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A new approach to A,B-difunctionalisation of cyclodextrins using bulky 1,3-bis[bis(aryl)chloromethyl]benzenes as capping reagents

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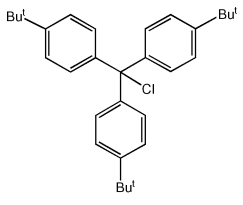
1,3-Bis[bis(4-*tert*-butylphenyl)chloromethyl]benzene and 1,3-bis[bis(4-anisyl)chloromethyl]benzene were employed as regioselective capping reagents for the preparation of C-6^{A},C-6^{B}-bridged, permethylated α- and β-CD derivatives; isolated yields up to 55% of proximally capped, methylated CDs were obtained, thus opening the way to the straightforward preparation of a wide range of A,B-functionalised CDs. As revealed by a single crystal X-ray diffraction study, the benzene-1,3-bis[bis(4-*tert*-butylphenyl)methyl] spacer is perfectly suited for A,B-capping of β-cyclodextrin.

Introduction

Chemical modification of natural cyclodextrins (CDs) gives access to a wide range of cavity-shaped molecules that find applications in many areas of contemporary chemistry.[1–4] Modification of CDs is usually achieved by substituting some or all of the hydroxyl groups present at the surface of the macrocycle. It is well known that the primary OH groups are the most nucleophilic ones and accordingly may be selectively functionalised with the secondary ones left unaffected.[5] Partial poly-substitution reactions at the primary face can also be achieved and efficient methologies for producing selectively di-,[6–9] tri-[10,11] and tetra-substituted[12,13] regioisomers have recently become available. However, the development of synthetic strategies leading to A,B-difunctionalised CDs still remains a challenge[14–17] and as a result, the latter have attracted less attention than other CD regioisomers, although recent work has underlined their relevance in homogeneous catalysis.[18] To date, direct proximal dialkylation of CDs cannot be achieved in yields higher than *ca.* 10% and does not give easy access to difunctionalised methylated CDs,[19] which are key starting materials for further modification, in particular for the introduction of phosphorus-based ligands. In some recent reports we have shown that supertrityl chloride **1** (^{S}TrCl) is a valuable alkylating agent suited for the selective formation of either A,B,D,E-tetra or A,D-diprotected, methylated α-CDs,[13,20] the selectivity of these reactions relying on the bulkiness of the supertrityl group. However, the efficiency of this reagent for A,B-dialkylation remains poor. We thought that A,B-disubstitution could be significantly improved by using synthons incorporating two bulky alkylating units separated by a rigid spacer, the length of which is compatible with the separation of two neighbouring glucose units.



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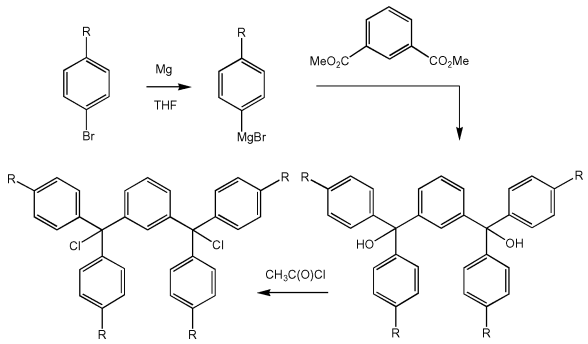
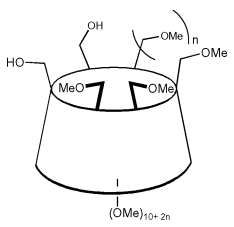
Results and discussion

The "bis-trityl" dichlorides used in this study, **2**–**4**, were conveniently prepared in three steps according to Scheme 1. Each synthesis starts with the preparation of a Grignard reagent derived from the appropriate aryl bromide. Reaction of the thus formed ArMgBr complex with dimethyl isophthalate and subsequent hydrolysis gave the expected bulky diol. Treatment of the latter with acetyl chloride afforded quantitavely the corresponding dichloride. All intermediates were purified by simple recrystallisation, chromatographic purification being unnecessary.



2 (R = OMe)
3 (R = Bu^t)
4 (R = H)

Scheme 1 Synthesis of 1,3-bis[bis(aryl)chloromethyl]benzenes.



11 n = 1
12 n = 2

Several bases were used to carry out the alkylation (Scheme 2). The best results for the capping reactions were obtained in DMF

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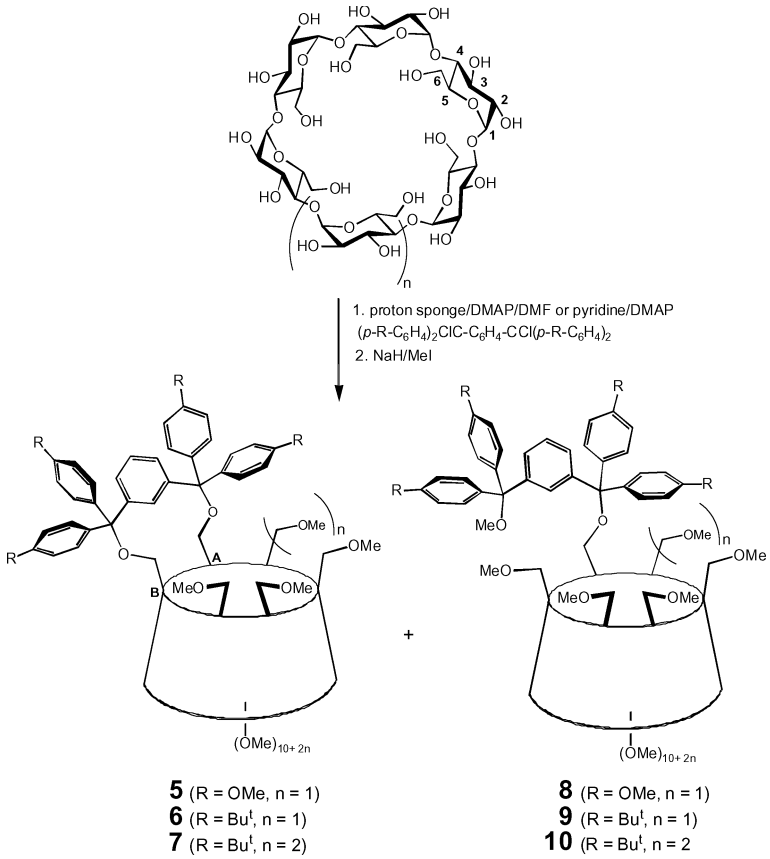

5 (R = OMe, n = 1)
6 (R = Bu^t, n = 1)
7 (R = Bu^t, n = 2)

8 (R = OMe, n = 1)
9 (R = Bu^t, n = 1)
10 (R = Bu^t, n = 2

Scheme 2 Formation of A,B-capped, methylated CDs.

using DMAP/proton sponge (method B, see experimental section) with a CD : dichloride ratio of 1 : 1 (Table 1). Using DMAP in pyridine (method A) gave slightly lower yields, but yields remained high when dichloride **2** was used. The resulting alkylation products were not isolated, but instead directly treated with MeI/NaH in order to methylate the remaining hydroxyl groups.

The latter step is necessary for product purification, the non-methylated species being too polar for chromatographic separation and also prone to ether cleavage. The highest yields were observed using the *tert*-butyl derivative **3** as capping agent, the corresponding disubstituted CDs **6** and **7** being isolated in 55 and 35% yield respectively (Table 1). The methoxy derivative **2**, which is also electron-rich, also gave rise to significant amounts of A,B-disubstituted species (up to 52% of **5** using method A). Conversely, when the non-substituted dichloride **4**,[21] which lacks such electron-donating groups, was employed, only traces of alkylated products were observed. Besides the expected A,B-capping products, the reaction mixture generally contained small amounts of "overtritylated" products and compounds resulting from monoalkylation (**8**, **9**, and **10**, respectively) together with unreacted starting material. The composition of the reaction mixture during the first alkylation step did not change significantly after 5 h. This could arise from a competing proton-catalysed ether cleavage. We noted that adding an excess of the capping reagent to the reaction mixture resulted in decreased yields of capped species **5**–**7**, as significant amounts of poly-substituted CDs were produced.

Table 1 Capping efficiency determined after methylation of the unreacted hydroxy groups

Entry	CD	Capping reagent	Method[a]	Products	Yield (%)
				5	52
1	α-CD	**2**	A	**8**	4
				5	29
2	α-CD	**2**	B	**8**	14
				6	46
3	α-CD	**3**	A	**9**	22
				6	55
4	α-CD	**3**	B	**9**	6
				7	35
5	β-CD	**3**	B	**10**	5

[a] See text and Experimental section for details.

The assignement of all capped species produced were made possible through derivatisation. Thus, deprotection of **5** (or **6**) and **7** with aqueous HBF_4 in MeCN afforded the diols **11** and **12**,[19] respectively. An X-ray diffraction study carried out on **7** confirmed the A,B-substitution pattern (Fig. 1). In the solid state the CD torus of **7** adopts a slightly elongated circular shape, with all glucose units in the standard $^4C_1$ conformation, those adjacent to the capped ones being slightly tilted towards the cavity centre. The longest O-4 $\cdots$ O′-4 separation is between units A and E (10.21 Å), while the O-4^C $\cdots$ O′-4^G separation is 8.94 Å. The bulky capping unit ideally fits with the O-6^A $\cdots$ O-6^B separation (5.63 Å *vs.* 5.30 Å on average) and covers *ca.* 60% (!) of the primary face surface.

In summary, by choosing a "bis-trityl" derivative that matches the separation between two adjacent glucose units in the rigid CD torus and tuning its reactivity by means of electron donor groups, we have managed for the first time to devise a reasonably high-yielding synthesis for A,B regioisomers of both α- and β-CD derivatives. We believe this methodology can be extended to the larger γ-CD as well as to other CD regioisomers just by changing the nature of the spacer separating both anchor points in the "bis-trityl" reagent. Overall, these results give easy access to a wide variety of valuable functionalised CD cavities.

Experimental

All manipulations were performed in Schlenk-type flasks under dry nitrogen. Solvents were dried by conventional methods and distilled immediately prior to use. $CDCl_3$ was passed down a 5 cm

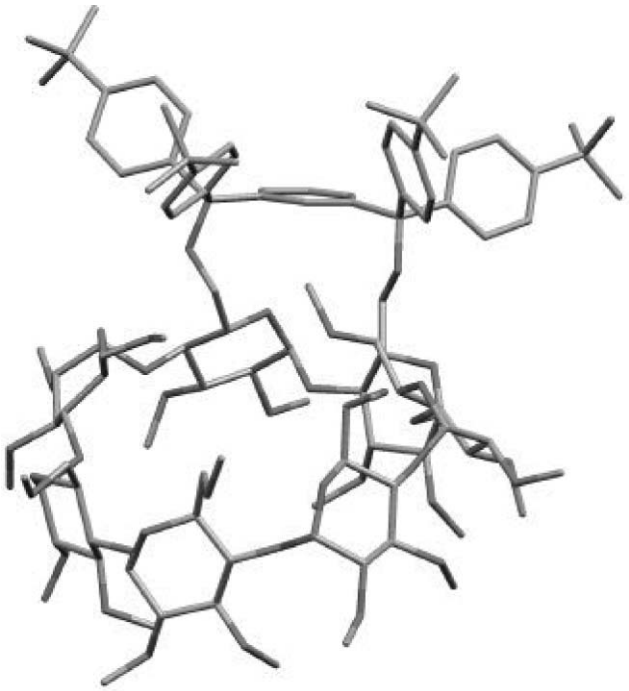

Fig. 1 Molecular structure of A,B-capped CD **7**. For clarity the solvent molecules are not shown.

thick alumina column and stored under nitrogen over molecular sieves (4 Å). Routine ^{1}H and $^{13}C\{^{1}H\}$ spectra were recorded with Bruker FT instruments (AC-200, AC-300, ARX-500). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (ref. 7.26 ppm and 77.0 ppm, respectively). Mass spectra were recorded either on a ZAB HF VG analytical spectrometer using *m*-nitrobenzyl alcohol as matrix or on a Bruker MicroTOF spectrometer (ESI) using CH_2Cl_2 as solvent.

1,3-Bis[bis(4-anisyl)chloromethyl]benzene (2)

In an oven-dried 1 L three-necked flask equipped with a condenser, dropping funnel, and nitrogen system were placed Mg turnings (5.257 g, 216.29 mmol) and an iodine crystal with dry THF (150 mL). A solution of 4-bromoanisole (40.454 g, 216.285 mmol) in dry THF (50 mL) was added dropwise over 1 h with gentle heating; when the reaction started the heat was removed. The reaction mixture, which turned grey, was stirred for 3 h without heating. A solution of dimethyl isophthalate (10.000 g, 51.495 mmol) in THF (40 ml) was added dropwise over 1 h. The mixture was stirred overnight at reflux under nitrogen, whereupon it was cooled to room temperature before being poured into a mixture of conc. H_2SO_4 (8 mL) and ice (300 g). The resulting suspension was extracted with Et_2O (3 × 300 mL). The combined organic extract was washed with water (300 mL), then dried over $MgSO_4$. Solvent removal *in vacuo* gave an orange solid, which was dissolved in Et_2O (250 mL). The solution was left to stand for 5 min, whereupon the product precipitated as a slightly orange solid. The latter was triturated in boiling Et_2O for 20 min, the suspension cooled to room temperature and filtered through a glass frit to afford the pure diol. The latter was then treated with boiling acetyl chloride (240 mL) for 40 h under nitrogen. Acetyl chloride was removed *in vacuo* and the product thoroughly dried to afford **2** as a red amorphous solid (24.560 g, 85%). Mp 88–90 °C. δ_H ($CDCl_3$, 300.1 MHz) 3.81 (s, 12 H, MeO), 6,76 (m, 8 H, AA′ part of AA′BB′ system), 6.95 (s, 1 H, H-2 of 1,3-phenylene), 7.11 (m, 8 H, BB′ part of AA′BB′ system), 7.29–7.33 (H-4,6 and H-5 of 1,3-phenylene). δ_C ($CDCl_3$, 75.5 MHz) 55.2 (MeO), 81.6 (C–Cl), 112.9 (CH of anisyl), 127.2 (C-2 or C-5 of 1,3-phenylene), 129.0 (C-4,6 of 1,3-phenylene), 130.8 (CH of anisyl), 131.2 (C-5 or C-2 of 1,3-phenylene), 137.4 (C_{quat} of anisyl), 145. 1 (C-1,3 of 1,3-phenylene), 158.9 (C_{quat} of anisyl). Elemental analysis found C, 73.35, H, 6.10; $C_{36}H_{32}O_4Cl_2 \cdot C_5H_{12}$ (599.56 + 72.15) requires C, 73.31, H, 6.6%.

1,3-Bis[bis(4-*tert*-butylphenyl)chloromethyl]benzene (3)

1,3-Bis[bis(4-*tert*-butylphenyl)chloromethyl]benzene was prepared from 4-bromo-*tert*-butylbenzene (61.453 g, 288.350 mmol) and dimethyl isophthalate (12.000 g, 61.795 mmol). The crude diol was recrystallised from heptane (400 mL) before being subjected to the above chlorination procedure to afford the pure product as a pale yellow solid (19.902 g, 46%). Mp 206–208 °C. δ_H ($CDCl_3$, 300.1 MHz) 1.31 (s, 36 H, Bu^t), 7.11 (m, 8 H, AA′ part of AA′BB′ system), 7.06–7.24 (3 H, H-4,5,6 of 1,3-phenylene), 7.27 (m, 8 H, AA′ part of AA′BB′ system), 7.44 (t, 1 H, ^{4}J 2 Hz, H-2 of 1,3-phenylene). δ_C ($CDCl_3$, 75.5 MHz) 31.1 (CH_3), 34.3 (C_{quat} of Bu^t), 81.0 (C–Cl), 124.3 (CH of Bu^t-phenyl), 126.4 (C-2 or C-5 of 1,3-phenylene), 128.1 (C-4,6 of 1,3-phenylene), 129.0 (CH of Bu^t-phenyl), 132.0 (C-2 or C-5 of 1,3-phenylene), 141.9 (C_{quat} of Bu^t-phenyl), 144.8 (C-1,3 of 1,3-phenylene), 150.3 (C_{quat} of anisyl). Elemental analysis found C, 81.71, H, 8.24; $C_{48}H_{56}Cl_2$ (703.89) requires C, 81.91, H, 8.02%.

Method A. To a mixed solution of α-CD (3.000 g, 3.084 mmol) and 4-dimethylaminopyridine (DMAP) (0.382 g, 3.125 mmol) in dry pyridine (70 mL) was added **2** (1.847 g, 3.081 mmol). The solution was stirred for 13 h at 70 °C, then evaporated to dryness. The residue was dissolved in DMF (100 mL) before sodium hydride (60% in oil) (4.49 g, 112.5 mmol) was added. The mixture was stirred for 1 h at ambient temperature whereupon it was cooled to 5 °C and MeI (13.680 g, *ca.* 6 mL, 96.380 mmol) was added carefully so that the temperature of the mixture did not exceed 35 °C. The solution was stirred for another 14 h before MeOH (50 mL), followed by water (300 mL), was added to destroy excess NaH. The cyclodextrin was subsequently extracted with Et_2O (3 × 200 mL). The organic extracts were washed with H_2O (200 mL), dried over $MgSO_4$ and finally evaporated to dryness. The brown residue was separated by column chromatography to afford the A,B-capped product **5** (2.761 g, 52%) together with the monosubstituted product **8** (0.218 g, 4%) and small amounts of less polar polytritylated products and permethylated α-CD (TM-α-CD) which were not recovered.

Method B. To a mixed solution of *β*-CD (8.000 g, 7.048 mmol), 1,8-bis(dimethylamino)naphthalene (4.521 g, 21.095 mmol) and DMAP (0.864 g, 3.11 mmol) in dry DMF (200 mL) was added **3** (4.962 g, 7.05 mmol). The solution was stirred for 13 h at 70 °C, then allowed to reach room temperature. After stirring for another hour, dry DMF (200 mL) was added and the mixture was cooled to 5 °C before NaH (60% in oil) (12.00 g, 300.0 mmol) was added. The mixture was stirred for 1 h at ambient temperature, then MeI (36.48 g, *ca.* 16 mL, 257.010 mmol) was added, the temperature of the mixture being kept below 35 °C. The solution was stirred for another 14 h before MeOH (50 mL), followed by H_2O (300 mL), was added to destroy excess NaH. The suspension was subsequently extracted with Et_2O (3 × 200 mL). The organic extracts were washed with water (200 mL), dried over $MgSO_4$ and finally evaporated to dryness. The dark yellow residue was separated by column chromatography to afford respectively the A,B-capped product **7** (5.072 g, 35%) together with the monosubstituted product **10** (0.730 g, 5%) and small amounts of less polar polytritylated compounds.

Benzene-1,3-bis[bis(4-anisyl)methyl]-6^A,6^B-capped permethylated α-CD (5)

R_f (EtOAc) = 0.21. Mp 180–182 °C. ES-TOF, *m*/*z*: 1724.8 ($M + H^+$). δ_H (300.1 MHz, $CDCl_3$) 2.75 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ 3.6 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ 9.9 Hz, H-2), 3.12–4.14 (35 H, H-2, H-3, H-4, H-5, H-6), 3.35 (s, 9 H, MeO), 3.44 (s, 3 H, MeO), 3.45 (s, 3 H, MeO), 3.46

(s, 3 H, MeO), 3.47 (s, 3 H, MeO), 3.48 (s, 3 H, MeO), 3.54 (s, 3 H, MeO), 3.56 (s, 3 H, MeO), 3.59 (s, 3 H, MeO), 3.61 (s, 3 H, MeO), 3.62 (s, 9 H, MeO), 3.63 (s, 3 H, MeO), 3.75 (s, 3 H, *Me*OAr), 3.76 (s, 3 H, *Me*OAr), 3.76 (s, 6 H, *Me*OAr), 4.21 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.7 Hz, H-1), 5.01 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.3 Hz, H-1), 5.07 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.15 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.0 Hz, H-1), 5.29 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 6.73–7.77 (20 H, aromatic H). δ_C (75.5 MHz, $CDCl_3$) 55.0 [×3], 55.1 (MeO on trityl), 57.5, 57.6, 57.7 [×2], 57.8, 57.9, 58.9, 59.0 [×2], 59.2, 61.6, 61.7 [×3], 61.7, 61.8 (MeO of CD), 61.5 [×2] (C-$6^{A,B}$), 70.1, 71.2, 71.2 [×3], 72.0 (C-5), 70.6, 71.1, 71.3 [×2] (C-$6^{C,D,E,F}$), 81.0 [×4], 81.3, 81.6, 81.7, 81.9 [×2], 82.0, 82.1 [×2], 82.1, 82.2, 82.3, 82.4, 82.5, 82.9 (C-2, C-3, C-4), 85.5, 87.3 (O*C*$(Ar)_3$), 99.5, 100.0, 100.2, 100.4 [×2], 100.7 (C-1), 112.8, 112.9, 113.1, 113.3, 127.2, 127.7 [×2], 129.4, 129.8, 130.6, 132.0, 133.9 (aromatic CH), 135.6, 136.2, 140.2, 140.3, 140.4, 141.8, 157.6, 157.7, 158.0, 158.1 (aromatic C_{quat}). Elemental analysis found C, 60.95, H, 7.26; $C_{88}H_{122}O_{34}$ (1723.93) requires C 61.31, H, 7.13%.

Benzene-1,3-bis[bis(4-*tert*-butylphenyl)methyl]-6^A,6^B-capped permethylated α-CD (6)

R_f (EtOAc–cyclohexane, 80 : 20, v/v) = 0.30. Mp 212–214 °C. ES-TOF, *m/z*: 1829.1 (M + H$^+$). δ_H ($CDCl_3$, 300.1 MHz) 1.27 (s, 9 H, Bu^t), 1.29 (s, 18 H, Bu^t), 1.29 (s, 9 H, Bu^t), 2.66 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ 3.6 Hz, $^3J_{H\text{-}2,H\text{-}3}$ 9.7 Hz, H-2), 3.13–4.17 (35 H, H-2, H-3, H-4, H-5, H-6), 3.32 (s, 3 H, MeO), 3.35 (s, 3 H, MeO), 3.36 (s, 3 H, MeO), 3.47 (s, 3 H, MeO), 3.49 (s, 3 H, MeO), 3.49 (s, 3 H, MeO), 3.52 (s, 3 H, MeO), 3.53 (s, 3 H, MeO), 3.57 (s, 6 H, MeO), 3.59 (s, 3 H, MeO), 3.59 (s, 3 H, MeO), 3.63 (s, 9 H, MeO), 3.64 (s, 3 H, MeO), 3.99 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.5 Hz, H-1), 5.02 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.3 Hz, H-1), 5.06 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.1 Hz, H-1), 5.09 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.1 Hz, H-1), 5.16 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 2.8 Hz, H-1), 5.37 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 6.89–7.77 (20 H, aromatic H). δ_C ($CDCl_3$, 75.5 MHz) 31.4 [×2], 31.4 (C(*C*H_3)$_3$), 34.2, 34.2 [×2], 34.3 (*C*$(CH_3)_3$), 57.5, 57.6, 57.7 [×4], 58.9, 59.0, 59.1, 59.3, 61.7 [×2], 61.8 [×2], 61.8, 61.9 (MeO), 60.3 [×2] (C-$6^{A,B}$), 69.8, 71.2, 71.3, 71.3, 71.4, 72.1 (C-5), 70.8, 71.0, 71.5 [×2] (C-$6^{C,D,E,F}$), 81.0 [×4], 81.1 [×2], 81.3, 81.7 [×2], 82.0, 82.1 [×3], 82.2, 82.3, 82.5 [×2], 83.2 (C-2, C-3, C-4), 85.6, 87.7 (O*C*$(Ar)_3$), 99.5, 100.1, 100.2, 100.4 [×2], 100.7 (C-1), 124.3, 124.4, 124.6, 124.8, 126.3, 127.7, 128.2, 128.4 [×2], 131.1, 132.7, 133.0 (aromatic CH), 139.7, 139.9, 140.8, 141.5, 144.7, 144.9, 148.6 [×2], 148.8, 149.0 (aromatic C_{quat}). Elemental analysis found C, 66.14, H, 8.27; $C_{100}H_{146}O_{30}$ (1828.26) requires C, 65.70, H, 8.05%.

Benzene-1,3-bis[bis(4-*tert*-butylphenyl)methyl]-6^A,6^B-capped permethylated β-CD (7)

R_f (EtOAc–cyclohexane, 80 : 20, v/v) = 0.27. Mp 199–201 °C. ES-TOF, *m/z*: 2033.1 (M + H$^+$). δ_H ($CDCl_3$, 300.1 MHz) 1.25 (s, 18 H, Bu^t), 1.26 (s, 9 H, Bu^t), 1.28 (s, 9 H, Bu^t), 2.72 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ 3.6 Hz, $^3J_{H\text{-}2,H\text{-}3}$ 9.6 Hz, H-2), 3.15–4.22 (41 H, H-2, H-3, H-4, H-5, H-6), 3.97 (s, 3 H, MeO), 3.17 (s, 3 H, MeO), 3.30 (s, 3 H, MeO), 3.31 (s, 3 H, MeO), 3.33 (s, 3 H, MeO), 3.38 (s, 3 H, MeO), 3.46 (s, 3 H, MeO), 3.48 (s, 3 H, MeO), 3.50 (s, 3 H, MeO), 3.52 (s, 3 H, MeO), 3.57 (s, 3 H, MeO), 3.58 (s, 3 H, MeO), 3.59 (s, 3 H, MeO), 3.60 (s, 3 H, MeO), 3.63 (s, 6 H, MeO), 3.64 (s, 3 H, MeO), 3.65 (s, 6 H, MeO), 4.23 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.4 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.09 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.12 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.6 Hz, H-1), 5.30 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.6 Hz, H-1), 5.31 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.6 Hz, H-1), 5.47 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.5 Hz, H-1), 6.95–7.66 (20 H, aromatic H). δ_C ($CDCl_3$, 75.5 MHz) 31.3 [×4] (C(*C*H_3)$_3$), 34.2 [×4] (*C*$(CH_3)_3$), 57.6, 58.1, 58.2, 58.5, 58.6 [×3], 58.8, 58.9, 59.0 [×2], 59.1, 60.9, 61.3, 61.3, 61.3, 61.6, 61.7, 61.9 (MeO), 62.1, 62.6 (C-$6^{A,B}$), 70.0, 70.8 [×4], 70.9, 71.6 (C-5), 71.1 [×2], 71.4, 71.5, 71.9 (C-$6^{C,D,E,F,G}$), 79.6 [×2], 80.2, 80.7, 80.9, 81.4, 81.5, 81.5, 81.6, 81.7 [×3], 81.8, 81.9, 82.0, 82.1, 82.2, 82.2 [×2], 82.5, 82.9 (C-2, C-3, C-4), 86.0, 87.6 (O*C*$(Ar)_3$), 98.0 [×2], 98.7, 98.8, 98.9 [×2], 99.2 (C-1), 124.3, 124.4 [×2], 124.5, 126.4, 126.6, 126.7, 127.5, 128.3, 130.6, 131.9, 134.1 (aromatic CH), 140.1, 140.3, 142.0, 142.1, 143.1, 144.9, 148.6, 148.7, 148.7, 148.8 (aromatic C_{quat}). Elemental analysis found C, 64.27, H, 8.12; $C_{109}H_{162}O_{35}$ (2032.46) requires C, 64.41, H, 8.03%. Crystals suitable for X-ray diffraction were grown by diffusion of heptane into a butanone solution of **7**.

6-*O*-{3-[Bis(4-anisyl)methoxymethyl]phenyl-bis(4-anisyl)methyl}-subtituted permethylated α-CD (8)

R_f (EtOAc) = 0.17. Mp 166–168 °C. ES-TOF, *m/z*: 1738 (M − OMe)$^+$. δ_H ($CDCl_3$, 300.1 MHz) 2.94 (s, 3 H, MeO on trityl), 2.99–4.11 (36 H, H-2, H-3, H-4, H-5, H-6), 3.13 (s, 3 H, MeO), 3.26 (s, 3 H, MeO), 3.36 (s, 3 H, MeO), 3.38 (s, 3 H, MeO), 3.39 (s, 3 H, MeO), 3.45 (s, 3 H, MeO), 3.48 (s, 3 H, MeO), 3.48 (s, 3 H, MeO), 3.49 (s, 3 H, MeO), 3.50 (s, 3 H, MeO), 3.58 (s, 3 H, MeO), 3.59 (s, 3 H, MeO), 3.64 (s, 6 H, MeO), 3.65 (s, 3 H, MeO), 3.67 (s, 3 H, MeO), 3.70 (s, 3 H, MeO), 3.78 (s, 9 H, *Me*OAr), 3.79 (s, 3 H, *Me*OAr), 4.88 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 2.9 Hz, H-1), 5.05 (4 H, H-1), 5.10 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.3 Hz, H-1), 6.75–7.63 (20 H, aromatic H). δ_C ($CDCl_3$, 75.5 MHz) 55.0 [×3], 55.1 (*Me*OAr), 57.5, 57.6, 57.7, 57.8, 58.0, 58.1, 58.2, 58.9 [×4], 61.5, 61.6, 61.7 [×2], 61.8, 61.9 (MeO of CD), 62.7 (C-6^A), 66.9 (C-6), 70.8, 71.0 [×2], 71.2 [×2], 71.8 (C-5), 70.9, 71.3, 71.4, 71.5 (C-6), 81.1, 81.1 [×2], 81.2, 81.3, 81.3, 81.4, 81.8, 81.9, 82.0, 82.1, 82.1 [×2], 82.3 [×2], 82.4 [×2], 82.5 (C-2, C-3, C-4), 85.7, 86.4 (O*C*$(Ar)_3$), 98.3, 99.8 [×2], 100.0, 100.1, 100.4 (C-1), 112.8 [×4], 125.0, 125.8, 127.4, 129.3, 129.8, 130.0, 130.3, 130.6 (aromatic CH), 135.6, 136.3, 136.7, 136.8, 143.4, 145.5, 158.1, 158.2, 158.3 [×2] (aromatic C_{quat}). Elemental analysis found C, 61.25, H, 7.36; $C_{90}H_{128}O_{35}$ (1770.00) requires C, 61.07, H, 7.29%.

6-*O*-{3-[Bis(4-*tert*-butylphenyl)methoxymethyl]phenyl-bis(4-*tert*-butylphenyl)methyl}-substituted permethylated α-CD (9)

R_f (EtOAc–cyclohexane, 80 : 20, v/v) = 0.24. FAB, *m/z*: 1872.9 (70%, M$^+$), 1841.9 (100%, (M − OCH_3)$^+$). δ_H ($CDCl_3$, 300.1 MHz) 1.28 (s, 36 H, Bu^t), 2.90 (s, 3 H, MeO on trityl), 2.93–4.14 (36 H, H-2, H-3, H-4, H-5, H-6), 3.11 (s, 3 H, MeO), 3.18 (s, 3 H, MeO), 3.31 (s, 3 H, MeO), 3.33 (s, 3 H, MeO), 3.37 (s, 3 H, MeO), 3.40 (s, 3 H, MeO), 3.46 (s, 9 H, MeO), 3.48 (s, 3 H, MeO), 3.56 (s, 6 H, MeO), 3.62 (s, 6 H, MeO), 3.64 (s, 3 H, MeO), 3.65 (s, 3 H, MeO), 3.69 (s, 3 H, MeO), 4.77 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.01 (m, 4 H, H-1), 5.07 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.1 Hz, H-1), 7.14–7.61 (20 H, aromatic H). δ_C ($CDCl_3$, 75.5 MHz) 31.3 [×2] (C(*C*H_3)$_3$), 31.4 [×2] (C(*C*H_3)$_3$), 34.3 [×4] (*C*$(CH_3)_3$), 51.9 (MeO on trityl), 57.5, 57.6, 57.7, 57.8, 58.2, 58.2, 58.3, 58.8 [×3], 58.9, 61.4, 61.6, 61.7 [2], 61.8, 61.8 (MeO of CD), 62.4 (C-6^A), 70.6, 70.9, 71.0, 71.1 [×2], 71.9 (C-5), 71.1, 71.2, 71.3, 71.4, 71.6 (C-$6^{B,C,D,E,F}$), 81.0, 81.1 [×3], 81.2, 81.5, 81.8, 81.9, 82.0, 82.1 [×3], 82.2 [×3], 82.3, 82.4 [×2] (C-2, C-3, C-4), 85.9, 86.7 (O*C*$(Ar)_3$), 97.6, 99.7, 99.8, 100.0 [×2], 100.4 (C-1), 124.1, 124.2 [×2], 124.3, 125.3, 126.0, 127.2, 128.3, 128.5, 128.7, 129.0, 129.7 (aromatic C), 140.4, 140.9, 141.1, 141.4, 143.1, 144.8, 149.2 [×2], 149.3 [×2] (aromatic C_{quat}). Elemental analysis found C, 65.09, H, 8.28; $C_{102}H_{152}O_{31}$ (1874.33) requires C, 65.36; H, 8.17.

6-*O*-{3-[Bis(4-*tert*-butylphenyl)methoxymethyl]phenyl-bis(4-*tert*-butylphenyl)methyl}-substituted permethylated β-CD (10)

R_f (EtOAc–cyclohexane, 80 : 20, v/v) = 0.13. ES-TOF, *m/z*: 2047.2 (M − CH_3O)$^+$, 2077 (M)$^+$. δ_H ($CDCl_3$, 300.1 MHz) 1.29 (s, 9 H, Bu^t), 1.29 (s, 18 H, Bu^t), 1.31 (s, 9 H, Bu^t), 2.87 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ 3.2 Hz, $^3J_{H\text{-}2,H\text{-}3}$ 9.3 Hz, H-2), 2.93 (s, 3 H, MeO on trityl), 2.99–3.90 (41 H, H-2, H-3, H-4, H-5, H-6), 3.14 (s, 3 H, MeO), 3.18 (s, 3 H, MeO), 3.22 (s, 3 H, MeO), 3.32 (s, 3 H, MeO), 3.35 (s, 3 H, MeO), 3.36 (s, 3 H, MeO), 3.38 (s, 3 H, MeO), 3.48 (s, 9 H, MeO), 3.50 (s, 3 H, MeO), 3.51 (s, 3 H, MeO), 3.55 (s, 3 H, MeO), 3.57 (s, 3 H, MeO), 3.62 (s, 3 H, MeO), 3.63 (s, 6 H, MeO), 3.65 (s, 3 H, MeO), 3.65 (s, 3 H, MeO), 4.74 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.06 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.2 Hz, H-1), 5.07

(d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.3 Hz, H-1), 5.15–5.18 (m, 3 H, H-1), 5.20 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ 3.4 Hz, H-1), 6.96–7.57 (20 H, aromatic H). Elemental analysis found C, 64.22, H, 8.17; $C_{111}H_{168}O_{36}$ (2078.55) requires C, 64.13, H, 8.15%.

$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F$-Hexadeca-*O*-methyl-α-cyclodextrin 11

Aqueous HBF_4 (34%, 1.15 mL) was added to a solution of **6** (1.000 g, 0.547 mmol) in MeCN (40 mL). The solution was stirred for 20 min at room temperature, whereupon Et_3N (2.5 mL) was added. Addition of H_2O (160 mL) caused the "bis-trityl-$(OH)_2$" to precipitate. The latter was filtered and the filtrate extracted with CH_2Cl_2 (4 × 80 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 80 mL) before being dried ($MgSO_4$) and evaporated to dryness, affording **11** as a colourless solid (0.630 g, 96%). R_f (CH_2Cl_2–MeOH, 85 : 15, v/v) = 0.22. Mp 113–115 °C. δ_H (300.1 MHz, $CDCl_3$) 2.39 (br s, 1 H, $OH^{A\text{ or }B}$), 2.61 (br s, 1 H, $OH^{B\text{ or }A}$), 3.38 (s, 3 H, MeO-6), 3.39 (s, 9 H, MeO-6), 3.47 (s, 3 H, MeO-2), 3.48 (s, 9 H, MeO-2), 3.49 (s, 3 H, MeO-2), 3.50 (s, 3 H, MeO-2), 3.63 (s, 6 H, MeO-3), 3.64 (s, 9 H, MeO-3), 3.65 (s, 3 H, MeO-3), 3.12–4.03 (36 H, H-2, H-3, H-4, H-5, H-6), 5.02 (d, $^3J_{H\text{-}2,H\text{-}1}$ 3.3 Hz, 1 H, H-1), 5.03–5.06 (4 overlapping d, 4 H, H-1), 5.08 (d, $^3J_{H\text{-}2,H\text{-}1}$ 3.3 Hz, 1 H, H-1). δ_C (75.5 MHz, $CDCl_3$) 57.64, 57.69 [×3], 57.75 and 57.77 (MeO-2), 58.75, 58.76 [×2] and 58.89 (MeO-6), 61.47, 61.50, 61.52 [×2] and 61.56 [×2] (MeO-3), 61.76 and 62.19 ($C\text{-}6^{A,B}$), 70.95, 70.99 [×2] and 71.07 ($C\text{-}5^{C,D,E,F}$), 71.29, 71.32 and 71.37 [×2] ($C\text{-}6^{C,D,E,F}$), 72.37 and 72.73 ($C\text{-}5^{A,B}$), 81.08 [×3], 81.13 [×3], 81.77, 81.82 [×2], 81.92 [×4], 81.98, 82.07 [×2], 82.19 and 82.51 (C-2, C-3, C-4), 99.36, 99.51, 99.59, 99.66, 99.69, 99.73 (C-1). Elemental analysis found C, 51.98, H, 7.53; $C_{52}H_{92}O_{30}$ (1197.27) requires C, 52.15, H, 7.75.

Collection and reduction of X-ray data

Single crystals were obtained by slow diffusion of heptane containing a small amount of hexane into a butanone solution of **7**. Due to the very high desolvatation abilities of this compound, the sample was captured inside the crystallisation solvent with oil, then very quickly mounted in a capillary and set in the 110 K nitrogen flow. $C_{109}H_{162}O_{35}\cdot\frac{3}{2}(C_7H_{16})\cdot\frac{1}{2}(C_4H_8O)\cdot\frac{1}{4}(C_6H_{14})$, M_r = 2240.28, orthorhombic, $P2_12_12_1$, a = 16.3780(3), b = 27.7666(4), c = 30.3256(5) Å, V = 13790.9(4) Å^3, Z = 4, D_x = 1.085 Mg m^{-3}, λ(MoKα) = 0.71073 Å, μ = 0.78 cm^{-1}, $F(000)$ = 4862, T = 120 K. The sample (0.22 × 0.14 × 0.10 mm) was studied on a NONIUS Kappa CCD with graphite monochromatised MoKα radiation. The cell parameters were obtained with Denzo and Scalepack[22] with 10 frames (ψ rotation: 1° per frame). Data collection[23] ($2\theta_{max}$ = 52.5°, 472 frames *via* 0.6° ω rotation and 15 s per frame, range *hkl*: *h* 0–19; *k* 0–33; *l* 0–36) gave 107 864 reflections. Data reduction with Denzo and Scalepack led to 13 094 independent reflections, from which 7957 had $I > 2.0\,\sigma(I)$. The structure was solved with SIR2002[24] which revealed the non-hydrogen atoms of the compound and one heptane molecule disordered over two positions. After further refinements, $\frac{1}{2}$ molecule of heptane and $\frac{1}{2}$ molecule of butanone were found, both lying outside the CD cavity. After structure solution, three residual carbon atoms (occupancy *ca.* 0.25) were found outside the CD which could be assigned to a hexane molecule near a special position. The whole structure was refined with SHELXL (huge option)[25] by the full-matrix least-squares technique (use of F^2 magnitude; x, y, z, β_{ij} for C and O atoms, x, y, z in riding mode for H atoms; 1527 variables and 7957 observations with $I > 2.0\,\sigma(I)$; calc. $w = 1/[\sigma^2(F_o^2) + (0.115P)^2 + 6.76\,P]$ where $P = (F_o^2 + 2\,F_c^2)/3$ with the resulting R = 0.082, R_w = 0.147 and S_w = 1.107, $\Delta\rho < 0.49$ e Å^{-3}. CCDC reference number 260388. See http://www.rsc.org/suppdata/ob/b5/b504012d/ for crystallographic data in CIF or other electronic format.

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