Selective Functionalization and Flexible Coupling of Cyclodextrins at the Secondary Hydroxyl Face

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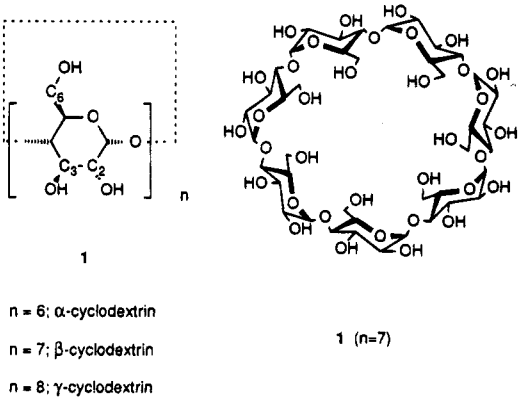
Methods are described for the chemo- and regioselective monofunctionalization of the secondary hydroxyl face of cyclodextrins. Monofunctionalization takes place either by nucleophilic epoxide opening of mono(2^A,3^A-anhydro)heptakis(6-*O*-*tert*-butyldimethylsilyl)-(2^AS)-β-cyclodextrin by ethylenediamine, lithium azide, or ammonia or by direct monoalkylation of one of the C(2)-hydroxyl groups of heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclodextrins with primary alkyl bromides, with cyano-, ethynyl-, or ester-containing functional groups. The latter route enables the synthesis of mono(2^A-*O*-(α-(4-(aminomethyl)tolyl))hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and its 2-aminomethyl isomer. These are lipophilic precursors for cyclodextrin derivatives having one reactive functional group and an enlarged molecular cavity formed by partial methylation of the secondary hydroxyl face. The direct monoalkylation route of the secondary face leaves the structure of the cavity intact, while this is distorted in the route using nucleophilic epoxide opening. Two amino-functionalized cyclodextrins were used for coupling reactions with a monofunctionalized calix[4]arene. In this way water-soluble cyclodextrin derivatives could be obtained of which the secondary faces were flexibly capped with a calix[4]arene moiety.

Introduction

Cyclodextrins **1**, a group of naturally occurring cyclic D-glucose oligomers, play an important role in supramolecular chemistry since they are soluble in water, contain a well-defined hydrophobic molecular cavity, and can be modified with various functional groups.[1] Especially the first two properties have given cyclodextrins widespread use as basis for inclusion compounds in analytical chemistry,[2] the food industry,[3] and the pharmaceutical industry,[4] since included guest molecules are protected from the environment. Chemical modifications of cyclodextrins bring about changes in the shape of the macrocyclic structure, in the size of the molecular cavity, in the ability to form hydrogen bonds, and in other physical properties. Thus, the binding properties and the catalytic behavior may be controlled by the introduction of functional groups. Especially in the late 1970s and the early 1980s, many reports were published on regio- and chemoselective introduction of functional groups by modifications of primary and, to a lesser extent, of secondary hydroxyl groups of cyclodextrins.[5] However, poor results in chemoselectivity, regioselectivity, and purification of the newly synthesized cyclodextrin derivatives appeared to be the major problems associated with this work.[6] The still on-going fundamental research toward the introduction of generally applicable functional groups, as is indicated by many recent publications in this field,[7] underlines the problems encountered in the development of standard procedures for the functionalization of cyclodextrins. The lack of these standards has certainly retarded the development of cyclodextrin-based molecular receptors.

Chart 1



The synthesis of selectively, chemically modified cyclodextrins is possible by using the differences in reactivity of the three types of hydroxyl groups.[8] The C(6)-hydroxyls, being primary alcohols, are more nucleophilic compared to the C(2)- and C(3)-hydroxyls which are secondary alcohols. The two types of secondary hydroxyls

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(1) Szejtli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, 1988.
(2) (a) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (b) Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457. (c) Schurig, V.; Nowotny, H.-P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939. (d) Cabrere, K.; Schwinn, G. *Kontakte (Darmstadt)* **1989**, 3. (e) Armstrong, D. W.; Jin, H. L. *Anal. Chem.* **1987**, *59*, 2237. (f) Armstrong, D. W.; Jin, H. L.; Pitha, J. *Anal. Chem.* **1990**, *62*, 217. (g) Armstrong, D. W.; Alak, A.; Bui, K.; DeMond, W.; Ward, T. *J. Incl. Phenom.* **1984**, *2*, 533.
(3) (a) Hashimoto, H. *Proceeding of the 4th International Symposium on Cyclodextrins*; Huber, O., Szejtli, J., Eds.; Kluwer Academic Publishers: Dordrecht, 1988; p 533. (b) Duchêne, D.; Wouessidjewe, D. *J. Coord. Chem.* **1992**, *27*, 223.
(4) Bekers, O.; Uijtendaal, E. V.; Beijnen, B. H.; Bult, A.; Undenberg, W. J. M. *Drug. Dev. Ind. Pharm.* **1991**, *17*, 1503.
(5) Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417.
(6) Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *J. Org. Chem.* **1991**, *56*, 7274.
(7) For a recent review see: Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.
(8) Rao, C. T.; Pitha, J. *Carbohydr. Res.* **1991**, *210*, 209.

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have different reactivity, primarily because of their different role in the belt of hydrogen bonds at the secondary face of the cyclodextrin. Temperature-dependent NMR studies indicate that in the interglycosidic hydrogen bond between C(2)-OH and C(3)-OH of two adjacent glucose units, the C(3)-OH is the predominant proton donor.[9] This leads to a more acidic C(2)-hydroxyl with a pK_a-value[10] of circa 12.1, and a less acidic C(3)-hydroxyl.[11] Cyclodextrin derivatives in which the hydroxyls of one, two, or all three types are modified uniformly have been reported. The reason for such modifications may be the enhancement of the solubility in water (*e.g.* by methylation[12]) or in organic solvents (*e.g.* by alkylation,[13] acylation,[14] or silylation[15]), and the activation of certain hydroxyls by the introduction of good leaving groups for further functionalization (*e.g.* by sulfonylation of the primary face[16]).

Selective introduction of functional groups to cyclodextrins has been extensively studied for the primary hydroxyl face of cyclodextrins, but less well for the secondary hydroxyl face. However, functionalization of the secondary hydroxyl face of cyclodextrins is important in view of applications of cyclodextrins as catalytically active compounds.[17] In that case, the catalytic functions can be attached to the more open face of the toroidal cyclodextrin molecule instead of to the narrow face of the primary side.

As for the primary hydroxyl face of cyclodextrins,[18] the most commonly used method for selective introduction of one functional group at the secondary face is via activation of one hydroxyl group by sulfonylation. Selective sulfonylation of one C(2)-hydroxyl of β-cyclodextrin was reported by Ueno and Breslow[19] using 3-(nitrophenyl)-4-toluenesulfonate as sulfonating reagent. Murakami *et al.*[20] described an alternative method for the regioselective tosylation of a C(2)-hydroxyl of cyclodextrins using di-*n*-butyltin oxide. A recent, convenient strategy for selective functionalization of C(2)-hydroxyls of cyclodextrins involves deprotonation of the more acidic C(2)-hydroxyl with sodium hydride, affording a cyclodextrin oxyanion which can react with electrophiles like 4-toluenesulfonyl chloride (circa 30% yield) and *N*-methyl-4-(chloromethyl)-2-nitroaniline (35%), to give exclusively the C(2)-substituted cyclodextrins.[21]

Substitution of secondary C(2)-sulfonates by nucleophiles does not take place directly, but via nucleophilic ring opening of the manno-epoxide which is formed by intramolecular substitution of the sulfonate group by a neighboring C(3)-hydroxyl.[22,23] The cyclodextrin manno-epoxide obtained in this way is known to be opened with various nucleophiles.[23-28]

Only very few examples are known of the introduction of a single functional group at the secondary face of cyclodextrins without prior sulfonylation. The water-soluble heptakis(2,6-di-*O*-methyl)-β-cyclodextrin[29] (DIMEB) can be modified at one of the C(3)-hydroxyls under strongly basic conditions for deprotonation. In this way a chiral ferrocenylphosphine ligand,[30] imidazole,[31] and a metalloporphyrin[32] have been attached to DIMEB by attack of a nucleophilic C(3)-oxyanion to an electrophilic spacer linked to the functional groups. Under relatively mild basic conditions (0.37 M aqueous NaOH), β-cyclodextrin can be selectively 2-hydroxypropylated at one of the C(2)-hydroxyl positions.[33] Finally, the fluorescent pyrenecarbonyl group has been attached directly (aselectively) to the secondary face of γ-cyclodextrin by a transacylation reaction using 4-(nitrophenyl)-1-pyrenecarboxylate as acyl donor.[34]

An important problem in the synthesis of secondary face monofunctionalized cyclodextrins remains the separation of the reaction mixtures. Because of the presence of many, more or less equally reactive hydroxyl groups, chemo- and regioselective monofunctionalization occurs only rarely. Consequently, comprehensive and scale-

(9) (a) Gillet, B.; Nicole, D. J.; Delpuech, J. J. *Tetrahedron Lett.* **1982**, *23*, 65. (b) Yamamoto, Y.; Inoue, Y. *J. Carbohydr. Chem.* **1989**, *8*, 29.

(10) (a) Gelb, R. I.; Schwartz, L. M.; Bradshaw, J. J.; Laufer, D. A. *Bioorg. Chem.* **1980**, *9*, 299. (b) Gelb, R. I.; Schwartz, L. M.; Laufer, D. A. *Bioorg. Chem.* **1982**, *11*, 274.

(11) Casu, B.; Reggiani, M.; Gallo, G. G.; Vigevani, A. *Tetrahedron* **1968**, *24*, 803.

(12) Szejtli, J. *J. Incl. Phenom. Mol. Recogn.* **1992**, *14*, 25.

(13) (a) Wenz, G. *Carbohydr. Res.* **1991**, *214*, 257. (b) Wenz, G.; von der Bey, E. *Proceedings of the 4th International Symposium on Cyclodextrins*; Huber, O., Szejtli, J., Eds.; Kluwer Academic Publishers: Dordrecht, 1988; p 133. (c) Hochgesand, A.; Wenz, G. *Minutes of the 5th International Symposium on Cyclodextrins*; Duchêne, D., Ed.; Editions de Santé: Paris, 1990; p 322. (d) Bates, P. S.; Parker, D.; Green, B. N. *J. Chem. Soc., Chem. Commun.* **1993**, 693. (e) Bates, P. S.; Parker, D.; Patti, A. F. *J. Chem. Soc. Perkin Trans. 2* **1994**, 657.

(14) Komiyama, M.; Yamamoto, H.; Hirai, H. *Chem. Lett.* **1984**, 1081.

(15) (a) Takeo, K.; Uemura, K.; Mitoh, H. *J. Carbohydr. Chem.* **1988**, *7*, 293. (b) Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203. (c) Fügedi, P. *Carbohydr. Res.* **1989**, *192*, 366. (d) Michalski, T. J.; Kendler, A.; Bender, M. L. *J. Incl. Phenom.* **1983**, *1*, 125. (e) Wife, R. L.; Reed, D. E.; Leworthy, D. P.; Barnett, D. M.; Regan, P. D.; Volger, H. C. *Advances in Inclusion Science, Proceedings of the 1st International Symposium on Cyclodextrins*; Szejtli, J., Ed.; Akademiai Kiado: Budapest, 1982; p 301.

(16) (a) Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *J. Org. Chem.* **1991**, *56*, 7274 and references cited herein. (b) Fujita, K.; Ohta, K.; Masunari, K.; Obe, K.; Yamamura, H. *Tetrahedron Lett.* **1992**, *33*, 5519. (c) Yamamura, H.; Ezuka, T.; Kawase, Y.; Kawai, M.; Butsugan, Y.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1993**, 636. (d) Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 80. (e) Yamamura, H.; Kawase, Y.; Kawai, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 585.

(17) (a) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242. (b) VanEtten, R. L.; Clowes, G. A.; Sebastian, J. F.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253. (c) Rama Rao, K.; Srinivasan, T. N.; Bhanumathi, N.; Sattur, P. B. *J. Chem. Soc., Chem. Commun.* **1990**, 10.

(18) (a) Melton, L. D.; Slessor, K. N. *Carbohydr. Res.* **1971**, *18*, 29. (b) Brown, S. E.; Coates, J. H.; Coghlan, D. R.; Easton, C. J.; van Eyk, S. J.; Janowski, W.; Lepore, A.; Lincoln, S. F.; Luo, Y.; May, B. L.; Schiesser, D. S.; Wang, P.; Williams, M. L. *Aust. J. Chem.* **1993**, *46*, 953. (c) Matsui, Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3030. (d) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860. (e) Wang, Y.; Ikeda, T.; Ueno, A.; Toda, F. *Chem. Lett.* **1992**, 863.

(19) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451.

(20) Murakami, T.; Hatara, K.; Morimoto, S. *Tetrahedron Lett.* **1987**, *28*, 321.

(21) Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275.

(22) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390.

(23) Murakami, T.; Harata, K.; Morimoto, S. *Chem. Lett.* **1988**, 553.

(24) Ikeda, H.; Nagano, Y.; Du, Y.; Ikeda, T.; Toda, F. *Tetrahedron Lett.* **1990**, *31*, 5045.

(25) Mortellaro, M. A.; Czarnik, A. W. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1635.

(26) Rama Rao, K.; Srinivasan, T. N.; Bhanumathi, N.; Sattur, P. B. *J. Chem. Soc., Chem. Commun.* **1990**, 10.

(27) Akkaya, E. U.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.

(28) Fornasier, R.; Scarpa, E.; Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Incl. Phenom. Mol. Recogn.* **1992**, *14*, 205.

(29) (a) Szejtli, J. *J. Incl. Phenom. Mol. Recogn.* **1992**, *14*, 25. (b) Szejtli, J. *J. Incl. Phenom.* **1983**, *1*, 135.

(30) Sawamura, M.; Kitayama, K.; Itp, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1829.

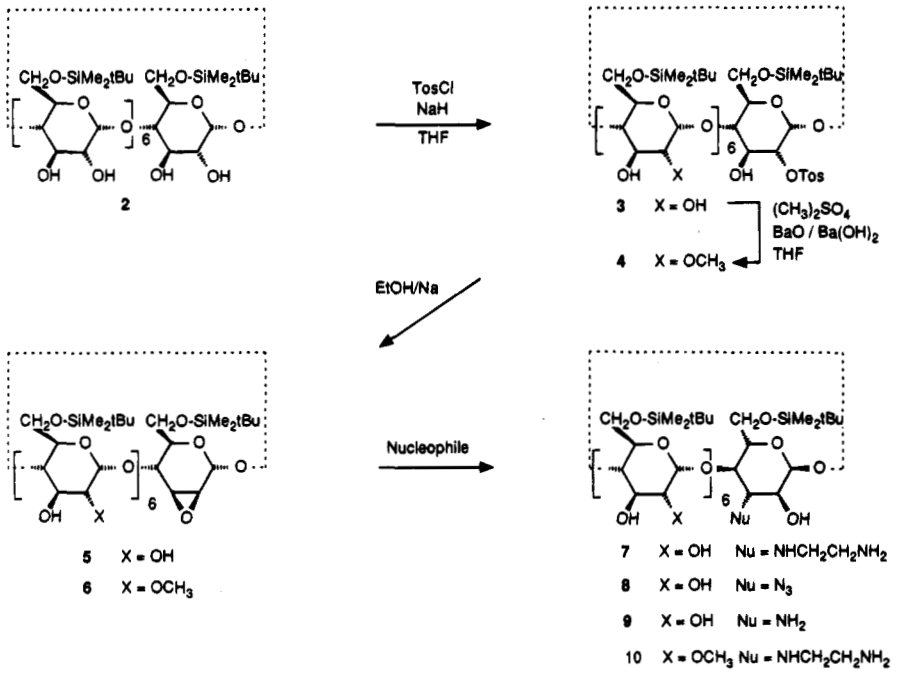
(31) (a) Ikeda, H.; Ikeda, T.; Toda, F. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1581. (b) Ikeda, H.; Kojin, R.; Yoon, C.-J.; Ikeda, T.; Toda, F. *J. Incl. Phenom. Mol. Recogn.* **1989**, *7*, 117.

(32) (a) Weber, L.; Imiolczyk, I.; Haufe, G.; Rehorek, D.; Hennig, H. *J. Chem. Soc., Chem. Commun.* **1992**, 301. (b) Weber, L.; Hommel, R.; Behling, J.; Haufe, G.; Hennig, H. *J. Am. Chem. Soc.* **1994**, *116*, 2400.

(33) Rao, C. T.; Lindberg, B.; Lindberg, J.; Pitha, J. *J. Org. Chem.* **1991**, *56*, 1327.

(34) Suzuki, I.; Ueno, A.; Osa, T. *Chem. Lett.* **1989**, 2013.

Scheme 1



limited purification methods using selective precipitation, recrystallization, reverse phase chromatography, and size exclusion chromatography are often needed, and moderate yields are unavoidable. The use of partially silylated cyclodextrins, in which the primary hydroxyls are converted to silyl ethers, turned out to be an important step for better defined synthetic routes to selectively modified cyclodextrins.[15] Silylated cyclodextrins are soluble in various organic solvents, can be purified on a large scale by common silica gel chromatography, and open possible routes to differentiate between the remaining C(2)- and C(3)-hydroxyls.[15,35,36] The first example was given by Pregel and Buncel[35] in their detailed report on the synthesis and characterization of mono(2-*O*-tosyl)-heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **3**.

In this paper we report the monofunctionalization of cyclodextrins at the secondary face by two methods. In the first method an amino-functionalized group is introduced at the C(3)-position of the cyclodextrin by prior tosylation of a secondary hydroxyl group of silylated cyclodextrin and subsequent nucleophilic ring-opening of the intermediate cyclodextrin manno-epoxide. The second method proceeds by direct and selective introduction of functional groups to the secondary hydroxyl face of silylated cyclodextrins via monoalkylation of the C(2)-oxyanion, leaving the configuration of all glucose units in the cyclodextrin intact. The second method was also followed in the synthesis of a secondary face tethered cyclodextrin dimer and for the synthesis of two novel cyclodextrin-calix[4]arene host molecules. For the latter compounds, silylated β-cyclodextrins, functionalized with an *o*- or *p*-aminoxylyl spacer, were coupled to a calix[4]-arene monoformyl derivative by reductive amination. After desilylation of the cyclodextrin residues two water-soluble cyclodextrin-calix[4]arene receptors were obtained of which the opening of the hydrophilic cavity at the secondary hydroxyl face is flexibly capped by the aryl residues of the calix[4]arene moiety.

Results and Discussion

Monofunctionalized Cyclodextrins. The synthesis of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **2** was performed by a modified procedure of Pregel *et al.*[35] Dry β-cyclodextrin was reacted in doubly distilled pyridine with 10 equiv of *tert*-butyldimethylsilyl chloride at room temperature for 16 h. After silica gel column chromatography, pure **2** was isolated in 82% yield. Silylation of α-cyclodextrin was performed according to Takeo *et al.*[15] by a reaction with 6.6 equiv of *tert*-butyldimethylsilyl chloride in dry DMF with imidazole as nitrogen base. Hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin was obtained in 88% yield after silica gel chromatography. The pure monotosylate **3** of silylated β-cyclodextrin could be obtained in 32% yield[37] after reaction of **2** with tosyl chloride and sodium hydride in THF and purification by column chromatography, besides 50% recovered starting material (Scheme 1). Monotosylate **3** was characterized as the C(2)-tosylate by ^{13}C NMR spectroscopy in accordance with previous reports.[19,23,35] Monotosylate **3** could be converted into the manno-epoxide **5** in 88% yield by reaction with sodium ethoxide in refluxing dry ethanol.[35] Nucleophilic attack on the manno-epoxide occurs exclusively at the C(3)-position because of steric reasons[22,23] and was performed with ethylenediamine, lithium azide, and ammonia. Epoxide opening of **5** with ethylenediamine was achieved in quantitative yield by reaction of **5** in refluxing ethanol in the presence of an excess of the nucleophile. Treatment of the epoxide with lithium azide in refluxing ethanol, followed by reduction of the azide with tri-*n*-butyltin hydride and azobis(isobutyronitrile), gave compound **9** in 85% yield. β-Cyclodextrin amine **9** could also be obtained in 83% yield via a shorter route by treatment of manno-epoxide **5** with an anhydrous solution of ammonia in dry ethanol.[37] β-Cyclodextrin derivatives with an increased water solubility could be obtained by partial

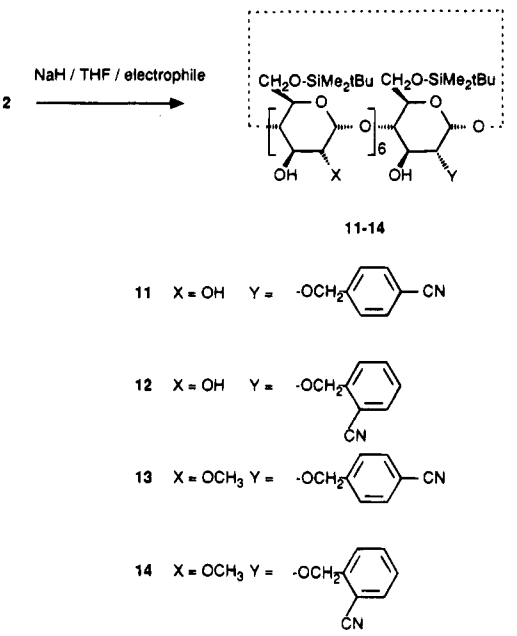
(35) Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130.
(36) Coleman, A. W.; Zhang, P.; Parrot-Lopez, H.; Ling, C.-C.; Miocque, M.; Mascrier, L. *Tetrahedron Lett.* **1991**, *32*, 3997.
(37) Venema, F.; Baselier, C. M.; Van Dienst, E.; Ruël, B. H. M.; Feiters, M. C.; Engbersen, J. F. J.; Reinhoudt, D. N.; Nolte, R. J. M. *Tetrahedron Lett.* **1994**, *35*, 1773.

methylation.[29] Methylation of the C(2)-hydroxyls of silylated, monofunctionalized β-cyclodextrins and subsequent removal of the silyl protecting groups give the possibility to obtain C(2)-methylated, monofunctionalized β-cyclodextrin derivatives. Under weakly basic conditions, the silylated β-cyclodextrin monotosylate **3** does not react to the manno-epoxide **5**, but only gives deprotonation of the remaining C(2)-hydroxyls. Thus, mono(2-*O*-tosyl)-heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **3** could be methylated at the remaining C(2)-oxygens by a reaction with dimethyl sulfate in THF using a mixture of barium oxide and barium hydroxide as the base. Mono(2-*O*-tosyl)-hexakis(2-*O*-methyl)-heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **4** was obtained in 89% yield after column chromatography (Scheme 1). The product was characterized by FAB mass spectrometry and NMR spectroscopy. FAB-MS showed that compound **4** was the major product, with small signals (<5%) for over- and undermethylated products.[38] The ^{13}C NMR showed an upfield shift of approximately 9 ppm for the C(2)-atoms after methylation, in accordance with the chemical shift reported in literature for DIMEB.[39] Compound **4** could be converted quantitatively into the corresponding manno-epoxide **6**. Reaction of this epoxide with excess of lithium azide in refluxing ethanol did not give ring opening; the starting compound was fully recovered. Probably the increased hydrophobic character of the secondary hydroxyl face due to the partial methylation hampers the nucleophilic attack of the azide anion. However, opening of the epoxide was achieved with ethylenediamine as nucleophile, yielding 75% of **10**.

In the former reactions, the presence of the silyl groups at the primary face of β-cyclodextrin gives rise to more easy modification of the secondary face and better purification of the cyclodextrin derivatives. However, the functionalization via the manno-epoxide is accompanied by a deformation of the cyclodextrin cavity since the reacting glucose unit is changed in configuration at the C(2) and C(3) atoms, giving a conformational change of this modified saccharide unit. This conformational change has been previously described by Breslow and Czarnick[22] and is recently fully confirmed by Lawrence and coworkers.[39] The influence of this deformed molecular cavity on the complexing behavior of cyclodextrins has not been established yet. However, by nucleophilic attack of a C(2) mono-oxyanion of silylated cyclodextrins to an electrophilic compound, cyclodextrin derivatives with a nondistorted cavity will be obtained (Scheme 2).

Reaction of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **2** with 1.5 equiv of sodium hydride and 1.2 equiv of α-bromo-*p*-toluonitrile in refluxing THF, gave mono(2-*O*-(α-(*p*-toluonitrile)))-heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **11** in 35% yield, after silica gel flash column chromatography, besides starting material (circa 50%) and low amounts of higher benzylated cyclodextrin derivatives which could easily be separated. A large downfield shift can be seen in the ^{13}C NMR spectrum of **11** ($CDCl_3$) for the modified C(2)-atom (circa 7 ppm) in accordance with the results of Ueno and Breslow[19] and proven correctly for a cyclodextrin modified with a functionalized benzyl group by Rong and D'Souza.[21] For the neighboring carbon atoms, only a small upfield shift (1 ppm) was observed for C(1) of the functionalized glucose moiety. Other, smaller changes in the carbohydrate region can be attributed to the asymmetry of the modified β-cyclodextrin. The spectrum showed further signals for the symmetric aromatic substituent at 142.7, 132.3, 129.2, and 112.2 ppm and for the nitrile carbon atom at δ 118.4 ppm. The proton NMR spectrum of **11** showed clearly the aromatic protons at 7.62 and 7.42 ppm (dd, $J = 8.3$ Hz, 4H) and the benzylic protons at 5.21 ppm (s, 2H). An upfield shift for some of the hydroxyl protons, probably due to disruption of the belt of intramolecular hydrogen bonds at the secondary face, and strong overlap of the other carbohydrate protons, render the spectrum very complex. A similar monofunctionalization of **2** was performed with α-bromo-*o*-toluonitrile to give the *ortho*-derivative **12**. After methylation of the remaining C(2)-hydroxyls of the nitrile-modified cyclodextrins **11** and **12**, according to the procedure described above for tosylated β-cyclodextrin **4**, nitriles **13** and **14** could be obtained in 90% yield after silica gel chromatography.

Scheme 2



The reduction of the nitrile functions of **13** and **14** to primary amines was successfully achieved with borane as the reducing agent. Reduction with lithium aluminum hydride led to partial decomposition of the cyclodextrin. Thus, reaction of the nitriles with a large excess of borane (as the dimethyl sulfide complex)[40] in THF (60 °C, overnight) gave the primary amines **15** and **16** in satisfactory yields (Chart 2). Also the non-methylated analogs could be obtained by the same procedure from reduction of **11** and **12**, but the resulting amines could not be obtained in a satisfactory pure form for elemental analysis by column chromatography. Going from the nitrile to the amine, a distinct change in the ^1H NMR spectrum is observed in the aromatic region. The double doublet of the aromatic protons observed for the nitrile coincide in case of the amine.

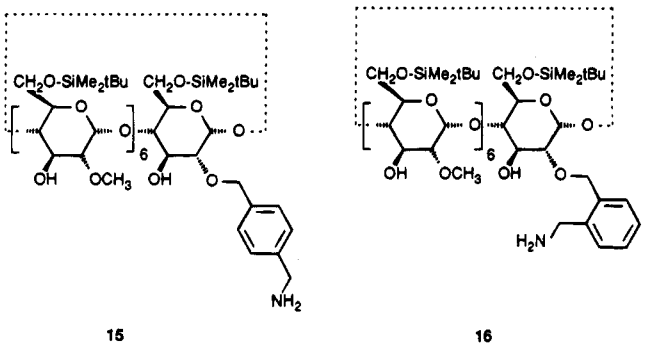
Similar reactions as described above for β-cyclodextrin were also successful for α-cyclodextrin analogs. Starting from hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin[15a] reaction with α-bromo-*p*-toluonitrile gave **11(α)** in 43% yield. The subsequent methylation yielded **13(α)** in 83%, and reduction of this compound to **15(α)** proceeded in

(38) Spencer, C. M.; Stoddart, J. F.; Zarzycki, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1323.

(39) Jiang, T.; Sukumaran, D. K.; Soni, S.-D.; Lawrence, D. S. *J. Org. Chem.* **1994**, *59*, 5149.

(40) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Synthesis* **1981**, 605.

Chart 2



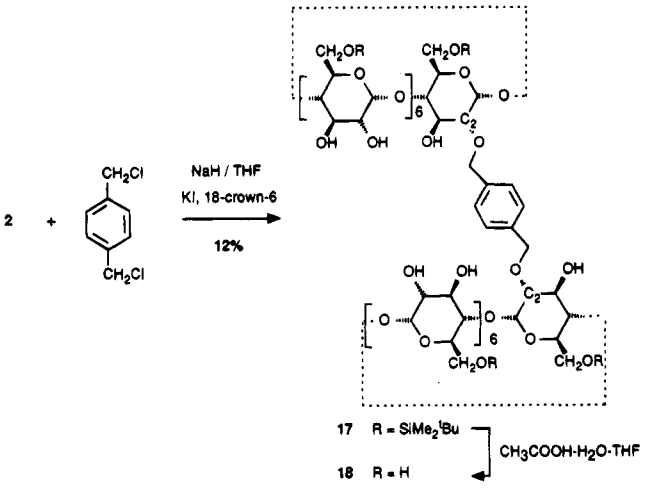
15 16

79% yield. However, the methylation of the remaining C(2)-hydroxyls after the monofunctionalization appeared to be less selective in this case. According to FAB-MS higher fractions of over- and undermethylated products were obtained which could not be separated by silica gel chromatography. The lack of selectivity for the C(2)-hydroxyls in the methylation reaction and, more in general in alkylation reactions,[41] is probably due to the higher flexibility of the hydroxyl groups at the secondary face of α-cyclodextrin. Because of the macrocyclic strain in α-cyclodextrin only four of the six possible hydrogen bonds are formed between neighboring C(2)- and C(3)-hydroxyl groups.[42] For this reason the C(2)- and C(3)-hydroxyls are better available for modification and differ less in reactivity, compared to the secondary hydroxyls in β-cyclodextrin which form a close, tight belt of hydrogen bonds.

Cyclodextrin Dimers. Various cyclodextrin dimers coupled with their primary hydroxyl faces have been reported in literature.[43] However, only a few examples are known of cyclodextrin dimers coupled with their secondary hydroxyl faces.[37,44] Some of the cyclodextrin dimers described in literature have shown to form complexes with large hydrophobic substrates with higher binding constants compared to the parent cyclodextrins due to the so-called chelate effect.[45]

On the basis of direct monofunctionalization of silylated cyclodextrin via selective deprotonation of a C(2)-hydroxyl, followed by coupling with an electrophilic compound, novel cyclodextrin dimers could be obtained in which the secondary faces of two cyclodextrins are connected by short xylyl spacers. The silylated reaction products could be easily purified and characterized and the cyclodextrin dimers which are obtained after desilylation of the primary hydroxyl groups are well soluble in water. By this procedure cyclodextrin dimers were obtained of which the conformation of the molecular cavities is retained.

Scheme 3



Thus, reaction of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **2** with 1.5 equiv of sodium hydride in refluxing THF with catalytic amounts of potassium iodide and 18-crown-6, followed by the addition of 0.5 equiv of α,α′-dichloro-*p*-xylene under highly diluted conditions, gave the cyclodextrin dimer **17** after silica gel column chromatography, in 12% yield, besides recovery of unreacted **2** (Scheme 3). Similarly, the *o*- and *m*-xylyl linked cyclodextrin dimers were obtained. Cyclodextrin dimer **17** was characterized by NMR spectroscopy and FAB-MS. The mass spectrum shows the dimer (MW 3,965), but the most prominent signal appears at MW 2,032 which can be assigned to the cleavage product in which one benzyl ether bond of the dimer is cleaved.

The final step in the synthesis of the water-soluble cyclodextrin dimers is the deprotection of the primary hydroxyls of the cyclodextrin moieties. Silylated cyclodextrin derivatives are usually deprotected with tetra-*n*-butylammonium fluoride (TBAF),[46] followed by selective precipitation of the cyclodextrins with methanol. However, in the case of **17** the desilylated cyclodextrin dimer **18** could not be separated from the TBAF salt by precipitation. Ion-exchange chromatography dramatically reduced the yield of the reaction product. A better alternative for the fluoride-mediated desilylation appeared to be the cleavage of the silyl ethers in an acetic acid–THF–water mixture (3:1:1, 80 °C for 12 h).[46] According to ^{1}H NMR, all silyl groups were removed after this step, but some of the hydroxyls had been acetylated. Additional treatment of the reaction product with 50% saturated NH_3 solution in MeOH[47] yielded pure **18** quantitatively.

Cyclodextrin-Calix[4]arene Receptors. As described above, partially silylated cyclodextrins can be

(41) For a detailed study of the (over)methylation of α- and β-cyclodextrins see: Tanimoto, T.; Kubota, Y.; Nakanishi, N.; Koizumi, K. *Chem. Pharm. Bull.* **1990**, *38*, 318–322. The possibility to separate the pure hexakis(2,6-di-*O*-methyl)-α-cyclodextrin and pentakis(2,6-di-*O*-methyl)mono(2,3,6-tri-*O*-methyl)-α-cyclodextrin from a crude reaction mixture by benzoylation, column separation, and debenzoylation is described in Alston, D. R.; Ashton, P. R.; Lilley, T. H.; Stoddart, J. F.; Zarzycki, R.; Slawin, A. M. Z.; Williams, D. J. *Carbohydr. Res.* **1989**, *192*, 295–281.

(42) (a) Sundararajan, P. R.; Rao, V. S. R. *Carbohydr. Res.* **1970**, *13*, 351. (b) Rees, D. A. *J. Chem. Soc.* **1970**, *B*, 877.

(43) (a) Fujita, K.; Ejima, S.; Imoto, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1277. (b) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296. (c) Coates, J. H.; Easton, C. J.; van Eyk, S. J.; Lincoln, S. F.; May, B. L.; Whalland, C. B.; Williams, M. L. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2619. (d) Petter, R. C.; Sikorski, C. T.; Waldeck, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 2325. (e) Wang, Y.; Ueno, A.; Toda, F. *Chem. Lett.* **1994**, 167. (f) Breslow, R. *Pure Appl. Chem.* **1990**, *62*, 1859. (g) Breslow, R. *Supramolecular Chemistry*; Balzani, V., De Cola, L., Eds.; Kluwer Academic Publishers: Dordrecht, 1992; p 411–428. (h) Breslow, R.; Chung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659. (i) Breslow, R. *Supramol. Chem.* **1993**, *1*, 111. (j) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1992**, *114*, 5882. (k) Deschenaux, R.; Greppi, A.; Ruch, T.; Kriemler, H.-P.; Raschdorf, F.; Ziessel, R. *Tetrahedron Lett.* **1994**, *35*, 2165.

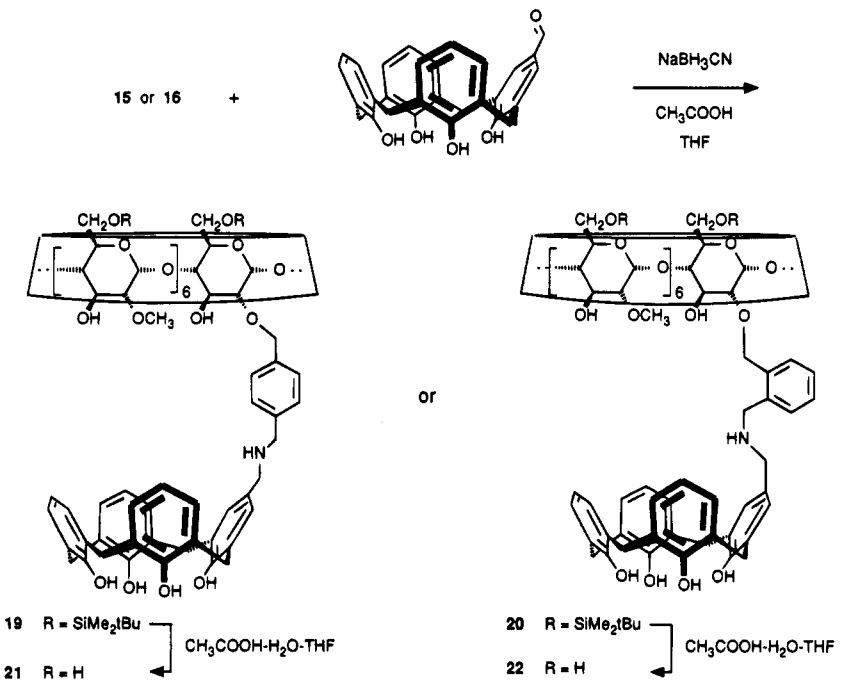
(44) (a) Harada, A.; Furue, M.; Nozakura, S. *Macromolecules* **1976**, *9*, 701. (b) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296. (c) Breslow, R. *Supramol. Chem.* **1993**, *1*, 111.

(45) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353 and references cited herein.

(46) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(47) Neilson, T.; Werstiuk, E. S. *Can. J. Chem.* **1971**, *49*, 493.

Scheme 4



modified in acceptable yields with amino-containing functional groups in such a way that the conformation of the macrocyclic cyclodextrin structure is not changed. In order to obtain cyclodextrins which are flexibly coupled at the secondary hydroxyl face,[48] the amino-functionalized cyclodextrin derivatives **15** and **16** were coupled to monoformylated calix[4]arene (25,26,27,28-tetrahydroxycalix[4]arene-5-carboxaldehyde)[49] by reductive amination (Scheme 4). In this coupling reaction sodium cyanoborohydride was used as the reducing agent in THF with a low amount of acetic acid to catalyze the intermediate imine formation. The coupled products **19** and **20** could be isolated in reasonable yields after flash silica gel chromatography. The FAB-MS of these coupled products showed various metastable cleavage signals besides the signal for the calculated molecular mass.

Like for the cyclodextrin dimer **17** the desilylation of the cyclodextrin-calix[4]arene receptors **19** and **20** proceeded most easily in acetic acid–THF–water mixture (3:1:1), followed by the ammonia-mediated workup procedure to obtain the water-soluble receptors **21** and **22**.

Concluding Remarks

The use of partially silylated cyclodextrins, in which the primary hydroxyl groups have been converted into silyl ethers, appeared to be an essential step to obtain well-defined cyclodextrin derivatives, selectively modified at the secondary hydroxyl face. Due to the solubility of these silylated cyclodextrins in organic solvents, various monofunctionalized silylated cyclodextrins could be obtained on gram-scale after flash silica gel chromatography. Two approaches have been applied for the monofunctionalization of the secondary hydroxyl face of the lipophilic silylated cyclodextrins. The first approach followed a synthetic route, which was already known for the functionalization of the secondary face of hydrophilic cyclodextrins, and involved prior tosylation of one of the secondary hydroxyls of the silylated cyclodextrin followed by a ring opening of the intermediate manno-epoxide by various nucleophiles. In this route the functional group is introduced at one of the C(3)-atoms, and the epoxide-opening results in a chair inversion of the modified saccharide residue and therefore in a structural change of the molecular cavity. The loss of symmetry found in the first route is clearly indicated by the very complicated NMR spectra of cyclodextrin derivatives obtained in this way, caused by extensive overlap of chemical shifts. The second route to monofunctionalization proceeded by direct monoalkylation of a C(2)-hydroxyl group under basic conditions and this reaction does not distort the conical structure of the cyclodextrin cavity. For example, monobenzylation of the secondary face with α-bromotoluonitrile yields a cyclodextrin derivative of which the nitrile function can be easily reduced, giving an amino-functionalized cyclodextrin which can be further functionalized.

The silylated β-cyclodextrin derivatives **15** and **16** could be coupled to a monoformylated calix[4]arene by reductive amination. After deprotection of the silylated primary hydroxyls of the cyclodextrin moiety two novel water-soluble cyclodextrin-calix[4]arene host molecules were obtained of which the entries at the secondary hydroxyl face of the hydrophobic cavities are shielded by flexible calix[4]arene moieties. The strongly enhanced complexation properties of these cyclodextrin-calixarenes with the fluorescent guests 1-anilino-8-naphthalenesulfonate and 2-*p*-toluidino-6-naphthalenesulfonate have been recently reported.[50]

Experimental Section

General. Mass spectra were obtained using *m*-nitrobenzyl alcohol (NBA) or glycerol as matrix. Elemental analyses are

(48) A β-cyclodextrin–calix[4]arene derivative in which the primary side of β-cyclodextrin is coupled via an ethylenediamine spacer with the lower rim of tetrakis(hydroxycarbonylmethoxy)calix[4]arene has been reported recently: D'Alessandro, F.; Gulino, F. G.; Impellizzeri, G.; Pappalardo, G.; Rizzarelli, E.; Sciotto, D.; Vecchio, G. *Tetrahedron Lett.* **1994**, *35*, 629.

(49) Van Dienst, E. Ph.D. Thesis: University of Twente, 1994, Chapter 4.

(50) Van Dienst, E.; Ruel, B. H. M.; Von Piekartz, I.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 1151.

not corrected for possible inclusion of solvent molecules. Melting points are uncorrected. All solvents were distilled prior to use. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl. Other reagents were of reagent grade and used without further purification. All reactions were carried out in an argon atmosphere. Chromatographic separations were performed on silica gel 60 (SiO_2, E. Merck, 0.040–0.063 mm, 230–240 mesh). Thin layer chromatography was performed on TLC aluminum sheets with silica gel $60F_{254}$. The cyclodextrin spots were visualized by dipping the sheets with 5% sulfuric acid in ethanol, followed by heating of the sheets.

Mono(2^A,3^A-anhydro)hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-(2^A*S*)-*β*-cyclodextrin (6). A solution of silylated cyclodextrin-tosylate **3**[37] (0.50 g, 0.24 mmol), dimethyl sulfate (0.5 mL, 5.2 mmol), barium oxide (0.5 g, 3.2 mmol), and barium hydroxide (0.5 g, 3.0 mmol) in THF (10 mL) was stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in chloroform (25 mL) and washed with 2 N HCl (2 × 25 mL) and water (25 mL). The organic phase was heated to reflux for 4 h with 1 N NaOH (15 mL) and methanol (5 mL). The organic phase was separated and washed with water until the water layer became pH-neutral, and finally with saturated aqueous NaCl (25 mL). After drying over $MgSO_4$ and filtration, the filtrate was concentrated in vacuo yielding methylated tosylate **4** in 96% (0.49 g, 0.23 mmol), mp 170–171 °C. The FAB mass spectra indicated small amounts of over- and undermethylated products. No signals from these products appeared in the ^1H NMR spectra, indicating that at least 95% of the product was the hexamethylated compound **4**: ^1H NMR ($CDCl_3$) δ 7.83 (t, J = 8.3 Hz, 2H), 7.28 (m, 2H), 5.19–4.86 (m, 14H), 4.2–3.3 (m, 53H), 3.55 (s), 3.15 (br d, 7H), 2.39 (s, 3H), 0.82 (m, 63H), 0.02 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 144.6, 133.6, 129.8, 129.3, 128.4, 128.2, 100.6–100.4, 99.5, 82.3–81.8, 79.7, 73.4–72.4, 71.9–71.6, 61.9–61.2, 60.4–59.9, 25.9, 21.6, 18.2, −5.1, −5.2; FAB MS (NBA) m/z calcd for $C_{97}H_{186}O_{37}SSi_7$: 2171.1, measured (+ve) 2195.1 (M + Na^+). This compound was further reacted for the formation of the epoxy derivative **6**. Therefore, a solution of **4** (0.25 g, 0.12 mmol) and sodium ethoxide (1.2 mL of a 0.1 M solution of sodium in ethanol, 0.12 mmol) in ethanol (10 mL) was heated to reflux for 2.5 h. The reaction product was precipitated by adding ice-cold water. After filtration, the residue (0.31 g) was purified by flash chromatography (SiO_2, CH_2Cl_2:CH_3OH = 95:5, R_f = 0.29) giving **6** in 83% yield (0.20 g, 0.10 mmol); mp 182 °C; ^1H NMR ($CDCl_3$) δ 5.12–4.73 (m, 13H), 3.96–3.39 (m, 53H), 3.67 (s), 3.18–3.05 (m, 7H), 0.85 (m, 63H), 0.03 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 102.6–100.0, 82.8–81.5, 74.3–73.2, 71.9–71.6, 61.6, 60.1, 25.9, 18.3, −5.2; FAB MS (NBA) m/z calcd for $C_{90}H_{178}O_{34}Si_7$ 1999.0, measured (+ve) 2022.9 (M + Na^+). Anal. Calcd for $C_{90}H_{178}O_{34}Si_7{\cdot}H_2O$: C 53.54, H 8.99. Found: C 53.37, H 8.99.

Mono(3^A-((2-aminoethyl)amino)-3^A-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-(2^A*S*),(3^A*S*)-*β*-cyclodextrin (7). A solution of the manno-epoxide **5**[35] (0.34 g, 0.18 mmol) in dry ethylenediamine (20 mL) was heated to reflux for 16 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (25 mL) and washed with water (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic phase was dried over $MgSO_4$, and after filtration, the filtrate was concentrated in vacuo giving **7** in 98% yield (0.32 g, 0.16 mmol); mp > 200 °C dec; ^1H NMR ($CDCl_3$) δ 4.88, 4.86 (br d, 6H), 4.77, 4.76 (d, 1H), 4.2–3.4 (m, 42H), 2.9–2.5 (m, 4H), 0.85 (m, 63H), 0.01 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 102.2, 81.7, 73.0–72.0, 62.0, 61.7, 29.8, 25.9, 18.2, −5.1; FAB MS (NBA) m/z calcd for $C_{86}H_{174}N_2O_{34}Si_7$ 1974.9, measured (+ve) 1977.0. Anal. Calcd for $C_{86}H_{174}N_2O_{34}Si_7$: C 52.28, H 8.8, N 1.42. Found: C 52.29, H 9.08, N 1.27.

Mono(3^A-azido-3^A-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-(2^A*S*),(3^A*S*)-*β*-cyclodextrin (8). Mono-epoxide **5** (0.50 g, 0.26 mmol) was dissolved in dry ethanol (20 mL), and lithium azide (0.03 g, 0.61 mmol) was added in one portion. The reaction mixture was heated to reflux for 4 days. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (25 mL) and saturated aqueous NaCl (25 mL) before it was dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness, giving pure **8** in quantitative yield (0.52 g, 0.25 mmol); mp 240 °C dec; ^1H NMR ($CDCl_3$) δ 4.95–4.85 (m, 6H), 4.63 (s, 1H), 4.2–3.3 (m, 42H), 1.3 (s, 9H), 0.85 (m, 54H), 0.05 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 104.9, 102.1, 101.3, 80.2, 73.7, 73.4, 72.4, 72.0, 63.1, 61.5, 25.9, 18.8, 17.7, −3.5, −4.7, −4.9; FAB MS (NBA) m/z calcd for $C_{84}H_{167}N_3O_{34}Si_7$ 1959.8, measured (+ve) 1965.8 (M + Li^+), 1982.1 (M + Na^+); IR (KBr) 2116.2 cm^{-1} (N_3). Anal. Calcd for $C_{84}H_{167}N_3O_{34}Si_7{\cdot}2H_2O$: C 50.55, H 8.64, N 2.11. Found: C 50.69, H 8.36, N 2.09. Karl-Fisher titration calcd for 2 H_2O: 1.80, found: 1.91.

Mono(3^A-amino-3^A-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-(2^A*S*),(3^A*S*)-*β*-cyclodextrin (9). By Azide Reduction.[50] To a solution of azide **8** (2.63 g, 1.34 mmol) in dioxane (60 mL) were added tri-*n*-butyltin hydride (Bu_3SnH) (1.08 mL, 4.03 mmol) and azobis(isobutyronitrile) (AIBN) (0.22 g, 1.34 mmol). The mixture was kept at reflux for 1 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 25 mL) and saturated aqueous NaCl (25 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated to dryness giving the crude reaction mixture. Flash chromatography gave the monoamine **9** in 85% yield (2.21 g, 1.15 mmol);

By Epoxide Opening with Ammonia. Epoxide **5** (3.05 g, 1.59 mmol) was dissolved in dry ethanol (50 mL) and saturated with NH_3(g). The reaction mixture was kept at 60–70 °C for 48 h in a closed carius tube. After evaporation of the solvent, the crude reaction product was purified by flash chromatography (EtOAc:MeOH:H_2O = 16:2:1, R_f = 0.05) giving pure **9** in 83% yield (1.90 g, 0.98 mmol); mp 250 °C dec; ^1H NMR ($CDCl_3$) δ 4.95–4.75 (m, 7H), 4.2–3.3 (m, 42H), 0.84 (m, 63H), 0.05 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 104.9, 102.9, 102.6, 102.3, 102.1, 101.8, 101.3, 82.5, 73.4–71.9, 61.9–61.5, 52.9, 25.9, 18.2, −5.1; FAB MS (NBA) m/z calcd for $C_{84}H_{169}NO_{34}Si_7$ 1932.0, measured (−ve) 1931.7, (+ve) 1933.6, 1955.4 (M + Na^+). Anal. Calcd for $C_{84}H_{169}NO_{34}Si_7{\cdot}3H_2O$: C 50.75, H 8.88, N 0.71. Found: C 50.68, H 8.75, N 0.64. Karl-Fisher titration calcd for 3 H_2O: 2.72, found: 2.62.

Mono(3^A-((2-aminoethyl)amino)-3^A-deoxy)hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis-(6-*O*-*tert*-butyldimethylsilyl)-(2^A*S*),(3^A*S*)-*β*-cyclodextrin (10). Opening of the epoxide **6** (0.25 g, 0.13 mmol) was performed in refluxing dry ethanol (15 mL) with ethylenediamine (6 mL). After 16 h the solvent was removed in vacuo, and the residue was dissolved in chloroform (25 mL) and washed with water (3 × 15 mL) and saturated aqueous NaCl (15 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness giving **10** in 75% yield (0.20 g, 0.10 mmol): mp 178 °C; ^1H NMR ($CDCl_3$) δ 5.2–4.7 (m), 4.1–3.3 (m, 53H), 6.61 (s), 3.2–3.05 (m, 7H), 2.9–2.75 (m, 4H), 0.85 (m, 63H), 0.00 (m, 42H); FAB MS (NBA) m/z calcd for $C_{92}H_{186}N_2O_{34}Si_7$ 2059.1, measured (+ve) 2059.3, 2194.0 (M + Cs^+), (−ve) 2191.3 (M + Cs^+). Anal. Calcd for $C_{92}H_{186}N_2O_{34}Si_7{\cdot}1.5H_2O$: C 52.92, H 9.12, N 1.35. Found: C 52.90, H 9.08, N 1.17. Karl-Fisher titration calcd for 1.5 H_2O: 1.29, found: 1.25.

Mono(2^A-*O*-(α-(4-toluonitrile)))heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-cyclodextrin (11). A solution of silylated *β*-cyclodextrin **2** (7.7 g, 4.0 mmol, dried for 8 h at 0.05 mmHg, 100 °C) and sodium hydride (0.14 g, 4.7 mmol, 80% slurry in oil) in THF (250 mL) was heated to reflux for 1.5 h. The electrophilic reagent α-bromo-4-toluonitrile (0.86 g, 4.7 mmol), dissolved in THF (50 mL), was added dropwise to the reaction mixture, which was kept at reflux for another 2.5 h. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with water (2 × 50 mL) and saturated aqueous NaCl (50 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness, and the residue (9.2 g) was purified by repeated flash chromatography (SiO_2, (i) EtOAc:CH_3OH:H_2O = 25:2:1, (ii) EtOAc, (iii) EtOAc:CH_3OH:H_2O = 25:2:1, R_f = 0.60) giving pure **11** in 35% yield (3.7 g, 1.8 mmol); mp 245–246 °C; ^1H NMR ($CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 6.60 (m, 2H), 6.53 (s, 1H), 6.28 (s, 1H), 5.93 (s, 1H), 5.84 (s, 1H), 5.29–4.61 (m, 7H), 5.21 (s, 2H), 4.88 (br s,

7H), 4.2–3.2 (m, 42H), 0.85 (s, 63H), 0.00 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 142.7, 132.3, 129.2, 118.4, 112.2, 102.9, 102.2, 101.9, 100.8, 82.0–81.5, 80.1, 73.9–72.3, 62.1–61.3, 25.9, 18.3, −5.1, −5.2; FAB MS (NBA) *m/z* calcd for $C_{92}H_{173}NO_{35}Si_7$ 2048.2, measured (−ve) 2047.3, (+ve) 2072.4 (M + Na^+); IR (KBr) 2231 cm^{-1} (CN). Anal. Calcd for $C_{92}H_{173}NO_{35}Si_7 \cdot H_2O$: C 53.44, H 8.54, N 0.68. Found: C 53.25, H 8.53, N 0.84.

Mono(2^A-*O*-(α-(2-toluonitrile))heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (12). Nitrile **12** was obtained in 18% yield (R_f = 0.25) in the same way as described for compound **11** using α-bromo-2-toluonitrile as the electrophilic reagent: mp 272–274 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.59–6.54 (m, 3H), 6.46 (s, 1H), 6.23 (s, 1H), 5.91 (s, 1H), 5.45 (s, 1H), 5.18–4.78 (m, 15H), 4.16–3.2 (m, 42H), 0.85 (m, 63H), 0.02 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 140.4, 132.6, 132.3, 131.3, 128.6, 117.7, 113.2, 103.0, 102.0, 100.2, 82.1–81.4, 80.0, 73.8–72.4, 61.6, 25.9, 18.3, −5.2; FAB MS (NBA) *m/z* calcd for $C_{92}H_{173}NO_{35}Si_7$ 2048.2, measured (−ve) 2047.3. Anal. Calcd for $C_{92}H_{173}NO_{35}Si_7 \cdot H_2O$: C 53.44, H 8.54, N 0.68. Found: C 53.53, H 8.59, N 0.58.

Mono(2^A-*O*-(α-(4-toluonitrile)))hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (13). A suspension of nitrile **11** (3.75 g, 1.8 mmol), dimethyl sulfate (3.5 mL, 36 mmol), barium oxide (3.5 g, 23 mmol), and barium hydroxide (3.5 g, 20 mmol) in THF (50 mL) was stirred for 24 h at room temperature. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (100 mL) and washed with 1 N HCl (2 × 50 mL) and water (50 mL). The organic phase was stirred overnight with 1 N NaOH (75 mL) and methanol (25 mL). The organic phase was separated, washed with water (4 × 50 mL) until the water phase was pH neutral and with saturated aqueous NaCl (50 mL). The organic solution was dried over $MgSO_4$ and filtered, and the filtrate was concentrated to dryness. The crude reaction product was further purified by flash chromatography (SiO_2, CH_2Cl_2:CH_3OH = 90:10, R_f = 0.64) giving pure **13** in 85% yield (3.3 g, 1.5 mmol), mp 161 °C. The FAB mass spectra indicated small amounts of over- and undermethylated products. No signals from these products appeared in the ^{1}H NMR spectra, indicating that at least 95% of the product was the hexamethylated compound **13**: ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.51 (m, 2H), 5.2–4.6 (m, 16H), 4.2–3.4 (m, 53H), 3.62 (s), 3.17 (d, *J* = 8.9 Hz, 7H), 0.81 (s, 63H), −0.02 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 143.0, 132.1, 128.4, 118.6, 111.6, 101.6, 100.9–100.3, 82.6–81.7, 73.5–72.3, 71.6, 62.0, 61.3, 61.1, 60.1, 60.0, 59.8, 25.9, 18.2, −4.8; FAB MS (NBA) *m/z* calcd for $C_{98}H_{185}NO_{35}Si_7$ 2132.1, measured (+ve) 2134.8, 2156.2 (M + Na^+). Anal. Calcd for $C_{98}H_{185}NO_{35}Si_7$: C 55.15, H 8.74, N 0.66. Found: C 55.22, H 9.13, N 0.66.

Mono(2^A-*O*-(α-(2-toluonitrile)))hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (14). Using the same procedure as described for **13**, nitrile **14** could be obtained in 82% yield from compound **12** (R_f = 0.54), mp 168 °C. The FAB mass spectra indicated small amounts of over- and undermethylated products. No signals from these products appeared in the ^{1}H NMR spectra, indicating that at least 95% of the product was the hexamethylated compound **16**: ^{1}H NMR ($CDCl_3$) δ 7.6 (m, 3H), 7.38 (m, 1H), 5.2–4.8 (m, 16H), 4.2–3.4 (m, 53H), 3.66 (s), 3.18 (d, *J* = 9.4 Hz, 7H), 0.84 (s, 63H), −0.01 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 141.1, 132.7, 132.5, 129.2, 128.0, 117.2, 111.8, 101.7, 101.0–100.3, 82.2–81.9, 72.9, 71.6, 61.5, 59.9, 25.7, 18.1, −5.4; FAB MS (NBA) *m/z* calcd for $C_{98}H_{185}NO_{35}Si_7$ 2132.1, measured (+ve) 2134.8, 2156.2 (M + Na^+). Anal. Calcd for $C_{98}H_{185}NO_{35}Si_7 \cdot H_2O$: C 54.69, H 8.67, N 0.65. Found: C 54.59, H 8.91, N 0.66.

Mono(2^A-*O*-(α-(4-(aminomethyl)tolyl))hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (15). A solution of nitrile **13** (3.0 g, 1.4 mmol) and borane (6.5 mL 10 M BH_3–dimethyl sulfide complex) in THF (100 mL) was heated overnight to 60 °C (boiling point of dimethyl sulfide) in a Claisen flask. During this period most of the dimethyl sulfide was distilled off. The reaction mixture was concentrated in vacuo, dissolved in acetone (5 × 25 mL), and again concentrated to remove all the dimethyl sulfide. The crude reaction mixture was dissolved in CH_2Cl_2 (100 mL) and washed with 2 N HCl (2 × 25 mL), water (25 mL), and saturated aqueous NaCl (25 mL). The organic phase was evaporated, dissolved in 2,2-dimethoxypropane, and again concentrated to dryness to remove all water. Flash column chromatography (SiO_2, CH_2Cl_2:CH_3OH = 90:10, R_f = 0.29) gave **15** in 70% yield (2.1 g, 1.0 mmol); mp 176–179 °C; ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (m, 4H), 5.17–4.65 (m, 16H), 4.2–3.3 (m, 55H), 3.64 (s), 3.18 (d, *J* = 9.8 Hz, 7H), 0.85 (s, 63H), 0.02 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 129.3, 128.8, 100.5, 82.3–81.9, 73.0, 71.6, 61.5, 60.0, 49.1, 48.9, 25.7, 18.1, −5.4; FAB MS (NBA) *m/z* calcd for $C_{98}H_{189}NO_{35}Si_7$ 2136.1, measured (+ve) 2138.1, 2159.7 (M + Na^+). Anal. Calcd for $C_{98}H_{189}NO_{35}Si_7 \cdot 3H_2O$: C 53.69, H 8.97, N 0.64. Found: C 53.56, H 9.03, N 0.66.

Mono(2^A-*O*-(α-(2-(aminomethyl)tolyl)))hexakis(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (16). According to the synthesis of **15**, amine **16** was obtained by reduction of nitrile **14** in a yield of 51% after flash column chromatography (R_f = 0.15); mp 169 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 1H), 7.55–7.20 (m, 3H), 5.22–4.63 (m, 16H), 4.2–3.25 (m, 55H), 3.61 (s), 3.17 (m, 7H), 0.84 (m, 63H), 0.05 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 135, 131, 129, 127, 100.7, 82.2–81.9, 73.0, 71.6, 61.5, 59.9, 25.7, 18.1, −5.2, −5.4, −5.5; FAB MS (NBA) *m/z* calcd for $C_{98}H_{189}NO_{35}Si_7$ 2136.1, measured (+ve) 2137.8, 2159.2 (M + Na^+). Anal. Calcd for $C_{98}H_{189}NO_{35}Si_7 \cdot 3H_2O$: C 53.69, H 8.97, N 0.64. Found: C 53.46, H 9.04, N 0.65. Karl-Fisher titration calcd for 3 H_2O: 2.46, found: 2.13.

Mono(2^A-*O*-(α-(4-toluonitrile)))hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (11(α)). The α-cyclodextrin toluonitrile derivative **11(α)** was obtained in 43% yield (R_f = 0.35) from silylated α-cyclodextrin[15a] in the same way as described for the β-cyclodextrin analog **11**: mp 280 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.37–5.92 (m, 5H, C(2)-O*H*s), 5.29–4.38 (m, 14H), 4.03–3.18 (m, 36H), 0.83 (s, 54H), 0.00 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 142.5, 132.3, 129.5, 118.4, 112.4, 103.7, 101.9, 101.6, 101.4, 100.8, 82.1, 81.6, 81.3, 80.9, 80.7, 80.6, 74.6–71.9, 62.1, 61.9, 61.5, 26.0, 18.4, −5.2; FAB MS (NBA) *m/z* calcd for $C_{80}H_{149}NO_{30}Si_6$ 1771.8, measured (+ve) 1796.0 (M + Na^+), (−ve) 1771.3. Anal. Calcd for $C_{80}H_{149}NO_{30}Si_6 \cdot H_2O$: C 53.63, H 8.50, N 0.78. Found: C 53.40, H 8.42, N 0.43.

Mono(2^A-*O*-(α-(4-toluonitrile)))pentakis(2^B,2^C,2^D,2^E,2^F-*O*-methyl)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (13(α)). The methylated α-cyclodextrin toluonitrile derivative **13(α)** was obtained in 85% yield (R_f = 0.54) in the same way as previously described for the β-cyclodextrin analog **13**, mp 136–138 °C. The FAB mass spectra indicated small amounts of over- and undermethylated products. No clear signals from these products appeared in the ^{1}H NMR spectra, indicating that at least 90% of the product was the pentamethylated compound **13(α)**: ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.26–4.44 (m, 14H), 4.07–3.16 (m, 45H), 3.60 (s), 0.83 (s, 54H), 0.00 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 143.2, 132.3, 128.4, 118.7, 111.7, 101.0, 100.5, 82.8–81.7, 73.9–72.2, 71.6, 61.9, 61.7, 60.0, 25.9, 18.3, −5.2; FAB MS (NBA) *m/z* calcd for $C_{85}H_{159}NO_{30}Si_6$ 1841.9, measured (+ve) 1866.3 (M + Na^+), (−ve) 1841.1. Anal. Calcd for $C_{85}H_{159}NO_{30}Si_6$: C 55.37, H 8.70, N 0.76. Found: C 55.36, H 8.77, N 0.69.

Mono(2^A-*O*-(α-(4-(aminomethyl)tolyl)))pentakis(2^B,2^C,2^D,2^E,2^F-*O*-methyl)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (15(α)). The aminofunctionalized α-cyclodextrin derivative **15(α)** was obtained by reduction of nitrile **13(α)**, using borane–dimethyl sulfide complex in THF as was described for the β-cyclodextrin analog **15**. The amine **15(α)** was obtained in 79% yield after flash column chromatography (R_f = 0.14); mp 174–176 °C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.30 (m, 4H), 4.9–3.1 (br m, 67H), 3.60 (s), 0.84 (s, 54H), 0.00 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 128.8, 100.5, 82.4, 81.9, 74.8–71.6, 61.8, 60.0, 25.9, 18.3, −5.2; FAB MS (NBA) *m/z* calcd for $C_{85}H_{163}NO_{30}Si_6$ 1845.9, measured (+ve) 1848.3. Anal. Calcd for $C_{85}H_{163}NO_{30}Si_6 \cdot 2H_2O$: C 54.20, H 8.94, N 0.74. Found: C 54.36, H 8.79, N 0.70.

α,α′-Bis[2-*O*-(heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin)]-*p*-xylene (17). A solution of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **2** (5.00 g, 2.6 mmol), sodium hydride (0.09 g, 2.9 mmol, 80%), potassium iodide (0.43 g, 2.6 mmol), and a catalytic amount 18-crown-6 in THF (500 mL) was heated to reflux for 1 h. After this time a solution of α,α′-dichloro-*p*-xylene (0.23 g, 1.3 mmol) in THF (50 mL) was added dropwise (50 μL/min) by using a perfusor, while the reaction mixture was kept to reflux for 16 h. The crude reaction product obtained after evaporation of the solvent was dissolved in chloroform (300 mL) and washed with 2 N HCl (2 × 100 mL), water (2 × 100 mL), and saturated aqueous NaCl (100 mL). The organic phase was concentrated to dryness and the cyclodextrin dimer **17** was obtained in 12% yield (0.62 g, 0.16 mmol) after repeated flash column chromatography (SiO_2, (i) EtOAc−CH_3OH−H_2O = 25:2:1 (ii) EtOAc (iii) EtOAc−CH_3OH−H_2O = 25:2:1, R_f = 0.17) besides recovery of unreacted starting material: mp 271 °C; ^1H NMR ($CDCl_3$) δ 7.50−7.25 (m, 4H), 6.7−6.5 (m, 6H), 6.3−5.8 (m, 6H), 5.4−4.4 (m, 18H), 4.89 (br s, 14H), 4.2−3.2 (m, 84H), 0.87 (s, 126H), 0.03 (s, 84H); ^{13}C NMR ($CDCl_3$) δ 136.6, 129.4, 128.2, 126.1, 102.1, 99.5, 81.9, 79.9, 74.1−71.9, 61.7, 25.9, 18.3, −5.1; FAB-MS (NBA) *m/z* calcd for $C_{176}H_{342}O_{70}Si_{14}$ 3967.8, measured (−ve) 3964.8 and signals of products obtained after cleavage of the benzyl ether bonds. Anal. Calcd for $C_{176}H_{342}O_{70}Si_{14}·2H_2O$: C 52.75, H 8.71. Found: C 52.47, H 8.80. Karl-Fisher titration calcd for 2 H_2O: 0.90, found: 1.04.

α,α′-Bis[2-*O*-β-cyclodextrin]-*p*-xylene (18). A solution of silylated dimer **17** (0.5 g, 0.13 mmol) in a mixture of acetic acid (30 mL), THF (10 mL), and water (10 mL) was heated to reflux for 16 h. After evaporation of the solvents the crude reaction mixture was stirred for 16 h in a half-saturated methanolic ammonia solution to deprotect acylated hydroxyl groups. The water-soluble dimer **18** was obtained in quantitative yield (0.30 g, 0.13 mmol) after evaporation of the solvent; mp 225 °C dec; ^1H NMR (D_2O) δ 7.5 (br s, 4H), 5.2 (br s, 4H), 5.1 (br s, 14H), 4.2−3.4 (m, 84H); ^{13}C NMR (D_2O) δ 137.3, 129.4, 102.0, 100.0, 81.4, 73.2, 71.9, 61.2; FAB MS (glycerol) *m/z* calcd for $C_{92}H_{146}O_{70}$ 2370.5, measured (+ve) 2372.1, (−ve) 2369.6 and signals (1235.0, 1133.3) of products obtained after benzyl bond cleavage. Anal. Calcd for $C_{92}H_{146}O_{70}·4H_2O$: C 45.19, H 6.35. Found: C 45.16, H 6.54. Karl-Fisher titration calcd for 4 H_2O: 2.95, found: 2.81.

***N*-(α-(25,26,27,28-Tetrahydroxycalix[4]arene-5-methyl))-mono(2^A-*O*-(α-(4-(aminomethyl)tolyl)))hexakis-(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (19).** A solution of amino cyclodextrin **15** (1.00 g, 0.47 mmol), formylcalix[4]arene[48] (0.21 g, 0.47 mmol), sodium cyanoborohydride (0.15 g, 2.4 mmol), and a catalytic amount of acetic acid in THF (20 mL) was stirred at room temperature for 6 h. After removal of the solvent in vacuo, the residue was dissolved in $CHCl_3$ (50 mL) and washed with 2 N HCl (2 × 25 mL), water (2 × 25 mL), and saturated aqueous NaCl (25 mL). The organic phase was concentrated to dryness, and the crude reaction mixture was purified by repeated flash column chromatography (SiO_2, (i) CH_2Cl_2−CH_3OH = 9:1 (ii) CH_2Cl_2 (iii) CH_2Cl_2−CH_3OH = 9:1, R_f = 0.53) giving **19** in 36% yield (0.44 g, 0.2 mmol) besides the recovery of starting materials; mp 208 °C; ^1H NMR ($CDCl_3$) δ 7.4−7.2 (m, 6H), 7.0 (m, 6H), 6.7 (m, 3H), 5.2−4.6 (m, 14H), 4.5−3.3 (m, 65H), 3.16 (d, *J* = 9.8 Hz, 7H), 0.87 (m, 64H), 0.02 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 148.8, 147.7, 136.3, 133.9, 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 122.2, 101.8, 100.7, 84.3, 82.3, 73.2, 71.7, 62.1, 61.7, 61.3, 60.3, 60.1, 52.9, 52.2, 31.7, 25.9, 18.3, −5.2; FAB-MS (NBA) *m/z* calcd for $C_{127}H_{213}NO_{39}Si_7$ 2572.3, measured (+ve) 2574.9, (−ve) 2572.9. Anal. Calcd for $C_{127}H_{213}NO_{39}Si_7·2H_2O$: C 58.43, H 8.38, N 0.54. Found: C 58.15, H 8.68, N 0.55. Karl-Fisher titration calcd for 2 H_2O: 1.38, found: 1.50.

***N*-(α-(25,26,27,28-Tetrahydroxycalix[4]arene-5-methyl))-mono(2^A-*O*-(α-(2-(aminomethyl)tolyl)))hexakis-(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (20).** Compound **20** was obtained by reductive coupling of **16** with formylcalix[4]arene following the procedure as described for **19**. After silica gel flash column chromatography (R_f = 0.51), **20** was obtained in 40% yield besides recovery of starting materials; mp 207 °C; ^1H NMR ($CDCl_3$) δ 7.5−7.2 (m, 6H), 7.1−7.0 (m, 6H), 6.8−6.65 (m, 3H), 5.3−4.8 (m, 14H), 4.4−3.2 (m, 65H), 3.17 (m, 7H), 0.88 (m, 64H), 0.03 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 148.9, 131.1−127.2, 122.2, 101.8, 101.0, 100.5, 83.0−81.5, 73.2, 71.8, 61.9, 60.1, 52.9, 52.2, 31.7, 25.9, 18.3, −5.2; FAB-MS (NBA) *m/z* calcd for $C_{127}H_{213}NO_{39}Si_7$ 2572.3, measured (+ve) 2575.5 (−ve) 2572.2. Anal. Calcd for $C_{127}H_{213}NO_{39}Si_7·7H_2O$: C 56.48, H 8.48, N 0.52. Found C 56.38, H 8.21, N 0.71.

***N*-(α-(25,26,27,28-Tetrahydroxycalix[4]arene-5-methyl))-mono(2^A-*O*-(α-(4-(aminomethyl)tolyl)))hexakis-(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)-β-cyclodextrin (21).** Cyclodextrin−calix[4]arene coupled product **19** (0.40 g, 0.16 mmol) was dissolved in a mixture of acetic acid (15 mL), THF (5 mL), and water (5 mL) and heated to reflux for at least 12 h. After evaporation of all solvents the crude reaction product was stirred for 16 h in half-saturated methanolic ammonia (40 mL) at room temperature. Concentration of the reaction mixture to dryness gave **21** in almost quantitative yield (0.27 g, 0.15 mmol); mp 200 °C dec; ^1H NMR (CD_3OD) δ 7.54, 7.46 (ABq, *J* = 7.8 Hz, 4H), 7.1 (m, 6H), 6.7 (m, 3H), 5.1, 5.0 (dd, *J* = 3.6 Hz, 7H), 4.0−3.4 (m, 65H), 3.3 (m, 7H); ^{13}C NMR (CD_3OD) δ 140.1, 134.2, 130.4, 130.1, 103.1, 102.4, 101.8, 85.1, 83.5, 81.1, 80.2, 74.3, 73.1, 61.8, 60.4, 32.0; FAB-MS (glycerol) *m/z* calcd for $C_{85}H_{115}NO_{39}$ 1773.0, measured (−ve) 1772.7. Anal. Calcd for $C_{85}H_{115}NO_{39}·7H_2O$: C 53.19, H 6.88, N 0.73. Found: C 53.14, H 6.71, N 0.71. Karl-Fisher titration calcd for 7 H_2O): 6.64, found: 6.71.

***N*-(α-(25,26,27,28-Tetrahydroxycalix[4]arene-5-methyl))-mono(2^A-*O*-(α-(2-(aminomethyl)tolyl)))hexakis-(2^B,2^C,2^D,2^E,2^F,2^G-*O*-methyl)-β-cyclodextrin (22).** Compound **22** was obtained in quantitative yield from **20** by desilylation following the procedure as described for **21**: mp 220 °C dec; ^1H NMR (CD_3OD) δ 7.4 (br m, 6H), 7.0 (br m, 6H), 6.7 (br m, 3H), 5.0, 4.9 (2 br s, 7H), 4.2−3.4 (m, 65H), 3.25 (br s, 7H); ^{13}C NMR (CD_3OD) δ 177.3, 130.5−129.0, 122.4, 101.5, 83.5, 82.8, 73.7, 72.2, 61.1, 60.4, 32.1; FAB-MS (glycerol) *m/z* calcd for $C_{85}H_{115}NO_{39}$: 1773.0, measured (−ve) 1772.1. Anal. Calcd for $C_{85}H_{115}NO_{39}·3H_2O$. C 55.29, H 6.71, N 0.76. Found: C 54.82, H 6.73, N 0.61. Karl-Fisher titration calcd for 3 H_2O: 2.96, found: 3.10.

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