Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 241–245

TETRAHEDRON LETTERS

Novel fluorinated amphiphilic cyclodextrin derivatives: synthesis of mono-, di- and heptakis-(6-deoxy-6-perfluoroalkylthio)-β-cyclodextrins

Sandrine Peroche and Hélène Parrot-Lopez*

Synthèse, Reconnaissance et Organisation Moléculaire et Biomoléculaire-UMR CNRS 5078, Université Claude Bernard-Lyon I, Domaine Scientifique de la Doua, Bât. J. Raulin, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne cedex, France

Received 11 September 2002; revised 12 November 2002; accepted 13 November 2002

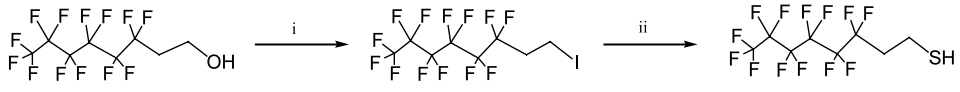
Abstract—A new series of fluorinated amphiphilic β-cyclodextrin derivatives has been synthesized. The strategy is based on the modification of the C-6 position of the mono-6-deoxy-6^A-*para*-tolylsulfonyl, di-6^A, 6^D-deoxy-6^A, 6^D-(*para*-tolylsulfonyl) and heptakis-(6-deoxy-6-iodo)-β-cyclodextrin precursors. The synthesis lead to mono-perfluoroalkylthio-, di-perfluoroalkylthio- and heptakis-perfluoroalkylthio-β-cyclodextrin in excellent yields (90–99%).

Cyclodextrins or cyclomaltoheptaoses (CDs) have significant potential as drug carriers arising from their ability to form inclusion complexes.[1] The potential utility of such inclusion phenomena includes solubilization,[2] encapsulation,[3] and transport of biologically active molecules.[4] Amphiphilic β-cyclodextrin derivatives are of considerable interest for pharmaceutical applications in view of their capacity for self-organization in water. With the aim of providing versatile carrier and delivery systems for hydrophilic and lipophilic drugs, liposomes,[5] nanoparticles,[6] vesicles[7] and micellar aggregates[8] have been prepared from amphiphilic cyclodextrins.

In recent years, in view of their unique hydrophobic and colloidal self-assembly properties, highly fluorinated surfactants have been increasingly studied.[9] Riess et al.[10] synthesized several surfactants with one or more perfluoroalkylated hydrophobic for possible application in the biomedical field. Films and fluorinated vesicles made from fluorinated surfactants are usually, more stable and less permeable than those made from standard surfactants. Vierling et al.[11] synthesized fluorinated liposomes by dispersion of fluorinated double-chain amphiphiles and phospholipids in aqueous solution; these fluorinated liposomes showed lower drug permeation across the liposomal bilayer, and the results of the toxicology studies were satisfactory. Thus, the combination of inclusion properties of the CDs and the useful amphiphilic properties of fluorocarbon chains should lead to molecules possessing novel physical, chemical and biological properties, and with higher hydrophobicity compared to their hydrocarbon analogs.[12]

In previous studies, amphiphilic cyclodextrins were obtained by the introduction of lipophilic groups at the upper and/or lower rims.[13] The substitution of the upper rim is more efficient and does not require protection and deprotection steps. The self-organization depends essentially on the number and the length of the hydrophobic chains; in view of the above, we have synthesized mono-, di- and heptakis-β-cyclodextrin derivatives substituted at C-6 by a perfluorohexylpropanethiol chain.

The hydrofluorocarbon thiol **3** is obtained from the 3-perfluorohexylpropan-1-ol **1** in two steps (Scheme 1)



1 **2** **3**

Scheme 1. Synthesis of the 3-perfluorohexylpropanethiol, **3**. *Reagents and conditions*: (i) P_2O_5 (6 equiv.), H_3PO_4 (85%, 6 mL), KI (2.6 equiv.), 120°C, 4 h; (ii) thiourea (2 equiv.), THF/H_2O (20:1) (42 mL), 80°C, 3 h followed by NH_4OH at 20°C.

* Corresponding author. E-mail: h.parrot@cdlyon.univ-lyon1.fr

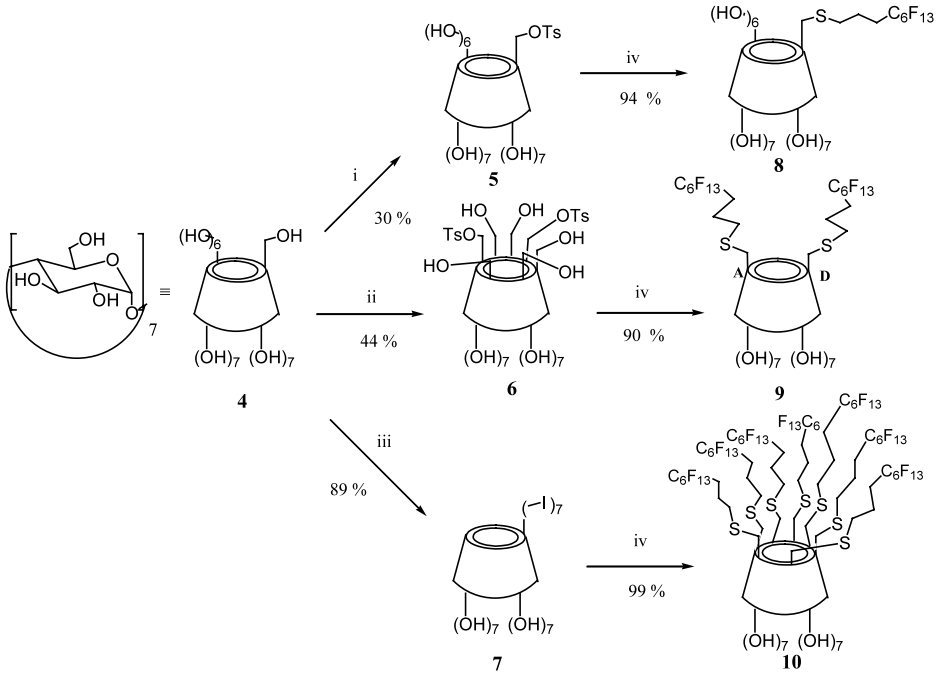
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02539-X

1,[14] available via a literature method, gives **2** (88% yield) in an elimination–addition reaction[15] in the presence of phosphoric acid and potassium iodide. In the second step, according to Pucci's method[16] **2** reacts with thiourea, to give after hydrolysis with NH_4OH the thiol derivative **3**.[17]

Fluorinated amphiphilic β-cyclodextrin derivatives **8** and **10** were synthesized from β-cyclodextrin **4** in two steps (Scheme 2). β-Cyclodextrin **4** was monotosylated at O-6 in pyridine at a temperature lower than 5°C[18] or fully substituted by iodide with iodine in presence of triphenylphosphine in DMF at 70°C[19] to yield **5** (30%) and **7** (89%), respectively. The thio-ether linkage is realized via nucleophilic displacement of the tosyl or iodide groups in presence of the 3-perfluorohexylpropanethiol **3**. For **8**, to a solution of **3** (490 mg, 0.38 mmol) in methanol (2 mL) is added a solution of MeONa in MeOH (1 M, 0.9 mL, 0.91 mmol). The mixture was stirred during 2 h at rt. The solvent is removed and anhydrous DMF (3 mL) is added to the residue under a nitrogen atmosphere. To this solution is added a solution of mono-6-*para*-tolylsulfonyl-β-cyclodextrin **5** (300 mg, 0.76 mmol) in anhydrous DMF (2 mL) drop wise. The reaction mixture was stirred for 24 h at 70°C and the reaction stopped by addition of acetone (20 mL). The precipitate was recovered by filtration, washed with acetone and purified by precipitation from ethanol. The product **8** was obtained in 94% yield.[20] The ^1H and ^{13}C NMR spectra were recorded in pyridine and were assigned by comparison with the corresponding spectra of **5**, the signals of the methyl and aromatic protons are absent. The monosubstitution at C-6 leads to a diminution in the molecular symmetry giving two doublets for the H-1 anomeric protons; a doublet at 5.60 ppm integrating for one proton was characteristic of the substituted glucopyranose and the doublet at 5.69 ppm integrating for 6 protons corresponds to the unsubstituted glucopyranose unities. The positive mode electrospray mass spectrum of **8** plus one sodium ion shows m/z ratio of 1533.5.

Similar experiments were carried out with heptakis (6-deoxy-6-iodo)-β-cyclodextrin **7**[19] (250 mg, 0.13 mmol) and **3** (14 equiv., 1.84 mmol). The fluorinated amphiphilic cyclodextrin **10** was isolated in the 99% yield.[21] MALDI mass spectrometry clearly demonstrates that **10** was heptasubstituted (m/z 3789 [**10**+Na]$^+$) and that under-substituted derivatives are absent. ^{19}F NMR shows the presence of perfluoroalkyl chains and the symmetrical nature of **10** is confirmed by the presence in the ^1H NMR of only a doublet ($J=3.2$ Hz) at 5.56 ppm for the H-1 β-cyclodextrin anomeric protons (Fig. 1).

The preparation of selectively modified cyclodextrins is a major synthetic challenge. The difficulty lies not only in the control of the number of *O*-alkylated sites but also in the reproducibility of the reaction. Recently, Sinaÿ et al.[22] described an elegant approach that consists of the regioselective deprotection of perbenzylated cyclodextrins **11**[23] (Scheme 3). The regioselective di-*O*-debenzylation at O-6^A, O-6^D is efficiently achieved in the presence of excess (140 equiv.) diisobutylaluminum hydride (DIBALH) (1.5 M) in toluene at 30°C for 2 h



Scheme 2. Synthesis of fluorinated amphiphilic β-cyclodextrins. *Reagents and conditions*: (i) *para*-tolylsulfonyl chloride (1 equiv., dry pyridine, 5°C); (ii) conditions in Scheme 3; (iii) PPh_3 (15 equiv.), DMF, I_2 (15.5 equiv.), 70°C, 18 h; (iv) 3-perfluorohexylpropanethiol **3** (2 equiv. for **8**, 4 equiv. for **9** and 14 equiv. for **10**), MeONa/MeOH (1 M), dry DMF, 70°C, 24 h.

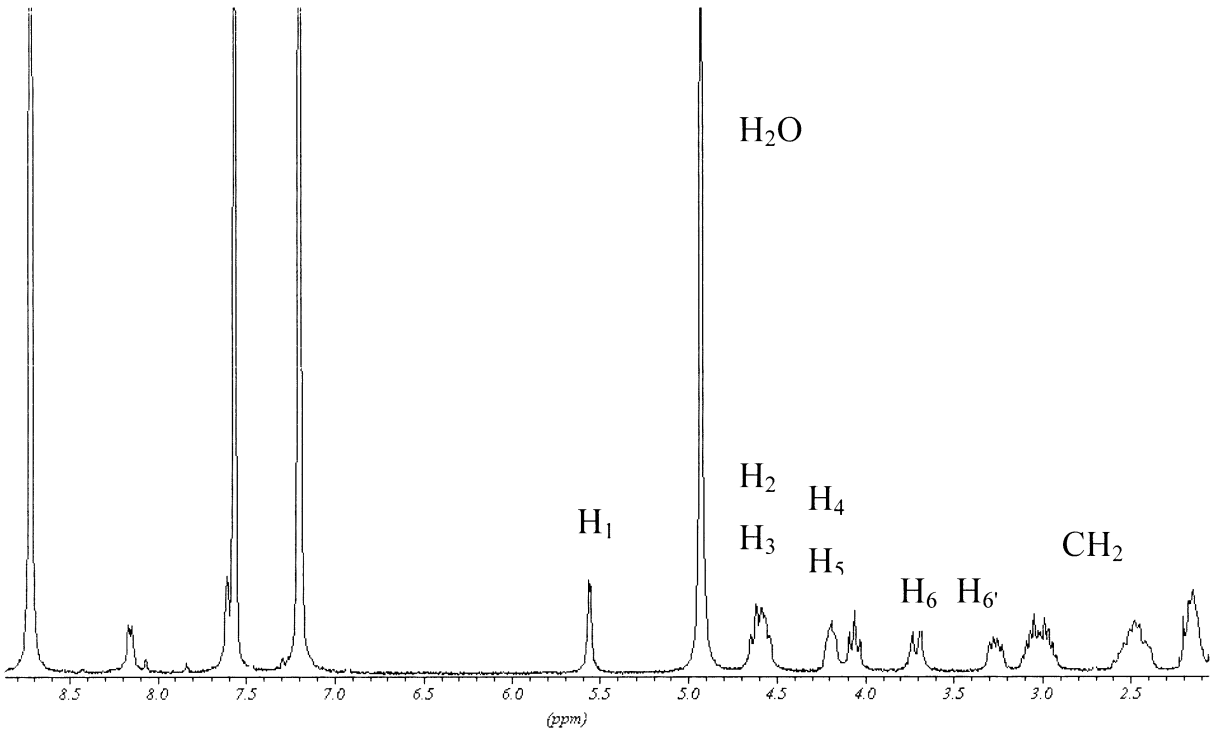
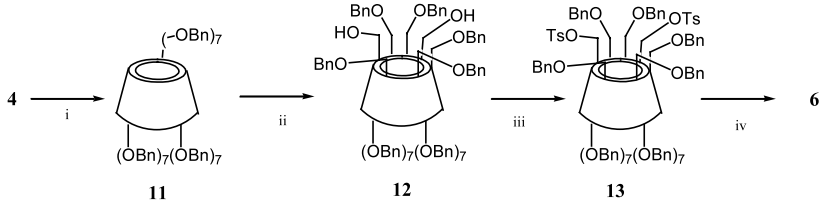


Figure 1. ^{1}H NMR spectrum in pyridine-d_5 of compound persubstitued at C-6, **10**.



Scheme 3. Synthesis of the AD regioisomers. *Reagents and conditions*: (i) benzyl chloride (27.5 equiv.), dry DMSO, 20°C, 7 h; (ii) DIBAL (140 equiv.), anhydrous toluene, 30°C, 2 h; (iii) *para*-tolylsulfonyl chloride (28 equiv.), dry pyridine, 20°C, 36 h; (iv) Pd/C 10%, Pd black, MeOH/formic acid (8:2), 20°C, 2 days.

(95% yield). The **AD** regioisomer **12** was identified by ^{1}H, ^{13}C NMR and electrospray mass spectrometry which are in agreement with literature values. The two free hydroxyl groups in the **AD** positions were activated by coupling of *para*-tolylsulfonyl groups. A mixture of **12** (2.20 g, 0.773 mmol) and *para*-tolylsulfonyl chloride (4.13 g, 21.66 mmol) in dry pyridine (100 mL) was stirred under nitrogen atmosphere at 25°C for 36 h. Chloroform was added and the mixture extracted. Organic layers were evaporated and the residue recrystallized in ethanol to give the novel β-cyclodextrin intermediate **13** in 99% yield.[24] The complete debenzylation (**13**, 800 mg, 0.25 mmol) in ethyl acetate (10 mL) in presence of Pd/C 10% (3 g, 2.8 mmol) in methanol/formic acid (8:2) (100 mL) gave the **AD** regioisomer **6** in 44% yield after 2 days. In the previous work of Hamada,[25] the ditosylated regioisomers **AB**, **AC** and **AD** were prepared directly from β-cyclodextrin in the presence of excess of *para*-tolylsulfonyl chloride in pyridine at rt. The **AD** regioisomer was separated from the reaction mixture by reversed-phase column (LiChroprep RP 18, $MeOH/H_2O$, 1:1) with a yield of <3%.

6^{A}, 6^{D}-Deoxy-6^{A}, 6^{D}-di-perfluorohexylpropanethiol-β-cyclodextrin **9** was accessible from the key intermediate **6** (120 mg, 0.08 mmol) in anhydrous DMF (2 mL) by nucleophilic displacement of the di-tosyl groups by the hydrofluorocarbon chain **3** (131 mg, 0.33 mmol).[26] Substitutions by two perfluoroalkylchains were confirmed by ^{19}F, ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts (pyridine-d_5) of H-$6^{A,D}$ and H-$6'^{A,D}$ at 3.36 and 3.59–3.66 ppm, respectively, indicated that the substitutions occurs at C-6A and C-6D position. The MALDI mass spectrum of **9** showed monocationic species corresponding to $[\mathbf{9}+Na]^{+}$: (m/z 1909) and $[9+K]^{+}$: (m/z 1925).

In conclusion, we have synthesized a series of novel perfluoroalkylated amphiphilic cyclodextrins in which the upper rim is mono, di and hepta functionalized with perfluorohexylpropanethiol chains. The thiolate chain was an excellent nucleophile and we have not observed competitive bridging reactions between O-3 and C-6 as was previously described by Stoddart et al.[27] The regioselective introduction of two chains in AD posi-

tions or hepta chains gives the new cyclodextrin in excellent yield. Studies on the aqueous self-organization properties of the molecules are currently being undertaken.

Acknowledgements

We are grateful to the MRET for financial support.

References

1. Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045–2076.
2. Duchêne, D. *News Trends in Cyclodextrin and Derivatives*; Edition de Santé: Paris, 1991.
3. Szejtli, J. *Med. Res. Rev.* **1994**, *14*, 353–386.
4. Szejtli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, 1998.
5. (a) Lin, J.; Creminon, C.; Perly, B.; Djedaïni-Pilard, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2639–2646; (b) Auzély-Velty, R.; Perly, B.; Taché, O.; Zemb, T.; Jéhan, P.; Guenot, P.; Dalbiez, J. P.; Djedaïni-Pilard, F. *Carbohydr. Res.* **1999**, *318*, 82–90.
6. Perrier, E.; Terry, N.; Rival, D.; Coleman, A. W. *Jpn. Kokai Tokkyo Koho* 2001, Jp 2001323002.
7. Ravoo, B. J.; Darcy, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 4324–4326.
8. Mazzaglia, A.; Ravoo, B. J.; Darcy, R.; Gambadauro, P.; Mallamace, F. *Langmuir* **2002**, *18*, 1945–1948.
9. (a) Riess, J. G.; Greiner, J. *Carbohydr. Res.* **2000**, *327*, 147–168; (b) Riess, J. G. *Tetrahedron* **2002**, *58*, 4113–4131; (c) Riess, J. G. *J. Drug Targeting* **1994**, *2*, 455–468.
10. (a) Krafft, M. P.; Riess, J. G. *Biochimie* **1998**, *80*, 489–514; (b) Krafft, M. P. *Adv. Drug Deliv. Rev.* **2001**, *47*, 209–228.
11. (a) Gadras, C.; Santaella, C.; Vierling, P. *J. Control. Rel.* **1999**, *57*, 29–34; (b) Guittard, F.; Geribaldi, S. *J. Fluorine Chem.* **2001**, *107*, 363–374.
12. Ling, C. C.; Darcy, R.; Risse, W. *J. Chem. Soc., Chem. Commun.* **1993**, 438–440.
13. (a) Tanaka, M.; Azumi, R.; Tachibana, H.; Nakamura, T.; Kawabata, Y.; Matsumoto, M.; Miyasaka, T.; Tagaki, W.; Nakahara, H.; Fukufa, K. *Thin Solid Films* **1994**, *244*, 832–835; (b) Greenhall, M. H.; Lukes, P.; Kataky, R.; Agbor, N. E.; Badyal, J. P.; Yarwood, J.; Parker, D.; Petty, M. C. *Langmuir* **1995**, *11*, 3997–4000; (c) Zhang, P.; Ling, C. C.; Coleman, A. W.; Parrot-Lopez, H.; Galons, H. *Tetrahedron Lett.* **1991**, *32*, 2769–2770; (d) Eddaoudi, M.; Coleman, A. W.; Bazkin, A.; Parrot-Lopez, H. *Langmuir* **1995**, *11*, 13–15.
14. Kotora, M.; Hajek, M.; Ameduri, B.; Boutevin, B. *J. Fluorine Chem.* **1994**, *68*, 49–56.
15. **1-Iodo-3-perfluorohexylpropane 2**: Yield: 88%; $R_f = 0.8$ (cyclohexane/ethyl acetate 55:5); IR ν (cm^{-1}): 2660 (C–H stretch), 1233–1120 (C–F stretch); ^1H NMR ($CDCl_3$) δ (ppm): 2.12–2.35 (m, 4H, H-2, H-3), 3.27 (t, 2H, H-1, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 4.2 (C_1), 24.7 (C_2), 32.3 (C_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ (ppm): −81.3 (m, 3F, CF_3), −114.1 (m, 2F, $\underline{CF_2}$-CH_2), −122.3 (m, 2F, CF_2), −123.3 (m, 2F, CF_2), −123.9 (m, 2F, CF_2), −126.5 (m, 2F, $\underline{CF_2}$-CF_3). MS ES m/z: $[M+Na]^+$ 511.
16. Barthélémy, P.; Ameduri, B.; Chabaud, E.; Popot, J. L.; Pucci, B. *Org. Lett.* **1999**, *1*, 1689–1692.
17. **3-Perfluorohexylpropanethiol 3**: Yield: 70%;. ^1H NMR ($CDCl_3$) δ (ppm): 1.41 (t, 1H, SH, $J = 8.2$ Hz), 1.89–2.01 (m, 2H, CH_2-CF_2), 2.14–2.35 (m, 2H, CH_2), 2.59–2.70 (m, 2H, CH_2-SH); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.7 (C_3), 25.0 (C_2), 29.7 (C_1);. ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ (ppm): −81.2 (m, 3F, CF_3), −114.3 (m, 2F, CF_2-CH_2), −122.3 (m, 2F, CF_2), −123.2 (m, 2F, CF_2), −123.8 (m, 2F, CF_2), −126.5 (m, 2F, CF_2-CF_3). MS ES m/z: $[M+Na]^+$ 417.
18. Khan, A. R.; Forgo, P.; Stine, K.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
19. Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed.* **1991**, *30*, 78–79.
20. **6^A-Deoxy, 6^A-(3-perfluorohexylpropanethio)-cyclomaltoheptaose 8**: yield 94%. Mp 230°C; IR ν (cm^{-1}) 3306 (OH free); 2926 (C–H stretch); 1237–1153 (C–F stretch); ^1H NMR (pyridine-d_5, 500 MHz) δ (ppm) 1.85–1.96 (m, 2H, CH_2-CH_2-SH), 2.18–2.39 (m, 2H, CH_2-SH), 2.89 (t, 2H, CH_2-CF_2, $J = 6.7$ Hz), 3.33–3.44 (dd, 1H, *H-6*^{A}, $J = 6.7$ and 13.0 Hz), 3.59–3.68 (m, 1H, *H-6′*^{A}), 4.28–5.52 (m, 30H, *H-2*, *H-3*, *H-4*, *H-5*, *H-6*), 5.60 (d, 1H, *H-1*^{A}, $J = 3.2$ Hz), 5.69 (d, 6H, *H-1*, $J = 3.2$ Hz), 6.46 (s, 6H, O*H-6*), 7.65 (m, 7H, O*H-2*), 7.86 (m, 7H, O*H-3*); ^{13}C NMR (pyridine-d_5) δ (ppm) 106.2 (C_1), 85.5 (C_4), 77.5, 77.3, 77.0 (C_2, C_3, C_5), 64 (C_6), 36.5 (C_6^A), 35.4 (CH_2-S-), 33.6 (CH_2-CF_2), 20.7 (CH_2-CH_2-S); ^{19}F (pyridine-d_5, $CFCl_3$) δ (ppm) −80.2 (m, 3F, CF_3), −112.9 (m, 2F, CF_2-CH_2), −121.1 (m, 2F, CF_2), −122.1 (m, 2F, CF_2), −122.6 (m, 2F, CF_2), −125.4 (m, 2F, CF_2-CF_3). ES MS (+) m/z: $[M+Na]^+$ 1533.5.
21. **Heptakis-[6-deoxy-6-(3-perfluorohexylpropanethio)]-cyclomaltoheptaose 10**: yield 99%; mp 210°C; IR ν (cm^{-1}) 3306 (OH free); 2926 (C–H stretch); 1237–1153 (C–F strech); ^1H NMR (pyridine-d_5, 500 MHz) δ (ppm): 2.14–2.21 (m, 2H, CH_2-CH_2-S), 2.38–2.60 (m, 2H, CH_2-S-), 2.70 (m, 2H, CH_2-CF_2), 3.27 (dd, 1H, H-6, $J = 7.6$ and 14.0 Hz), 3.70 (m, 1H, H-6′), 4.06 (t, 1H, H-5, $J = 9.0$ Hz), 4.21 (m, 1H, H-4), 4.49–4.71 (m, 2H, H-2, H-3), 5.56 (d, 1H, H-1, $J = 3.2$ Hz), 7.60 (d, 1H, OH-3, $J = 2.0$ Hz), 8.15 (d, 1H, OH-2, $J = 6.0$ Hz); ^{13}C NMR (pyridine-d_5) δ (ppm): 105.7 (C_1), 88.4 (C_4), 76.7, 76.3, 75.8 (C_2, C_3, C_5), 36.0 (C_6), 34.7 (CH_2-S-), 31.9 (CH_2-CF_2), 22.8 (CH_2-CH_2-S); ^{19}F NMR (pyridine-d_5, $CFCl_3$) δ (ppm): −80.8 (m, 3F, CF_3), −113.5 (m, 2F, CF_2-CH_2), −121.5 (m, 2F, CF_2), −122.5 (m, 2F, CF_2), −122.8 (m, 2F, CF_2), −125.9 (m, 2F, CF_2-CF_3); Maldi MS *m/z:* $[M+Na]^+$ 3789.
22. Pearce, A. J.; Sinaÿ, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3610–3612.
23. Sato, T.; Nakamura, H.; Ohno, Y.; Endo, T. *Carbohydr. Res.* **1990**, *199*, 31–35.
24. **6^A, 6^D-*para*-Tolylsulfonyl-6^B,6^C,6^E,6^F,6^G-benzyl-2,3-*O*-perbenzyl-cyclomaltoheptaose 13**: Yield: 99%; mp 64°C; $R_f = 0.4$ (ethyl acetate/cyclohexane, 1:4); IR ν (cm^{-1}): 3078–3001 (C–H), 1597–1438 (C–H arom.), 1375 (O-SO_2).^1H NMR ($CDCl_3$) δ (ppm): 2.13 and 2.14 (s, 6H, CH_3), 3.19–3.30 (m, 4H), 3.39–5.42 (m, 82H), 5.61 (d, 2H, H-1^A and H1^D; $J = 3.8$ Hz), 6.91–7.40 (m, 95H, CH arom), 7.66 (m. 4H, CH arom tosyl). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.11 (CH_3), 66.3 (C_6^A, C_6^D), 69.8 (C_6), 73.8 (C_2, C_3, C_5, CH_2), 79.6 (C_4^A, C_4^D), 81.6 ($C_4^{B,C,E,F,G}$), 99.2 (C_1), 1127.4–128.8 (CH-benzyl), 130.4 (CH-tosyl), 128.7–140.0 (C-arom). ES.MS (+) *m/z:* 1600.6 $[M+2Na]^{++}/2$.

25. Narita, M.; Hamada, F.; Suzuki, I.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2751–2758.
26. **6^{A}, 6^{D}-Deoxy-6^{A}, 6^{D}-di-(3-perfluorohexylpropanethio)-cyclomaltoheptaose 9**: yield 90%; mp 230°C; IR ν (cm^{-1}) 3306 (OH), 2926 (C–H stretch), 1237–1153 (C–F stretch); ^{1}H NMR (pyridine-d_5, 500 MHz) δ (ppm): 1.82–2.01 (m, 4H, CH_2-CH_2-SH), 2.10–2.42 (m, 4H, CH_2-SH), 2.89 (t, 2H, CH_2-CF_2, $J=6.7$ Hz), 3.36 (m, 2H, H-$6^{A,D}$), 3.66 (m, 2H, H-$6'^{A,D}$), 4.02–5.75 (m, 30H, H-2, H-3, H-4, H-5, H-6), 5.69 (m, 7H, H-1), 6.51 (s, 5H, OH-6), 7.65 (m, 7H, OH-2), 7.89 (m, 7H, OH-3); ^{13}C NMR (pyridine-d_5) δ (ppm): 104.7 and 104.2 (C_1), 86.5 (C_4), 77.9–74.1 (C_2, C_3, C_5), 61.7 (C_6), 34.4 (C_6^{A}), 32.7 (C_7), 30.3 (C_9), 21.0 (C_8); ^{19}F NMR (pyridine-d_5, $CFCl_3$) δ (ppm): −81.3 (m, 3F, CF_3), −114.0 (m, 2F, CF_2-CH_2), −122.3 (m, 2F, CF_2), −123.3 (m, 2F, CF_2), −123.7 (m, 2F, CF_2), −126.6 (m, 2F, CF_2-CF_3); Maldi MS m/z: $[M+Na]^+$ 1909, $[M+K]^+$ 1925.
27. Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 80–81.