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Synthesis and characterisation of some lipophilic per(2,6-di-*O*-alkyl)cyclomalto-oligosaccharides

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ABSTRACT

Cyclomalto-hexa-, -hepta-, and -octa-ose (cyclodextrins; α-, β-, and γ-CD) were alkylated severally using propyl, butyl, pentyl, 3-methylbutyl, and dodecyl bromides and NaOH in methyl sulfoxide at 23°. After reaction for 3–9 days, the per(2,6-di-*O*-alkyl)-CDs were formed. The regiospecifity of these alkylations was higher than for methylations. The best yields of crystalline products were obtained for the butyl derivatives of α- and β-CD (37% and 41%, respectively). The homogeneity of the pattern of substitution was verified by degradation analysis, f.a.b.-m.s., and n.m.r. spectroscopy.

INTRODUCTION

Cyclomalto-hexa-, -hepta-, and -octa-ose (α-, β-, and γ-CD) are chiral host compounds[1], but, due to their hydrophilicity, applications are restricted to aqueous systems[2]. For applications of CDs in inert organic solvents[3,4], hydrophobic derivatives are necessary. Among may CD derivatives[5], the alkyl ethers are of special interest because they are highly soluble in most organic solvents and stable.

Hexakis(2,6-di-*O*-methyl)-αCD[6] (**1a**) and heptakis(2,6-di-*O*-methyl)-βCD[7,8] (**1b**) were usually synthesised by the procedure of Kuhn and Trischmann[9], which involves treatment of αCD and βCD with $Ba(OH)_2 \cdot 8\ H_2O/BaO$ and methyl sulfate in *N,N*-dimethylformamide–methyl sulfoxide at 0°. This procedure was claimed initially to alkylate preponderantly at positions 2 or 6, but it was shown later[10–12] that mixtures with broad distributions of substituents were obtained. The isolation of **1a** and **1b** from these mixtures by chromatography was difficult[10,12] and isolation as the benzoates was recommended[13]. For the preparation of heptakis(2,6-di-*O*-ethyl)-βCD (**2**), βCD was ethylated by the above procedure[14], but a mixture of products was found[11].

A straightforward procedure to obtain per(2,6-di-*O*-alkyl)-CD derivatives (**3–7**) is now described together with the verification of the pattern of substitution.

RESULTS AND DISCUSSION

Synthesis. — The alkylation of CDs with long-chain alkyl bromides (*e.g.*, pentyl bromide) under the conditions[9] noted above was slow and a d.s. of 2 was not reached. The methylation of monosaccharides with methyl iodide/NaOH in methyl sulfoxide is

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rapid and complete[15]. Application of this method to βCD with pentyl bromide at 23° for 3 days gave a mixture of lipophilic pentyl ethers[16] that was analysed by degradation analysis[17,18]. The crude product (yield ~95%) contained 8% of mono-, 79% of 2,6-di-, and 11% of 2,3,6 tri-*O*-pentyl "anhydroglucose" units. Chromatography gave 53% of a product that contained 94.4% of 2,6-di- and 5.6% of 2,3,6 tri-*O*-pentyl "anhydroglucose" units, from which nearly pure heptakis(2,6-di-*O*-pentyl)-βCD (**5b**; overall yield, 5%; 98.4% of 2,3,6 tri-*O*-pentyl "anhydroglucose" units) was isolated by recrystallisation. The rate of reaction was dependent on the proportion of water in the reaction mixture; 0.5–1% increased the rate, but higher proportions reduced the yield due to hydrolysis of the alkylating agent. Sometimes, an induction period (up to 3 days) was observed but this did not influence the final yield. Elevation of the temperature accelerated the alkylation but reduced the regiospecifity, *e.g.*, after reaction for 1 day at 40°, the crude product (yield ~95%) contained 14% of mono-, 74% of 2,6-di-, and 11% of 2,3,6 tri-*O*-pentyl "anhydroglucose" units.

In order to test the scope of this alkylation method, the reactions of each of a series of *n*-alkyl bromides were investigated with βCD and a general procedure was developed for the preparation of the per(2,6-di-*O*-alkyl)-CDs **3**–**7**. The yields after chromatography increased from 0% for ethyl bromide to 60% for dodecyl. Ethylation gave heptakis(2,3,6-tri-*O*-ethyl)-βCD as the major product. The yield of the final recrystallisation dropped with increasing length of the alkyl chain. Heptakis(2,6-di-*O*-butyl)-βCD (**4b**) was synthesised in the highest yield (41%) and in the highest purity.

Crystalline per(2,6-di-*O*-butyl) derivatives of α- (**4a**) and γ-CD (**4c**) were also prepared. The rate of butylation of the CDs increased in the series $\alpha < \beta < \gamma$ (completion after 7, 5, and 3 days, respectively) and the yields (**4a**, 37%; **4b**, 41%; and **4c**, 10%) reflected an increase in overalkylation. For comparison, the facility of methylation increases in the order $\beta \leqslant \alpha << \gamma$ (ref. 11). These differences of the reactivities of CDs might be due to the increase of the flexibility with increase in the size of macrocycle, with consequent higher accessibility of the OH groups and a lower discrimination of HO-3. Also, the recognition of the size of macrocycle by reactants might be the cause[11].

The sensitivity of the 2,6-di-*O*-alkylation of CDs towards steric effects was also investigated by using branched alkyl bromides. 1-Methylbutyl bromide and 3,3-dimethylbutyl bromide did not give any lipophilic CD ether. Only with 3-methylbutyl bromide did alkylation of βCD occur and 36% of crystalline heptakis(2,6-di-*O*-3-methylbutyl)-βCD (**6**) was isolated.

Characterisation of the products. — In contrast to the per-2,6-di-*O*-methyl (**1a** and **1b**) and -ethyl (**2**) derivatives, the propyl and the longer-chain alkyl derivatives **3**–**6** were not hydrophilic. The solubility of **3**–**6** in water was < 0.1%, and, in such polar solvents as methanol or methyl sulfoxide, they were only moderately soluble at 23°. On the other hand, **3**–**6** were highly soluble in heptane, toluene, and chloroform.

The homogeneity of the alkylated CDs was analysed by several independent

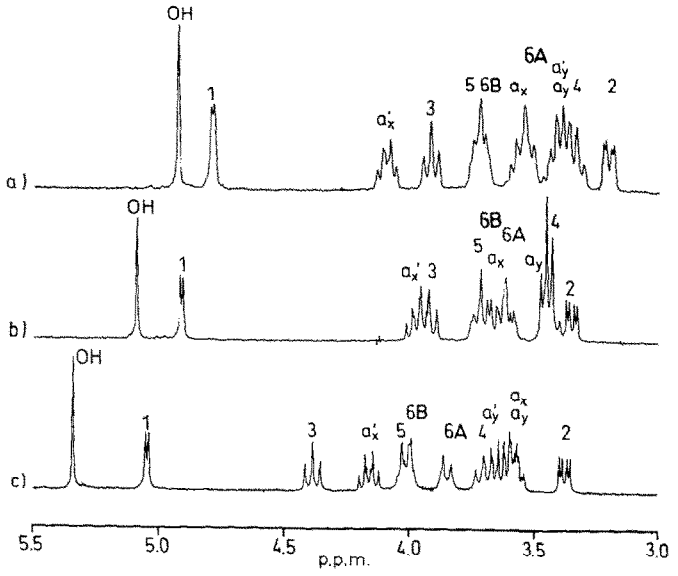

Fig. 1. Partial ^{1}H-n.m.r. spectra (region of the carbohydrate protons) at 20° of **5b** in (*a*) cyclohexane-d_{12}, (*b*) $CDCl_3$, (*c*) toluene-d_8.

methods. T.l.c. was sensitive to the d.s. because of the change of polarity caused by the alkylation of an OH group, and this effect became more pronounced as the length of the alkyl chain increased. Small amounts (> 5%) of over- or under-alkylated by-products were detectable. The sensitivity of ^{1}H-n.m.r. spectroscopy (300 MHz) for these by-products was even higher (> 3%). The signal of H-1 is shifted markedly downfield when HO-3 is alkylated [δ of H-1 in toluene, 5.04 for **5b** and 5.52 for heptakis(2,3,6-tri-*O*-pentyl)-βCD[19]]. As the symmetry of the CD is lost by partial overalkylation, even one over-alkylated glucose residue is easily detectable[13]. The H-1 signals of recrystallised **3**, **4a–c**, **5a**, **5b** (Fig. 1), and **6** were sharp and demonstrated the symmetry.

The best resolved ^{1}H-n.m.r. spectra of the 2,6-di-*O*-alkyl-CDs were obtained on solutions in toluene, as shown for **5b** in Fig. 1. The chemical shifts of the resonances of the inner (H-3) and outer (H-1) carbohydrate protons are dependent upon the solvent, which could reflect inclusion effects or changes in conformation.

The ^{1}H signals of **5b** were assigned by the COSY spectrum shown in Fig. 2. As the ^{1}H-n.m.r. spectra of the other compounds were similar to that of **5b**, analogous assignments were made and confirmed where necessary by homodecoupling measurements. The chemical shifts of, for example, the H-1 resonance are nearly independent of the length of the alkyl chain. Consequently, the βCD macrocycles of **3**, **4b**, **5b**, **6**, and **7** appear to have similar conformations. On the other hand, the chemical shift of the HO-3 resonance is dependent on the size of the CD macrocycle (δ 5.08 for **4a**, 5.32 for **4b**, and 5.42 for **4c**), which could reflect the strength of the hydrogen bonds between HO-3 and O-2. The temperature dependence of the chemical shift of the HO-1 signal (δ 5.32 at 20°, 5.22 at 60°, and 5.11 at 100°) supported this conclusion.

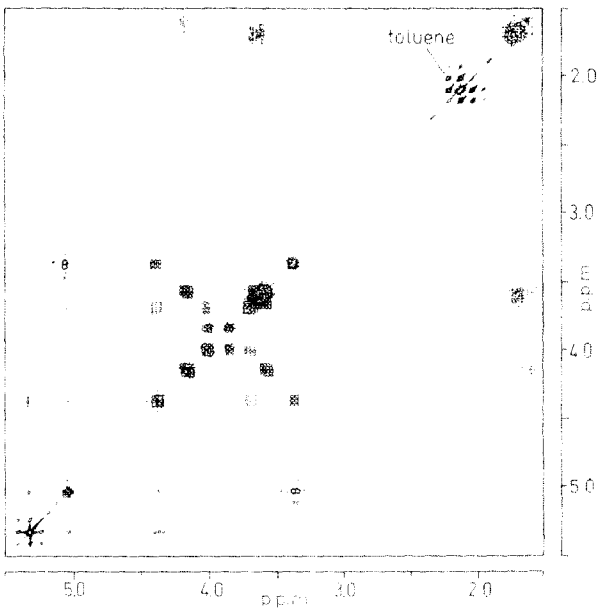

Fig. 2. Partial ^{1}H-COSY n.m.r. spectrum at 20° of **5b** in toluene-d_8.

The geminal protons of three methylene groups (*e.g.*, of **5b**) were non-equivalent, the signals of H-6A and H-6B were split by 0.18 p.p.m., those of one of the α-methylene groups (a_x) by 0.55 p.p.m., and those of the other α-methylene group (a_y) by 0.10 p.p.m. (measured on solutions in toluene at 20°). A similar splitting (~0.10 p.p.m.) of the signals of H-6,6 was observed for **1a**[20], **1b**[13], and heptakis(2,3,6-tri-*O*-methyl)-β-CD[21], and was attributed to hindered rotation of the C-5–C-6 bond[23]. In order to evaluate this possibility, the temperature dependence of the ^{1}H-n.m.r. spectrum of **5b** in toluene was checked up to 100°. However, since there was no significant shift of the signals of these methylene protons as the temperature was increased (*e.g.*, for a'_x, δ 4.15 at 20°, 4.12 at 60°, and 4.09 at 100°; *cf.* for H-1, δ 5.05 at 20°, 5.03 at 60°, and 5.01 at 100°), these splittings are due to the diastereotopic environments. The splitting of the signals of the α-methylene groups should decrease with increasing distance to a stereogenic[22] centre. The α-methylene group at O-2 (a_2) is closer to the chiral C-2 than the α-methylene group at O-6 (a_6) is to chiral C-5. Therefore, the signal with the higher splitting (a_x) should be associated with a_2. At longer distances, small diastereotopic splittings were also observed. For the 3-methylbutyl derivative **6**, there was non-equivalence of the 2 geminal methyl groups at the end of the alkyl chain; the signals of the methyl protons H-d_5 and H-d_6 were each split by 0.02 p.p.m. and the signals for C-d_5 and C-d_6 were split by 0.07/0.14 p.p.m.. This effect cannot be explained by the influence of one stereogenic centre (C-2 or C-5) alone, but by the chiral effect of the CD macrocycle.

Mass spectrometry is known to be an unambiguous method for the detection of over- or under-alkylated CD products[11]. The f.a.b.-mass spectrum of recrystallised **5b** showed only one major signal corresponding to the **5b**·Na^+ ion (Fig. 3). Unfortunately,

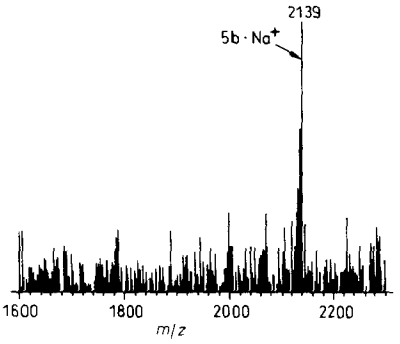

Fig. 3. F.a.b.-mass spectrum of recrystallised **5b**.

the signal-to-noise ratio of ~4 was quite low due to the low solubility of **5b** in the matrix.

The per(2,6-di-*O*-alkyl)-CDs described above may have value as intermediates for the synthesis of more sophisticated host–guest systems based on CDs.

EXPERIMENTAL

General methods. — Methyl sulfoxide was stored over molecular sieves (0.4 nm) and contained <0.03% of water. Tetrahydrofuran, *tert*-butyl methyl ether, and light petroleum (b.p. 30–75°) were freshly distilled. The CDs, which were commercial products, were used without further purification, and contained 10–12% of water. Melting points were measured with a differential scanning calorimeter DSC-30 (Mettler) with heating at 5°/min. Optical rotations were measured on solutions in $CHCl_3$ at 23° with a IBZ Messtechnik instrument. I.r. spectra (films on NaCl discs) were recorded with a Perkin–Elmer 1430 spectrometer. F.a.b.-m.s. was performed using a primary atom beam of Xe atoms with a Kratos MS80RF spectrometer coupled to a DS90 data system, with 3-nitrobenzyl alcohol containing a trace of triton X100 as the matrix. N.m.r. spectra (^1H, 300.13 MHz; ^{13}C, 75.46 MHz) were obtained with a Bruker AW 300 spectrometer at 20°. For ^1H–^1H COSY spectra, 1024 × 8 free-induction decays were acquired with 4K data points and a sweep width of 2000 Hz; for ^1H–^{13}C-COSY spectra, 256 × 80 free induction decays were acquired with 16K data points for ^{13}C (sweep width 11 000 Hz) and 0.5K data points for ^1H (sweep width 1200 Hz). All chemical shifts are referenced to internal Me_4Si. The ^{13}C-n.m.r. signals were assigned by using the DEPT technique or by ^1H–^{13}C-COSY spectroscopy.

The carbons of the alkyl chains are designated, a, b, c, *etc.*, starting with the position α to the oxygen. The subscripts 2 or 6 designate the location of the alkyl group at position 2 or 6; if this position could not be assigned, subscripts x or y are used. Diastereotopic protons at C-6 are distinguished by A and B; diastereotopic substituents at a C atom of a side chain by apostrophes (*e.g.*, H-a_x,a'_x), respectively. Numbers of protons are given per "anhydroglucose" unit.

*Synthesis of per(2,6-di-*O*-alkyl)-CDs.* — Each alkylation reaction was performed

at 23° under nitrogen. A solution of the CD (5 mmol) in methyl sulfoxide (150 mL) that contained 20 × *n* mmol each of alkyl bromide and freshly powdered sodium hydroxide (*analytical* grade) (*n* is the size of the CD macrocycle) was stirred for 2 days (the formation of a fine white precipitate of NaBr indicated the onset of the reaction). More NaOH and alkyl bromide (10 × *n* mmol each) were added and the mixture was stirred for 3 days. The reactions were monitored by t.l.c. on Silica Gel 60 (Merck), using *tert*-butyl methyl ether–light petroleum mixtures (*A*, 7:3; *B*, 3:7; *C*, 15:85) with detection by charring with 2% sulfuric acid in ethanol or with molybdato phosphoric acid spray. As soon as only one major product was observed, each mixture was worked-up; otherwise, the addition of the reagents was repeated and the total reaction time was prolonged up to 7 days. The resulting brownish suspension was poured into water (300 mL) and extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined extracts were washed twice with water and half-concentrated brine, and concentrated *in vacuo* (100 Pa). Drying over inorganic salts caused loss of product. The crude product was fractionated by l.c. (over-pressure 0.02 MPa) on Silica Gel 60 (500 g, 40–63 μm) with a 10–30% gradient of *tert*-butyl methyl ether in light petroleum. The final product was dried *in vacuo* at 60° for 16 h and crystallised from methanol at 5°.

Heptakis(2,6-di-O-propyl)-βCD (**3**). — The reaction of βCD (2.55 g, 2 mmol) with propyl bromide (56 + 28 mmol) and NaOH (56 + 28 mmol) for 5 days yielded **3** (2.2 g, 63%) after chromatography. After recrystallisation, **3** (0.55 g, 16%) was obtained with m.p. 256° (dec.), $[\alpha]_D$ +82° (*c* 0.92); R_f 0.44 (solvent *A*), 0.08 (solvent *B*); ν_{max} 3430s, 2960s, 2930s, 2870s, 1465m, 1360m, 1180s, 1090s cm^{-1}. N.m.r. data: ^{1}H (toluene-d_8), δ 5.30 (s, 1 H, HO-3), 5.01 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.36 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 4.07 (dt, 1 H, J_{a_x,a'_x} 9.2, $J_{a_x,b}$ 7.1 Hz, H-a$'_x$), 4.02–3.95 (m, 2 H, H-5,6B), 3.83 (dd, 1 H, $J_{6A,6B}$ 9.1, $J_{5,6A}$ < 3 Hz, H-6A), 3.64 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.60–3.41 (m, 3 H, H-a$_x$,a$_y$,a$'_y$), 3.33 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.2 Hz, H-2), 1.78–1.50 (m, 4 H, H-b), 0.99 (t, 3 H, $J_{b,c}$ 7.4 Hz, H-c$_x$), 0.84 (t, 3 H, $J_{b,c}$ 7.4 Hz, H-c$_y$); ^{13}C (CDCl$_3$), δ 101.8 (C-1), 83.5 (C-4), 80.4 (C-2), 74.6 (C-a$_x$), 73.5 (C-3), 73.0 (C-a$_y$), 70.4 (C-5), 69.1 (C-6), 22.9 (C-b$_x$), 22.7 (C-b$_y$), 10.5 (C-c$_x$), 10.1 (C-c$_y$).

Anal. Calc. for $C_{84}H_{154}O_{35}$: C, 58.5; H, 9.0. Found: C, 58.1; H, 8.9.

Hexakis(2,6-di-O-butyl)-αCD (**4a**). — The reaction of αCD (15.4 g, 14 mmol) with butyl bromide (336 + 168 + 168 mmol) and NaOH (336 + 168 + 168 mmol) for 7 days yielded **4a** (12.9 g, 56%, after chromatography; 8.5 g, 37%, after recrystallisation), m.p. 161°, $[\alpha]_D$ +72° (*c* 1), R_f 0.17 (solvent *B*); ν_{max} 3460s, 2970s, 2940s, 2880s, 1470m, 1370m, 1160s, 1090s, 1050 cm^{-1}. N.m.r. data: ^{1}H (toluene-d_8), δ 5.08 (s, 1 H, HO-3), 4.96 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.32 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.0 Hz, H-3), 4.09 (dt, 1 H, J_{a_x,a'_x} 9.4, $J_{a'_x,b}$ 6.7 Hz, H-a$'_x$), 4.03 (m, 1 H, H-6B), 3.96 (dd, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 3.7 Hz, H-5), 3.79 (dd, 1 H, $J_{6A,6B}$ 10.4, $J_{5,6A}$ 3.7 Hz, H-6A), 3.70 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 3.64–3.52 (m, 2 H, H-a$_x$,a$'_y$), 3.48 (dt, 1 H, J_{a_y,a'_y} 9.3, $J_{a_y,b}$ 6.6 Hz, H-a$_y$), 3.31 (dd, 1 H, $J_{1,2}$ 3.3, $J_{2,3}$ 9.0 Hz, H-2), 1.68–1.52 (m, 4 H, H-b), 1.51–1.41 (m, 2 H, H-c$_x$), 1.38–1.30 (m, 2 H, H-c$_y$), 0.94 (t, 3 H, $J_{c,d}$ 7.2 Hz, H-d$_x$), 0.87 (t, 3 H, $J_{c,d}$ 7.2 Hz, H-d$_y$); ^{13}C (CDCl$_3$), δ 101.4 (C-1), 83.5 (C-4), 79.7 (C-2), 73.8 (C-3), 72.3 (C-a$_x$), 71.4 (C-a$_y$), 70.4 (C-5), 69.3 (C-6), 31.8 (C-b$_x$), 31.7 (C-b$_y$), 19.2 (C-c$_x$), 18.9 (C-c$_y$), 13.9 (C-d$_x$), 13.7 (C-d$_y$).

Anal. Calc. for $C_{84}H_{156}O_{30}$: C, 61.3; H, 9.5. Found: C, 61.1; H, 9.4.

*Heptakis(2,6-di-*O*-butyl)-βCD* (**4b**). — The reaction of βCD (6.4 g, 5 mmol) with butyl bromide (140 + 70 mmol) and NaOH (140 + 70 mmol) for 5 days yielded **4b** (4.9 g, 51%, after chromatography; 3.8 g, 40%, after recrystallisation), m.p. 198°, $[\alpha]_D$ +75° (*c* 1.1); R_F 0.19 (solvent *B*); ν_{max} 3410s, 2960s, 2930s, 2860s, 1470m, 1160s, 1090s, 1040m cm^{-1}. N.m.r. data: ^1H (toluene-d_8), δ 5.32 (s, 1 H, HO-3), 5.02 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.37 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 4.13 (dt, 1 H, $J_{a'_x,a_x}$ 13.8, $J_{a'_x,b}$ 9.4 Hz, H-a'$_x$), 4.00 (m, 1 H, H-5), 3.96 (m, 1 H, H-6B), 3.83 (dd, 1 H, $J_{6A,6B}$ 9.2, $J_{5,6A}$ < 3 Hz, H-6A), 3.67 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 3.63–3.51 (m, 3 H, H-a$_x$,a$_y$,a'$_y$), 3.34 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.5 Hz, H-2), 1.72–1.52 (m, 4 H, H-b), 1.51–1.41 (m, 2 H, H-c$_y$), 1.39–1.30 (m, 2 H, H-c$_x$), 0.96 (t, 3 H, J_{c_x,d_x} 7.3 Hz, H-d$_x$), 0.88 (t, 3 H, J_{c_y,d_x} 7.3 Hz, H-d$_y$); ^{13}C ($CDCl_3$), δ 101.8 (C-1), 83.5 (C-4), 80.4 (C-2), 73.5 (C-3), 72.7 (C-a$_x$), 71.2 (C-a$_y$), 70.4 (C-5), 69.1 (C-6), 31.8 (C-b$_x$), 31.7 (C-b$_y$), 19.3 (C-c$_x$), 19.0 (C-c$_y$), 13.9 (C-d$_x$), 13.8 (C-d$_y$).

Anal. Calc. for $C_{98}H_{182}O_{35}$: C, 61.3; H, 9.5. Found: C, 61.2; H, 9.4.

*Oktakis(2,6-di-*O*-butyl)-γCD* (**4c**). — The reaction of γCD (14.6 g, 10 mmol) with butyl bromide (320 + 160 mmol) and NaOH (320 + 160 mmol) for 3 days yielded **4c** (5.7 g, 26%, after chromatography; 2.2 g, 10%, after recrystallisation) as white needles, m.p. 219°, $[\alpha]_D$ +82° (*c* 1); R_F 0.12 (solvent *B*); ν_{max} 3420s, 2960s, 2940s, 2880s, 1470m, 1360m, 1170s, 1090s, 1050m cm^{-1}. N.m.r. data: ^1H (toluene-d_8), δ 5.42 (s, 1 H, HO-3), 5.09 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.31 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 4.16 (dt, 1 H, J_{a_x,a'_x} 9.2, $J_{a'_x,b}$ 6.7 Hz, H-a'$_x$), 4.06 (m, 1 H, H-5), 4.01 (m, 1 H, H-6B), 3.85 (dd, 1 H, $J_{6A,6B}$ 9.7, $J_{5,6A}$ < 3 Hz, H-6A), 3.65 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.64–3.52 (m, 3 H, H-a$_x$,a$_y$,a'$_y$), 3.35 (dd, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 9.2 Hz, H-2), 1.71–1.56 (m, 4 H, H-b), 1.54–1.42 (m, 2 H, H-c$_x$), 1.40–1.32 (m, 2 H, H-c$_y$), 0.95 (t, 3 H, J_{c_x,d_x} 7.3 Hz, H-d$_x$), 0.90 (t, 3 H, J_{c_y,d_y} 7.3 Hz, H-d$_y$); ^{13}C ($CDCl_3$), δ 101.8 (C-1), 83.3 (C-4), 80.8 (C-2), 73.4 (C-3), 72.8 (C-a$_x$), 71.2 (C-a$_y$), 70.5 (C-5), 69.2 (C-6), 31.82 (C-b$_x$), 31.76 (C-b$_y$), 19.3 (C-c$_x$), 19.0 (C-c$_y$), 13.9 (C-d$_x$), 13.8 (C-d$_y$).

Anal. Calc. for $C_{112}H_{208}O_{40}$: C, 61.3; H, 9.5. Found: C, 61.3; H, 9.4.

*Hexakis(2,6-di-*O*-pentyl)-αCD* (**5a**). — The reaction of αCD (17.5 g, 16 mmol) with pentyl bromide (384 + 192 mmol) and NaOH (384 + 192 mmol) for 3 days yielded **5a** (17.1 g, 65%) after chromatography. Slow concentration of a solution in methanol gave **5a** (1.5 g, 6%), m.p. 103°, $[\alpha]_D$ +70° (*c* 0.9); R_F 0.33 (solvent *B*); ν_{max} 3420s, 2950s, 2930s, 2860s, 1460m, 1360m, 1155s, 1090s, 1050s cm^{-1}. N.m.r. data: ^1H (toluene-d_8), δ 5.12 (s, 1 H, HO-3), 4.98 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.34 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 4.10 (dt, 1 H, J_{a_x,a'_x} 9.3, $J_{a'_x,b}$ 7.8 Hz, H-a'$_x$), 4.06–3.99 (m, 1 H, H-5), 3.97 (m, 1 H, H-6B), 3.79 (dd, 1 H, $J_{6A,6B}$ 10.0, $J_{5,6A}$ < 3 Hz, H-6A), 3.72 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.65–3.50 (m, 3 H, H-a$_x$,a$_y$,a'$_y$), 3.34 (dd, 1 H, $J_{1,2}$ 3.2, $J_{2,3}$ 9.2 Hz, H-2), 1.73–1.53 (m, 4 H, H-b), 1.44–1.34 (m, 4 H, H-c), 1.32–1.30 (m, 4 H, H-d), 0.92 (t, 3 H, J_{d_x,e_x} 7.1 Hz, H-e$_x$), 0.89 (t, 3 H, J_{d_y,e_y} 7.1 Hz, H-e$_y$); ^{13}C ($CDCl_3$), δ 101.5 (C-1), 83.6 (C-4), 80.0 (C-2), 73.9 (C-3), 72.7 (C-a$_x$), 71.9 (C-a$_y$), 70.5 (C-5), 69.4 (C-6), 29.5 (C-b$_x$); 29.4 (C-b$_y$), 28.3 (C-c$_x$), 27.9 (C-c$_y$), 22.6 (C-d$_x$), 22.5 (C-d$_y$), 14.0 (C-e).

Anal. Calc. for $C_{96}H_{180}O_{30}$: C, 63.6; H, 10.0. Found: C, 64.0; H, 10.0.

*Heptakis(2,6-di-*O*-pentyl)-βCD* (**5b**). — The reaction of βCD (12.7 g, 10 mmol)

with pentyl bromide (280 + 140 mmol) and NaOH (280 + 140 mmol) for 3 days yielded **5b** (11.2 g, 53%). Slow concentration of a solution in methanol at room temperature gave **5b** (1.0 g, 5%), m.p. 129°, $[\alpha]_D$ +71° (*c* 0.8); R_F 0.34 (solvent *B*); ν_{max} 3420s, 2920s, 2960s, 2860s, 1470m, 1360m, 1160s, 1090s, 1040m cm^{-1}. N.m.r. data: ^{1}H (toluene-d_8): δ 5.33 (s, 1 H, HO-3), 5.05 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.37 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.4 Hz, H-3), 4.15 (dt, 1 H, $J_{a'x,ax}$ 9.5, $J_{a'x,b}$ 7.0 Hz, H-a'$_x$), 4.02 (m, 1 H, H-5), 4.00 (m, 1 H, H-6B), 3.84 (dd, 1 H, $J_{6A,6B}$ 9.5, $J_{5,6A}$ < 3 Hz, H-6A), 3.68 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.4 Hz, H-4), 3.66–3.53 (m, 3 H, H-a'$_y$,a$_x$,a$_y$), 3.37 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.4 Hz, H-2), 1.75–1.50 (m, 4 H, H-b), 1.50–1.20 (m, 8 H, H-c,d), 1.00–0.85 (dt, 6 H, H-e); ^{13}C ($CDCl_3$), δ 101.9 (C-1), 83.6 (C-4), 80.5 (C-2), 73.5 (C-3), 73.0 (C-a$_x$), 71.6 (C-a$_y$), 70.6 (C-5), 69.2 (C-6), 29.44 (C-b$_x$), 29.38 (C-b$_y$), 28.3 (C-c$_x$), 27.9 (C-c$_y$), 22.6 (C-d$_x$), 22.5 (C-d$_y$), 14.1 (C-e$_x$), 14.0 (C-e$_y$).

Anal. Calc. for $C_{112}H_{210}O_{35}$: C, 63.6; H, 10.0. Found: C, 63.6; H, 9.9.

Heptakis[2,6-di-O-(3-methylbutyl)]-βCD (**6**). — The reaction of βCD (5.1 g, 4 mmol) with 3-methylbutyl bromide (112 + 56 + 56 mmol) and NaOH (112 + 56 + 56 mmol) after 9 days yielded **6** (3.7 g, 44%, after chromatography; 3.0 g, 36%, after recrystallisation), m.p. 189°, $[\alpha]_D$ +69° (*c* 0.95); R_F 0.39 (solvent *B*); ν_{max} 3460s, 2960s, 2920s, 2870m, 1470m, 1360m, 1160m, 1090s, 1050s cm^{-1}. N.m.r. data: ^{1}H (toluene-d_8), δ 5.32 (s, 1 H, HO-3), 5.01 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.36 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 4.21 (dt, 1 H, $J_{ax,a'x}$ 9.2, $J_{a'x,b}$ 7.1 Hz, H-a'$_x$), 3.99 (m, 2 H, H-5,6B), 3.83 (dd, 1 H, $J_{6A,6B}$ 9.2, $J_{5,6A}$ < 3 Hz, H-6A), 3.68 (m, 1 H, H-a$_x$), 3.66 (m, 1 H, H-4), 3.64–3.54 (m, 2 H, H-a$_y$,a'$_y$), 3.34 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.2 Hz, H-2), 1.90–1.72 (m, 2 H, H-c$_x$,c$_y$), 1.69–1.52 (m, 3 H, H-b$_y$, b$_x$, b'$_x$), 1.49–1.37 (m, 1 H, H-b'$_y$), 0.97 (d, 3 H, $J_{c,d}$ 6.38 Hz, H-d$_x$), 0.95 (d, 3 H, $J_{c,d}$ 6.78 Hz, H-d'$_x$), 0.93 (d, 3 H, $J_{c,d}$ 6.76 Hz, H-d$_y$), 0.91 (d, 3 H, $J_{c,d}$ 6.46 Hz, H-d'$_y$); ^{13}C ($CDCl_3$), δ 101.8 (C-1), 83.5 (C-4), 80.4 (C-2), 73.5 (C-3), 71.3 (C-a$_x$), 70.4 (C-5), 69.9 (C-a$_y$), 69.1 (C-6), 38.51 (C-b$_x$), 38.45 (C-b$_y$), 25.04 (C-c$_x$), 24.77 (C-c$_y$), 22.81 (C-d$_x$), 22.74 (C-d'$_x$), 22.42 (C-d$_y$), 22.28 (C-d'$_y$).

Anal. Calc. for $C_{112}H_{210}O_{35}$: C, 63.6; H, 10.0. Found: C, 63.7; H, 9.9.

Heptakis(2,6-di-O-dodecyl)-βCD (**7**). — The reaction of βCD (3.8 g, 3 mmol) with dodecyl bromide (84 + 42 mmol) and NaOH (84 + 42 mmol) for 6 days was performed using some modifications. After 2 days, the reaction mixture was diluted 1:1 by the addition of tetrahydrofuran in order to increase the solubility of the alkylated products, the reaction time was prolonged to 7 days, and the addition of the reagents was repeated after 4 days. After chromatography, **7** was obtained as a colourless oil (6.7 g, 64%), m.p. −0.5°, $[\alpha]_D$ +43° (*c* 1.3); R_F 0.71 (solvent *B*); ν_{max} 3460s, 2940s, 2850s, 1470s, 1360s, 1160s, 1090s, 1040s cm^{-1}. N.m.r. data: ^{1}H (toluene-d_8), δ 5.37 (s, 1 H, HO-3), 5.10 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.41 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 4.22 (dt, 1 H, $J_{ax,a'x}$ 9.2, $J_{a'x,b}$ 6.9 Hz, H-a'$_x$), 4.05 (m, 2 H, H-5,6B), 3.89 (dd, 1 H, $J_{6A,6B}$ 9.0, $J_{5,6A}$ < 3 Hz, H-6A), 3.75 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.70–3.53 (m, 3 H, H-a$_x$,a$_y$,a'$_y$), 3.42 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.2 Hz, H-2), 1.80–1.63 (m, 4 H, H-b), 1.52–1.50 (m, 4 H, H-c), 1.37–1.31 (m, 32 H, H-d,e,f,g,h,i,j,k), 0.95 (t, 3 H, H-l$_x$), 0.94 (t, 3 H, H-l$_y$); ^{13}C ($CDCl_3$), δ 97.9 (C-1), 80.5 (C-4), 80.36 (C-2), 78.1 (C-3), 74.2 (C-a$_x$), 71.6 (C-a$_y$), 71.3 (C-5), 69.5 (C-6), 32.0 (C-b), 30.7–29.5 (C-c,d,e,f,g,h,i), 26.4–26.2 (C-j), 22.7 (C-k), 16.9 (C-l).

Anal. Calc. for $C_{210}H_{406}O_{35}$: C, 72.2; H, 11.7. Found: C, 72.0; H, 11.6.

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