-5A), 4.28 (m, 1H, H-1′a), 4.95–5.07 (m, 9H, H-1 and H-3′), 5.69 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 75 MHz, assignments by DEPT and HSQC): δ (ppm): 28.8–29.3 (CH_3 Boc), 49.2 (C-6A), 51.3 (C-1′), 58.5–62.1 (2-O*C*H$_3$, 3-O*C*H$_3$, 6-O*C*H$_3$), 71.0–71.8 (C-5, C-6), 79.7 (O–*C* Boc), 80.7–82.4 (C-2, C-3, C-4), 98.4 (C-1A), 99.4–100.5 (C-1), 116.5 (C-3′), 134.1 (C-2′), 155.3 (*C*=O Boc); MALDI-TOF-MS: $[M+Na]^+$ 1576.7, $[M+K]^+$ 1592.7; $C_{70}H_{123}NO_{36}$.

4.1.4. General procedure for metathesis reactions. To a solution of **3** (1.0 equiv) in freshly distilled CH_2Cl_2 (0.25 M) was added under argon the alkene (2.5 equiv) and Grubbs catalyst [$Cl_2(PCy_3)_2Ru$=CHPh] (15% mol/mol for **4**, **5** and 20% mol/mol for **6**). The solution was stirred at 50 °C and the reaction can be monitored by TLC (Et_2O/MeOH, 90/10). After stirring for 18 h (46 h for **6**), the solvent was evaporated and the black solid was subjected to column chromatography (SiO_2, Et_2O/MeOH, step gradient: 100/0 to 96/4 (100/0 to 95/5 for **6**) to afford the product.

4.1.4.1. Mono-(6^A-deoxy-6^A-(1-*N*-non-2-ene-*N*-*tert*-butoxycarbonylamino))-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 4. Yield: 70%; R_f (Et_2O/MeOH, 90/10)=0.63; mp (dec): 68 °C; $[\alpha]_D$ +133 (*c* 0.990, $CHCl_3$); IR (cm^{-1}, KBr): 2929 (C–H), 1697 (C=O), 1164 (C–O–C), 1037 (C–N); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm): 0.81 (s, 3H, H-9′, $^3J_{H\text{-}9'/H\text{-}8'}$=6.5 Hz), 1.21–1.32 (m, 8H, H-5′, H-6′, H-7′, H-8′), 1.43 (s, 9H, C*H*$_3$ Boc), 1.98 (q, 2H, H-4′, $^3J_{H\text{-}4'/H\text{-}5'}$=$^3J_{H\text{-}4'/H\text{-}3'}$=7.0 Hz), 2.75 (m, 1H, H-6aA), 3.04 (t, 1H, H-4A, $^3J_{H\text{-}4A/H\text{-}5A}$=$^3J_{H\text{-}4A/H\text{-}3A}$=9.0 Hz), 3.09–3.13 (m, 7H, H-2), 3.30–3.82 (m, 93H, H-3, H-4, H-5, H-6a, H-6b, 2-OC*H*$_3$, 3-OC*H*$_3$, 6-OC*H*$_3$, H-1′b), 4.03 (m, 1H, H-5A), 4.35 (d, 1H, H-1′a, $^2J_{H\text{-}1'a/H\text{-}1'b}$=13.0 Hz), 4.94 (br s, 1H; H-1), 5.03 (m, 5H, H-1), 5.11 (br s, 1H, H-1), 5.30 (m, 1H, H-2′), 5.46 (m, 1H, H-3′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 14.5 (C-9′), 23.0 (C-8′), 28.9–29.6 (C-5′, C-6′, CH_3 Boc), 32.1 (C-7′), 32.7 (C-4′), 48.9 (C-6A), 51.2 (C-1′), 58.8–62.1 (2-O*C*H$_3$, 3-O*C*H$_3$, 6-O*C*H$_3$), 71.0–72.0 (C-5, C-6), 79.5 (O–*C* Boc), 80.7–82.6 (C-2, C-3, C-4), 98.4 (C-1A), 99.8–100.5 (C-1), 133.4 (C-2′), 133.9 (C-3′), 155.3 (*C*=O Boc); MALDI-TOF-MS $[M+Na]^+$ 1662.7, $[M+K]^+$ 1676.7; $C_{76}H_{135}NO_{36}$.

4.1.4.2. Mono-(6^A-deoxy-6^A-(1-*N*-3-phenyl-prop-2-ene-*N*-*tert*-butoxycarbonylamino))-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 5. Yield: 73%; R_f (Et_2O/MeOH, 90/10)=0.55; mp (dec): 95 °C; $[\alpha]_D$ +135 (*c* 1.005, $CHCl_3$); IR (cm^{-1}, KBr): 2930 (C–H), 1700 (C=O), 1170 (C–O–C), 1036 (C–N); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm): 1.46 (s, 9H, C*H*$_3$ Boc), 2.80 (m, 1H, H-6aA), 3.07–3.13 (m, 8H, H-2, H-4A), 3.29–3.85 (m, 93H, H-3, H-4, H-5, H-6a, H-6b, 2-OC*H*$_3$, 3-OC*H*$_3$, 6-OC*H*$_3$, H-1′b), 4.06 (m, 1H, H-5A), 4.57 (d, 1H, H-1′a, $^2J_{H\text{-}1'a/H\text{-}1'b}$=14.0 Hz), 5.03 (m, 6H, H-1), 5.12 (br s, 1H, H-1A), 6.08 (m, 1H, H-2′), 6.38 (d, 1H, H-3′, $^3J_{H\text{-}3'/H\text{-}2'}$=15.0 Hz), 7.16 (t, 1H, H_{para}, $^3J_{H_{para}/H_{meta}}$=7.3 Hz), 7.24 (t, 2H, H_{meta}, $^3J_{H_{meta}/H_{para}}$=$^3J_{H_{meta}/H_{ortho}}$=7.3 Hz), 7.30 (d, 2H, H_{ortho}, $^3J_{H_{ortho}/H_{meta}}$=7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 28.9–29.4 (CH_3 Boc), 49.5 (C-6A), 51.5 (C-1′), 58.0–62.3 (2-O*C*H$_3$, 3-O*C*H$_3$, 6-O*C*H$_3$), 71.1–71.5 (C-5, C-6), 79.7 (O–*C* Boc), 81.9–82.6 (C-2, C-3, C-4), 98.5 (C-1A), 99.6–100.6 (C-1), 125.6 (C-3′), 126.7 (C_{ortho}), 128.1 (C_{para}), 129.0 (C_{meta}), 132.1 (C-2′), 137.0 (C_{ipso}), 155.3 (*C*=O Boc); MALDI-TOF-MS $[M+Na]^+$ 1652.9, $[M+K]^+$ 1668.9; $C_{76}H_{127}NO_{36}$.

4.1.4.3. Mono-[6^A-deoxy-6^A-(1-*N*-5,8-dioxy-non-2-ene-*N*-*tert*-butoxycarbonylamino)]-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 6. Yield: 53%; R_f (Et_2O/MeOH: 90/10)=0.20; mp (dec): 76 °C; $[\alpha]_D$ +113 (*c* 1.005, $CHCl_3$); IR (cm^{-1}, KBr): 2928 (C–H), 1698 (C=O), 1164 (C–O–C), 1038 (C–N); ^1H NMR ($CDCl_3$, 500 MHz, assignments by COSY and HSQC): δ (ppm): 1.43 (s, 9H, CH_3 Boc), 2.71 (m, 1H, H-6aA), 3.03 (t, 1H, H-4A, $^3J_{H\text{-}4A/H\text{-}5A}$=$^3J_{H\text{-}4A/H\text{-}3A}$=9.0 Hz), 3.10–3.12 (m, 7H, H-2), 3.31–3.84 (m, 100H, H-3, H-4, H-5, H-6a, H-6b, 2-OC*H*$_3$, 3-OC*H*$_3$, 6-OC*H*$_3$, H-1′b, H-6′, H-7′, H-9′), 4.01 (m, 4H, H-4′, H-5A), 4.46 (d, 1H, H-1′a, $^2J_{H\text{-}1'a/H\text{-}1'b}$=13.5 Hz), 4.94 (br s, 1H, H-1A), 5.03 (m, 5H, H-1), 5.11 (br s, 1H, H-1), 5.60 (m, 2H, H-2′, H-3′); ^{13}C NMR ($CDCl_3$, 125 MHz, assignments by DEPT and HSQC): δ (ppm): 28.9–29.4 (*C*H$_3$ Boc), 49.2 (C-6A), 50.9 (C-1′), 58.5–62.2 (2-O*C*H$_3$, 3-O*C*H$_3$, 6-O*C*H$_3$, C-9′), 69.9 (C-6′), 70.2–72.0 (C-5, C-6, C-7′), 72.3 (C-4′), 79.6 (–O–*C*– Boc), 81.3–83.1 (C-2, C-3, C-4), 84.4 (C-4A), 98.5 (C-1A), 99.6–100.0 (C-1), 129.2 (C-2, C-3′), 155.2 (–*C*=O Boc); HR-MALDI-TOF-MS $[M+Na]^+$ 1664.8884, $[M+K]^+$ 1680.8875; $C_{74}H_{131}NO_{38}$.

4.1.5. Mono-[6^A-deoxy-6^A-(1-*N*-3-perfluorohexylprop-2-ene-*N*-*tert*-butoxy-carbonylamino)]-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 7. To a solution of **3** (0.25 M) in freshly distilled CH_2Cl_2 (0.390 g, 0.251 mmol) and 1H,1H,2H-perfluoro-1-octene (73 μL, 3.220 mmol, 13 equiv) was added under argon Hoveyda–Grubbs catalyst ($C_{31}H_{38}Cl_2N_2ORu$) (32 mg, 51 μmol, 20% mol/mol). The solution was stirred at 50 °C and the reaction can be monitored by TLC (Et_2O/MeOH, 90/10). After stirring for 9 days, the solvent was evaporated and the black solid was subjected to column chromatography (SiO_2, Et_2O/MeOH, step gradient: 100/0 to 95/5) to afford **7**. Yield: 27%; R_f (Et_2O/MeOH, 90/10)=0.80; mp (dec): 74 °C; $[\alpha]_D$ +111 (*c* 0.670, $CHCl_3$); IR (cm^{-1}, KBr): 2932 (C–H), 1701 (C=O), 1243–1180 (C–F), 1165 (C–O–C), 1039 (C–N); ^1H NMR ($CDCl_3$, 500 MHz, assignments by COSY and HSQC): δ (ppm):

1.43 (s, 9H, CH_3 Boc), 2.73 (m, 1H, H-6aA), 3.08–3.10 (m, 8H, H-2, H-4A), 3.27–3.85 (m, 93H, H-3, H-4, H-5, H-6a, H-6b, 2-OCH_3, 3-OCH_3, 6-OCH_3, H-1′b), 4.00 (m, 1H, H-5A), 4.58 (m, 1H, H-1′a), 5.02–5.04 (m, 7H, H-1), 5.58 (m, 1H, H-3′), 6.32 (d, 1H, H-2′, $^3J_{\text{H-2′/H-3′}}$=16.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, assignments by DEPT and HSQC): δ (ppm): 28.6–29.2 (*C*H_3 Boc), 50.1 (C-6A, C-1′), 58.3–61.9 (2-O*C*H_3, 3-O*C*H_3, 6-O*C*H_3), 71.2–72.0 (C-5, C-6), 80.3 (–O–*C*– Boc), 81.1–83.8 (C-2, C-3, C-4), 98.4 (C-1A), 99.7–100.7 (C-1), 108.4–118.7 (C-4′, C-5′, C-6′, C-7′, C-8′, C-9′), 117.5 (C-3′), 139.4 (C-2′), 155.6 (–*C*=O Boc); ^{19}F NMR ($CDCl_3$, 280 MHz): δ (ppm): −81.3 (s, 3F, F-9′), −110.1 to −113.9 (m, 2F, F-4′), −122.1 (m, 2F, F-5′), −123.4 to −123.6 (m, 4F, F-6′, F-7′), −126.6 (m, 2F, F-8′); ES (+) *m*/*z*: $[M+Na]^+$ 1894.9, $[M+2+Na]^{2+}$ 959.0; $C_{76}H_{122}F_{13}NO_{36}$.

4.1.6. Boc-homodimer 8. To a solution (0.25 M) in freshly distilled CH_2Cl_2 of **3** (0.400 g, 0.257 mmol) was added under argon the Grubbs catalyst [$Cl_2(PCy_3)_2Ru$=CHPh] (30 mg, 36 μmol, 14% mol/mol). The solution was stirred at 50 °C and the reaction can be monitored by TLC (Et_2O/MeOH, 90/10). After stirring for 21 h, the solvent was evaporated and the black solid was subjected to column chromatography (SiO_2, Et_2O/MeOH, step gradient: 100/0 to 90/10) to afford **8**. Yield: 60%; R_f (Et_2O/MeOH, 75/25)=0.58; mp (dec): 107 °C; $[\alpha]_D$ +136 (*c* 0.825, $CHCl_3$); IR (cm^{-1}, KBr): 2930 (C–H), 1698 (C=O), 1165 (C–O–C), 1039 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 1.41 (s, 18H, CH_3 Boc), 2.67 (m, 2H, H-6aA), 3.03 (t, 2H, H-4A, $^3J_{\text{H-4A/H-5A}}$=$^3J_{\text{H-4A/H-3A}}$=9.0 Hz), 3.11 (dd, 14H, H-2, $^3J_{\text{H-2/H-1}}$=3.0 Hz, $^3J_{\text{H-2/H-3}}$=9.5 Hz), 3.27–3.78 (m, 186H, H-3, H-4, H-5, H-6a, H-6b, 2-OCH_3, 3-OCH_3, 6-OCH_3, H-1′b), 4.01 (m, 2H, H-5A), 4.49 (m, 2H, H-1′a), 4.94 (br s, 2H, H-1A), 5.02 (m, 10H, H-1), 5.09 (m, 2H, H-1), 5.44 (m, 2H, H-2′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 28.9–29.3 (*C*H_3 Boc), 49.2 (C-6A), 50.8 (C-1′), 58.5–62.2 (2-O*C*H_3, 3-O*C*H_3, 6-O*C*H_3), 70.2–72.1 (C-5, C-6), 79.7 (–O–*C*– Boc), 80.4–83.1 (C-2, C-3, C-4), 98.7 (C-1A), 99.5–100.8 (C-1), 128.4 (C-2′), 155.4 (–*C*=O Boc); MALDI-TOF-MS $[M+Na]^+$ 3103.4, $[M+K]^+$ 3119.3; $C_{138}H_{242}N_2O_{72}$.

4.1.7. Procedure for Boc deprotection of 4. A solution of compound **4** (0.150 g, 91.5 μmol) in trifluoroacetic acid (6 mL) was stirred overnight at room temperature. The solution was then diluted with water (30 mL). The organic layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with a saturated solution of Na_2CO_3 (60 mL), dried over Na_2SO_4. The solvent was evaporated to afford **9**.

4.1.7.1. Mono-(6^A-deoxy-6^A-non-2-enamino)-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 9. Yield: 94%; R_f (Et_2O/MeOH, 85/15)=0.17; mp (dec): 80 °C; $[\alpha]_D$ +130 (*c* 1.000, $CHCl_3$); IR (cm^{-1}, KBr): 2928 (C–H), 1652 (C=C), 1155 (C–O–C), 1036 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz, assignments by COSY and HSQC): δ (ppm): 0.84 (t, 3H, H-9′, $^3J_{\text{H-9′/H-8′}}$=6.5 Hz), 1.13–1.29 (m, 8H, H-5′, H-6′, H-7′, H-8′), 1.98 (q, 2H, H-4′, $^3J_{\text{H-4′/H-5′}}$=$^3J_{\text{H-4′/H-3′}}$=7.0 Hz), 2.88 (dd, 1H, H-6aA, $^2J_{\text{H-6aA/H-6bA}}$=12.0 Hz, $^3J_{\text{H-6aA/H-5A}}$=6.5 Hz), 3.08–3.13 (m, 8H, H-2, H-6bA), 3.17–3.33 (m, 20H, H-1′, 6-OCH_3), 3.44–3.57 (m, 68H, H-3, H-4, H-6a, H-6b, 2-OCH_3, 3-OCH_3), 3.74–3.79 (m, 7H, H-5), 5.04–5.09 (m, 7H, H-1), 5.46 (m, 1H, H-2′), 5.58 (m, 1H, H-3′); ^{13}C NMR ($CDCl_3$, 125 MHz, assignments by DEPT and HSQC): δ (ppm): 14.4 (C-9′), 22.9 (C-8′), 28.9–29.6 (C-5′, C-6′), 32.0 (C-7′), 32.8 (C-4′), 49.6 (C-6A), 51.8 (C-1′), 58.6–61.8 (2-O*C*H_3, 3-O*C*H_3, 6-O*C*H_3), 69.5–71.7 (C-5, C-6), 80.4–83.3 (C-2, C-3, C-4), 99.1–99.6 (C-1), 128.5 (C-2′), 129.3 (C-3′); ES (+) *m*/*z*: $[M+H]^+$ 1538.6, $[M+Na]^+$ 1560.6; $C_{71}H_{127}NO_{34}$.

4.1.7.2. Mono-(6^A-deoxy-6^A-(3-phenyl-prop-2-enamino))-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 10. Yield: 82%; R_f (Et_2O/MeOH, 90/10)=0.11; mp (dec): 91 °C; $[\alpha]_D$ +137 (*c* 1.050, $CHCl_3$); IR (cm^{-1}, KBr): 2927 (C–H), 1652 (C=C), 1162 (C–O–C), 1034 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz, assignments by COSY and HSQC): δ (ppm): 3.05 (dd, 1H, H-6aA, $^2J_{\text{H-6aA/H-6bA}}$=11.9 Hz, $^3J_{\text{H-6aA/H-5A}}$=6.5 Hz), 3.15–3.20 (m, 8H, H-2, H-6bA), 3.23–3.39 (m, 18H, 6-OCH_3), 3.51–3.65 (m, 70H, H-3, H-4, H-6a, H-6b, 2-OCH_3, 3-OCH_3, H-1′), 3.79–3.90 (m, 7H, H-5), 5.11–5.15 (m, 7H, H-1), 6.29 (dt, 1H, H-2′, $^3J_{\text{H-2′/H-1′}}$=15.6 Hz, $^3J_{\text{H-2′/H-1′}}$=6.2 Hz), 6.55 (d, 1H, H-3′, $^3J_{\text{H-3′/H-2′}}$=15.6 Hz), 7.23–7.27 (m, 1H, H_{para}), 7.30 (t, 2H, H_{meta}, $^3J_{H_{meta}/H_{para}}$=$^3J_{H_{meta}/H_{ortho}}$=7.5 Hz), 7.36 (d, 2H, H_{ortho}, $^3J_{H_{ortho}/H_{meta}}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, assignments by DEPT and HSQC): δ (ppm): 50.2 (C-6A), 52.7 (C-1′), 59.2–62.3 (2-O*C*H_3, 3-O*C*H_3, 6-O*C*H_3), 70.5–72.3 (C-5, C-6), 80.6–83.8 (C-2, C-3, C-4), 99.6 (C-1A), 99.7–100.0 (C-1), 127.1 (C_{ortho}), 127.9 (C-3′), 128.4 (C_{para}), 129.4 (C_{meta}), 131.7 (C-2′), 137.6 (C_{ipso}); ES (+) *m*/*z*: $[M+H]^+$ 1530.9, $[M+H+Na]^{2+}$ 777.0; $C_{71}H_{119}NO_{34}$.

4.1.7.3. Mono-(6^A-deoxy-6^A-(5,8-dioxy-non-2-enamino))-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 11. Yield: 94%; R_f (Et_2O/MeOH, 80/20)=0.20; mp (dec): 65 °C; $[\alpha]_D$ +107 (*c* 0.500, $CHCl_3$); IR (cm^{-1}, KBr): 2926 (C–H), 1684 (C=C), 1162 (C–O–C), 1038 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 2.94 (m, 1H, H-6aA), 3.07 (dd, 1H; H-6bA, $^2J_{\text{H-6bA/H-6aA}}$=9.8 Hz, $^3J_{\text{H-6bA/H-5A}}$=3.0 Hz), 3.12 (dd, 7H, H-2, $^3J_{\text{H-2/H-1}}$=3.3 Hz, $^3J_{\text{H-2/H-3}}$=9.3 Hz), 3.17–3.32 (m, 23H, H-1′, H-9′, 6-OCH_3), 3.43–3.57 (m, 74H, H-3, H-4, H-6a, H-6b, 2-OCH_3, 3-OCH_3, H-3′, H-4′), 3.74–3.80 (m, 7H, H-5), 3.93 (d, 2H, H-4′, $^3J_{\text{H-4′/H-3′}}$=3.0 Hz), 5.04–5.07 (m, 7H, H-1), 5.73 (m, 2H, H-2′, H-3′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 49.3 (C-6A), 50.5–51.2 (C-1′), 58.8–61.9 (2-O*C*H_3, 3-O*C*H_3, 6-O*C*H_3, C-9′), 69.8 (C-6′), 71.3–71.8 (C-5, C-6, C-7′), 72.3 (C-4′), 80.5–83.2 (C-2, C-3, C-4), 99.2–99.5 (C-1), 127.8–128.5 (C-2′, C-3′); ES (+) *m*/*z*: $[M+H]^+$ 1542.9, $[M+H+Na]^{2+}$ 783.1; $C_{69}H_{123}NO_{36}$.

4.1.7.4. Mono-(6^A-deoxy-6^A-(3-perfluorohexylprop-2-enamino))-hexakis-(6^B,6^C,6^D,6^E,6^F,6^G-*O*-methyl)-heptakis-(2,3-di-*O*-methyl)-cyclomaltoheptaose 12. Yield: 89%; R_f (Et_2O/MeOH, 90/10)=0.40; mp (dec): 64 °C; $[\alpha]_D$ +99 (*c* 0.515, $CHCl_3$); IR (cm^{-1}, KBr): 2932 (C–H), 1653 (C=C), 1242–1191 (C–F), 1146 (C–O–C), 1040 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 3.06 (m, 1H, H-6aA),

3.09–3.20 (m, 8H, H-2, H-6bA), 3.23–3.38 (m, 20H, H-1′, 6-OCH_3), 3.51–3.65 (m, 68H, H-3, H-4, H-6a, H-6b, 2-OCH_3, 3-OCH_3), 3.81–3.86 (m, 7H, H-5), 5.10 (d, 3H, H-1, $^3J_{H\text{-}1/H\text{-}2}$=2.6 Hz), 5.13 (br s, 4H, H-1), 5.84 (m, 1H, H-3′), 6.50 (d, 1H, H-2′, $^3J_{H\text{-}2'/H\text{-}3'}$=15.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 50.8 (C-6A), 51.5 (C-1′), 59.7–63.5 (2-OCH_3, 3-OCH_3, 6-OCH_3), 69.8–72.9 (C-5, C-6), 81.4–84.4 (C-2, C-3, C-4), 100.3–100.6 (C-1), 108.4–118.7 (C-4′, C-5′, C-6′, C-7′, C-8′, C-9′), 129.3 (C-3′), 143.4 (C-2′); ^{19}F NMR ($CDCl_3$, 280 MHz): δ (ppm): −81.4 (t, 3F, F-9′, $^3J_{F\text{-}9'/F\text{-}8'}$=9.6 Hz), −110.8 to −113.7 (m, 2F, F-4′), −122.3 (m, 2F, F-5′), −123.5 to −123.8 (m, 4F, F-6′, F-7′), −126.8 (m, 2F, F-8′); ES (+) *m/z*: $[M+Na]^+$ 1794.8, $[M+H]^+$ 1773.0, $[M+2Na]^{2+}$ 909.0, $[M+H+Na]^{2+}$ 898.0; $C_{71}H_{114}F_{13}NO_{34}$.

4.1.7.5. Homodimer 13. Yield: 91%; R_f (Et_2O/MeOH, 70/30)=0.07; mp (dec): 104 °C; $[\alpha]_D$ +140 (*c* 1.015, $CHCl_3$); IR (cm^{-1}, KBr): 2926 (C–H), 1654 (C=C), 1163 (C–O–C), 1037 (C–N); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 2.99 (m, 2H, H-6aA), 3.06 (dd, 2H; H-6bA, $^2J_{H\text{-}6bA/H\text{-}6aA}$=9.5 Hz, $^3J_{H\text{-}6bA/H\text{-}5A}$=3.0 Hz), 3.12 (dd, 14H, H-2, $^3J_{H\text{-}2/H\text{-}1}$=2.5 Hz, $^3J_{H\text{-}2/H\text{-}3}$=9.5 Hz), 3.17–3.32 (m, 40H, H-1′, 6-OCH_3), 3.43–3.58 (m, 136H, H-3, H-4, H-6a, H-6b, 2-OCH_3, 3-OCH_3), 3.73–3.78 (m, 14H, H-5), 5.04 (d, 8H, H-1, $^3J_{H\text{-}1/H\text{-}2}$=2.8 Hz), 5.06 (br s, 6H, H-1), 5.64 (m, 2H, H-2′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 49.5–49.7 (C-6A), 51.8–52.2 (C-1′), 58.5–61.9 (2-OCH_3, 3-OCH_3, 6-OCH_3), 70.5–71.7 (C-5, C-6), 80.5–83.2 (C-2, C-3, C-4), 99.3–99.4 (C-1), 130.6 (C-2′); ES (+) *m/z*: $[M+H]^+$ 2880.7, $[M+2H]^{2+}$ 1441.4, $[M+3H]^{3+}$ 968.6; $C_{128}H_{226}N_2O_{68}$.

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