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Control of the Regioselectivity for New Fluorinated Amphiphilic Cyclodextrins: Synthesis of Di- and Tetra(6-deoxy-6-alkylthio)- and 6-(Perfluoroalkypropanethio)-α-cyclodextrin Derivatives

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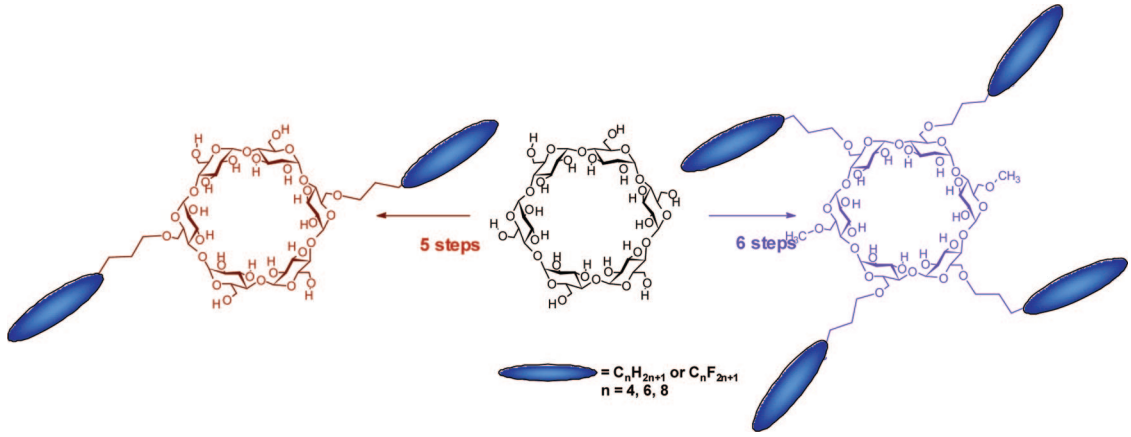
Received June 18, 2008



Twelve new di- and tetraderivatized α-cyclodextrin molecules having either alkylthio and perfluoroalkylpropanethio functions at the primary face have been synthesized by using the procedure of Sinaÿ for di-*O*-debenzylation of perbenzylated α-cyclodextrins. A new strategy of protection/deprotection has been developed for introducing the lipophilic chains. The coupling reaction involves the reaction between the appropriate α-cyclodextin derivative, regioselectively modified at C-6 positions by a good leaving group (*O*-mesityl for disubstituted or iodine for tetrasubstituted derivatives), with the thioalkyl or the thioperfluoroakylpropane chains. These nucleophilic reagents are obtained from the in situ basic hydrolysis of the alkylisothiouronium bromides or perfluoalkylropropane and the isothiouronium iodides. These multistep reactions give the desired amphiphilic α-cyclodextrins in good overall yields of 33% to 58%.

Introduction

Modified cyclodextrins (CDs) with pendant lipophilic groups at the primary[1] or at the secondary faces[2] are of considerable interest in supramolecular chemistry, especially for pharmaceutical applications.[3] Their capacity for self-organization in water allowed the preparation of various self-assembled structures including vesicles,[4] nanospheres,[5] nanocapsules,[6] solid-lipid nanoparticles,[7] and liquid crystals.[8] Their self-organizational properties depend on the nature, the number, and the length of hydrophobic chains at the different faces. Due to their potential

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10.1021/jo801111b CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/22/2008

activity in biomedical research, fluorine-containing organic compounds have attracted scientific attention.[9] Furthermore, it has been demonstrated that vesicles and nanocapsules made from fluorinated surfactants are usually more stable and less permeable than those made from nonfluorinated surfactants.[10] For example, Skiba et al.[6] described the synthesis of nanocapsules made from the 2,3-di-*O*-decafluorooctanoyl-β-cyclodextrin, suitable vehicles for oxygen solubilization.

In our research group, β-cyclodextrin derivatives, selectively substituted at the C-6 position by one, two, or seven perfluorohexylpropanethio chains, have been synthesized and studied.[11] These novel derivatives were obtained by thioalkylation of β-CD derivatives having tosyl or iodo groups at the C-6 position. Nevertheless, for β-cyclodextrin derivatives, the lipophilic−hydrophilic balance is very strongly shifted to lipophilicity and may reflect the noncompatibility of the 7-fold symmetry of these heptamers toward water[12] and also toward chain organization in the assemblies. We thus moved our attention to the use of α-cyclodextrin derivatives so as to favor both the interactions with water and the organization of the molecular assemblies.[13]

Recently, *per*-alkylthio and *per*-perfluoroalkylpropanethio-α-cyclodextrin derivatives and their *O*-2, *O*-3 methylated analogues have been synthesized.[14] Unfortunately, the nonmethylated molecules are highly insoluble in aqueous, organic, or fluorous solvents. The *O*-2, *O*-3 methylated analogues have shown higher solubilities in organic solvents and their interfacial properties could be studied. The assembly properties of the molecules at the air−water interface show a clear difference between alkylthio and perfluoroalkylpropanethio derivatives, with higher molecular areas and collapse pressures observed for the later.[14]

Due to the low solubility of the derivatives persubstituted at the primary face and nonmodified at the secondary face in common solvents, another strategy has been used to lead to more soluble α-cyclodextrin derivatives, with the introduction of only two or four hydrophobic chains at the primary face.

To selectively synthesize di- and tetrasubstituted derivatives, many strategies have been developed in the past for differentiating the primary hydroxyl groups of cyclodextrins. Only two recent methods present high yield along with a controlled regioselectivity: Fujita et al.[15] have synthesized 6^A-6^B, 6^A-6^C, and 6^A-6^D disubstituted α-CDs derivatives using mesitylsulfonyl chloride in pyridine, and these compounds have been separated by using reversed phase chromatography, leading to yields ranging from 7% to 14%. In the same way with an excess of sulfonyl reagent, tetrasubstituted α-CDs were obtained with less than 4% yield. An elegant method is to use bridging reactants to introduce sulfonyl groups at the primary face. Tabushi et al. used geometrically well-defined disulfonyl arenes to control the regioselectivity of the difunctionalization.[16−18] This strategy was then used by Breslow et al.[19] to functionalize two adjacent D-glucose units at the C-6 position of β-CD.

Coleman et al.[20] showed that use of the well-known sterically hindered methodology via use of the trityl group leads to tri -and tetrafunctionalized α-CDs, depending on the stoichiometry of the reagents. The complete separation of the different regioisomers was achieved by chromatography column after *per*-methylation of the secondary face. Methylated analogues were then obtained in 15−30% yield. More recently, Poorters et al.[21] used the supertrityl protecting group (sTrCl = tris(4-*tert*-butylphenyl)methyl chloride) for the selective tetrafunctionalization of α-CD, leading to the tetraprotected α-CD in position 6^A,6^B,6^D,6^E in 47% yield.

A far more elegant alternative approach is the regioselective deprotection of perfunctionalized cyclodextrins, thus combining the advantageous aspects of the first two methods mentioned above.

Sinaÿ et al.[22] have demonstrated that DIBAL-promoted de-*O*-benzylation of perbenzylated cyclodextrins occurs with remarkably high regioselectivity, giving access to either mono-6-*O*-debenzylated or 6^A,6^D-di-*O*-debenzylated derivatives.

We have used this strategy to synthesize di- and tetradebenzylated α-cyclodextrins in view of their further modification for the synthesis of new amphiphilic derivatives.

Here we describe the multistep syntheses of di- and tetra(6-deoxy-6-alkylthio)-α-cyclodextrins and di- and tetra(6-deoxy-6-perfluoroalkylpropanethio)-α-cyclodextrins. We also present the preparation of di- or tetrasubstituted α-cyclodextrins modified at the primary face by good leaving groups, through an easy synthetic route with high yield and controlled regioselectivity.

Results and Discussion

Perbenzylation of α-CD (**1**) was achieved by using the method described by Lecourt et al.[23] Perbenzylated α-CD **2** was prepared by direct benzylation of α-CD in DMSO with benzyl chloride and NaH during 12 h at room temperature. Compound **2** was then obtained in 90% yield after column purification (EtOAc in cyclohexane gradient) (Scheme 1).

The procedure described by Pearce et al.[22] has been followed for the selective deprotection of the perbenzylated intermediate. The mechanism of this remarkable reaction was determined in 2004, according to numerous results obtained by the same group.[23] The supposed mechanism implies two sequential reactions of *O*-debenzylation. Selectivity for the primary face has been explained by the high density of benzyl groups on the secondary face. The first debenzylation takes place on only one glucosidic unit. Because of the steric hindrance caused by the aluminum alkoxide, the second DIBAL pair is forced to interact with the most distant glucosidic unit. The authors claimed that the steric hindrance is strengthened by the presence of the benzyl groups. A single debenzylation is usually obtained with 30 equiv of DIBAL per α-CD while in the case of di-*O*-debenzylation,

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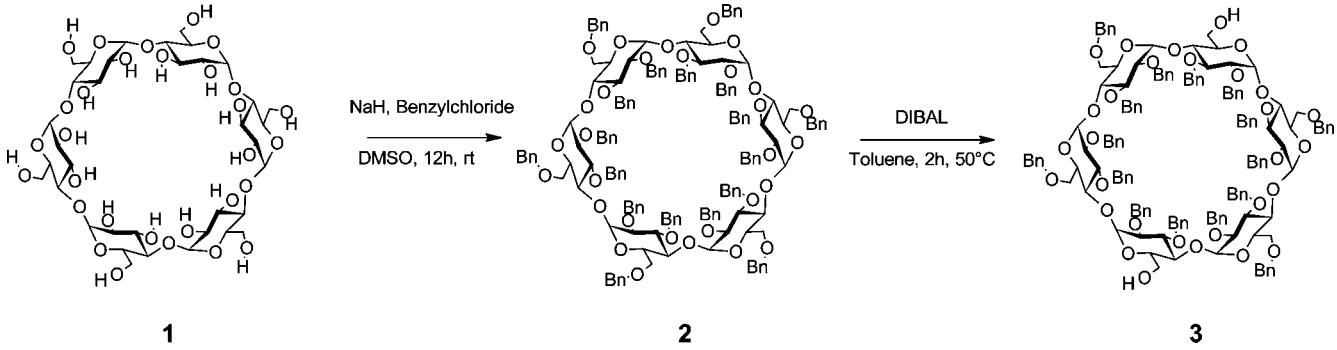
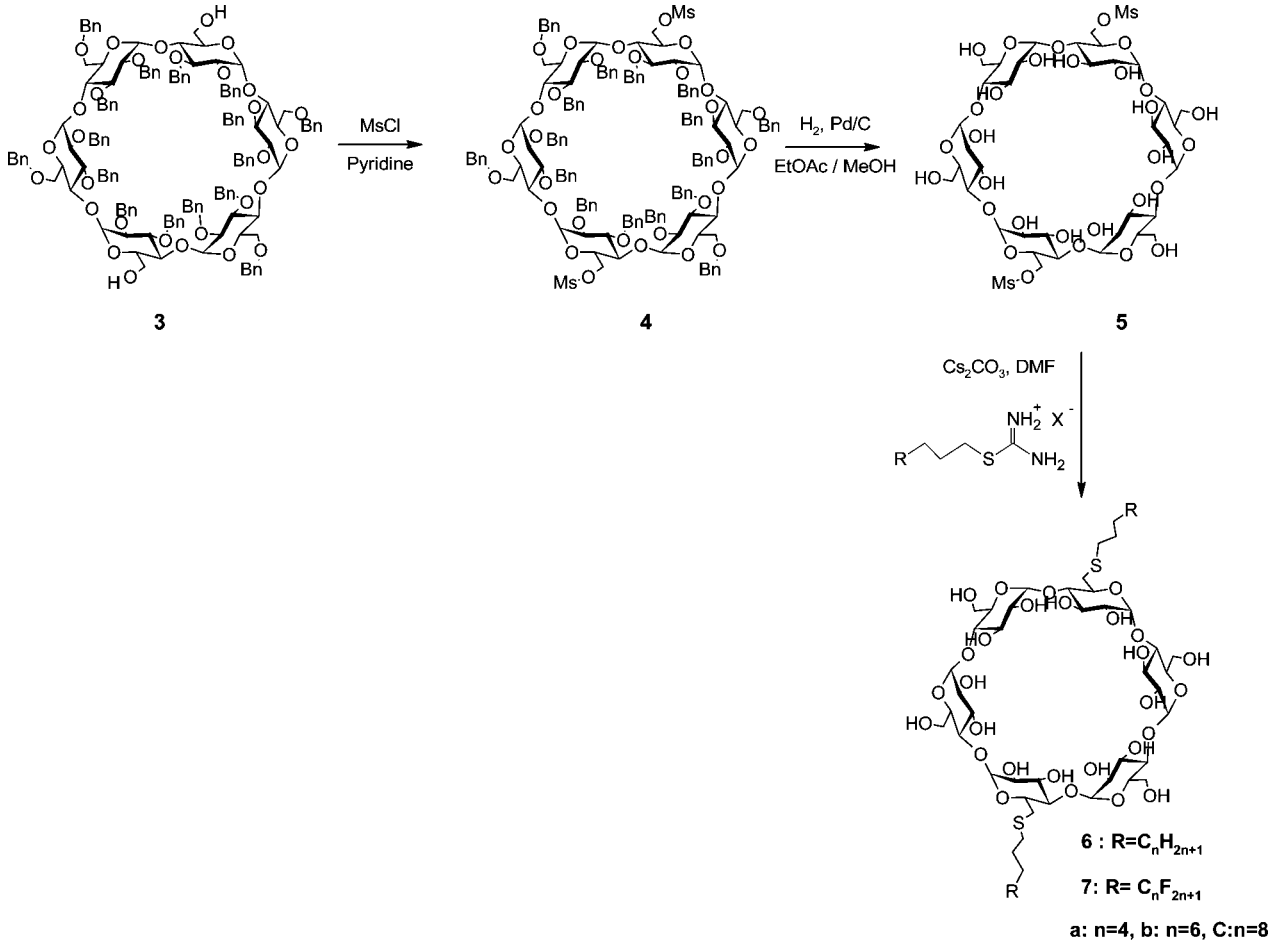
SCHEME 1. Synthesis of the Tetrabenzylated α-Cyclodextrin 3



SCHEME 2. Synthesis of Disubstituted Amphiphilic α-Cyclodextrins 6 and 7



120 equiv are needed, indicating the steric hindrance at the primary face after the formation of the first intermediate.[22]

Treatment of **2** with excess diisobutylaluminium (120 equiv DIBAL) in anhydrous toluene at 50 °C during 2 h gave the desired di-*O*-debenzylated compound **3** in 91% yield. This compound was characterized by ^{13}C and ^{1}H NMR and by positive mode electrospray mass spectroscopy and the obtained data are consistent with those given in the literature.[23]

To synthesize difunctionalized α-cyclodextrins, it is necessary to adopt a strategy of protection, activation, and deprotection of the hydroxyl groups:

In view of further deprotection of the benzyl groups by hydrogenation, the chosen leaving groups should be stable with regard to these conditions and also activate hydroxyl groups. For these reasons, in was decided to introduce sulfonyl groups, as iodide or bromide moieties would be cleaved under catalytic hydrogenation conditions. Use of the *p*-toluenesulfonyl group led to a mixture of derivatives—monotosylated, ditosylated, and even monochlorotosylated compounds—and thus use of tosyl-chloride has been excluded. Activation of hydroxyl groups with methanesulfonyl chloride in anhydrous pyridine led to the desired compound **4** in quantitative yield (Scheme 2).

Synthesis of **4** has already been described[24] under different conditions (CH_2Cl_2, Et_3N) but the product was neither isolated nor characterized. ^{1}H NMR characterization of this compound shows the disappearance of the peak at 3.19 ppm, corresponding

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TABLE 1. Yields of the Coupling Reaction between Isothiouronium Salts and Compound 5

R	compd	yield (%)
C_4H_9	**6a**	56
C_6H_{13}	**6b**	53
C_8H_{17}	**6c**	77
C_4F_9	**7a**	52
C_6F_{13}	**7b**	54
C_8F_{17}	**7c**	56

to the alcohol functionality, and the appearance of a singlet at 2.60 ppm, corresponding to the methanesulfonyl protons. In the ^{13}C NMR, the carbon of the methanesulfonyl group appears at 37.6 ppm and those of the glucosidic unit bearing these groups at 70.4 ppm. Introduction of two methanesulfonyl groups is confirmed by positive mode electrospray mass spectroscopy, which shows the presence of monocharged ion at *m*/*z* ratio 2571.2 ($[M + H]^+$) and 2592.7 ($[M + Na]^+$), corresponding to the desired compound.

After the introduction of the activating groups, deprotection of all benzyl groups was undertaken via catalytic hydrogenation in an AcOEt:MeOH 1:1 mixture, using stoichiometric quantities of Pd/C under H_2 at 10 bar pressure; the catalytic proportions described by Sinaÿ et al.[22] were not effective here. Compound **5** is obtained in 92% yield. ^1H NMR shows the disappearance of all the benzyl protons, the anomeric protons appear as three doublets at 4.80, 4.87, and 4.90 ppm, two triplets corresponding to the primary alcohol functions appear at 4.57 and 4.63 ppm. ^{13}C NMR shows the disappearance of both aromatic and benzylic carbon atoms and the conservation of the carbon of the methylsulfonate group at 37.5 ppm. Mass spectroscopy shows only one peak for *m*/*z* 1129.3 ($[M + H]^+$). $6^A,6^D$-Di-*O*-methylsulfonyl-α-cyclodextrin **5** is thus obtained with controlled regioselectivity in 75% yield starting from native α-cyclodextrin **1**. This intermediate compound **5** is the precursor for the syntheses of all the disubstituted amphiphilic derivatives.

For the introduction of perfluoroalkyl chains, we have developed a new strategy using a polar reaction between a perfluoroalkylpropanethiol and a cyclodextrin bearing a suitable leaving group.[14] The traditional radical reaction method using Hein and Meintchen's procedure[25] led to mixtures of substituted cyclodextrins.[26] The use of a precursor to generate this thiol in situ is preferred because of the facile oxidative dimerization of the perfluoropropanethiol.

Using the procedures of Garcia-Lopez et al.,[27] compound **5** reacts with hydrocarbonated isothiouronium salts or their perfluoroalkylpropane analogues[12] in the presence of cesium carbonate in DMF to give **6** and **7** with good yields (Table 1), after 4 days at 60 °C.

2-Dimensional NMR spectroscopy (HSQC, HMBC, and TOCSY-HSQC) has allowed the complete assignment of all proton and carbon signals (see the Supporting Information). The success of the coupling reaction in this series was confirmed by ^{13}C NMR spectroscopy. For **7a**, for example, the ^1H NMR shows singlets for H-$6a^A$, H-$6b^A$, H-$6a^D$, and H-$6b^D$ at 3.23 ppm. Signals of the propyl chain grafted on sulfur atom are found at 1.92 ppm for $CH_2CH_2CF_2$, 2.28 ppm for CH_2CF_2, and 2.61 ppm for SCH_2. It is worth noting that H-1, H-3, and H-4 signals are found in the form of three doublets for H-1 and three triplets for H-3 and H-4, respectively. On the other hand, H-2 and H-5 protons are grouped together and are found under the shape of widened singlets.

Concerning the ^{13}C NMR, the chemical shift at 34.2 ppm, corresponding to C-6^A and C-6^D, is characteristic of the success of the perfluorobutylpropanethio chain coupling. Furthermore, the presence of 3 different signals for all the cyclodextrin core carbons indicates a 2-fold symmetry of the CD. Mass spectrometry of **7a** confirms the presence of only $[M + H]^+$ at 1547.4 and $[M + K]^+$ at 1563.4.

All compounds in the series **6** and **7** have been characterized in this way. Further details are given in the Experimental Section.

Concerning tetrasubstituted α-cyclodextrins, they have been synthesized from $6^A,6^B,6^D,6^E$-tetra-*O*-benzylper-2,3-di-*O*-benzyl-α-cyclodextrin **3** in four steps, as described in Scheme 3.

The protecting group we have to introduce on free hydroxyl groups of compound **3** has to present many characteristics. It should be stable against benzylic ether cleavage conditions in the presence of Pd/C, against dehydration conditions (100 °C under vacuum during 12 h at least) necessary for iodine substitution of the four hydroxyl groups, and against iodination reaction in the presence of PPh_3/I_2, warming at 80 °C during 15 h. Furthermore, this protecting group has to be easily cleaved in not too basic conditions to avoid intramolecular nucleophilic substitution of iodine atoms by hydroxyl groups in the O-3 position, which would lead to the formation of a 3,6-anhydro-α-CD derivative.

Introduction of silyl or acetyl protecting groups on compound **3** failed because of the nonselective deprotection of the benzyl groups in the following step: unfortunately both silyl and acetyl groups are cleaved under debenzylation conditions. For this reason, we chose to introduce methyl groups at the free hydroxyl groups in compound **3**. In the presence of sodium hydride and methyl iodide in DMF, compound **8** is obtained in 98% yield. Hydrogenolysis of the benzyl ether groups is then realized by using 0.5 equiv of Pd/C, under 1 atm of H_2 in an AcOEt/MeOH 1/1 mixture. Compound **9** is obtained in 98% yield and characterized by NMR and mass spectroscopy. Because of the selectivity of iodination for the primary face, we have chosen to introduce iodine atoms in the presence of PPh_3/I_2 for activating these positions. Solid/liquid extraction was used for purification of compound **10**, which was obtained in 64% yield. ($6^A,6^B,6^C,6^D$-tetradeoxy-$6^A,6^B,6^C,6^D$-tetraiodo)-($6^C,6^F$-di-*O*-methyl)-α-cyclodextrin **10** has been characterized by use of HSQC-TOCSY, HSQC, and HMBC (see the SI).

In the ^1H NMR, the anomeric protons are found as three distinct doublets at 5.41, 5.48, and 5.50 ppm for respectively H-1^B and H-1^E, H-1^C and H-1^F, and H-1^A and H-1^D. The presence of a signal due to the methyl protons as a singlet at 3.50 ppm demonstrates the retention of these functions during the iodination reaction. ^{13}C NMR shows that each type of carbon atom is present as three different peaks, showing the 2-fold symmetry of the molecule and thus the success of the tetraiodination. In the ^{13}C NMR spectra, each type of carbon of the CD skeleton is observed as three separate peaks, indicating a 2-fold symmetry for compound **10**, consistent with tetraiodination. The four different C6 species, each linked to an iodine, are observed at 9.0 and 10.9 ppm respectively for (C-6^A, C-6^D) and (C-6^B, C-6^E), characteristic of the chemical shifts of a methylenic carbon bearing an

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SCHEME 3. Synthesis of Tetrasubstituted Amphiphilic α-Cyclodextrins xs 211 and 12

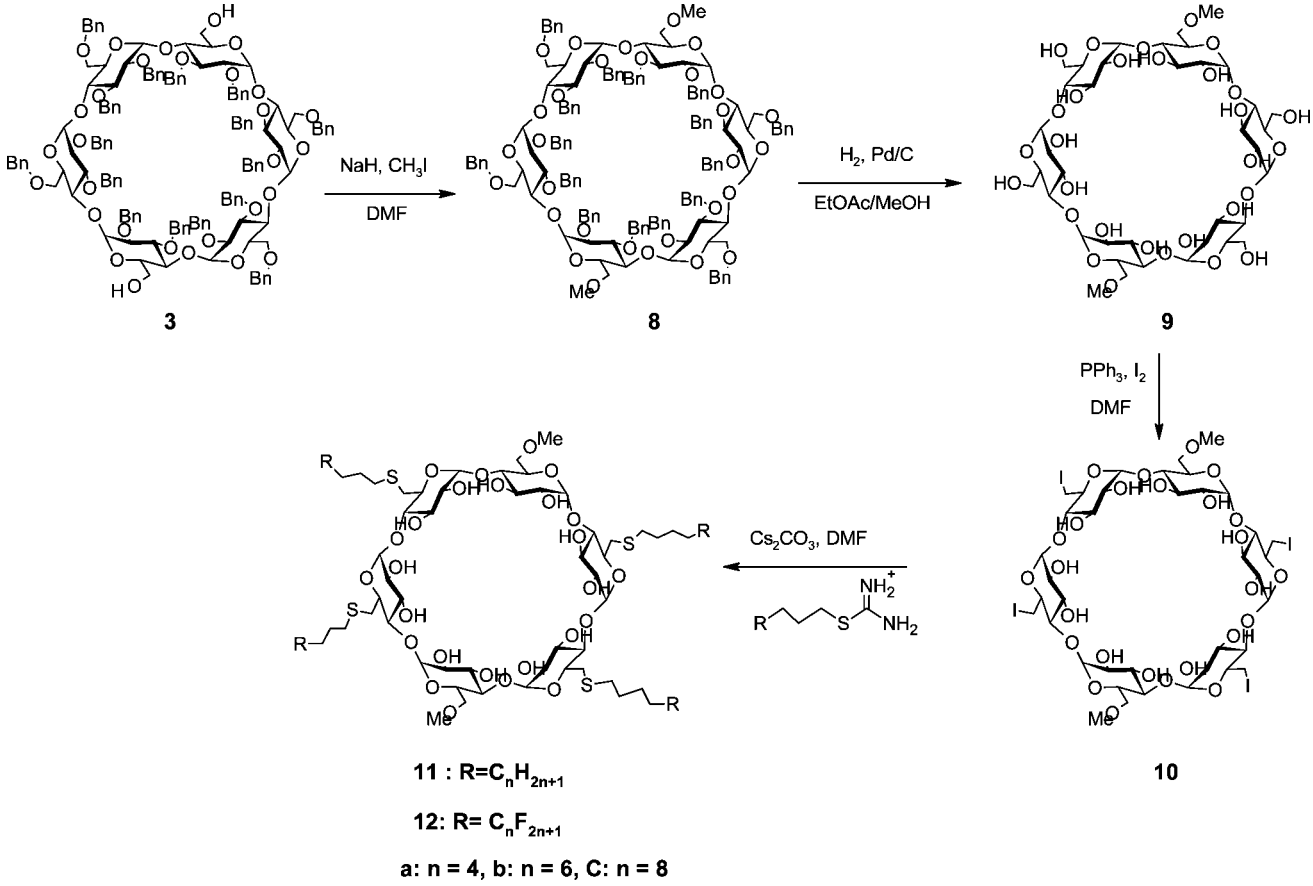

TABLE 2. Yields of the Coupling Reaction between Isothiouronium Salts and Compound 10

R	compd	yield (%)
C_4H_9	**11a**	86
C_6H_{13}	**11b**	81
C_8H_{17}	**11c**	65
C_4F_9	**12a**	85
C_6F_{13}	**12b**	93
C_8F_{17}	**12c**	86

iodine atom. Finally, it is worth noting that there is a quite important difference of chemical shifts between C-3, C-4, C-5, and C-6 of glucosidic units bearing iodine and those bearing a methyl group. ESI MS experiments in negative mode show only one peak for $[M + Cl]^-$ at 1474.9 supporting the absence of mono-, di-, or triiodinated side products. The tetraiodo derivative **10** has been synthesized in 50% yield starting from native α-CD and is a good general candidate for tetrafunctionalization of α-CD. Coupling of perfluoroalkylpropane or hydrocarbonated chains to **10**, via the isothiourionium salts, was undertaken in anhydrous DMF, as previously described for compounds **6** and **7**, and affords compounds **11a−c** and **12a−c** in good yields (Table 2).

These tetrafunctionalized derivatives **11** and **12** are insoluble in most common organic solvents and were thus characterized by solid NMR spectroscopy, as previously described for *O*-6-alkylthio- and perfluoroalkylpropanethio-α-cyclodextrins.[14] Thus success of the coupling to yield **12c** is observed in CPMAS ^{13}C NMR by the disappearance of the signals at 9.0 and 10.9 ppm, corresponding to the C-6 carbons of glucosidic units bearing iodine atoms. The peaks arising from carbon atoms of the propyl spacer and $C6^{A,B,D,E}$ are found between 20.4 and 32.2 ppm: 20.4 ppm for $\boldsymbol{C}H_2-CH_2-CF_2$ and 29.2 − 32.2 ppm for $\boldsymbol{C}H_2-CF_2$, $\boldsymbol{C}H_2-S$, and $\boldsymbol{C}6^{A,B,D,E}$. The *O*-methyl carbons are found at 58.5 ppm. Carbons of the perfluoroalkylated chain are found at 110.3 and 118.6 ppm, in two distinct multiplets (Figure 1).

The ^{19}F solid state NMR spectrum remains unchanged, indicating that the perfluorooctyl chain has not been cleaved. Mass spectroscopy experiments have been performed to prove that there are no less substituted products. For example, for the compound **12b**, only monomolecular ions at 1072.1 $[M + K + H]^{2+}$, 2505.0 $[M + H]^+$, and 2526.8 $[M + Na]^+$ have been observed indicating the presence of only tetrasubstituted α-cyclodextrin. Similar spectra were observed for all tetraderivatives.

The hydrocarbonated analogues have been characterized in a similar manner. For **11c**, the solid state NMR CPMAS ^{13}C spectrum allowed observation of the analogous signals for the carbon atoms of the CD core (Figure 2). The carbon atoms of the undecanoyl chain are observed at 14.2 and 23.0 ppm and a set of peaks centered at 31.2 ppm is observed, corresponding to the CH_3, CH_2CH_3, and CH_2 carbon atoms, respectively. As previously noted, success of the coupling reaction is demonstrated by the disappearance of the signals corresponding to those carbon atoms linked to iodine atoms, at 9.0 and 10.9 ppm. Finally, the electrospray mass spectrum confirms the presence of the tetrathioalkylated derivatives and the absence of understituted derivatives. For **11c**, only monomolecular ions at 1570.5 $[M + H]^+$ and 1592.2 $[M + Na]^+$ are observed.

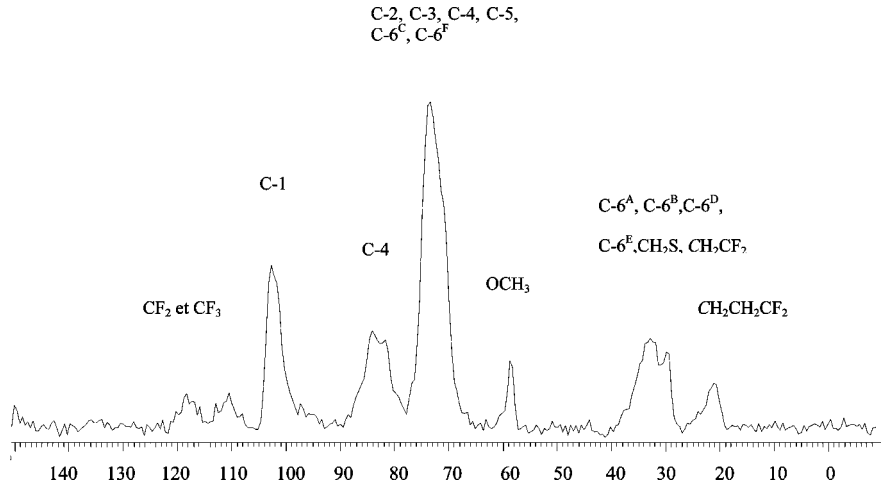

FIGURE 1. ^{13}C solid state NMR (CPMAS, 125 MHz) of compound **12c**.

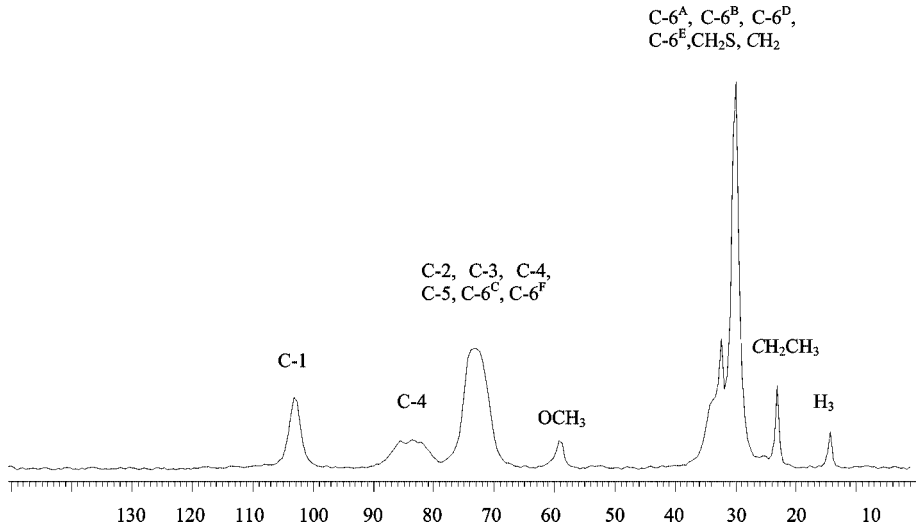

FIGURE 2. ^{13}C solid state NMR (CPMAS, 125 MHz) of compound **11c**.

Conclusion

We have developed two new synthetic routes allowing access to di- and tetrasubstituted α-cyclodextrins bearing methanesulfonyl or iodo groups. The two synthetic intermediates have been obtained in excellent yields, with perfectly controlled regioselectivities, and are key products for further di- or tetrafunctionalizations of α-CD. Di- and tetrasubstituted amphiphilic α-cyclodextrins bearing perfluoroalkylpropanethio and alkylthio chains have finally been synthesized in good yields, 39−58%, in 5 steps for the disubstituted amphiphilic α-cyclodextrin derivatives, and 33−47% in 6 steps for the tetrasubstituted derivatives. Whereas tetrafunctionalised derivatives are not soluble in most common solvents, disubstituted compounds have comparable solubilities as native α-cyclodextrin (DMF, DMSO, and pyridine), except in water.

A series of amphiphilic cyclodextrins having potentially various values of hydrophobic/hydrophilic balance, depending of the number (2, 4, or 6[12]), the length (C_4, C_6, or C_8), and the nature (fluorinated or hydrocarbonated) of these grafted chains, is then available for studying their behavior in aqueous medium, their self-organization at the air/water interface, and in aqueous medium in the form of nanoparticles to transport biologically active compounds.

Experimental Section

Syntheses: 6^A,6^D-Di-*O*-methylsulfonyl-6^B,6^C,6^E,6^F-tetra-*O*-benzyl(per-2,3-di-*O*-benzyl)-α-cyclodextrine (4). To a solution of **3**[22] (3.50 g, 1.45 mmol) in anhydrous pyridine (50 mL) under argon at 0 °C was added dropwise methylsulfonyl chloride (900 μL, 11.6 mmol, 8 equiv). The reaction mixture was stirred during 3 h at room temperature under argon and the reaction monitored by TLC (cyclohexane/EtOAc: 6/2). The reaction was quenched by adding saturated $NaHCO_3$ solution (50 mL). The organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated and the resulting solution containing pyridine was coevaporated three times with toluene to afford **4** with quantitative yield. Mp 56 °C dec. IR ν (cm^{-1}) 3030 (C−H Ar), 2925 (C−H), 1354 (C−SO_2−C), 1092 (C−O−C). $[\alpha]^{22}_D$ +31 (*c* 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C, assignments by COSY, DEPT, HSQC, and HMBC) δ (ppm) 2.60 (s, 6H, CH_3 mesyl), 3.35 (dd, 2H, 2 × H-2, J = 3.2 and 9.8 Hz), 3.41 (dd, 2H, 2 × H-2, J = 3.2 Hz and 9.8 Hz), 3.47−3.52 (m, 4H, $H\text{-}2^A$, $H\text{-}2^D$, 2 × H-6b), 3,60 (t, 2H, $H\text{-}4^A$, $H\text{-}4^D$, J = 9,0 Hz), 3.72 (d, 2H, 2 × H-6b, J = 10.5 Hz), 3.90−4.26 (m, 22H, $H\text{-}3^A$, $H\text{-}3^B$, $H\text{-}3^C$, $H\text{-}3^D$, $H\text{-}3^E$, $H\text{-}3^F$, $H\text{-}4^B$, $H\text{-}4^C$, $H\text{-}4^E$, $H\text{-}4^F$, $H\text{-}5^A$, $H\text{-}5^B$, $H\text{-}5^C$, $H\text{-}5^D$, $H\text{-}5^E$, $H\text{-}5^F$, $H\text{-}6a^A$, $H\text{-}6a^B$, $H\text{-}6a^C$, $H\text{-}6a^D$ $H\text{-}6a^E$, $H\text{-}6a^F$), 4.29−4.57 (m, 20H, H benz., $H\text{-}6b^A$, $H\text{-}6b^D$), 4.81−4.95 (m, 12H, $H\text{-}1^B$, $H\text{-}1^C$, $H\text{-}1^E$, $H\text{-}1^F$, H benz.), 5.02 (d, 2H, H benz., J = 11.4 Hz), 5.11 (d, 2H, $H\text{-}1^A$ and $H\text{-}1^D$, J = 3,6 Hz), 5.17 (d, 2H, H benz., J = 10,8

Hz), 5.34 (d, 2H, H benz., $J = 11.1$ Hz), 7.09−7.29 (m, 80H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz assignments by DEPT, HSQC, and HMBC) δ (ppm) 37.6 (CH_3 mesyl), 69.3, 69.6 (C-6^B, C-6^C, C-6^E, C-6^F), 70.0 (C-5^A, C-5^D), 70.4 (C-6^A, C-6^D), 71.9, 72.4 (C-5^B, C-5^C, C-5^E, C-5^F), 72.8, 73.1, 73.4, 73.8, 73.9, 75.4, 76.3, 76.5 (C benz.), 78.5 (C-2^A, C-2^D), 79.4, 79.6 (C-2^B, C-2^C, C-2^E, C-2^F), 80.3 (C-4^A, C-4^D), 80.9, 81.1, 81.9 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F, C-4^B, C-4^C, C-4^E, C-4^F), 98.9, 100.4 (C-1^B, C-1^C, C-1^E, C-1^F), 100.7 (C-1^A, C-1^D), 127.1−128.7 (CH_{ar}), 138.6−139.9 (C_{Ar}). MS (ESI) *m/z* 1308.2 $[(M + 2Na)/2]^{2+}$, 2571.2 $[M + H]^+$, 2592.7 $[M + Na]^+$. HRMS calcd for $C_{122}H_{136}O_{34}S_2Na$ 2291.8252, found 2291.8238.

6^A,6^D-Di-*O*-methylsulfonyl-α-cyclodextrin (5). To a solution of **4** (0.258 g, 100 μmol) in a 1:1 EtOAc/MeOH mixture (20 mL) was added 10% Pd/C (0.106 g, 100 μmol, 1 equiv) The reaction mixture was stirred during 24 h at room temperature under 10 bar H_2 atmosphere. The reaction was monitored by TLC (*n*-BuOH/ethanol/water: 5/4/3). The mixture was then filtered (Celite) into a separating funnel, washing thoroughly with MeOH. The solvent is then evaporated under vacuum to afford **5** as a white powder, in 92% yield. Mp 156 °C dec. IR ν (cm^{-1}) 3310 (O−H), 2931 (C−H), 1332 (C−SO_2−C), 1075 (CH−OH). $[\alpha]^{22}{}_D{}^{22}$ +145 (*c* 1.0 in DMSO). ^1H NMR (DMSO-d_6, 300 MHz, 25 °C, assignments by COSY, DEPT, HSQC) δ (ppm) 3.19 (s, 6H, CH_3 mesyl), 3.30−3.48 (m, 12H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^B, H-4^C, H-4^D, H-4^E, H-4^F), 3.52−3.81 (m, 18H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, H-5^B, H-5^C, H-5^E, H-5^F, H-$6a^B$, H-$6a^C$, H-$6a^E$, H-$6a^F$, H-$6b^B$, H-$6b^C$, H-$6b^E$, H-$6b^F$), 3.91−3.93 (m, 2H, H-5^A, H-5^D), 4.31 (d, 2H, H-$6b^A$, H-$6b^D$, $J = 9.6$ Hz), 4.52 (dd, 2H, H-$6a^A$, H-$6a^D$, $J = 3.8$ and 10.7 Hz), 4.57 (t, 2H, OH-6, $J = 6.3$ Hz), 4.63 (t, 2H, OH-6, $J = 5.3$ Hz), 4,80 (d, 2H, H-1^A, H-1^D, $J = 3.0$ Hz), 4,87 (d, 2H, 2 × H-1, $J = 3.0$ Hz), 4.90 (d, 2H, 2H-1, $J = 3.0$ Hz), 5.45−5.63 (m, 12H, OH-2, OH-3).^{13}C NMR (DMSO-d_6, 75 MHz assignments by DEPT and HSQC) δ (ppm) 37.5 (CH_3 mesyl), 60.7, 61.3 (C-6^B, C-6^C, C-6^E, C-6^F), 69.6 (C-5^A, C-5^D), 70.3 (C-6^A, C-6^D), 72.6, 72.9, 73.1 (C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F, C-5^B, C-5^C, C-5^E, C-5^F), 73.9 (C-3^A, C-3^D), 74.0 (C-3^B, C-3^C, C-3^E, C-3^F), 82.6, 83.0, 83.4 (C-4^A, C-4^B, C-4^C, C-4^D, C-4^E, C-4^F), 102.5 (C-1^A, C-1^D), 102.7(C-1^B, C-1^C, C-1^E, C-1^F). MS (ESI) *m/z* 1129.3 $[M + H]^+$, 1146.3 $[M + NH_4]^+$, 1151.3 $[M + Na]^+$, 1167.3 $[M + K]^+$, 1219.3 $[M + Na - H]^+$. HRMS calcd for $C_{38}H_{64}O_{34}S_2Na$ 1151.2618, found 1151.2609.

General Procedure for the Preparation of 6^A,6^D-Dideoxy-6^A,6^D-dialkylthio-α-cyclodextrins (6a−c). Dry Cs_2CO_3 (1.73 g 5.31 mmol, 12 equiv) was added to a solution of alkylisothiouronium bromide[14] (4 equiv) in anhydrous DMF (10 mL) and the mixture was stirred for 2 h at room temperature under argon. A solution of **5** (0.500 g, 1equiv) in anhydrous DMF (10 mL) was then added dropwise to the suspension during 1 h. The reaction mixture was stirred for 4 days at 60 °C under argon and the reaction monitored by TLC (*n*-BuOH/ethanol/water: 5/4/3). The product was then precipitated from cold acetone (500 mL). The precipitated was filtered off, then washed with acetone, water, then MeOH.

6^A,6^D-Dideoxy-6^A,6^D-diheptanethio-α-cyclodextrin (6a). The methanolic filtrate was evaporated under vacuum to afford **6a** as a white powder. Yield 53%. Mp 209 °C dec. IR ν (cm^{-1}) 3313 (O−H), 2925 et 2850 (C−H), 1075 (CH−OH). ^1H NMR (pyridine-d_5, 500 MHz, assignements by TOCSY, HMBC, and HSQC) δ (ppm) 0.86 (m, 6H, CH_3), 1.30 (br s, 12H, CH_2−CH_2−CH_2−CH_3), 1.38−1.49 (m, 4H, CH_2−CH_2−CH_2−S), 1.62−1.72 (m, 4H, CH_2−CH_2−S), 2.74−2.84 (m, 4H, CH_2−S), 3.19 (dd, 2H, H-$6a^A$, H-$6a^D$, $J = 6.2$ and 13.4 Hz), 3.37 (d, 2H, H-$6b^A$, H-$6b^D$, $J = 13.4$ Hz), 4.10 (m, 8H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^D), 4.38 (t, 2H, H-4^C, H-4^F, $J = 9.0$ Hz), 4.42 (t, 2H, H-4^B, H-4^E, $J = 9.2$ Hz), 4.47 (d, 4H, H-$6b^B$, H-$6b^C$, H-$6b^E$, H-$6b^F$, $J = 9.4$ Hz), 4.51−4.59 (m, 10H, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-$6a^B$, H-$6a^C$, H-$6a^E$, H-$6a^F$), 4.69 (t, 2H, H-3^A, H-3^D, $J = 8.9$ Hz), 4.71 (t, 2H, H-3^C, H-3^F, $J = 8.6$ Hz), 4.76 (t, 2H, H-3^B, H-3^E, $J = 8.2$ Hz), 5.54 (br s, 4H, H-1^A, H-1^C, H-1^D, H-1^F), 5.61 (d, 2H, H-1^B, H-1^E, $J = 2.9$ Hz), 6.38 (t, 2H, OH-6^B, OH-6^E, $J = 5.5$ Hz), 6.46 (t, 2H, OH-6^C, OH-6^F, $J = 5.0$ Hz), 7.38−7.45 (m, 6H, OH-3), 7.65 (br s, 2H, OH-C2^B, OH-C2^E), 7.76 (br s, 2H, OH-C2^C, OH-C2^F). ^{13}C NMR (pyridine-d_5, 125 MHz, assignments by TOCSY, HMBC, and HSQC) δ (ppm) 14.4 (CH_3), 23.1 (CH_2−CH_3), 28.8 (CH_2−CH_2−CH_2−S), 29.3 (CH_2−CH_2−CH_2−CH_2−S), 30.0 (CH_2−CH_2−S), 32.1 (CH_2−CH_2−CH_3), 33.7 (CH_2−S), 34.6 (C-6^A, C-6^D), 61.3 (C-6^B, C-6^C, C-6^E, C-6^F), 72.7 (C-5^A, C-5^D), 73.9−74.0 (C-5^B, C-5^C, C-5^E, C-5^F, C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 74.7 (C-3^A, C-3^D), 74.8 (C-3^C, C-3^F), 74.9 (C-3^B, C-3^E), 83.1 (C-4^B, C-4^C, C-4^E, C-4^F), 86.2 (C-4^A, C-4^D), 103.4 (C-1^A, C-1^D), 103.8 (C-1^B, C-1^E), 103.9 (C-1^C, C-1^F). MS (ESI) *m/z* 1201.5 $[M + H]^+$, 1218.5 $[M + NH_4]^+$. HRMS calcd for $C_{50}H_{88}O_{28}S_2Na$ 1223.4801, found 1223.4812.

6^A,6^D-Dideoxy-6^A,6^D-dinonanethio-α-cyclodextrine (6b). The methanolic filtrate was evaporated under vacuum to afford **6b** as a white powder. Yield 77%. Mp 213 °C dec. IR ν (cm^{-1}) 3317 (O−H), 2923 and 2850 (C−H), 1072 (CH−OH). ^1H NMR (pyridine-d_5, 300 MHz, assignment by TOCSY, HMBC, and HSQC) δ (ppm) 0.85 (m, 6H, CH_3), 1.31−1.34 (m, 20H, CH_2−CH_2−CH_2−CH_2−CH_2−CH_2−CH_3), 1.42−1.50 (m, 4H, CH_2−CH_2−CH_2−S), 1.66−1.76 (m, 4H, CH_2−CH_2−S), 2.77−2.87 (m, 4H, CH_2−S), 3.22 (dd, 2H, H-$6a^A$, H-$6a^D$, $J = 6.2$ and 13.5 Hz), 3.41 (d, 2H, H-$6b^A$, H-$6b^D$, $J = 13.5$ Hz), 4.12 (m, 8H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^D), 4.38 (t, 2H, H-4^C, H-4^F, $J = 9.3$ Hz), 4.41 (t, 2H, H-4^B, H-4^E, $J = 9.2$ Hz), 4.48 (d, 4H, H-$6b^B$, H-$6b^C$, H-$6b^E$, H-$6b^F$, $J = 3.2$ Hz), 4.54−4.64 (m, 10H, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-$6a^B$, H-$6a^C$, H-$6a^E$, H-$6a^F$), 4.74 (t, 2H, H-3^A, H-3^D, $J = 9.2$ Hz), 4.77 (t, 2H, H-3^C, H-3^F, $J = 9,3$ Hz), 4.80 (t, 2H, H-3^B, H-3^E, $J = 9.2$ Hz), 5.57 (br s, 4H, H-1^A, H-1^C, H-1^D, H-1^F), 5.64 (d, 2H, H-1^B, H-1^E, $J = 2.0$ Hz), 6.50 (t, 2H, OH-6^B, OH-6^E, $J = 5.2$ Hz), 6.58 (t, 2H, OH-6^C, OH-6^F, $J = 5.2$ Hz), 7.38−7.45 (m, 6H, OH-3), 7.65 (br s, 2H, OH-C2^B, OH-C2^E), 7.76 (br s, 2H, OH-C2^C, OH-C2^F). ^{13}C NMR (pyridine-d_5, 75 MHz, assignments by TOCSY, HMBC, and HSQC) δ (ppm) 14.5 (CH_3), 23.2 (CH_2−CH_3), 29.0 (CH_2−CH_2−CH_2−S), 29.7, 29.9, 30.1 (CH_2−CH_2−CH_2−CH_2−CH_2−CH_2−S), 30.1 (CH_2−CH_2−S), 32.5 (CH_2−CH_2−CH_3), 33.9 (CH_2−S), 34.8 (C-6^A, C-6^D), 61.5 (C-6^B, C-6^C, C-6^E, C-6^F), 72.7 (C-5^A, C-5^D), 74.0−74.3 (C-5^B, C-5^C, C-5^E, C-5^F, C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 74.9 (C-3^A, C-3^D), 75.0 (C-3^C, C-3^F), 75.1 (C-3^B, C-3^E), 83.3 (C-4^B, C-4^C, C-4^E, C-4^F), 86.4 (C-4^A, C-4^D), 103.6 (C-1^A, C-1^D), 103.9 (C-1^B, C-1^E), 104.0 (C-1^C, C-1^F). MS (ESI) *m/z* 648.6 $[M + K + H]^{2+}$, 1257.6 $[M + H]^+$, 1274.5 $[M + Na]^+$, 1295.4 $[M + K]^+$. HRMS calcd for $C_{54}H_{96}O_{28}S_2Na$ 1279.5427, found 1279.5429.

6^A,6^D-Dideoxy-6^A,6^D-diundecanethio-α-cyclodextrin (6c). The precipitate was reprecipitated in warm EtOH (10 mL), filtered, and dried under vacuum to afford **6c** as a white powder. Yield 62%. Mp 213 °C dec. IR ν (cm^{-1}) 3325 (O−H), 2922 and 2853 (C−H), 1073 (CH−OH). ^1H NMR (DMSO-d_6, 500 MHz, assignment by TOCSY, HMBC, HSQC) δ (ppm) 0.87 (t, 6H, CH_3, $J = 7.0$ Hz), 1.26 (br s, 28H, 14 CH_2), 1.34−1.35 (m, 2H, CH_2−CH_2−CH_2−S), 1.42−1.48 (m, 4H, CH_2−CH_2−S), 2.50 (s, 4H, CH_2−S), 2.67 (dd, 2H, H-$6a^A$, H-$6a^D$, $J = 8.3$ and 13.8 Hz), 2.93 (d, 2H, H-$6b^A$, H-$6b^D$, $J = 8.3$ Hz), 3.28−3.35 (m, 8H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^D), 3.44 (t, 2H, 2 × H-4, $J = 9.3$ Hz), 3.46 (t, 2H, 2 × H-4, $J = 9.5$ Hz), 3.54 (d, 4H, H-$6b^B$, H-$6b^C$, H-$6b^E$, H-$6b^F$, $J = 9.4$ Hz), 3.62−3.66 (m, 4H, H-5^B, H-5^C, H-5^E, H-5^F), 3.71−3.77 (m, 8H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, 2 × H-6a), 3.81 (t, 2H, H-5^A, H-5^D, $J = 8.5$ Hz), 3.90 (d, 2H, 2 × H-6a, $J = 10.8$ Hz), 4.80 (br s, 4H, H-1^A, H-1^B, H-1^D, H-1^E), 4.84 (br s, 2H, H-1^C, H-1^F), 4.45 (br s, 2H, 2 × OH-6), 4.55 (br s, 2H, 2 × OH-6), 5.62 (br s, 6H, OH II^{ary}), 5.78 (br s, 2H, OH II^{ary}). ^{13}C NMR (DMSO-d_6, 125 MHz, assignment by TOCSY, HMBC, HSQC) δ (ppm) 15.0 (CH_3), 23.1 (CH_2−CH_3), 28.3 (CH_2−CH_2−CH_2−S), 29.3, 29.9, 29.9, 30.1, 30.3 (CH_2), 29.5 (CH_2−CH_2−S), 32.4 (CH_2−CH_2−CH_3), 33.2 (CH_2−S), 34.3 (C-6^A, C-6^D), 60.3 (C-6^B, C-6^C, C-6^E, C-6^F), 72.0 (C-5^A, C-5^D), 72.8−72.9 (C-5^B, C-5^C, C-5^E, C-5^F, C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 74.0 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F), 82.7 (C-4^B, C-4^C, C-4^E, C-4^F),

86.6 (C-4^A, C-4^D), 102.5, 102.9 (C-1^A, C-1^B, C-1^D, C-1^E), 103.1 (C-1^C, C-1^F). MS (Maldi) *m/z* 1335.8 [M + Na]$^+$, 1351.7 [M + K]$^+$. HRMS calcd for $C_{58}H_{104}O_{28}S_2Na$ 1335.6053, found 1335.6047.

General Procedure for the Preparation of 6^A,6^D-Dideoxy-6^A,6^D-di(3-perfluoroalkylpropanethio)-α-cyclodextrins (7a−c). Dry Cs_2CO_3 (1.84 g 5.65 mmol, 7.5 equiv) was added to a solution of 3-perfluoroalkylpropane isothiouronium iodide[14] (3.76 mmol, 5 equiv) in anhydrous DMF (20 mL) and the mixture was stirred for 1 h at room temperature under argon. A solution of **5** (0.850 g, 0.75 mmol, 1 equiv) in anhydrous DMF (15 mL) was then added dropwise to the suspension during 40 min. The reaction mixture was stirred for 4 days at 80 °C under argon and the reaction monitored by TLC (*n*-BuOH/ethanol/water: 5/4/3). After cooling, the product was precipitated from cold acetone (500 mL). The precipitated was filtered off, thenwashed with acetone, water (10 mL), and then MeOH (50 mL).

6^A,6^D-Dideoxy-6^A,6^D-di(3-perfluorobutylpropanethio)-α-cyclodextrine (7a). The methanolic filtrate was evaporated under vacuum to afford compound **7a** as a white powder in 52% yield. Mp 235 °C dec. IR ν (cm^{-1}) 3368 (O−H), 2930 (C−H), 1231−1151 (C−F), 1080 (C−O−C). ^{1}H NMR (pyridine-d_5, 500 MHz, assignment by TOCSY, HMBC, HSQC) δ (ppm) 1.92 (qi, 4H, CH_2−CH$_2$−S, J = 7.2 Hz), 2.28 (tt, 4H, CH_2−CF$_2$, J = 8.5 and 19.1 Hz), 2.61−2.90 (m, 4H, CH$_2$−S), 3.23 (br s, 4H, H-6a^A, H-6a^D, H-6b^A, H-6b^D), 4.08−4.14 (m, 6H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F), 4.18 (t, 2H, H-4^A, H-4^D, J = 8.8 Hz), 4.25 (t, 2H, H-4^C, H-4^F, J = 8.8 Hz), 4.34 (t, 2H, H-4^B, H-4^E, J = 9.2 Hz), 4.35−4.44 (m, 6H, H-6a^B, H-6a^E, H-6b^B, H-6b^C, H-6b^E, H-6b^F), 4.50−4.52 (m, 8H, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-6a^C, H-6a^F), 4.68 (t, 2H, H-3^A, H-3^D, J = 8.8 Hz), 4.71 (t, 2H, H-3^C, H-3^F, J = 8.9 Hz), 4.73 (t, 2H, H-3^B, H-3^E, J = 9.2 Hz), 5.51(d, 2H, H-1^A, H-1^D, J = 3.2 Hz), 5.53 (d, 2H, H-1^C, H-1^F, J = 3.1 Hz), 5.58 (d, 2H, H-1^B, H-1^E, J = 2.9 Hz), 6.43 (t, 2H, OH-6^B, OH-6^E, J = 6.0 Hz), 6.52 (t, 2H, OH-6^C, OH-6^F, J = 5.6 Hz), 7.40−7.49 (m, 6H, OH-3), 7.61 (br s, 2H, OH-C2^B, OH-C2^E), 7.61 (br s, 2H, OH-C2^C, OH-C2^F). ^{13}C NMR (pyridine-d_5, 125 MHz, assigment by TOCSY, HMBC, HSQC) δ (ppm) 20.9 (*C*H$_2$−CH$_2$−S), 29.7 (*C*H$_2$−CF$_2$, J = 21.8 Hz), 32.7 (CH$_2$−S), 34.2 (C-6^A, C-6^D), 61.3 (C-6^B, C-6^E), 61.7 (C-6^C, C-6^F), 72.5 (C-5^A, C-5^D), 73.86 (C-5^B, C-5^E), 73.94 (C-2^A, C-2^C, C-2^D, C-2^F), 74.1 (C-2^B, C-2^E), 74.2 (C-5^C, C-5^F), 74.8 (C-3^A, C-3^D), 74.9 (C-3^C, C-3^F), 75.0 (C-3^B, C-3^E), 83.1 (C-4^B, C-4^E), 83.4 (C-4^C, C-4^F), 85.6 (C-4^A, C-4^D), 103.4 (C-1^A, C-1^D), 103.7 (C-1^B, C-1^E), 103.8 (C-1^C, C-1^F). ^{19}F NMR (pyridine-d_5, 280 MHz, CFCl$_3$) δ (ppm) −82.3 (t, 3F, CF$_3$, J = 9.1 Hz), −113.1 (m, 2F, CH$_2$−CF_2), −123.4 (m, 2F, CF$_2$), −125.1 (m, 2F, CF_2−CF$_3$). MS (Maldi) *m/z* 1547.4 [M + Na]$^+$, 1563.4 [M + K]$^+$. HRMS calcd for $C_{50}F_{18}H_{70}O_{28}S_2Na$ 1547.3105, found 1547.3104.

6^A,6^D-Dideoxy-6^A,6^D-di(3-perfluorohexylpropanethio)-α-cyclodextrin (7b). The precipitate was reprecipitated in warm EtOH (10 mL), filtered, and dried under vacuum to afford **7b** as a cream powder in 54% yield. Mp 238 °C dec. IR ν (cm^{-1}) 3324 (O−H), 2924 (C−H), 1233−1144 (C−F), 1077 (C−O−C). ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 1.76 (qi, 4H, CH_2−CH$_2$−S, J = 7.3 Hz), 2.29 (tt, 4H, CH_2−CF$_2$, J = 7.3 and 19.2 Hz), 2.66 (t, 4H, CH$_2$−S, J = 7.3 Hz), 2.83 (dd, 2H, H-6a^A, H-6a^D, J = 5.8 and 12.9 Hz), 2.99 (d, 2H, H-6b^A, H-6b^D, J = 12.9 Hz), 3.28−3.32 (m, 6H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F), 3.35 (t, 2H, H-4^A, H-4^D, J = 8.8 Hz), 3.42 (t, 2H, 2*H-4, J = 8.9 Hz), 3.43 (t, 2H, 2 × H-4, J = 8.9 Hz), 3.62−3.66 (m, 10H, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-6b^B, H-6b^C, H-6b^E, H-6b^F), 3.74−3.77 (m, 8H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, 2 × H-6a), 3.85 (br s, 2H, 2 × H-6a), 4.48 (br s, 2H, OH-6), 4.53 (br s, 2H, OH-6), 4.78 (d, 4H, H-1^A, H-1^B, H-1^D, H-1^E, J = 1.6 Hz), 4.83 (d, 2H, H-1^C, H-1^F, J = 3.1 Hz), 5.54−5.59 (br s, 6H, OH II^{ary}), 5.63−5.66 (br s, 2H, OH II^{ary}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 20.1 (*C*H$_2$−CH$_2$−S), 29.0 (*C*H$_2$−CF$_2$, J = 20.3 Hz), 31.2 (CH$_2$−S), 33.0 (C-6^A, C-6^D), 59.8 (C-6^B, C-6^E), 60.0 (C-6^C, C-6^F), 70.8 (C-5^A, C-5^D), 72.0−72.3 (C-5^B, C-5^C, C-5^E, C-5^F, C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 73.1 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F), 81.8 (C-4^B, C-4^E), 82.2 (C-4^C, C-4^F), 84.7 (C-4^A, C-4^D), 101.6 (C-1^A, C-1^D), 101.9 (C-1^B, C-1^E), 102.1 (C-1^C, C-1^F). ^{19}F NMR (DMSO-d_6, 280 MHz, CFCl$_3$) δ (ppm) −81.2 (t, 3F, CF$_3$, J = 9.8 Hz), −114.0−114.2 (m, 2F, CH$_2$−CF_2), −122.6 (m, 2F, CF$_2$), −123.5 (m, 2F, CF$_2$), −123.6 (m, 2F, CF$_2$), −123.9 (m, 2F, CF$_2$), −126.7 (m, 2F, CF_2−CF$_3$). MS (Maldi) *m/z* 1747.3 [M + Na]$^+$, 1763.2 [M + K]$^+$. HRMS calcd for $C_{54}H_{70}F_{26}O_{28}S_2Na$ 1747.2978, found 1747.2973.

6^A,6^D-Dideoxy-6^A,6^D-di(3-perfluorooctylpropanethio)-α-cyclodextrin (7c). The precipitate was reprecipitated in warm EtOH (10 mL), filtered, and dried under vacuum to afford **7c** as a cream powder in 56% yield. Mp 245 °C dec. IR ν (cm^{-1}) 3325 (O−H), 2925 (C−H), 1236−1147 (C−F), 1078 (C−O−C). ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 1.74 (m, 4H, CH_2−CH$_2$−S), 2.27 (tt, 4H, CH_2−CF$_2$, J = 7.9 and 18.6 Hz), 2.64 (t, 4H, CH$_2$−S, J = 6.2 Hz), 2.77 (dd, 2H, H-6a^A, H-6a^D, J = 6.2 and 13.0 Hz), 2.99 (d, 2H, H-6b^A, H-6b^D, J = 13.0 Hz), 3.26 (dd, 2 × H-2, J = 2.7 and 9.1 Hz), 3.28 (dd, 2 × H-2, J = 2.7 and 7.8 Hz), 3.30 (dd, 2 × H-2, J = 2.7 and 9.9 Hz), 3.33−3.42 (m, 4H, 4 × H-4), 3.44 (t, 2H, 2 × H-4, J = 9.2 Hz), 3.58−3.60 (m, 10H, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-6b^B, H-6b^C, H-6b^E, H-6b^F), 3.73−3.84 (m, 8H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, H-6a^B, H-6a^C, H-6a^E, H-6a^F), 4.52 (br s, 2H, OH-6), 4.56 (br s, 2H, OH-6), 4.78 (d, 4H, H-1^A, H-1^B, H-1^D, H-1^E, J = 2.7 Hz), 4.83 (d, 2H, H-1^C, H-1^F, J = 2.7 Hz), 5.61 (br s, 12H, OH II^{ary}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 19.8 (*C*H$_2$−CH$_2$−S), 28.5 (*C*H$_2$−CF$_2$, J = 21.7 Hz), 30.8 (CH$_2$−S), 32.7 (C-6^A, C-6^D), 59.6 (C-6^B, C-6^E), 59.8 (C-6^C, C-6^F), 70.7 (C-5^A, C-5^D), 71.6−72.1 (C-5^B, C-5^C, C-5^E, C-5^F, C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 72.9 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F), 81.4 (C-4^B, C-4^E), 81.9 (C-4^C, C-4^F), 84.9 (C-4^A, C-4^D), 101.3 (C-1^A, C-1^D), 101.7 (C-1^B, C-1^E), 102.0 (C-1^C, C-1^F). MS (Maldi) *m/z* 1947.5 [M + Na]$^+$, 1963.4 [M + K]$^+$. HRMS calcd for $C_{58}F_{34}H_{70}O_{28}S_2Na$ 1947.2860, found 1947.2858.

6^A,6^D-Di-*O*-methyl-6^B,6^C,6^E,6^F-tetra-*O*-benzyl(per-2,3-di-*O*-benzyl)-α-cyclodextrin (8). To a solution of **3**[22] (10.00 g, 4,14 mmol) in anhydrous DMF (40 mL) under argon was added at 0 °C NaH (95%, 0.628 g, 24.85 mmol, 6 equiv). The reaction mixture was stirred during 1 h at room temperature under argon. Methyl iodide (1.55 mL, 24.85 mmol, 6 equiv) was then added dropwise in 5 min. The mixture was stirred at room temperature for 3 h and the reaction was monitored by TLC (cyclohexane/AcOEt: 6/2). The reaction was quenched by adding MeOH (10 mL), then water (100 mL). The organic layer was extracted with diethyl ether (3 × 50 mL) and organic layers were combined, washed with brine (100 mL), dried on Na_2SO_4, and then evaporated under vacuum. The crude product was purified by flash chromatography (SiO_2, eluent gradient 0−20% EtOAc in cyclohexane) to afford compound **8** as a white foam. Yield 98%. IR ν (cm^{-1}) 3030 (C−H ar), 2926 (C−H), 1091 (C−O−C). ^{1}H NMR ($CDCl_3$, 300 MHz, assignment by COSY, DEPT, HSQC) δ (ppm) 3.13 (s, 6H, CH$_3$), 3.36 (d, 2H, H-6a^A, H-6a^D, J = 10.5 Hz), 3.41−3.60 (m, 10H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-6a^B, H-6a^C, H-6a^E, H-6a^F), 3.74 (d, 2H, H-6b^A, H-6b^D, J = 10.2 Hz), 3.85−4.15 (m, 22H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, H-4^A, H-4^B, H-4^C, H-4^D, H-4^E, H-4^F, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-6b^B, H-6b^C H-6b^E, H-6b^F), 4.34−4.55 (m, 20H, H benz.), 4.83−4.89 (m, 6H, H benz.), 5.00 (d, 2H, 2 × H-1, J = 3.3 Hz), 5.04 (d, 2H, 2 × H-1, J = 3.6 Hz), 5.06 (d, 2H, 2 × H-1, J = 3.6 Hz), 5.13−5.23 (m, 6H, H benz.), 7.07−7.30 (m, 80H, H$_{Ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz, assigment by COSY, DEPT, HSQC) δ (ppm) 59.5 (CH$_3$), 69.6 (C-6^B, C-6^C, C-6^E, C-6^F), 71.5 (C-5^B, C-5^C, C-5^E, C-5^F), 71.9 (C-6^A, C-6^D), 72.0 (C-5^A, C-5^D), 73.2, 73.5, 73.8, 75.8, 76.0, 76.7 (C benz.), 79.3, 79.5, 79.5, 79.7, 79.8 (C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F, C-4^B, C-4^C, C-4^E, C-4^F), 80.4 (C-4^A, C-4^D), 81.4 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F), 99.2, 99.4 (C-1^A, C-1^B, C-1^C, C-1^D, C-1^E, C-1^F), 127.4−128.8 (CH$_{ar}$), 138.7−139.89 (C$_{Ar}$). MS (ESI) *m/z* 1222.2 [(M + 2H)/2]$^{2+}$, 1244.2 [(M + 2Na)/2]$^{2+}$, 2442.9 [M + H]$^+$, 2465.0 [M + Na]$^+$. HRMS calcd for $C_{150}H_{160}O_{30}Na$ 2464.0892, found 2464.0894.

6^A,6^D-Di-*O*-methyl-α-cyclodextrin (9). To a solution of **8** (9.48 g, 3.88 mmol) in a 1:1 EtOAc/MeOH mixture (100 mL) was added 10% Pd/C (2.05 g, 100 mmol, 0.5 equiv). The reaction mixture

was stirred during 46 h at room temperature under 1 bar H_2 atmosphere. The reaction achievement was monitored by TLC (*n*-BuOH/EtOH/H_2O: 5/4/3). The mixture was then filtered off on Celite, which was washed with water. After evaporation under vacuum, compound **9** was obtained as a white powder: Yield: 98%. Mp 227 °C dec. IR ν (cm^{-1}) 3330 (O−H), 2919 (C−H), 1076 (CH−OH). $[\alpha]^{22}_D$ +141 (*c* 1.03 in H_2O). ^1H NMR (D_2O, 300 MHz, assigment by COSY, DEPT, HSQC) δ (ppm) 3.39 (s, 6H, CH_3), 3.54−3.65 (m, 12H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^B, H-4^C, H-4^D, H-4^E, H-4^F), 3.77−4.01 (m, 24H, H-3^A, H-3^B, H-3^C, H-3^D, H-3^E, H-3^F, H-5^A, H-5^B, H-5^C, H-5^D, H-5^E, H-5^F, H-$6a^A$, H-$6a^B$, H-$6a^C$, H-$6a^D$, H-$6a^E$, H-$6a^F$, H-$6b^A$, H-$6b^B$, H-$6b^C$, H-$6b^D$, H-$6b^E$, H-$6b^F$), 4.78−4.85 (d, 6H, H-1^A, H-1^B, H-1^C, H-1^D, H-1^E, H-1^F, J = 2.4 Hz). ^{13}C NMR (D_2O, 75 MHz, assignment by DEPT, HSQC) δ (ppm) 58.9 (CH_3), 60.8 (C-6^B, C-6^C, C-6^E, C-6^F), 71.0 (C-5^A, C-5^D), 71.1 (C-6^A, C-6^D), 72.0 (C-2^A, C-2^B, C-2^C, C-2^D, C-2^E, C-2^F), 72.5 (C-5^B, C-5^C, C-5^E, C-5^F), 73.8 (C-3^A, C-3^B, C-3^C, C-3^D, C-3^E, C-3^F), 82.0 (C-4^B, C-4^C, C-4^E, C-4^F), 82.1 (C-4^A, C-4^D), 102.0 (C-1^B, C-1^C, C-1^E, C-1^F), 102.2 (C-1^A, C-1^D). MS (ESI) *m/z* 520.1 $[(M + H + K)/2]^{2+}$, 1001.4 $[M + H]^+$, 1018.4 $[M + NH_4]^+$, 1023.2 $[M + Na]^+$. HRMS calcd for $C_{38}H_{64}O_{30}Na$ 1023.3380, found 1023.3378.

(6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetraiodo)di(6^C,6^F-*O*-methyl)-α-cyclodextrin (10). Compound **9** was dried under vacuum at 100 °C during 15 h before use. To a solution of triphenylphosphine (13.21 g, 50.00 mmol, 16 equiv) in anhydrous DMF (60 mL) under argon was added iodine (12.78 g, 50.00 mmol, 16 equiv). After 10 min of stirring at room temperature, a solution of **9** (3.15 g, 3.15 mmol) in anhydrous DMF (30 mL) was added dropwise. The reaction mixture was then stirred at 80 °C during 23 h under argon and the reaction achievement monitored by TLC (*n*-BuOH/EtOH/H_2O: 5/4/3). The solution was then concentrated under vacuum to remove 50 mL of DMF. A 3 M sodium methanolate solution (19 mL) was then added at 0 °C and the reaction mixture was stirred at room temperature for 1 h. Iced ethanol (800 mL) was then poured into the solution to precipitate the compound, which was then filtered off and washed with EtOH. The brown solid was extracted with EtOH overnight with a Soxhlet apparatus to afford **10** as a powder. Yield 64%. Mp 208 °C dec. IR ν (cm^{-1}) 3343 (O−H), 2916 (C−H), 1079 (CH−OH). $[\alpha]^{22}_D$ +85 (*c* 0.53 in DMF). ^1H NMR (pyridine-d_5, 500 MHz, assigment by TOCSY, HMBC, HSQC) δ (ppm) 3.50 (s, 6H, CH_3), 3.80 (dd, 2H, H-$6b^B$, H-$6b^E$, J = 6.7 and 11.0 Hz), 3.85 (t, 2H, H-4^B, H-4^E J = 9.2 Hz), 3.87−3.90 (m, 2H, H-$6b^C$, H-$6b^F$), 3.93−3.95 (m, 8H, H-4^C, H-4^F, H-5^C, H-5^F, H-$6a^A$, H-$6a^D$, H-$6a^C$, H-$6a^F$), 3,99 (dd, 2H, H-$6b^A$, H-$6b^D$, J = 4.6 and 10.8 Hz), 4.03−4.06 (m, 4H, H-5^B, H-5^E, H-$6a^B$, H-$6a^E$), 4.08−4.11 (m, 8H, H-2^A, H-2^B, H-2^C, H-2^D, H-2^E, H-2^F, H-4^A, H-4^D), 4.43 (dd, 2H, H-5^A, H-5^D, J = 4.6 and 9.5 Hz), 4.63 (t, 2H, H-3^A, H-3^D, J = 9.6 Hz), 4.67 (t, 2H, H-3^B, H-3^E, J = 9.2 Hz), 4.70 (t, 2H, H-3^C, H-3^F, J = 8.2 Hz), 5.41 (d, 2H, H-1^C, H-1^F, J = 2.9 Hz), 5.48 (d, 2H, H-1^A, H-1^D, J = 3.1 Hz), 5.50 (d, 2H, H-1^B, H-1^E, J = 2.9 Hz), 7.08 (br s, 14H, OH-2, OH-3). ^{13}C NMR (pyridine-d_5, 125 MHz, assigment by HMBC, HSQC) δ (ppm) 9.0 (C-6^B, C-6^E), 10.9 (C-6^C, C-6^F), 59.3 (O−CH_3), 70.4 (C-5^C, C-5^F), 71.3 (C-5^B, C-5^E), 71.9 (C-6^A, C-6^D), 72.1 (C-5^A, C-5^D), 73.6 (C-2^B, C-2^E), 73.66 (C-2^A, C-2^D), 73.7 (C-2^C, C-2^F), 74.09 (C-3^B, C-3^E), 74.11 (C-3^C, C-3^F), 73.8 (C-3^A, C-3^D), 83.2 (C-4^A, C-4^D), 87.5 (C-4^B, C-4^E), 87.6 (C-4^C, C-4^F), 103.4 (C-1^C, C-1^F), 103.45 (C-1^A, C-1^D), 103.5 (C-1^B, C-1^E). MS (ESI) *m/z* 732.1 $[(M + H + Na)/2]^{2+}$, 740.2 $[(M + H + K)/2]^{2+}$, 1463.0 $[M + Na]^+$. HRMS calcd for $C_{38}H_{60}O_{26}I_4Na$ 1462.9450, found 1462.9446.

General Procedure for the Preparation of 6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetraalkylthiodi(6^C,6^F-O-methyl)-α-cyclodextrin (11a−c). Dry Cs_2CO_3 (1.900 g, 5.83 mmol, 24 equiv) was added to a solution of alkylisothiouronium bromide[14] (16 equiv) in anhydrous DMF (20 mL) and the mixture was stirred for 2 h at room temperature under argon. A solution of **10** (0.350 g, 0.24 mmol, 1 equiv) in anhydrous DMF (15 mL) was then added dropwise to the suspension during 20 min. The solution was stirred at 80 °C for 90 h under argon. After cooling, the product was precipitated from cold acetone (500 mL), then the precipitate was filtered off, washed with acetone (100 mL) and water (50 mL), and then reprecipitated from warm EtOH (10 mL) to afford the desired compound as a white powder.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetraheptanethiodi(6^C,6^F-*O*-methyl)-α-cyclodextrin (11a). Yield 86%. Mp 188 °C dec. IR ν (cm^{-1}) 3325 (O−H), 2923 and 2854 (C−H), 1232−1148 (C−F), 1083 (CH−OH). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 14.2 (CH_3), 23.0 (CH_2−CH_3), 29.3−33.8 (CH_2, C-6), 58.6 (OCH_3), 73.3 (C-2, C-3, C-5), 81.4−85.5 (C-4), 102.9 (C-1). MS (ESI) *m/z* 1457.4 $[M + H]^+$, 1479.7 $[M + Na]^+$. HRMS calcd for $C_{66}H_{120}O_{26}S_4Na$ 1479.6848, found 1479.6853.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetranonanethiodi(6^C,6^F-*O*-methyl)-α-cyclodextrin (11b). Yield 81%. Mp 198 °C dec. IR ν (cm^{-1}) 3315 (O−H), 2922 and 2853 (C−H), 1230−1149 (C−F), 1085 (CH−OH). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 14,2 (CH_3), 23.0 (CH_2−CH_3), 29.7−32.2 (CH_2, C-6), 58.5 (OCH_3), 72.2 (C-2, C-3, C-5), 83.1−85.5 (C-4), 102.6 (C-1). MS (ESI) *m/z* 1570.5 $[M + H]^+$, 1592.2 $[M + Na]^+$. HRMS calcd for $C_{74}H_{136}O_{26}S_4Na$ 1591.8100, found 1591.8105.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetraundecanethiodi(6^C,6^F-*O*-methyl)-α-cyclodextrin (11c). Yield 65%. Mp 203 °C dec. IR ν (cm^{-1}) 3321 (O−H), 2921 and 2852 (C−H), 1228−1148 (C−F), 1085 (CH−OH). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 14.2 (CH_3), 23.0 (CH_2−CH_3), 29.7−34.2 (CH_2, C-6), 59.0 (OCH_3), 73.1 (C-2, C-3, C-5), 83.5−85.5 (C-4), 103.0 (C-1). MS (ESI) *m/z* 868.9 $[M + K + NH_4]^{2+}$, 1682.8 $[M + H]^+$, 1704.9 $[M + Na]^+$. HRMS calcd for $C_{82}H_{152}O_{26}S_4Na$ 1703.9352, found 1703.9360.

General Procedure for the Preparation of 6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetra(3-perfluoroalkylpropanethio)di(6^C,6^F-*O*-methyl)-α-cyclodextrin (12a−c). Dry Cs_2CO_3 (1.63 g, 5.00 mmol, 24 equiv) was added to a solution of 3-perfluoroalkylpropane isothiouronium iodide[14] (16 equiv) in anhydrous DMF (20 mL) and the mixture was stirred for 1 h at room temperature under argon. A solution of **10** (0.300 g, 0.18 mmol, 1 equiv) in anhydrous DMF (10 mL) was then added dropwise to the suspension during 20 min. The solution was stirred at 80 °C for 90 h under argon. After cooling, the product was precipitated from cold acetone (500 mL), then the precipitate was filtered off, washed with acetone (100 mL) and water (50 mL), and then reprecipitated from warm EtOH (10 mL) to afford the desired compound as a white powder.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetra(3-perfluorobutylpropanethio)di(6^C,6^F-O-methyl)-α-cyclodextrin (12a). Yield 85%. Mp 213 °C dec. IR ν (cm^{-1}) 3339 (O−H), 2929 (C−H), 1238−1145 (C−F), 1088 (C−O−C). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 19.9 (CH_2−CH_2−S), 29.3−32.3 (CH_2−CF_2, CH_2−S, C-6), 58.1 (OCH_3), 67.4−73.6 (C-2, C-3, C-5), 82.0−84.4 (C-4), 102.1 (C-1), 106.5−120.2 (CF_2 and CF_3). ^{19}F NMR (470 MHz, MAS 10 and 12 kHz, RD = 4 s, $PhCF_3$) δ (ppm) −81.3 (m, 3F, CF_3), −113.3 (m, 2F, CH_2−CF_2), −123.7 (m, 2F, CF_2), −125.5 (m, 2F, CF_2−CF_3). MS (ESI) *m/z* 1072.1 $[M + K + H]^{2+}$, 2105.2 $[M + H]^+$, 2127.5 $[M + Na]^+$. HRMS calcd for $C_{66}H_{84}F_{36}O_{26}S_4Na$ 2127.3457, found 2127.3465.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetra(3-perfluorohexylpropanethio)di(6^C,6^F-*O*-methyl)-α-cyclodextrin (12b). Yield 93%. Mp 231 °C dec. IR ν (cm^{-1}) 3337 (O−H), 2924 (C−H), 1235−1143 (C−F), 1086 (C−O−C). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 20.4 (CH_2−CH_2−S), 29.2−32.1 (CH_2−CF_2, CH_2−S, C-6), 58.1 (OCH_3), 73.1 (C-2, C-3, C-5), 82.0−83.6 (C-4), 103.1 (C-1), 108.9−118.1 (CF_2 and CF_3). ^{19}F NMR (470 MHz, MAS 10 and 12 kHz, RD = 4 s, $PhCF_3$) δ (ppm) −81.4 (m, 3F, CF_3), −113.7 (m, 2F, CH_2−CF_2), −121.5 to −122.7 (m, 6F, CF_2), −126.2 (m, 2F, CF_2−CF_3). MS (ESI) *m/z* 1072.1 $[M + K + H]^{2+}$, 2505.0 $[M + H]^+$, 2526.8 $[M + Na]^+$. HRMS calcd for $C_{74}H_{84}F_{52}O_{26}S_4Na$ 2527.3201, found 2527.3212.

6^A,6^B,6^D,6^E-Tetradeoxy-6^A,6^B,6^D,6^E-tetra(3-perfluorooctylpropanethio)di(6^C,6^F-O-methyl)-α-cyclodextrin (12c). Yield 86%. Mp 245 °C dec. IR ν (cm^{-1}) 3326 (O−H), 2922 (C−H), 1238−1145

(C−F), 1089 (C−O−C). ^{13}C NMR (125 MHz, CP, HP Dec, MAS 10 kHz, RD = 4 s) δ (ppm) 20.4 (CH_2−CH_2−S), 29.2−32.2 (CH_2−CF_2, CH_2−S, C-6), 58.5 (OCH_3), 73.6 (C-2, C-3, C-5), 81.5−84.0 (C-4), 102.9 (C-1), 110.3−118.6 (CF_2 and CF_3). ^{19}F NMR (470 MHz, MAS 10 and 12 kHz, RD = 4 s, $PhCF_3$) δ (ppm) −81.4 (m, 3F, CF_3), −113.1 (m, 2F, CH_2−CF_2), −1212 tp −122.2 (m, 10F, CF_2), −126.0 (m, 2F, CF_2−CF_3). MS (ESI) *m/z* 2906.4 $[M + H]^+$, 2928.2 $[M + Na]^+$, 2943.2 $[M + K]^+$. HRMS calcd for $C_{82}H_{84}F_{68}O_{26}S_4Na$ 2927.2946, found 2927.2952.

Acknowledgment. We thank the Ph.D. fellowship from the French National Ministry of Education and Research, Dr. Anne Baudoin (Laboratoire de Chimie Organométallique de Surface, LCOMS, CNRS UMR 9986, CPE Lyon) for solid state NMR, and Natali Henriques and Christian Duchamp for mass spectroscopy analysis (Centre Commun de Spectrométrie de Masse, UMR5246, Université Claude Bernard Lyon1).

Supporting Information Available: General experimental procedures, spectral/analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801111B