# Unusual hydrogen-bonding differences in stereoisomeric 6-*C*-alkylated cyclodextrins †

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***Received (in Cambridge, UK) 17th July 2002, Accepted 18th October 2002***
***First published as an Advance Article on the web 22nd November 2002***

The Grignard reaction of perbenzylated β-cyclodextrin derivatives containing one 6-aldehydo group, or two 6-aldehydo groups in the A and D rings, was investigated. The reaction gave the stereoisomeric secondary alcohols expected for 1,2-addition in diastereomeric ratios of about 1 : 3 ratio for the 6*R*- and 6*S*-isomers. Surprisingly the 6*R*-isomers were consistently found to be much less polar in terms of chromatographic retention times than the 6*S*-isomers. The polarity difference, which disappeared upon acetylation or oxidation, was interpreted as being caused by the presence or absence of intramolecular hydrogen bonding. This was supported by their IR spectra. The configurations of the diastereomers were determined by hydrolysis of the cyclodextrin and comparison of the modified glucose residues with reference compounds. Modelling studies suggest that 6-*C*-alkylation restricts the conformation around the C5–C6 bond such that the 6*S*-isomer will adopt a *gg* conformation, which has the hydroxy group pointing outwards, while the 6*R*-isomer will adopt a *gt* conformation, which has the OH group pointing towards the inner face of the cyclodextrin.

## Introduction

Cyclodextrins are readily available cyclic amylose oligomers consisting of 6, 7, 8 or 9 glucose units (Fig. 1).[1] These compounds are referred to as α, β, γ, and δ-cyclodextrins respectively. Because of their ability to bind hydrophobic substrates in their cavity, cyclodextrins are attractive compounds as starting materials for the synthesis of artificial enzymes[2] and molecular machines.[3] Though many interesting enzyme mimics have been made, a limiting factor in this research is probably the difficult and often low yielding methods available for the preparation of modified cyclodextrins.[4] Consequently new and elegant ways of modifying these compounds are required and are indeed continuously being developed.[5]

Recently a new very powerful method with which to modify cyclodextrins was disclosed by Pearce and Sinaÿ.[6] They found that perbenzylated cyclodextrins could be selectively mono- or di-6-debenzylated with DIBAL-H in high yield. Particularly remarkable was the fact that dideprotection occurred selectively in the A and D glucose units of the substrate. Thus from perbenzylated β-cyclodextrin[7] (**2**) the diol **3** was obtained in excellent yield (Scheme 1).[6]

In a program in which the goal was to synthesise artificial enzymes using modified cyclodextrins, we have investigated diol **3** as a starting material in the synthesis of mimics of proteases and glycosidases containing two catalytic groups. In this paper we report some surprising results in the investigation of the Grignard reaction of aldehydes, such as the dialdehyde **4**, that are obtained from Pearce and Sinaÿ's alcohol **3** (Scheme 1).

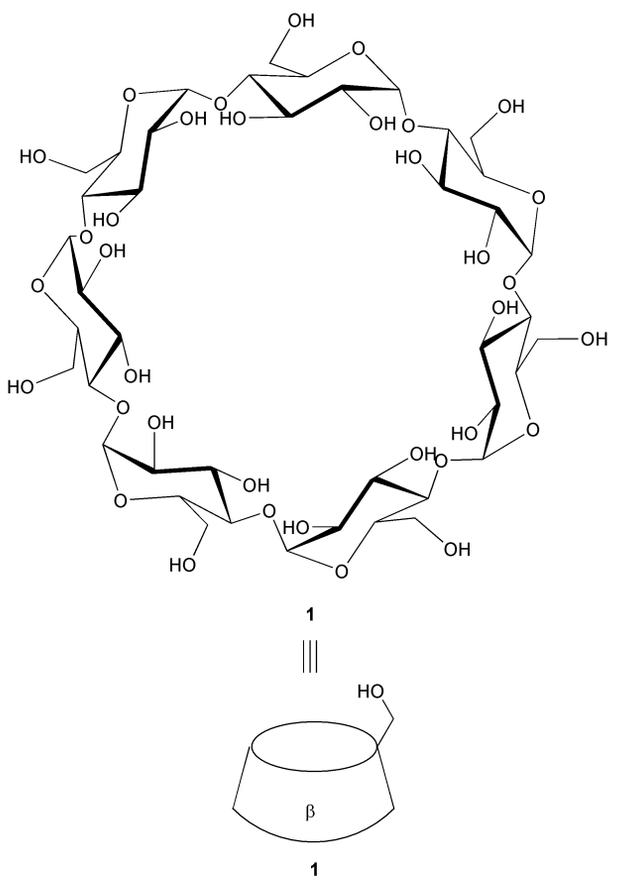


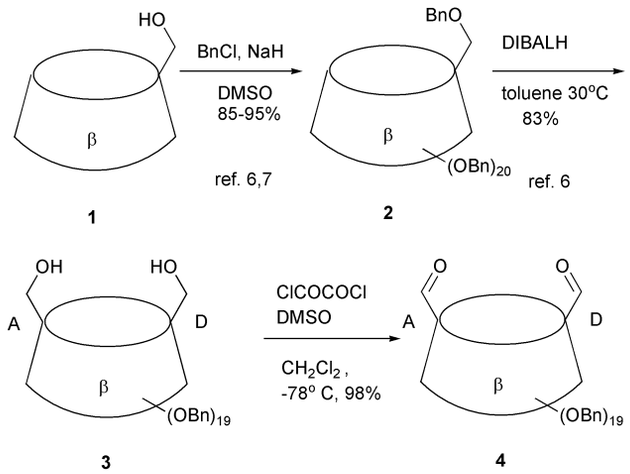

**Fig. 1** Structure and simplified representation of β-cyclodextrin (**1**).

## Results and discussion

The Grignard reaction of an aldehyde is likely to result in stereoisomers. In fact because of the absence of $C_2$ symmetry in β-cyclodextrin, the outcome of Grignard additions to the dialdehyde **4** may result in four stereoisomers, a ($6^{A}R$,$6^{D}R$), ($6^{A}S$,$6^{D}S$), ($6^{A}R$,$6^{D}S$) and a ($6^{A}S$,$6^{D}R$) isomer (Fig. 2). This problem may theoretically be overcome by improving stereoselectivity by employing chelation-controlled conditions[8] or by eliminating the stereocenter by deoxygenation of the resulting secondary alcohols.

† Electronic supplementary information (ESI) available: IR spectra of compounds **5** and **7** in $CH_2Cl_2$ solution. See http://www.rsc.org/suppdata/p1/b2/b207033m/

 DOI: 10.1039/b207033m




**Scheme 1** Preparation of dialdehyde **4**.

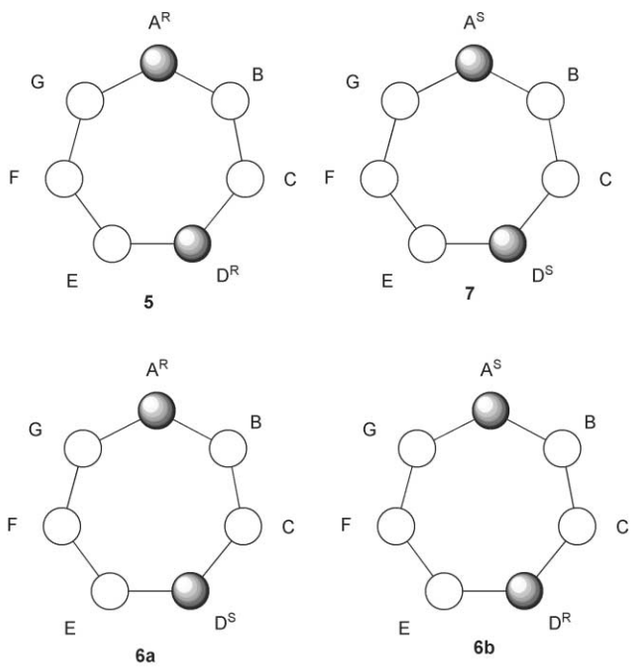



**Fig. 2** The consequences of diastereoisomerism in the A and D ring of β-cyclodextrin are four isomers due to the lack of symmetry β-cyclodextrin. Shown are the products obtained by reaction of dialdehyde **4** with allylmagnesium bromide.

With a standard Swern oxidation of the diol **3** it was possible to obtain the dialdehyde **4** in 98 % yield (Scheme 1). Pearce and Sinaÿ have reported that two of the anomeric protons in **3** are shifted downfield compared to the other five.[6] This downfield shift disappears in the dialdehyde **4** presumably because it is associated with the presence of the OH groups—the formation of **4**, or disappearance of **3**, can thus be readily monitored by $^1$H-NMR.

When allylmagnesium bromide was reacted with **4** several products were obtained (Scheme 2). TLC showed three spots with remarkably different $R_f$ values ($R_f$ = 0.88, 0.51 and 0.30), which suggested the formation of by-products. However after chromatographic separation all three fractions showed the presence of the allyl group in the $^1$H-NMR spectra, and had molecular weights identical to the expected product according to electrospray mass spectroscopy. Therefore the data suggests that the three fractions were stereoisomers. This observation can be explained by a large difference in polarity between the *R*- and *S*-isomeric alcohols formed in the reaction. In that case the chromatographic difference would be largest between 6$^A$*R*,6$^D$*R* and 6$^A$*S*,6$^D$*S* isomers, while 6$^A$*R*,6$^D$*S* and 6$^A$*S*,6$^D$*R* isomers would have similar polarity and intermediate polarity compared to the stereohomogenous isomers.

From the reaction of **4** with $CH_2$=$CHCH_2MgBr$ the three fractions were separated by chromatography giving, in order of elution, 6% **5**, 34% of a mixture of **6a** and **6b** and 28% of **7**. A similar experiment between **4** and *n*-BuMgBr gave the products **8**, **9a/9b** and **10**. Again a very large polarity difference was observed between the three compound fractions. From the chromatography separations, fractions of **8** and **9a/9b** were obtained, while **10** coeluted with reduction products and could not be obtained pure.

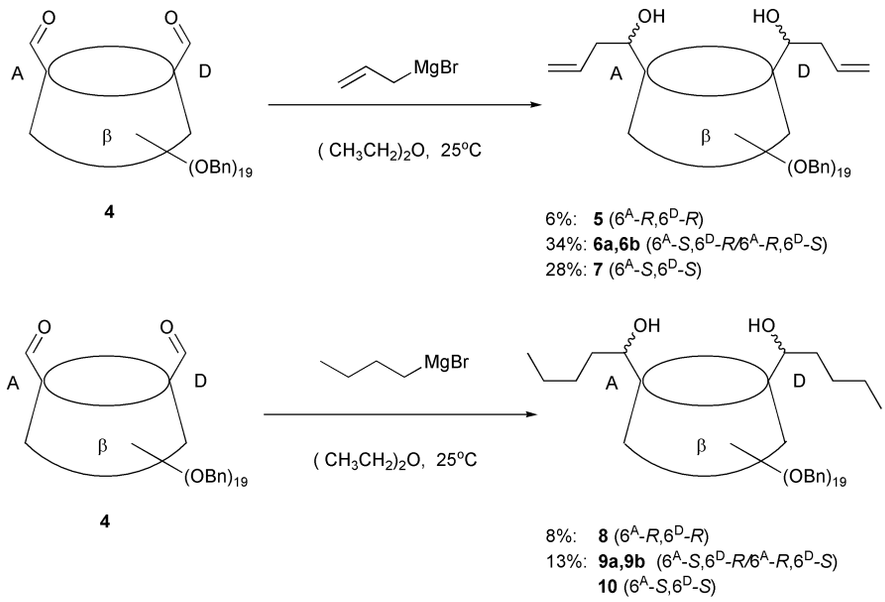
Swern oxidation of **5**, **6** and **7** in each case gave products that were identical on TLC, consistent with all three compounds affording the same ketone **11** (Scheme 3).

When the diols **5**, **6** and **7** were acetylated with pyridine and acetic anhydride three diacetates **12**, **13** and **14** were obtained. These three compounds had very similar polarity as one might expect from stereoisomers. Also noted was that while **6** and **7** increased slightly in lipophilicity upon acetylation **5** actually became more polar (see Experimental section). This suggests that the polarity difference between the compounds is caused by the presence or absence of H-bonds between the solid-phase and the compound. Compounds **6** and **7** can donate hydrogen bonds to silica gel but this ability vanishes upon acetylation making compounds **12** and **13** less polar. Compound **5** on the other hand does not H-bond to silica gel presumably because of an effective intramolecular H-bond. Acetylation of **5** in contrast to normal cases therefore decreases the lipophility. Compound **12** is actually more polar than **5** apparently because the carbonyl groups of the acetates bind more effectively to silica than an occupied OH.

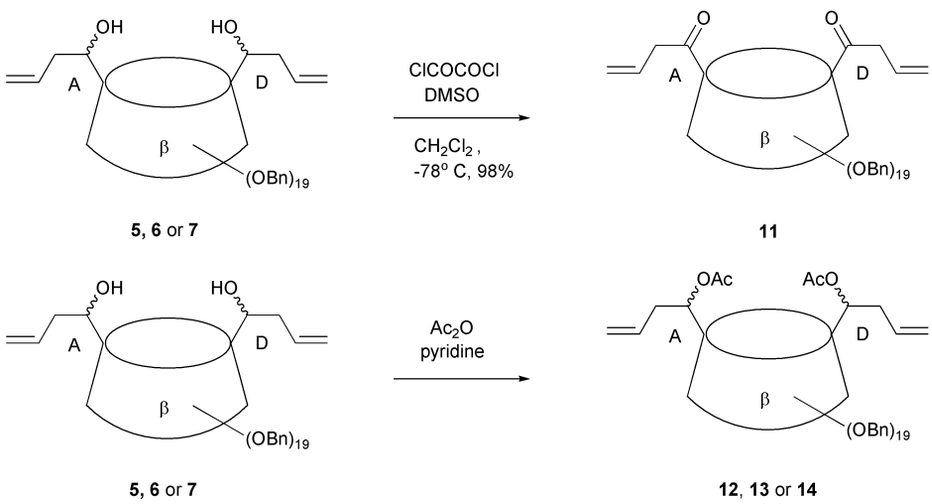
It is also noteworthy that acetylation of the stereoisomers proceed with widely different rates. While diacetylation of **7** was complete after 12 h at room-temperature, diacetylation of **6** required 55 °C for 36 h, and diacetylation of **5** required 60 h at 55 °C to complete.

To determine the stereochemistry of the products, **8** and **9** were degraded to monosaccharides and compared with the known two diastereomeric *C*-butyl analogues of D-glucose.[9] Thus **8** and **9** were debenzylated by hydrogenation with Pd/C to the butylcyclodextrins **16** and **17** (Scheme 4). The characteristic difference in chromatographic retention times was also seen in the unprotected compounds (**16**, $R_f$ = 0.64; **17**, $R_f$ = 0.54). Each of the compounds was hydrolysed with Amberlite IR 120 ($H^+$) to form a 2 : 5 mixture of 6-*C*-butylglucose **18** and glucose which were separated by chromatography. The samples of **18** thus obtained were compared with synthetic samples of (6*R*)-6*C*-butylglucose (**18a**) and (6*S*)-6*C*-butylglucose (**18b**) that were obtained using the published method.[9] The samples were compared in two ways: they were either acetylated to acetate **19** and analysed by HPLC, which allowed the retention times to be compared or directly compared with the $^{13}$C-NMR spectra of **18**. Both experiments clearly showed that **8** was a *RR*-isomer while **9** contained both *R* and *S*. The 6*R*- and 6*S*-isomers of **18** could be distinguished from the chemical shifts of several carbon atoms. The 6*S*-isomer has a clear signal at 68.7 ppm in the α-anomer,[9] while the lowest signals from oxygenated carbons in the 6*R*-isomer are at 71.3 ppm. Similarly the 6*R*-isomer had a clear signal at 78.7 ppm that was higher than any signals from the monoxygenated carbons in the 6*S*-isomer. The sample of **18** obtained from **9** showed signals both at 78.7 and 68.7, while the signal at 68.7 was absent in the sample from **8**. The stereoisomeric peracetates **19** had different HPLC retention times (6*S*: 14.6 min, 6*R*: 16.4 min, 4% iPrOH in hexane, 0.5 ml min$^{-1}$, silica gel). The sample of **19** obtained from **9** gave both peaks, while the sample from **8** gave a sole peak at 16.4 min.

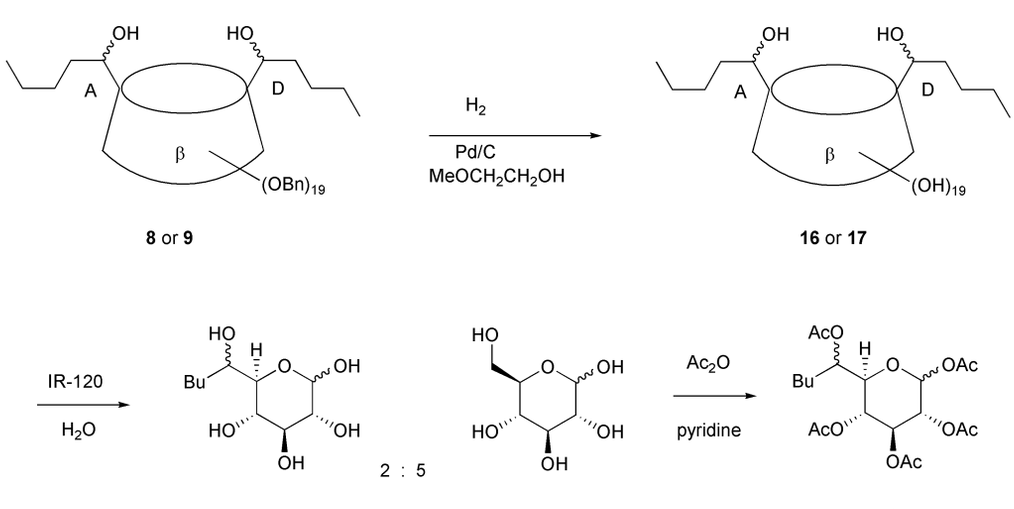
Therefore the *RR*-isomer was the least polar stereoisomer, *RS* and *SR* had intermediate polarity and the *SS*-isomer was the most polar. Based on the polarity of the analogues, **5** was




**Scheme 2** Reaction of dialdehyde **4** with allylmagnesium bromide and butylmagnesium bromide with 4 stereoisomers given in both cases.



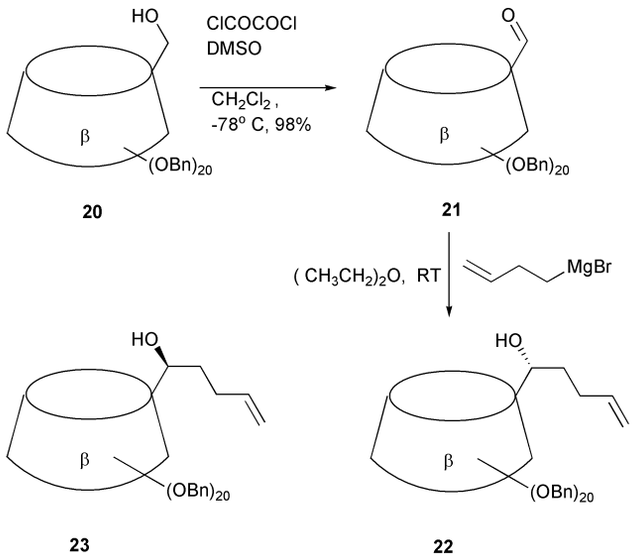

**Scheme 3** Swern oxidation of each of the stereoisomers **5**, **6** and **7** gives one ketone **11**, while acetylation affords acetates **12**, **13** and **14**, respectively, with similar polarity.




**Scheme 4** Deprotection and degradation of cyclodextrin derivatives **8** and **9** to glucose and **18**. The stereochemistry of **18** was determined by comparison with known substances.

assigned the *RR* stereochemistry, **6** the *RS*/*SR* and **7** the *SS* stereochemistry.

The same polarity difference was observed in the mono-substituted compounds. The monool **20**[5] was oxidised to the monoaldehyde **21** using the Swern procedure (Scheme 5). Reaction of monoaldehyde **21** with butenylmagnesium bromide gave the stereoisomeric products **22** ($R_f$ = 0.83) and **23** ($R_f$ = 0.49), which were assigned *R* and *S* stereo-




**Scheme 5** Synthesis of and reaction of monoaldehyde **21** with butenylmagnesium bromide.

chemistry, respectively, based on their widely different polarity.

In an unsubstituted glucose the hydroxymethyl group will adopt a mixture of three staggered conformers, named *gg*, *gt* and *tg*, of which *gg* and *gt* predominate probably due to the *gauche* effect.[10,11] Studies of various cyclodextrin derivatives have likewise shown that the *tg* conformer is virtually non-existent.[12] It is likely that 6-*C*-alkyl groups can limit possible conformers further. If a 6-*C*-methyl group is added to a β-cyclodextrin model (to form model **24**, Fig. 3) inspection of the

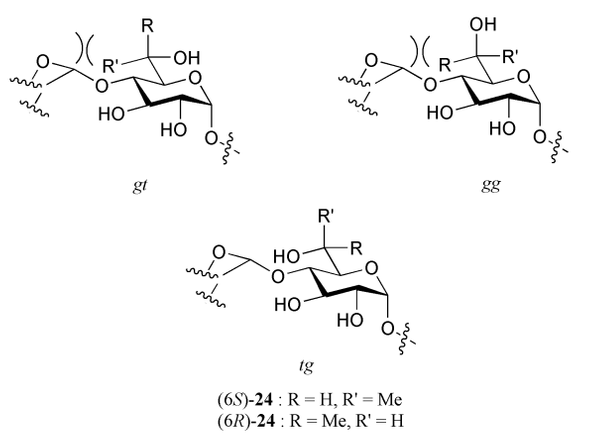



**Fig. 3** The hydroxymethyl rotamers of a cyclodextrin are shown here for the two stereoisomers of hypothetical $6^A$-*C*-methyl-β-cyclodextrin **24**. The three conformations shown are the possible staggered conformations *gt*, *gg* and *tg*. (For an explanation of this nomenclature, see ref. 10). Modelling shows that steric hindrance causes the *gt* conformation to be unfavourable for the $6^A$*S*-isomer and the *gg* conformation to be unfavourable for the $6^A$*S*-isomer.

conformers reveal that the methyl group conflicts with the O5 of the neighbouring sugar residue (Fig. 3) when the *S*-isomer is in the *gt* conformation or the *R*-isomer is in the *gg* conformation. This was confirmed by analysis of the total energy (MM2, chem3D ultra 6.0) of the three staggered C5–C6 bond conformers, which showed that the conformer having a methyl *trans* to O5 was considerably less stable than the two other conformers due to a high van der Waals energy contribution. Steric repulsion therefore makes certain conformers unlikely in 6-*C*-alkylated derivatives, which means that *6S*-**24** is likely to be in the *gg* conformation, while *6R*-**24** mainly adopts the *gt* conformation (Fig. 3). Consequently **5** is in a *gt*,*gt* having both OH groups oriented towards the interior of the ring, and **7** is in a *gg*,*gg* conformation with the OH groups pointing towards the exterior. This rigidity around the C5–C6 bond of the A,D units is interesting as the loss of flexibility can increase potential catalytic activity of an artificial enzyme system by limiting the number of conformers of the molecule.

While it appears reasonable that the stereoisomer with OH groups pointing outward is more polar, it remains unclear whether this alone can cause the large differences in $R_f$ observed and whether intramolecular hydrogen bonding also plays a role. The acetylation experiments, which clearly show that the *R*-isomer is less reactive, suggests that this isomer is hydrogen-bonded. To clarify this point IR spectra of **5** and **7** were recorded in dilute solution in dichloromethane (see supplementary information †). Both spectra contained a narrow peak at 3700 $cm^{-1}$ corresponding to a non-bonded OH and a broad peak at 3450 $cm^{-1}$ corresponding to a H-bonded OH.[11] However in the spectrum of **5** the 3450 $cm^{-1}$ band was much more intense, while in **7** the 3700 $cm^{-1}$ band was stronger, confirming that **5** has more hydrogen bonds than **7**. Since the solution is dilute and since **5**, having inwardly pointing OH groups, is less likely than **7** to have intermolecular H-bonds, the H-bonds in **5** must be intramolecular.

In summary we have found that the Grignard reaction of aldehydes on the primary rim of β-cyclodextrin gives stereoisomeric secondary alcohols of which the *R*-isomers are consistently much less polar and less reactive than the *S*-isomers. With the assistance of modelling this was explained by the the *S*-isomers being forced into a *gg* conformation, so that the 6-OH group points outwards allowing it to participate better in interactions with other molecules. The *R*-isomers were shown to participate in intramolecular hydrogen bonding probably with the O6 of the E or G unit.

## Experimental

### General

Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Pyridine was dried over potassium hydroxide before use. Evaporation was carried out on a rotary evaporator with the temperature kept below 40 °C. Glassware used for water-free reactions was dried for 2 hours at 130 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC-plates (Merck, 60, $F_{254}$) were visualized by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% $H_2SO_4$ and heating until coloured spots appeared. $^1$H-NMR, $^{13}$C-NMR and COSY spectra were recorded on a Varian Gemini 200 instrument. Spectra in $CDCl_3$ were referenced to tetramethylsilane (TMS); chemical shifts are given in ppm. Mass spectra were carried out on a Micromass LC-TOF instrument. The IR spectra were performed on a Perkin Elmer FT-IR paragon 1000 instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter and are in units of $10^{-1}$ deg $cm^2$ $g^{-1}$.

### $6^A$-*aldehydo*-$2^A$,$2^B$,$2^C$,$2^D$,$2^E$,$2^F$,$2^G$,$3^A$,$3^B$,$3^C$,$3^D$,$3^E$,$3^F$,$3^G$,$6^B$,$6^C$,$6^D$,$6^E$,$6^F$,$6^G$-Icosa-*O*-benzyl-β-cyclodextrin (21)

A solution of oxalyl chloride (51.2 μl, 0.6 mmol) in dry distilled $CH_2Cl_2$ (1.0 ml) was stirred at −78 °C under nitrogen. DMSO (84.4 μl, 1.2 mmol) in $CH_2Cl_2$ (1.0 ml) was added dropwise over 5 min. After stirring for 20 min the alcohol **20**[5] (350 mg, 0.12 mmol) in $CH_2Cl_2$ (4.0 ml) was added dropwise over 5 min. After stirring for 120 min triethylamine (165 μl, 1.2 mmol) was added and stirring was continued for another 30 min. The reaction mixture was warmed up to room temperature and water (10 ml) was slowly added. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent

was removed by evaporation. The residue was purified by chromatography using the eluent EtOAc : pentane 1 : 3 to give 318 mg of the aldehyde **21** (91%) as a colorless foam. TLC of the aldehyde using EtOAc : pentane 1 : 3 as eluent, gave a tailed spot. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 9.42 (d, C*H*O, 62%, $J_{5,6}$ 2.2 Hz), 7.30–6.90 (m, 100H, Ph), 5.51 (d, $(OH)_2CH$, 26%, $J_{5,6}$ = 3.6 Hz), 5.36 (d, 26%, $J_{5,6}$ = 3.6 Hz), 5.20–4.92 (m, 13H, H-1, C*H*Ph), 4.90–4.42 (m, 34H, C*H*Ph), 4.08–3.60 (m, 28H, H-3, H-4, H-5, H-6b), 3.55–3.10 (m, 13H, H-2, H-6a).

### 6$^A$-*C*-But-3-enyl-2$^A$,2$^B$,2$^C$,2$^D$,2$^E$,2$^F$,2$^G$,3$^A$,3$^B$,3$^C$,3$^D$,3$^E$,3$^F$,3$^G$,6$^B$, 6$^C$,6$^D$,6$^E$,6$^F$,6$^G$-icosa-*O*-benzyl-β-cyclodextrin (22 and 23)

4-Bromobut-1-ene (27μl, 0.27 mmol) was slowly added to a stirred suspension of Mg turnings (12 mg, 0.54 mmol) in diethyl ether (2 ml) under nitrogen. After two hours the solution containing the Grignard reagent was added dropwise at room temperature to a stirred solution of the aldehyde **21** (48 mg, 34 μmol) in diethyl ether (5 ml) under nitrogen. The reaction mixture was left stirring for 1 hour. After that time TLC showed three spots and no traces of the starting material. 5 ml of saturated ammonium chloride in water was added at 0 °C. Extraction of the water phase with diethyl ether (3 × 10 ml) was done, and the combined organic extracts was dried ($MgSO_4$). After removal of the solvent *in vacuo*, the crude product was chromatographed with EtOAc : pentane 1 : 3 to afford 8 mg (16%) of **22**. $R_f$ = 0.83. $[a]_D$ = +30.14. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 7.30–6.90 (m, 100H, Ph), 5.75–5.55 (m, 1H, =CH-), 5.21(d, H-1, $J_{1,2}$ = 3.5 Hz, 1H), 5.19–4.55 (m, 24H, H-1, C*H*Ph, =C*H*$_2$), 4.55–4.20 (m, 24H, C*H*Ph), 4.08–3.65 (m, 27H; H-3, H-4, H-5, H-6a), 3.60–3.35 (m, 12H, H-2, H-6b), 3.22 (dd, $J_{2,3}$ = 10 Hz, $J_{1,2}$ = 3.5 Hz, 1H, H-2), 2.42 (br s, 1H, OH), 2.10–1.90 (m, 2H, C*H*$_2$CH=), 1.40–1.20 (m, 2H, C*H*$_2$CH$_2$). MS (ES) *m*/*z* = 1517.8. Calculated for $C_{186}H_{198}O_{35}Na_2$ = 1517.7.

Further elution afforded 16 mg (33%) of **23**. $R_f$ = 0.49. $[a]_D$ = +40.38.$^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 7.30–6.90 (m, arom, 100H), 5.75–5.55 (m, 1H, CH=), 5.40 (d, $J_{1,2}$ = 4.1 Hz, 1H, H-1), 5.20–4.10 (m, 48H, H-1, C*H*Ph, =CH$_2$), 4.10–3.65 (m, 28H, H-3, H-4, H-5, H-6a), 3.65–3.20 (m, 13H, H-2, H-6b), 2.10–1.90 (m, 2H, C*H*$_2$CH=), 1.40–1.20 (m, 2H, C*H*$_2$CH$_2$). MS (ES) *m*/*z* = 1517.2. Calculated for $C_{186}H_{198}O_{35}Na_2$ = 1517.7

Finaly 11 mg of the alcohol **20** ($R_f$ = 0.37) was obtained. Overall yield of alkylated products: 49%.

### 6$^A$,6$^D$-*dialdehydo*-2$^A$,2$^B$,2$^C$,2$^D$,2$^E$,2$^F$,2$^G$,3$^A$,3$^B$,3$^C$,3$^D$,3$^E$,3$^F$,3$^G$,6$^B$, 6$^C$,6$^E$,6$^F$,6$^G$-Nonadeca-*O*-benzyl-β-cyclodextrin (4)

A solution of oxalyl chloride (236 μl, 2.7 mmol) in dry distilled $CH_2Cl_2$ (3.0 ml) was stirred at −78 °C under nitrogen. DMSO (389 μl, 5.5 mmol) in $CH_2Cl_2$ (3.0 ml) was added dropwise over 10 min. After stirring for 20 min the diol (781 mg, 0.55 mmol) in $CH_2Cl_2$ (8.0 ml) was added dropwise over 10 min. After stirring for 120 min triethylamine (760 μl, 5.5 mmol) was added and stirred for another 30 min. The reaction mixture was warmed up to room temperature and water (15 ml) was slowly added. The phases were separated, and the water phase was extracted with $CH_2Cl_2$ (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed by evaporation. The residue was purified by chromatography using the eluent EtOAc : pentane 1 : 3, to give 768 mg of the dialdehyde **4** (98%) as a colorless foam. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 9.42 (m, C*H*O, 60%), 7.20–6.90 (m, Ph, 95H), 5.20–4.10 (m, 45H, H-1, C*H*Ph), 4.10–3.60 (m, 28H, H-3, H-4, H-5, H-6a), 3.60–3.10 (m, 12H, H-2, H-6b)

### 6$^A$,6$^D$-Di-*C*-prop-2-enyl-2$^A$,2$^B$,2$^C$,2$^D$,2$^E$,2$^F$,2$^G$,3$^A$,3$^B$,3$^C$,3$^D$,3$^E$,3$^F$, 3$^G$,6$^B$,6$^C$,6$^E$,6$^F$,6$^G$-nonadeca-*O*-benzyl-β-cyclodextrin (5, 6 and 7)

Allyl bromide (243 μl, 2.8 mmol) was slowly added to a stirred suspension af Mg turnings (14 mg, 5.6 mmol) in diethyl ether (4 ml) under nitrogen. After two hours the solution containing the Grignard reagent was added dropwise at room temperature to a stirred solution of the dialdehyde **4** (500 mg, 0.35 mmol) in diethyl ether (20 ml) under nitrogen. The reaction mixture was left stirring for 1 hour and after that time TLC showed three spots and no traces of the starting material. 20 ml of saturated ammonium chloride in water was added at 0 °C. Extraction of the water phase with diethyl ether (3 × 20 ml) was done, and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent *in vacuo*, the crude product was chromatographed with EtOAc : pentane 1 : 3 to afford 30 mg (6%) of **5**. $R_f$ = 0.88. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 7.10–6.70 (m, Ph, 95H), 5.60–5.35 (m, 2H, CH=), 5.35–5.25 (m, 2H, H-1), 5.15–4.00 (m, 47H, H-1, C*H*Ph, =CH$_2$), 4.00–3.40 (m, 28H, H-3, H-4, H-5, H-6), 3.40–3.00 (m, 12H, H-2, H-6), 2.0–1.8 (m, 4H, C*H*$_2$CH=). MS (ES) *m*/*z* = 1486.6. Calculated for $C_{181}H_{192}O_{35}Na_2$ = 1485.7.

Further elution afforded 175 mg (34%) of a mixture of **6a** and **6b**. $R_f$ = 0.51. $^1$H NMR (200 MHz, $CDCl_3$, 20 °C) $\delta_H$: 7.30–6.90 (m, arom, 95H), 5.75–5.50 (m, 2H, CH=), 5.35–5.25 (m, 2H, H-1), 5.20–4.10 (m, 47H, H-1, C*H*Ph, CH$_2$=), 4.10–3.60 (m, 28H, H-3, H-4, H-5, H-6), 3.60–3.20 (m, 12H, H-2, H-6), 2.2–1.9 (m, 4H, C*H*$_2$CH=). MS (ES) *m*/*z* = 1486.6. Calculated for $C_{181}H_{192}O_{35}Na_2$ = 1485.7.

Further elution afforded 145 mg (28%) of **7**. $R_f$ = 0.30.$^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 7.30–6.90 (m, arom, 95H), 5.75–5.50 (m, 4H, H-1, $CH_2CHCH_2$), 5.20–4.10 (m, 47H, H-1, C*H*Ph, $CH_2CHCH_2$), 4.10–3.60 (m, 32H, H-3, H-4, H-5, H-6), 3.60–3.20 (m, 12H, H-2, H-6), 2.00 (br s, 2H, OH), 1.75–1.60 (m, 4H, C*H*$_2$CH=). MS (ES) *m*/*z* = 1485.9. Calculated for $C_{181}H_{192}O_{35}Na_2$ = 1485.7.

### 6$^A$,6$^D$-Di-*C*-butyl-2$^A$,2$^B$,2$^C$,2$^D$,2$^E$,2$^F$,2$^G$,3$^A$,3$^B$,3$^C$,3$^D$,3$^E$,3$^F$,3$^G$,6$^B$, 6$^C$,6$^E$,6$^F$,6$^G$-nonadeca-*O*-benzyl-β-cyclodextrin (8 and 9)

Butyl bromide (680 μl, 6.3 mmol) was slowly added to a stirred suspension af Mg turnings (304 mg, 13 mmol) in diethyl ether (10 ml) under nitrogen. After two hours the solution containing the Grignard reagent was added dropwise at room temperature to a stirred solution of the dialdehyde **4** (1100 mg, 0.77 mmol) in diethyl ether (40 ml) under nitrogen. The reaction mixture was left stirring for 4 hours. After that time 40 ml of saturated ammonium chloride in water was added at 0 °C. Extraction of the water phase with diethyl ether (3 × 40 ml) was carried out, and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent *in vacuo*, the crude product was chromatographed with EtOAc : pentane 1 : 3 to afford 97 mg (8%) of **8**. $R_f$ = 0.59. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 7.30–6.90 (m, Ph, 95H), 5.41–5.35 (m, 2H, H-1), 5.22 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.20–4.75 (m, 20H, H-1, CHPh), 4.75–4.10 (m, 22H, CHPh), 4.08–3.60 (m, 28H; H-3, H-4, H-5, H-6), 3.60–3.20 (m, 12H, H-2, H-6′), 2.42 (br s, 2*H*, OH), 1.50–0.90 (m, 12H, C*H*$_2$C*H*$_2$-C*H*$_2$CH$_3$), 0.90–0.70 (m, 6H, $CH_2CH_2CH_2CH_3$). MS (ES) *m*/*z* = 1501.67. Calculated for $C_{183}H_{200}O_{35}Na_2$ = 1501.68.

Further elution afforded 153 mg (13 %) of **9a**/**9b**. $R_f$ = 0.46. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$ 7.40–6.90 (m, arom, 95H), 5.50 (d, 1H, $^3J$(1,2) = 3.9 Hz, H-1), 5.43 (d, 1H, $^3J$(1,2) = 3.9 Hz, H-1), 5.40 (d, 1H, $^3J$(1,2) = 3.9 Hz, H-1), 5.30–4.20 (m, 42H, H-1, C*H*Ph), 4.20–3.60 (m, 28H, H-3, H-4, H-5, H-6), 3.60–3.20 (m, 12H, H-2, H-6′), 2.25 (br s, 2H, O*H*), 1.50–1.10 (m, 12H, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.10–0.80 (m, 6H, $CH_2CH_2CH_2CH_3$). MS (ES) *m*/*z* = 1501.8. Calculated for $C_{183}H_{200}O_{35}Na_2$ = 1501.7.

Further elution afforded an inseparable mixture containing the more polar dibutyl isomer (**10**) and byproducts.

### Oxidation of 5, 6 or 7

Oxidation of 8–33 mg of **5**, **6** or **7** was carried out as described in the synthesis of **4**. To 33 mg alcohol was added 1.5 ml $CH_2Cl_2$, 20 μl oxalyl chloride in 1 ml $CH_2Cl_2$, 30 μl DMSO in 1 ml $CH_2Cl_2$, and 70 μl $Et_3N$. The final $CH_2Cl_2$ extracts were analysed by TLC. $R_f$ value (**11**): 0.5 (EtOAc : pentane 1:4).

### Acetylation of 5, 6 or 7

Acetylation of **5**, **6** or **7** was carried out by dissolving 10 mg of the substance in a mixture of 1 ml acetic anhydride and 1 ml pyridine. The temperature was kept at 25 °C for the reaction of **7** and at 55 °C for the reaction of **5** and **6**. The reaction was followed by TLC and stopped when the starting material had disappeared ($R_f$ in EtOAc : pentane 1 : 3; **5**: 0.88, **6**: 0.51, **7**: 0.30) and a new spot appeared ($R_f$ in EtOAc : pentane 1 : 3; **12**: 0.59, **13**: 0.57, **14**: 0.43). The time required was 60 h for **5**, 36 h for **6** and 12 h for **7**. The excess reagents were evaporated, and the structure of the product confirmed by MS analysis; **12**: MS(ES) *m*/*z* = 1527.8, **13**: MS(ES) *m*/*z* = 1527.5, **14**: MS(ES) *m*/*z* = 1527.5. Calculated for $C_{185}H_{196}O_{37}Na_2$ = 1527.7.

### $6^A$,$6^D$-Di-*C*-butyl-β-cyclodextrin 16 and 17

**8** (97 mg) was dissolved in 20 ml 2-methoxyethanol under nitrogen. Palladium on carbon (10%, 30 mg) was added, and a hydrogen atmosphere (1 atm) introduced. After 24 hours TLC (EtOAc : pentane 1 : 3) showed the disappearance of a starting material and the appearance of a new spot when BuOH : EtOH : $H_2O$ 5 : 4 : 3 was the eluent. The mixture was then filtered through Celite and washed thoroughly with 3 × 10 ml EtOH : $H_2O$ 1 : 1. The filtrate was evaporated to afford 35 mg (86%) of **16**. $R_f$ = 0.64. MS (ES) *m*/*z* = 1269.50. Calculated for $C_{50}H_{86}O_{35}Na$ = 1269.48.

In the same way 90 mg of **9** was debenzylated to afford 31 mg (82%) of **17**. $R_f$ = 0.54. MS (ES) *m*/*z* = 1269.4852. Calculated for $C_{50}H_{86}O_{35}Na$ = 1269.4847.

### Hydrolysis of the $6^A$,$6^D$-*C*-butylated β-cyclodextrins

To a solution of **16** (35 mg) in water (10 ml) was added 8 ml Amberlite IR-120 ($H^+$), and the mixture was stirred at 100 °C for 24 hours. At that time TLC showed two spots using the eluent $H_2O$ : iPrOH : EtOAc 1 : 2 : 6. The resin was removed by filtration and the filtrate was stirred at room temperature for 1 hour in the presence of Amberlite ($OH^-$). The resin was removed by filtration, and the solvent was evaporated. Chromatography of the residue in $CH_2Cl_2$ : MeOH 5 : 1 afforded 7 mg 6-*C*-butylglucose (**18**) and 20 mg glucose.

To a solution of **17** (31 mg) in water (10 ml) was added 8 ml Amberlite IR-120 ($H^+$), and the mixture was stirred at 100 °C for 24 hours. At that time TLC showed two spots in $H_2O$ : iPrOH : EtOAc 1 : 2 : 6. The resin was removed by filtration, and the filtrate was stirred at room temperature for 1 hour in the presence of Amberlite ($OH^-$). The resin was removed by filtration, and the solvent was evaporated. Chromatography of the residue in $CH_2Cl_2$ : MeOH 5 : 1 afforded 7 mg 6-*C*-butylglucose (**18**) and 22 mg glucose.

### (6*S*)-Butyl-1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (19b)

(6*S*)-Butyl-D-glucopyranose[9] **18b** (20 mg) was dissolved in 2 ml pyridine : acetic anhydride 1 : 1 and kept at room temperature under nitrogen for 12 hours. The solvent was removed by evaporation, and the residue was purified by column chromatography (EtOAc : pentane 1 : 3) to afford 35 mg (92 %) of **19b**. $R_f$ = 0.53. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 6.35 (d, 1H, *J* = 3.6 Hz, H-1α), 5.64 (d, 1H, *J* = 8.0 Hz, H-1β), 5.43 (t, 1H, *J* = 9.8 Hz, H-3α), 5.22 (t, 1H, *J* = 8.8 Hz, H-3β), 5.14–4.97 (m, 6H, H-2α,β, H-4α,β, H-6α,β), 4.01 (dd, 1H, *J* = 10.4 Hz, 2.2 Hz, H-5α), 3.69 (dd, 1H, *J* = 9.8 Hz, 2.2 Hz, H-5β), 2.17 (s, 3H, $COCH_3$), 2.11 (s, 6H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.07 (s, 6H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.70–1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.40–1.10 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.70–1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.87 (t, 1H, *J* = 6.1 Hz, $CH_2CH_2CH_2CH_3$). MS (ES) *m*/*z* = 469.1685. Calculated for $C_{20}H_{30}O_{11}Na$ = 469.1686.

### (6*R*)-6-*C*-Butyl-1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (19a)

(6*R*)-Butyl-D-glucopyranose (12 mg) was dissolved in 2 ml pyridine : acetic anhydride 1 : 1 at room temperature under nitrogen for 12 hours. The solvent was removed by evaporation, and the residue was purified by column chromatography (EtOAc : pentane 1 : 3) to afford 20 mg (88%) of **19a**. $R_f$ = 0.50. $^1$H NMR (200 MHz, $CDCl_3$) $\delta_H$: 6.30 (d, 1H, *J* = 3.8 Hz, H-1α), 5.66 (d, 1H, *J* = 7.8 Hz, H-1β), 5.44 (t, 1H, *J* = 9.6 Hz, H-3α), 5.22 (t, 1H, *J* = 9.4 Hz, H-3β), 5.08 (dd, 1H, *J* = 9.6 Hz, 3.8 Hz, H-2α), 5.06–4.98 (m, 3H, H-4α,β, H2-β), 4.96–4.82 (m, 2H, H-6α,β), 4.08 (dd, 1H, *J* = 10.8 Hz, 2.2 Hz, H-5α), 3.77 (dd, 1H, *J* = 9.8 Hz, 2.2 Hz, H-5β), 2.15 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.07 (s, 6H, $COCH_3$), 2.05 (s, 6H, $COCH_3$), 2.01 (s, 6H, $COCH_3$), 1.99 (s, 6H, $COCH_3$), 1.70–1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.40–1.10 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.70–1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.87 (t, 1H, *J* = 6.1 Hz, $CH_2CH_2CH_2CH_3$). MS (ES) *m*/*z* = 469.1689. Calculated for $C_{20}H_{30}O_{11}Na$ = 469.1686.

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