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Taming of the DIBAL Promoted Debenzylation of α-Cyclodextrin. Kinetics, Substituent Effects and Efficient Synthesis of Lings Tetrol**

Mikael Bols*[a] and Victor Friis[a]

Abstract: The kinetics of the reaction of perbenzyl α-cyclodextrin was studied varying the concentration of DIBAL and substrate, and the temperature. The initial debenzylation was found to be 1st order in substrate and follow the relationship $0.0675 + 0.179[DIBAL]^2$ with respect to the concentration of DIBAL. The second and the third debenzylation which led to the $3^A,6^A,6^D$-triol (Lings triol) were both found to be 1st order in substrate concentration and zero order in DIBAL concentration. Longer reaction times with DIBAL in high concentration gave further debenzylation to comparatively complex mixtures containing the 2B,$3^A,6^A,6^D$-tetrol and the $3^A,6^A,6^C,6^D$-tetrol. In contrast reaction at 0.1 M DIBAL gave the symmetrical $3^A,6^A$,3D,6D-tetrol (Lings tetrol) in 60% yield. The effect of chlorine or methyl substitution of the phenyl groups of perbenzyl α-cyclodextrin was also investigated. Per 4-chlorobenzyl slowed down the reaction with DIBAL, while 4-methylbenzyl increased the reaction rate, but still gave the corresponding 6 A-monool or $6^A,6^D$-diol products. A Hammett reaction constant of −4.9 was found for the first debenzylation showing a high degree of positive charge in the transition state. The per(2,4-dichlorobenzyl)-α-cyclodextrin-derivative was completely resistant to DIBAL, however upon addition of trimethyl aluminium this derivative also reacted to give the $6^A,6^D$-diol product.

Introduction

Selective reduction of benzyl groups in perbenzylated cyclodextrins using diisobutyl aluminium hydride (DIBAL) has for the last decades been one of the most useful methods of preparing pure partially deprotected cyclodextrin derivatives.[1,2] When used on α-cyclodextrin (**1**) this reaction transforms the perbenzyl derivative **2** to first the monool **3** by selective debenzylation of one of the 6-primary O-benzyl derivatives and subsequently forms the diol **4** by selective debenzylation of another primary benzyl group on the D-sugar opposite the previous debenzylation at the A-ring (Figure 1, Scheme 1).

A selection of yields from this reaction under different conditions is shown in Table 1. Particularly the diol **4** can be isolated in remarkable high yield despite the many possibilities of side-reactions,[3] but also **3** can be obtained in reasonable yield. This chemistry has allowed efficient preparation of a range of supramolecular catalysts or receptors frequently with bridges spanning the primary face.[4–7] A mechanism has been proposed that involves two molecules of DIBAL for each debenzylation with one molecule acting as a Lewis acid and the other as the reducing agent.[2,8,9] Steric hindrance is the primary reason for the observed selectivity in that 1) the primary rim benzyl groups are more accessible reacting faster that the secondary rim benzyl groups and 2) after reaction of one benzyl group the diisobutylaluminate attached to the oxygen shields or hinders attack at the B,C,E & F sites, so that only debenzylation at the D-site is seen.[2] DIBAL can also reductively remove silyl groups[10,11] and O-methyl groups[12] from the primary rim of the cyclodextrin and does so with the same A,D selectivity as observed with **2**.

While the reaction of **2** almost appear to stop after removal of two of the 18 benzyl groups this is not the case. Lings group showed that if the reaction was left for a long time and performed with DIBAL in hexane (rather than DIBAL in toluene) the triol **5** and the tetrol **6** could be isolated in 32% and 10% yield, respectively (Scheme 1, Table 1).[13] These debenzylations are interesting in that removal of secondary benzyl groups occurs and with a degree of selectivity for the already modified A,D glucose-residues. It is also interesting that secondary debenzylation is not observed in the similar reaction with β-cyclodextrin.[14]

DIBAL reaction on the secondary rim of the cyclodextrin was also observed when per-O-methylated cyclodextrins were treated with DIBAL. In those cases de-O-methylation was predominant leading to $3^A,2^B$-diol formation in 50% yield.[15,16]

The stimulus for this work was the following: A perusal of the literature (Table 1) and our own experience revealed quite clearly that there were many inconsistencies in yields and reaction times reported in different studies that justified a kinetic study of the reaction. For example a comparison of experiments all focused on synthesis of monool **3** (Table 1,

[a] Prof. Dr. M. Bols, V. Friis
Department of chemistry, University of Copenhagen
Universitetsparken 5, 2100, Copenhagen (Denmark)
E-mail: bols@chem.ku.dk

[**] DIBAL = diisobutyl aluminum hydride

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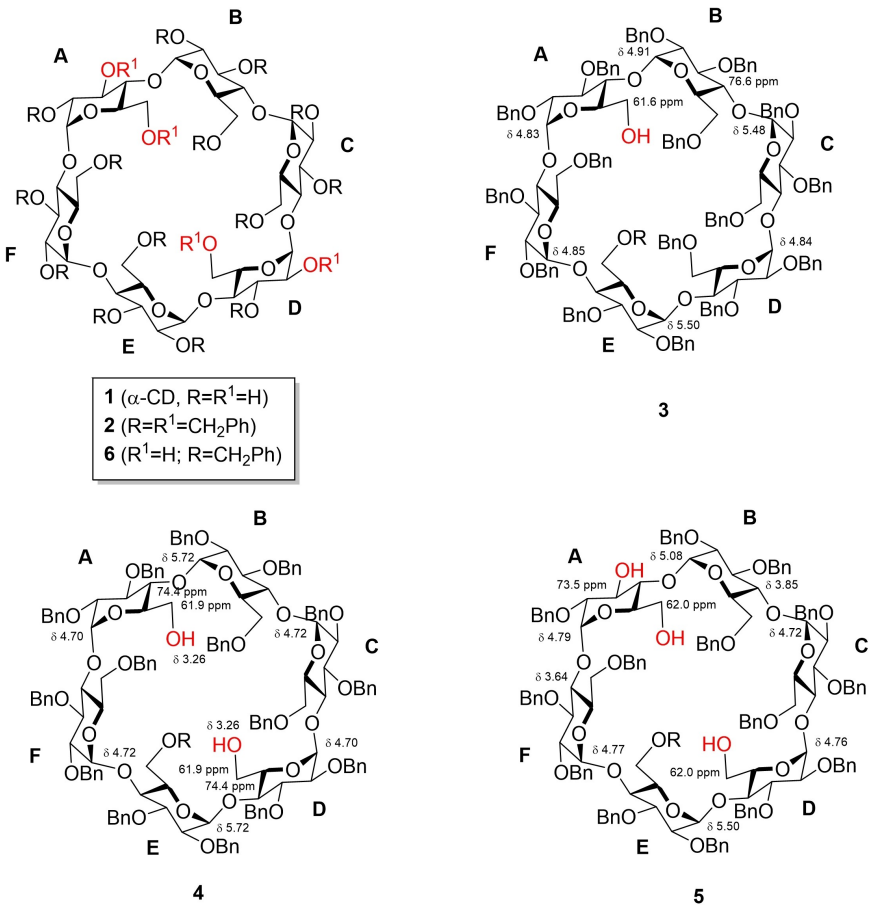
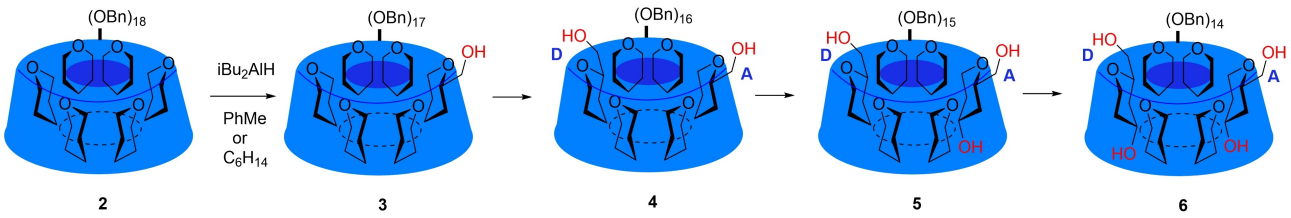


Figure 1. Structure of α-cyclodextrins **1**–**6**.



Scheme 1. The reaction of perbenzylated α-cyclodextrin with iBu_2AlH.

entries 2,5,9,12,13 and 14) show several curiosities - sometimes a higher yield of **3** was obtained even though the reaction time was shorter (entry 2 vs. entry 5) or the temperature lower (entry 2 vs. entry 13). Secondly the Ling groups interesting study of secondary rim debenzylation is the only study of the products of prolonged reaction times.[13] Ling suggested that the formation of **5** and **6** was related to their use of DIBAL in hexane and a slow reaction making the study of rates of further interest.

In this work we report the results of this 'revisitation' of the reaction of benzylated α-cyclodextrin with DIBAL and the following new findings: 1) The reaction of **2** with excess DIBAL is first order in **2** and a mixture of zero and second order in DIBAL concentration. 2) The reaction of **3** to **4** and **4** to **5** are zero order in the concentration of DIBAL. 3) Perbenzyl α-cyclodextrins with chloro or methyl substituted phenyl groups also undergo the debenzylation reaction but with a powerful substituent effect. 4) Further reaction of **2** with DIBAL in toluene leads to **5** and subsequently **6** or other tetrols dependending on the concentration of DIBAL.

Results and Discussion

*NMR assignment of **3**–**5***. The ^{1}H NMR spectra of **2**, **3**, **4** and **5** in $CDCl_3$ have outlying signals sufficiently different that the progress of debenzylation might be determined by spectra at different times during the reaction as a basis for a kinetic

Table 1. Selected reaction conditions and results from literature on the reaction of perbenzyl α-cyclodextrin (**2**) and DIBAL.

Entry	Group	Solvent	[2] [mM][a]	[DIBAL] [M][a]	T [°C]	Time [h]	3	4	5	6
1	Sinaÿ 2000[1]	Toluene	4.2	0.5	50	2	–	82%	–	–
2	Sinaÿ 2000[1]	Toluene	3.3	0.1	25	1.33	64%	21%	–	–
3	Sollogoub 2004[2]	Toluene	100	1.5	50	0.33	-	87%	–	–
4	Bols 2019[17]	Toluene	43	0.87	60	2	-	76%	–	–
5	Bols 2005[18]	Toluene	3	0.1	25	21	26%	-	–	–
6	Bols 2005[18]	Toluene	3	0.1[c]	25	21	10%	64%	–	–
7	Bols 2005[18]	Toluene	3	0.1[d]	25	21	19%	23%	–	–
9	Bols 2005[18]	Toluene	3	0.03	25	21	7%	-	–	–
10	Bols 2005[18]	Toluene	3	0.03[c]	25	1.5	47%	10%	–	–
11	Sollogoub 2008[3]	Toluene	33	1	50	3	–	82%	–	–
12	Sollogoub 2008[3]	Toluene	100	1	50	0.5	49%	-	–	–
13	Sollogoub 2008[3]	Toluene	500	1	50	2	58%	-	–	–
14	Ling 2009[13]	Hexane[b]	30	0.15	50	12	60%	20%	–	–
15	Ling 2009[13]	Hexane[b]	22 mM	0.9 M	50	24	15%	50%	8%	–
16	Ling 2009[13]	Hexane[b]	22 mM	0.9 M	50	96	–	5%	32%	10%

[a] [**2**] and [DIBAL] means concentration of substrate and DIBAL at the start of the reaction. [b] Small content of toluene present. [c] 4 A molecular sieves added. [d] 3 A molecular sieves added.

study.[3,13] However in order to prevent any misinterpretation of the complex ^{1}H and ^{13}C spectra of **3**, **4** and **5** they were recorded at 800 MHz and assigned using COSY, HSQC, 1D and 2D TOCSY, HMBC and ROESY spectra as follows: From the resolved ^{13}C NMR spectra each of the ^{1}H signals could be identified, even in heavily overlapped areas of the proton spectra, using the phase sensitive HSQC spectra, which also identified which of the protons were at C-6 or benzylic. The TOCSY spectra were used to determine which protons were connected to the same monosaccharide unit extracting 6 sets for **3** and **5** and 3 sets for **4** - by HSQC the corresponding ^{13}C sets were obtained. HMBC and NOESY spectra were used to identify correlations between anomeric protons and H-4 or C-4 in the preceding monosaccharide or correlations between anomeric carbon and H-4. The modified residues (A and D) where determined by identifying the H-6 protons either by their C–H correlation to the characteristic up field C-6 carbon signals or, for compound **4**, a COSY correlation to the visible alcohol proton. This gave the assignments shown in Tables 2–4. Specifically the following ROESY or HMBC observations were important for the assignments (see also Figure 1).

For **3** the ^{13}C signal at 61.6 ppm identifies the debenzylated CH_2 group and by HSQC and TOCSY residue A and a ROESY crosspeak between H-4^{A} and H-1^{B} at 4.91 ppm is seen. Also for **3** a HMBC crosspeak between C-4^{B} (76.6 ppm) and H-1^{C} at 5.48 ppm, a ROESY crosspeak between H-1^{C} and and H-4^{B} (at δ 4.01), a ROESY crosspeak between the H-1^{D} (at δ 4.84) and H-4^{C} (at δ 4.12) are seen. Finally in **3** the anomeric signal at δ 5.50 (H-5^{E}) has an HMBC crosspeak with C-4^{D} (at 75.9 ppm) and a ROESY crosspeak between H-1^{E} and H-4^{D}.

For **4** the ^{13}C signal at 61.9 ppm and a OH signal at d 3.26 identifies the debenzylated CH_2OH group and by HSQC and TOCSY residues A and D. Also in **4** a HMBC correlation between C4$^{A/D}$ at 74.4 ppm and an anomer at 5.72 ppm is seen thereby identifying residues B and E, and a ROESY correlation between H-4$^{A/D}$ and H-1$^{B/E}$ confirms this.

For **5** the ^{13}C signal at 62.0 ppm for C-6 and 73.5 ppm for C-3 identifies the double debenzylated A residue, while ROESY

Table 2. ^{1}H and ^{13}C NMR chemical shifts of monool **3**.

	A[a]	B	C	D	E	F
H-1	4.83	4.91	5.48	4.84[b]	5.50	4.85[b]
H-2	3.40	3.43	3.54	3.43	3.53	3.43
H-3	4.11	4.08	4.19	4–4.1	4.18	4–4.1
H-4	4.04	4.02	4.12	3.85–4	3.95	3.85–4
H-5	3.90	3.88	3.85	3.85–4	3.93	3.85–4
H-6 a	3.83	3.88 (4.1)	4.1 (3.95)	3.93	3.93	3.93
H-6 b	3.65	3.43	3.47	3.53[c]	3.72	3.68[c]
Bn	4.25–4.55(20H), 4.67(2H), 4.80–4.95(8H), 5.17(1H), 5.21(1H), 5.32(1H), 5.37(1H)					
Ar	7.06–7.32 (85H)					
C-1	98.1	98.23[b]	98.5	98.17[b]	98.15	98.9
C-2	79.5	79.1[c]	78.6[c]	79.3[c]	78.1[d]	79.7[c]
C-3	81.51	80.93	81.3	80.8	80.95	81.46
C-4	80.3[g]	76.6	80.5	75.9[f]	80.0[g]	81.12[f]
C-5	71.9[h]	71.8	71.6	71.4[e]	72.0[h]	71.5[e]
C-6	61.6	69.1	69.3	69.5	69.6	69.4
Bn	72.52, 72.53, 73.0, 73.1, 73.2, 73.3, 73.39, 73.41, 73.46, 73.49, 73.8, 74.7, 74.8, 76.0 (x2), 76.2, 76.3					
Ar	(6 C), 138.0–138.6 (11 C), 126.8–128.5 (85 C)					

[a] The letters **A** to **F** refers to each of the monosaccharides using normal cyclodextrin nomenclature as of Figure 1. [b–h] Shifts may be interchanged.

Table 3. ^{1}H and ^{13}C NMR chemical shift of diol **4**.

	A[a]	B	C	D	E	F
H-1	4.7	5.72	4.72	4.7	5.72	4.72
H-2	3.41	3.57	3.41	3.41	3.57	3.41
H-3	4.09	4.20	4.02	4.09	4.20	4.02
H-4	3.86	3.96	3.76	3.86	3.96	3.76
H-5	3.93	3.93	3.93	3.93	3.93	3.93
H-6a	~3.73	4.01	3.9	~3.73	4.01	3.9
H-6b	3.64	3.73	3.76	3.64	3.73	3.76
OH	3.26	–	–	3.26	–	–
Bn	4.31(2H), 4.36(2H), 4.41(2H), 4.45(2H),4.5–4.55(10H), 4.76(6H), 4.88(4H), 5.18(2H), 5.44(2H)					
Ar	7.04–7.32 (80H)					
C-1	98.4	98.0[b]	97.8[b]	98.4	98.0[b]	97.8[b]
C-2	79.9[c]	77.9	79.2[c]	79.9[c]	77.9	79.2[c]
C-3	81.8	81.1	80.8	81.8	81.1	80.8
C-4	74.4	81.2	81.9	74.4	81.2	81.9
C-5	72.2[d]	71.8[d]	71.4[d]	72.2[d]	71.8[d]	71.4[d]
C-6	61.9	69.7	69.8	61.9	69.7	69.8
Bn	72.4, 73.2, 73.5(x3), 74.1, 76.2 & 76.6					
Ar	139.2–139.2 (6 C), 137.8–138.6 (10 C), 126.3–128.4 (80 C)					

[a] The letters **A** to **F** refers to each of the monosaccharides using normal cyclodextrin nomenclature as of Figure 1. [b–d] Shifts may be interchanged.

Table 4. ^{1}H and ^{13}C NMR chemical shift of triol **5**.

	A[a]	B	C	D	E	F
H-1	4.79	5.08	4.72	4.76	5.60	4.77
H-2	3.27	3.61	3.40	3.43	3.56	3.38
H-3	4.22	4.25	4.03	4.11	4.012	3.99
H-4	3.41	3.85	3.83	3.79	3.94	3.64
H-5	3.79	3.97	3.89	4.07	3.94	3.92
H-6a	3.60	3.74	3.88	3.71	3.69	3.85
H-6b	3.61	3.97	3.67	3.65	4.08	3.75
Bn	4.4–4.6 (17H), 4.7–4.84 (5H), 4.85(1H), 4.88(1H), 4.91(1H), 4.97(1H), 5.15(1H), 5.21(1H), 5.31(1H), 5.51(1H)					
Ar	7.07–7.43 (75H)					
C-1	100.5	100.7	99.3	98.0	98.6	97.9
C-2	77.4	78.2	78.8	79.9	77.7	79.7
C-3	73.5	81.3	80.7	81.6	80.81	80.83
C-4	81.8	82.3	81.4	76.0	80.8	82.7
C-5	71.6	72.2	71.9	71.4	71.7	72.3
C-6	62.0	69.7[b]	70.0[b]	62.0	69.4[b]	70.1[b]
Bn	72.3,72.4,72.6, 72.8, 72.9, 73.4(x3), 73.5, 74.2, 74.5, 75.9, 76.1, 76.5, 76.6					
Ar	(5 C), 137.6–138.8 (10 C), 126.5–128.6 (75 C)					

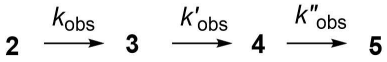
[a] The letters **A** to **F** refers to each of the monosaccharides using normal cyclodextrin nomenclature as of Figure 1. [b] Shifts may be interchanged.

crosspeaks between H-4^{A} (δ 3.41) and an anomer at δ 5.08 (H-1^{B}), between H-1^{A} (δ 4.79) and a signal at δ 3.64 (H-4^{F}), between the H-1^{C} at δ 4.72 and H-4^{B} at δ 3.85, and between the H-1^{D} at δ 4.76 and H-4^{C} at δ 3.83 are seen. Finaly in **5** the anomeric signal at 5.60 (H-1^{E}) has a ROESY cross-peak with a signal at 3.79 (H-4^{D}).

From Table 1–3 we see that each of the partially debenzylated compounds **3**–**5** have one or two of the anomeric signals at unusually low field (δ 5.4–5.8) while the remainder are at δ 4.8–5.0 and closer to the expected value of anomeric protons of benzylated α-glucosides. These signals are not, as one might think, the H-1 on the debenzylated residues, **A** or **D**, but often from **B** or **E** i.e. the residues right behind the modified sugar. So the likely explanation for the outlying signals are that the removing some benzyl groups create holes so that some anomeric protons are less shielded by aromatic ring currents.

These outlying anomeric signals can be used to determine the composition of **2**,**3**,**4** and **5** in a partially debenzylated mixture as the doublet at δ 5.72 is indicative of 2 protons from **4**, the doublets at δ 5.50 and δ 5.48 each holds 1 proton from **3**, the doublet at δ 5.08 holds 6 protons from **2** and d 5.60 holds one proton from **5**. There is some overlap between H-1 of **2** and a H-1 in **5**, which have to be taken into account in the rare cases where **2** and **5** are present simultaneously.

*Kinetics of the reaction of **2**.* The rate of reaction of **2** with excess DIBAL was measured with the goal of obtaining the pseudofirst order rate constant k_{obs} shown in Scheme 2. Practically this was done by taking out samples of the reaction of **2** with excess DIBAL and working it up in the usual manner whereby one gets an NMR such as shown in Figure 2 that by integration provides the relative composition of the components (in shown case it contains 65% **2**, 33% **3** and 2% **4**) and hence the concentration of that compound at the time of



Scheme 2. Pseudo first-order reactions k_{obs}, k'_{obs} and k''_{obs} determined when DIBAL concentration is kept constant.

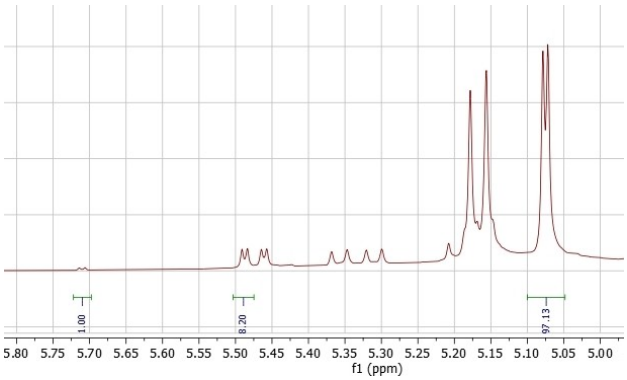


Figure 2. The area from δ 5.0–5.8 of the 500 MHz ^{1}H NMR spectrum of the product from reaction of **2** (15.4 mM) with DIBAL (1.5 M) at 50 °C for $^1/_2$ h. From integrals it is seen that the product 65% **2**, 33% of **3** and 2% **4**.

sampling. As the concentration of DIBAL is important DIBAL stock solutions were titrated in advance using a published method.[19]

Two different series of concentrations were performed either with a) 100 equivalents of DIBAL and different dilutions or b) a fixed starting concentration of **2** and 20–190 equivalents of DIBAL. A plot of the natural logarithm of the mole fraction of remaining **2** at a given time gave linear relationship in all cases (Figure 3) in agreement with pseudofirst order kinetics. From such plots the pseudofirst order rate constants at different DIBAL concentrations and temperature 50 °C were determined. This gave the rate constants shown in Table 5 which include data from the series with fixed equivalents or fixed substrate concentration as there appeared to be no major difference. We see that k_{obs} is essentially independent of the concentration of DIBAL until about 0.5 M DIBAL at which point the rate increases much with the increase of [DIBAL]. There therefore must be part of the reaction which is zero-order in DIBAL concentration.

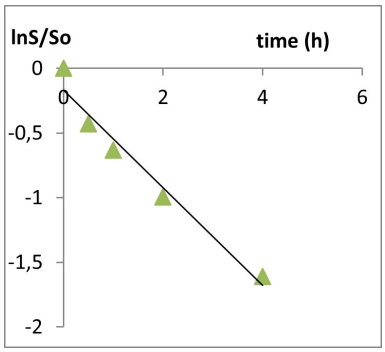


Figure 3. The fit of the product composition vs. time at [DIBAL] = 1.5 M.

Table 5. Experimental pseudo first order kinetic constants for the reaction of **2** to **3** (Scheme 2) and calculated times ($t^1/_2$) required for 50% conversion. Reactions were performed in toluene at 50 C with starting concentration of **2** of 1–16 mM.

DIBAL [M]	k_{obs} [h^{-1}]	Calc $T^1/_2$ [h]
0.1	0.069 ± 0.012	10
0.3	0.10 ± 0.02	8.3
0.375	0.049 ± 0.005	7.5
0.5	0.097 ± 0.011	6.2
0.6	0.14 ± 0.01	5.2
0.75	0.15 ± 0.01	4.1
0.9	0.16 ± 0.02	3.3
1	0.23 ± 0.03	2.8
1.2	0.46 ± 0.02	2.1
1.5	0.38 ± 0.04	1.5
1.7	0.49 ± 0.05	1.2
2.1	0.86 ± 0.08	0.81
2.8	2.6 ± 0.1	0.47

The simplest mathematical model that can explain the rate dependence of DIBAL is a polynomium of the form $k_{obs} = k_0 + k_n[DIBAL]^n$ where k_0 is the rate constant of the zero order reaction and k_n is the rate of the concentration dependent component and n is the multiplicity of the DIBAL dependence. In order to determine k_0, k_n and n we converted the equation to logarithmic form, $\ln(k_{obs} - k_0) = \ln k_n + n\ln[DIBAL]$, and plotted $\ln|k_{obs} - k_0|$ versus ln[DIBAL] for different values of k_0. For a value of $k_0 = 0.0675$ h^{-1} we get an excellent fit of the data with $n = 2$ and $r^2 = 0.96$ (Figure 4). This means (1) is valid:

$$k_{obs} = 0.0675 + 0.179[DIBAL]^2 \ (h^{-1}) \quad (1)$$

with DIBAL concentration given in M.

We suggest the following explanation for the observed kinetics: In this reaction where the medium is very unpolar complexation of DIBAL to the cyclodextrin is likely to precede every reaction. If this complexation is very efficiently and complete it will not influence the rate. On the other hand if the complexation equilibrium is far to the right it will influence the rate and the concentration of DIBAL will affect the rate. The zero order reaction is therefore caused by the slow internal

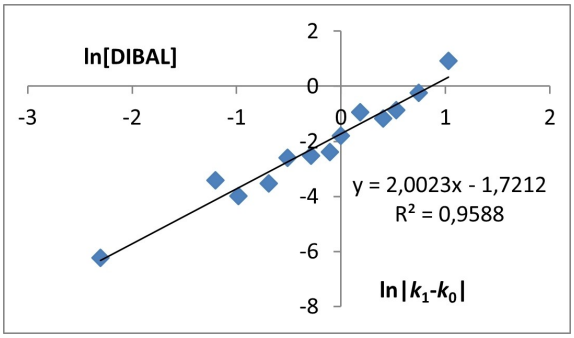


Figure 4. Double logarithmic plot of $k_{obs}-k_0$ (where $k_0 = 0.0675$ h^{-1}) versus [DIBAL] for the reaction of **2** with excess DIBAL in toluene at 50 °C. We see that the slope equal to the multiplicity in [DIBAL] is 2. The intercept is $\ln k_n$ and giving $k_n = 0.179$ M^{-2} h^{-1}.

reduction of the quantitatively preformed cyclodextrin-DIBAL complex (Figure 5). The second order reaction is a result of two additional equivalents of DIBAL participating. The first equivalent makes a less favored complex to the other lone pair of O[6], while the second equivalent acts as a reducing agent.

Support for this mechanism comes from the influence of temperature on k_{obs}: An Arrhenius plot of the reaction of **2** to **3** in 1.5 M DIBAL at 30–70 C is shown in Figure 6. The activation energy is 42.9 kJ/mol, and the activation entropy is calculated to −130 J/mol° or (−31 cal/mol°). This low activation entropy reveal a high degree of order in the transition state similar to that of a Diels-Alder reaction (−36 cal/mol°).[20] At this concentration of DIBAL the reaction is mainly the second order component and the high degree of order fits with the proposed mechanism. An Arrhenius plot was also made at 0.1 M DIBAL where the zero order component is the predominant reaction (Figure 7). Here the activation energy was 51.3 kJ/mol, and the activation entropy is calculated to −114 J/mol° or (−27 cal/mol°). So also here the transition state is highly ordered fitting with the complexation of DIBAL.

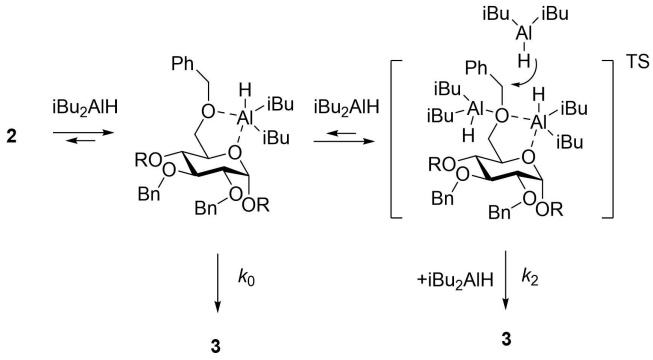


Figure 5. Proposed mechanism for the reduction of **2**.

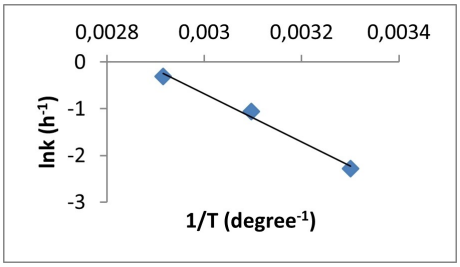


Figure 6. Arrhenius plots for the reaction of **2** to **3** at 1.5 M DIBAL in toluene.

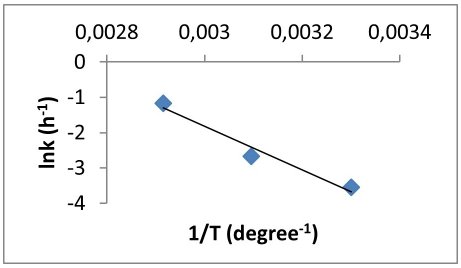


Figure 7. Arrhenius plots for the reaction of **2** to **3** at 0.1 M DIBAL in toluene.

From the relationship $k_{obs} = 0.0675 + 0.179[DIBAL]^2$ the half-lives of **2** ($t^1/_2$) can be calculated as $\ln 2/k_{obs}$ and they are listed in Table 5. We see that the half-life of **2** is 10 h at 0.1 M DIBAL and does not fall much before the DIBAL concentration is increased to 0.6 Mm where $t^1/_2$ is 5 h. At DIBAL concentrations typically used in many preparative reactions such as 1.0 M or 1.5 M the half-life of **2** is 3 h and 1.5 h respectively. These rates are considerably lower than in several of the preparative experiments reported by us and others (table 1, entries 1,3–4,11–13), which appears to run much faster. The present rate data are much more in accordance with the experiments reported by Lings group (Table 1, entries 14–16) and the difference is so significant that Ling actually states that "the debenzylations went much slower than it was reported." suggesting that this was due to the solvent in Lings experiments being hexane and not toluene.[13]

*Kinetics of the reaction of **3**.* The kinetics of the reaction of the monool **3** to diol **4** was also studied. Determination of rate constant for that reaction, k'_{obs}, at 50 °C gave the data shown in Table 6. We see that the rate of the reaction is essentially independent of the concentration of DIBAL over a large span of concentration with a mean rate of $k'_{obs} = 0.25\ h^{-1}$ i.e. the reaction is zero order in DIBAL concentration. There may be several physical explanations to this behavior but the simplest is to invoke the mechanism originally proposed[1] for formation of **4** i.e. an intramolecular reduction by the diisobutylaluminate attached to the monool (Figure 8, left).

*Kinetics of the reaction of **4**.* When **4** is reacted with DIBAL in toluene we find that the initial product of reaction is triol **5** similarly to what Ling reported using DIBAL in hexanes.[13] Triol **5** reacts further to tetrols (see below) but since no other triol appears to be formed a good determination of the rate from **4** to **5** can be determined if the reaction is only progressed to around 50% completion. The rate constant at 50 °C is seen in table 6. The reaction is also independent of the concentration of DIBAL with a mean k''_{obs} of 0.008 h^{-1} – about 30 times slower that the reaction from monool **3** to diol **4**. The simplest explanation for the zero order kinetics is an intramolecular mechanism: The diisobutylaluminate attached to the 6-OH of the A-pyranose perform a reduction of the 3-O-Benzyl group in the same pyranose (Figure 8, right).

Further reaction with DIBAL. The reactions beyond diol **4** are slow reactions and we therefore tried to push the reactions

Table 6. Rate constant for reaction **3** to **4** (k'_{obs}) and **4** to **5** (k''_{obs}) with DIBAL (large excess) in toluene at 50 °C. ND means not determined. Mean is the average of the determined values.

[DIBAL] [M]	k'_{obs} [h^{-1}]	k''_{obs} [h^{-1}]
0.3	0.27 ± 0.04	ND
0.6	ND	0.0096 ± 0.0022
0.9	0.21 ± 0.04	ND
1.0	0.27 ± 0.04	ND
1.5	0.24 ± 0.07	0.0073 ± 0.0005
2.8	ND	0.0071 ± 0.0005
Mean	0.25	0.0080

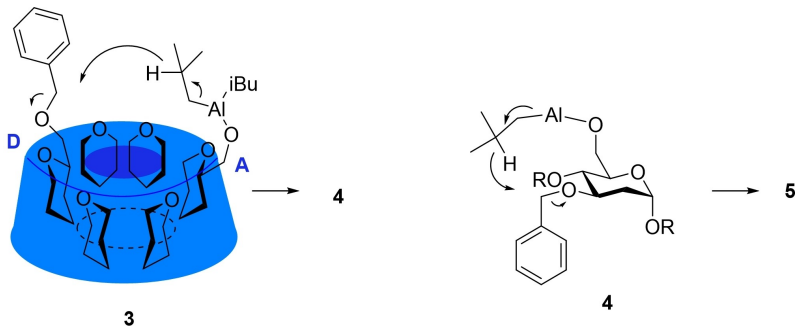


Figure 8. Mechanisms for formation of **4** and **5** that accords with the kinetics observed.

with concentrated DIBAL solutions. Reaction with of **2** with 2.8 M DIBAL in toluene at 50 °C had after 40 minutes only 5% **2** is left and after 3 h all cyclodextrin has essentially been converted to **4**. After 12 h 29% of the triol **5** has formed and after 24 h the mixture contains 43% triol **5**, 42% diol **4** and 15% other products have started to formed. These other compounds must all originate from **4**, and it is clear that the primary product from **4** is **5**, but it is difficult to exclude that there could be another triol formed in small amounts but we have not isolated it. Since **5** reacts, the isolated yield of **5** was never high which is similar to the observations of Ling on the reactions in hexane.[13] For example in a preparative experiment we reacted **2** with 2.8 M DIBAL in toluene for 72 h at 50 °C and obtained 21% of **5**.

Ling's tetrol **6** was not observed in our experiments with 1.5 or 2.8 M DIBAL in toluene. However two other tetrols were obtained. The least polar of these compounds was the 2B,3 A,6 A,6D-tetrol **7** which was isolated in 20% yield from the reaction of **2** with 2.8 M DIBAL in toluene at 50 °C for 73 h. From the same experiment a polar tetrol **8** which was debenzylated at the 3 A,6 A,6 C,6D-position was isolated in 3% yield. In another preparative experiment, where **2** was reacted with 2.8 M DIBAL in toluene at 80 C for 42 h, **8** was isolated in 18% yield. Compounds **7** and **8** are most likely formed from **5**.

The structure of compounds **7** and **8** were identified from 800 MHz ^{1}H, ^{13}C, COSY, HSQC, 2D TOCSY and ROESY spectra similarly as was done in the assignment of **3**–**5** described above. The assignments are shown in table 7 and 8. Particularly important for the assignment of **7** was that several OH protons were visible in the ^{1}H spectrum and that one of them (δ 2.99) coupled with a H-2 proton (δ 3.76) revealing that 2-debenzylation had occurred. Moreover the ^{13}C signal a 62.03 ppm signal for C-6 and 73.32 ppm signal for C-3 identified a 3,6-double-debenzylated A residue, and ROESY crosspeaks between H-4^{A} (δ 3.42) and the anomer at δ 5.20 (H-1B) revealed that the B-residue was the 2-O-debenzylated residue. For **8** the assignment was based on ROESY crosspeaks between H-1^{E} and H-4^{D} (δ 3.79), between H-1^{B} and H-4^{A} (δ 3.46), between H-1^{D} (δ 4.68) and a signal at δ 3.95 (H-4^{E}), between the H-1^{C} at δ 4.79 and H-4^{B} at δ 3.67, and between the H-1^{A} at δ 4.78 and H-4^{F} at δ 3.67.

While we did not observe Lings tetrol **6** in the above experiments with high concentrations of DIBAL, the kinetic evidence showing that the reaction of **4** to **5** was 0 order and potentially intramolecular led us to investigate the reaction of **4**

Table 7. ^{1}H and ^{13}C NMR chemical shift of tetrol **7**.

	A[a]	B	C†	D	E	F†
H-1	4.80	5.20	4.80	4.80	5.64	4.80
H-2	3.26	3.76	3.48	3.46	3.58	3.41
H-3	4.19	4.12	4.04	4.12	4.09	4.03
H-4	3.42	3.85	3.89	3.81	3.95	3.66
H-5	3.95	3.91	3.80	4.16	3.98	3.95
H-6 a	3.66	3.90[b]	3.92[b]	3.70	4.04[b]	4.10[b]
H-6 b	3.77	3.79[b]	3.70[b]	3.70	3.79[b]	3.70[b]
OH	2.88	2.99	–	3.18	–	–
Bn	5.45 (d,1H), 5.30 (d,1H), 5.22 (d,1H), 5.18 (d,1H), 4.38–4.96 (m, 24H)					
Ar	7.07–7.41 (70H)					
C-1	98.09	101.17	100.30	97.82	98.58	99.21
C-2	77.49	72.08	79.17	79.98	77.57	79.66
C-3	73.32	81.72	80.42	81.54	80.77	80.66
C-4	82.08	81.93	81.35	76.35	80.70	82.81
C-5	71.89	72.80	71.79	71.34	71.73	72.30
C-6	62.03	70.18[b]	70.06[b]	62.13	69.66[b]	69.29[b]
Bn	76.67, 76.24, 75.87, 75.85, 74.43, 73.46, 73.45, 73.42, 73.41, 73.22, 73.15, 72.71, 72.56, 72.45					
Ar	137.89–139.68 (14 peaks, C-ipso), 126.5–128.7 (m)					

[a] The letters **A** to **F** refers to each of the monosaccharides using normal cyclodextrin nomenclature as of Figure 1. [b] Shifts may be interchanged.

Table 8. ^{1}H and ^{13}C NMR chemical shift of tetrol **8**.

	A[a]	B	C	D	E	F
H-1	4.78	5.06 (d)	4.79	4.68	5.57 (d)	4.84
H-2	3.27 (dd)	3.55(dd)	3.46	3.45	3.56 (dd)	3.39 (dd)
H-3	4.22	4.22	4.04	4.10	4.13	4.01
H-4	3.46	3.67	3.70	3.79	3.95	3.67
H-5	3.79	3.80	3.95	3.46	3.80	3.97
H-6 a	3.70	4.06	4.01[b]	3.72[b]	3.82	3.85
H-6 b	3.64	3.70	3.82[c]	3.72[c]	3.76	3.76
OH	2.78	–	3.13[d]	2.41[d]	–	–
Bn	5.44 (d,1H), 5.28 (d,1H), 5.20 (d,1H), 5.17 (d,1H), 4.37–4.95 (24H)					
Ar	7.05–7.40 (m, 70H)					
C-1	100.11	100.37	99.21	97.91	98.49	98.03
C-2	77.53	77.90	81.28	79.96	78.35	79.54
C-3	73.40	81.06	80.45	77.36	80.88	80.85
C-4	78.60	82.60	81.88	81.57	80.41	82.27
C-5	71.49	73.52[b]	72.13	71.60[b]	73.40[b]	71.70
C-6	61.68	69.39	62.88[c]	61.96[c]	70.35	70.11
Bn	76.42, 76.33, 76.02, 75.99, 74.57, 74.09, 73.69, 73.62, 73.43, 73.12, 72.89, 72.70, 72.46, 72.25					
Ar	137.5–139.7 (14 peaks, C-ipso), 126.6–128.7 (m)					

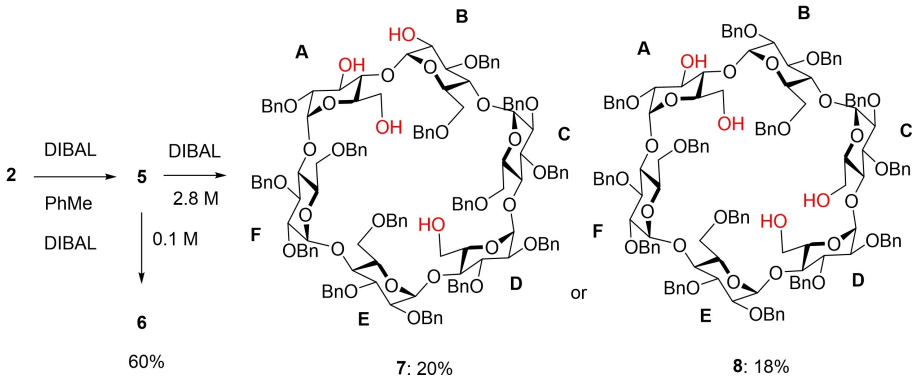
[a] The letters **A** to **F** refers to each of the monosaccharides using normal cyclodextrin nomenclature as of Figure 1. [b–d] Shifts may be interchanged.

at low concentrations of DIBAL that would be expected to favor an intramolecular reaction rather than intermolecular reactions. Indeed, these counterintuitive reaction conditions led to preferred formation of Lings tetrol **6**. Reaction of **2** with 0.1 M DIBAL for 10 days at 70 C gave **6** as the essentially sole product left in the reaction according to NMR though TLC shows other minor spots of higher and lower polarity indicating several biproducts and starting materials being present in small amounts (Scheme 3). A similar result is obtained when **4** was reacted with 0.1 M DIBAL for 6 days at 90 C and **6** could be isolated in 60% yield. The remarkable finding that **6** is formed almost exclusively at low DIBAL concentration and almost not at high DIBAL concentration we believe is because it is formed by intramolecular reduction by the aluminates bound to the 6-OH groups as outlined above (Figure 8). At high concentrations this reaction is outcompeted by other intermolecular debenzylation leading to products such as **7** and **8**.

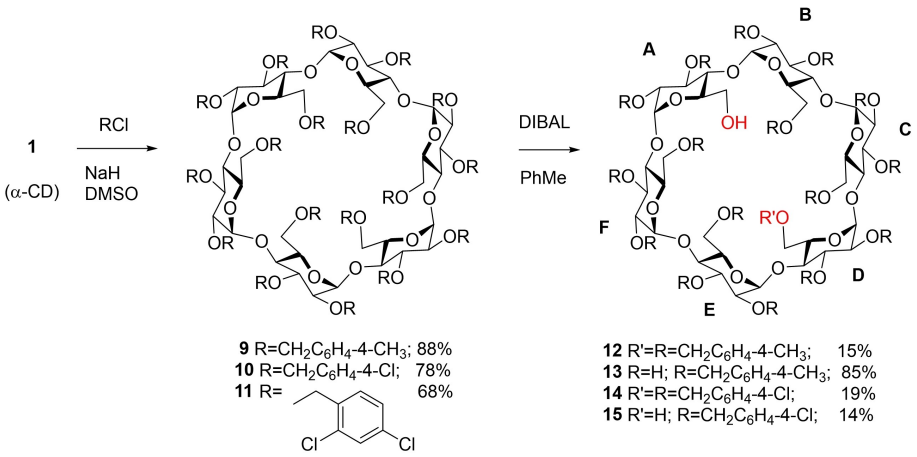
Investigation of benzyl substituents. We also investigated the influence of substitution in the benzyl groups by preparing perbenzylated α-cyclodextrin with 4-methyl, 4-chloro- and 2,4-dichloro substitution as outlined in Scheme 3: By alkylation of **1** with the benzyl chlorides and sodium hydride in DMSO the derivatives **9**–**11** were obtained in 68–88% yield (Scheme 4). Using benzyl bromides rather than chlorides in this reaction does not give any product presumably due to Kornblum oxidation of the bromide.

Reaction of **9**–**11** with DIBAL in toluene was investigated (Scheme 4). The 4-methyl-analogue **9** reacted considerably faster than **2** but still giving the analogues mono- and diols **12** and **13**. The 4-chloro-analogue **10** was on the other hand very sluggish yet still eventually gave first monool **14** and then diol **15**. The identity of these new derivatives were easy to establish because the ^{1}H-spectra of **13** and **15** showed the compounds were symmetrical and were extremely similar to the ^{1}H-spectrum of **4**. Furthermore it was clearly seen that **12** and **14** were formed first and then completely converted to **13** and **15**, respectively leaving no doubt of the structures that were also confirmed by MS.

The pseudo first order rate constants for the reaction of **9** to **12** and **10** to **13** was compared to that for the reaction for **2** to **3** and plotted against the Hammett σ_p^+ constants used for reactions where direct conjugation between the reaction center



Scheme 3. Formation of **5**, **6**, **7** and **8**.



Scheme 4. Synthesis of substituted perbenzyl α-cyclodextrins **9**–**11**.

and possible.[20] The plot (Figure 9) gives a straight line with a ρ of −4.9. This fits a mechanism where there is a high degree of positive charge at the benzylic center such as shown in Figure 10. Other reactions with a similar low ρ-value are solvolysis of benzhydryl ($\rho = -4.1$) or dimethylbenzyl ($\rho = -4.54$) while solvolysis of ordinary benzylic chlorides only has $\rho = -2.18$.[20,21] This speaks of a transition state where the complexation of two aluminium atoms to O5 and O6 (Figure 10) makes the O6 a good leaving group that to high degree have broken the bond to benzylic carbon in the transition state.

The per(2,4-dichlorobenzyl) derivative **11** did not react with DIBAL in toluene – even after 2 days at 50 °C with 1.5 M DIBAL no product was observed. This is not surprising given the powerful negative influence on rate even one chlorine atom has. However if $AlMe_3$ is added to the reaction **11** begins to react eventually leading to formation of the diol **16** which was obtained in 60% yield (Scheme 5). As above **16** is readily identified by its symmetry and great resemblance of the ^1H NMR with that of **4**. The rationale behind this reaction is that scrambling of alkyl groups on aluminium readily occurs as has been described by Ziegler and collaborators.[22] Therefore dimethylaluminium hydride and methylisobutylalumnium hydride is formed (Scheme 5) and are obviously able to debenzylate the 2,4-dichlorobenzyl groups. For comparison if trimethylaluminum is added to the reaction of **2** with DIBAL a

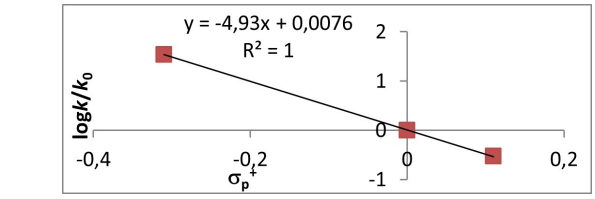


Figure 9. Hammett plot for the reaction of **2** to **3** at 1.5 M DIBAL in toluene.

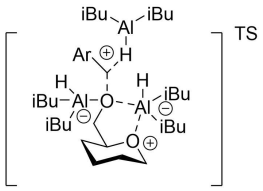
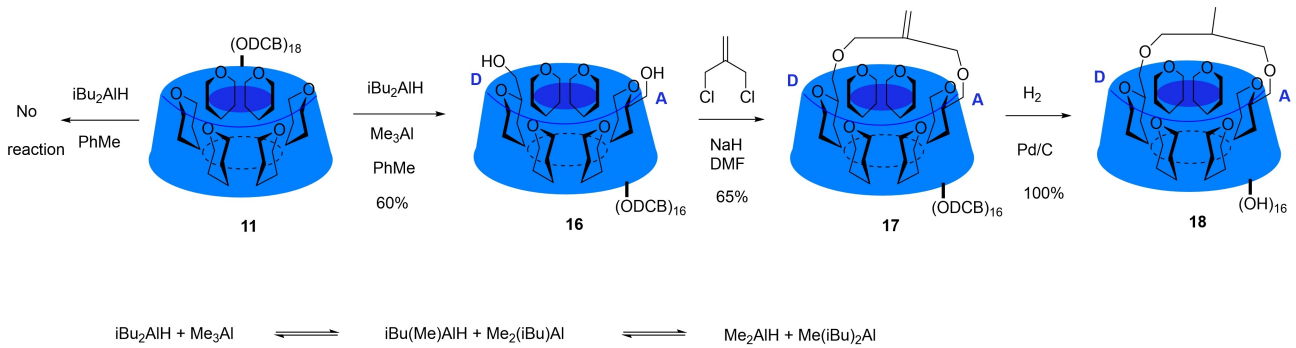


Figure 10. Transition state of the debenzylation of the primary benzyl has a high degree of positive charge at benzylic carbon.



Scheme 5. Resistance of **11** to DIBAL, and its succeptebility to DIBAL/$AlMe_3$.

complex mixture of products is seen. Neither **2** or **11** reacts with trimethyl aluminum alone.

Compound **16** can be converted to the bridged derivative **17** in the manner previously described for **4** reacting with 1.1 equiv. of methallyl dichloride and NaH in DMF. This gave a 65% yield of **17** (Scheme 4). Hydrogenation and hydrogenolysis gave the known unprotected cyclodextrin **18** in quantitative yield.[23]

Conclusion

The DIBAL promoted debenzylation of perbenzyl α-cyclodextrin (**2**) has a second order and a zero order dependency of the DIBAL concentration meaning there is two routes to the monool **3**. Both routes are likely to involve complexation of DIBAL to the O5 and O6 of the monosaccharide attacked as has previously been suggested,[2] which is supported by the finding that the activation entropy is very low pointing at an highly ordered transition state. The debenzylation of monool **3** to diol **4** was found to be zero order in DIBAL concentration as was the debenzylation of diol **4** to Lings triol **5** and we believe the most likely explanation for this is that the reaction is intramolecular with the aluminate attached to the debenzylated alcohol acting as an internal reducing reagent either from residue 6-OH of residue A to 6-OBn of residue D or to the 3-OBn of residue A. Supporting this hypothesis is the finding that Lings tetrol **6** is formed selectively when the reaction is conducted at low DIBAL concentration and not at all at high concentration where intermolecular reactions appear to dominate. The rate of debenzylation of **2** is highly dependent on substitution with $\rho = -4.9$ showing a very positively charged transition state. The observation that towards DIBAL totally unreactive per(2,4-dichloroperbenzyl)-α-cyclodextrin **11** can be converted to diol **16** when trimethyl aluminum is added to the reaction indicates that sterical hindrance from the substituents on aluminum is nevertheless important for these reactions. This will be investigated in the future.

Experimental Section

General information. Dry solvents were tapped from a PureSolv solvent purification system. Reactants were purchased from commercial sources and used without further purification. HRMS were recorded on a Bruker Solarix XR mass spectrometer analyzing TOF. Generally NMR spectra were recorded on a 500 MHz Bruker instrument with a cryoprobe. The 800 MHz spectra were recorded on a Bruker Avance Neo spectrometer with 5 mm CPTXO Cryoprobe C/N–H–D optimized for direct ^{13}C detection. Chemical shifts (δ) are reported in ppm relative to the residue solvent signals or other solvent present. Flash chromatography was carried out on a Büchi Pure Chromatography Instrument C-805 using silica columns. Neat DIBAL was taken from a sure-Pac™ metal container using the plastic bag technique: The DIBAL container was placed in a plastic bag that was fitted with a valve using duct tape and evacuated and filled with nitrogen several time to ensure no oxygen left in the bag. Then the container was opened and neat DIBAL withdrawn using a syringe. [1]

General procedure for studying the kinetics of reactions of benzylated cyclodextrin with DIBAL: A sample of **2**, **9**, **10** or **11** (200 mg) was dissolved in X ml dry toluene in a dry round-bottomed flask fitted with a septum and stirring bar under nitrogen. Y ml DIBAL either as a 1.5 M solution in toluene or neat (see general information) was added with a syringe. In experiments with fixed number of equivalents of DIBAL, X was 0, 5, 10, 15 or 70 ml and Y was 5 ml., while in experiments with fixed concentration of cyclodextrin X was 1,2,3 or 4 ml, while Y was 1,2,3 or 4 ml so that $X+Y=5$ ml. The reaction was stirred at fixed temperature, normally 50 °C, controlled by an oil bath. At different times samples (0.3–2 ml depending on volume) were extracted with a syringe, added to 50 ml toluene and was washed with 50 ml 1 M H_2SO_4 and saturated $NaHCO_3$ in a separating funnel. The organic layer was dried with sodium sulfate, filtered, concentrated and analyzed by ^1H NMR in $CDCl_3$. The relative content of **2**, **3**, **4** & **5** in the sample was determined by comparing the integrals of peaks at δ 5.72 (d, 2H, 4), 5.60 (d, 1H, 5), 5.50 (d, 1H, 3) & 5.08 (d, 6H, 2). Compound **5** has a benzyl proton at δ 5.51 (Table 4) that overlaps with **3** and has to be subtracted in the very rare cases where **3** and **5** are present in the same sample.

$2^{A-F},3^{B-C},3^{E-F},6^{B-C},6^{E-F}$-tetradeca-*O*-benzyl-α-cyclodextrin (6): To a solution of diol **4** (0.8 g, 0.33 mmol) in dry toluene (240 mL) in a round-bottomed flask fitted with septum and stirring bar and a nitrogen atmosphere was added 17.5 ml DIBAL (1.5 M in toluene). The mixture was stirred at 90 C using an oil bath for 6 days. The toluene phase was washed with 100 ml 1 M H_2SO_4 and 50 ml water, dried using sodium sulphate, filtered and concentrated. The residue was subjected to silica gel flash chromatography in a solvent gradient of heptane-EtOAc 1:0→3:1→1:1→0:1 gave tetrol **6** (0.45 g, 60%) as a clear syrup. NMR showed it identical to the compound reported by Lings group.[13,14]

$2^{A,C-F},3^{B-F},6^{B-C},6^{E-F}$-tetradeca-*O*-benzyl-α-cyclodextrin (7): To a solution of perbenzyl α-cyclodextrin 2 (1.27 g, 0.51 mmol) in dry toluene (3 mL) in a round-bottomed flask fitted with septum and stirring bar and a nitrogen atmosphere was added 3 ml neat DIBAL giving a concentration of 2.8 M DIBAL. The mixture was stirred at 50 °C using an oil bath for 3 days. Toluene (50 ml) and 1 ml isopropanol was added to destroy the excess DIBAL and the organic layer was washed with 50 ml 1 M H_2SO_4 and 20 ml saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated. The residue (1.08 g) was subjected to silica gel flash chromatography in a solvent gradient of heptane-EtOAc 1:0→4:1→1:1→0:1 giving diol **4** (170 mg, 14%, R_f 0.85 in EtOAc:p-ether 2:3), triol **5** (241 mg, 21%, R_f 0.65 in EtOAc:p-ether 2:3), tetrol **7** (214 mg, 20%, R_f 0.25 in EtOAc:p-ether 2:3) and tetrol **8** (34 mg, 3%, R_f 0.08 in EtOAc:p-ether 2:3). NMR (800 MHz, $CDCl_3$) see table 7. HRMS (ESI). Calc for $C_{134}H_{144}O_{30}+K^+$: 2272.9413. Found: 2272.9837.

$2^{A-F},3^{B-F},6^{B,E-F}$-tetradeca-*O*-benzyl-α-cyclodextrin (8): To a solution of perbenzyl α-cyclodextrin 2 (1.32 g, 0.51 mmol) in dry toluene (3 mL) in a round-bottomed flask fitted with septum and stirring bar and a nitrogen atmosphere was added 3 ml neat DIBAL giving a concentration of 2.8 M DIBAL. The mixture was stirred at 80 C using an oil bath for 2 days. Toluene (50 ml) and 1 ml isopropanol was added to destroy the excess DIBAL and the organic layer was washed with 50 ml 1 M H_2SO_4 and 50 ml saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated. The residue (1.4 g) was subjected to silica gel flash chromatography in a solvent gradient of heptane-EtOAc 1:0→0:1 giving diol **4** (94 mg, 8%), triol

[1] The procedure can be seen in the following video: http://www.pittelkow.kiku.dk/synmet/synmet_videoer/The%20plastic%20bag%20technique.mp4

5 (164 mg, 14%) and tetrol **8** (206 mg, 18%, R_f 0.44 in diethyl ether). NMR (800 MHz) see table 8. HRMS (ESI). Calc for $C_{134}H_{144}O_{30}+Na^+$: 2256.9674. Found: 2256.9765.

Octadeca-*O*-(4-methylbenzyl)-α-cyclodextrin (9): To a solution of dry α-cyclodextrin (1.0 g, 1.03 mmol) in DMSO (20 mL) was added NaH (1.5 g, 60%, 36 equiv., 37 mmol) under nitrogen atmosphere. After bubbling had subsided 4-methylbenzylchloride (5 ml, 5.2 g, 36 equiv., 37 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Then the reaction was quenched by addition of 5 ml ethanol, toluene (50 ml) was added, and the organic phase was washed with H_2SO_4 (1 M, 50 mL) with some NaCl added for better phase-separation and 3 times with brine (3× 50 ml). The organic layer was dried with Na_2SO_4, filtered and concentrated on the rotary-evaporator to an oily residue (5.64 g). Silica gel flash chromatography in a solvent gradient of heptane-EtOAc 1:0→4:1 gave octadeca-O-(4-methylbenzyl)-α-cyclodextrin **9** (2.56 g, 88%) as a clear syrup. $R_f=0.67$ (p-ether/EtOAc: 3/1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.88–7.27 (m, 72H, ArH), 5.08 (bs, 6H, H1), 5.07 (d, $J=10.6$ Hz, 6H, BnH), 4.78 (d, $J=10.6$ Hz, 6H, BnH), 4.49 (d, $J=12.2$ Hz, 6H, BnH), 4.42 (d, $J=12.2$ Hz, 6H, BnH), 4.34 (d, $J=11.9$ Hz, 6H, BnH), 4.21 (d, $J=11.9$ Hz, 6H, BnH), 4.09 (t, $J=8.9$ Hz, 6H, H3), 4.03 (t, $J=8.8$ Hz, 6H, H4), 3.97 (dd, $J=11.3$, 3.0 Hz, 6H, H6a), 3.84 (bd, $J=9.4$ Hz, 6H, H5), 3.41 (m, 12H, H2 & H6b), 2.26 (s,18H,$ArCH_3$), 2.25 (s,18H,$ArCH_3$), 2.19 (s,18H,$ArCH_3$). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 137.20, 136.98, 136.60, 136.44, 135.62, 135.45 (Ar-ipso), 129.21, 129.08, 128.95, 128.76, 128.04, 127.98, 127.84, 127.74 (ArH), 98.17 (C1), 81.24, 79.00, 78.67 (C2,C3,C4), 75.58(Bn), 73.38(Bn), 72.68(Bn), 71.61(C5), 69.09(C6), 21.32 (ArMe), 21.27 (ArMe), 21.18 (ArMe). HRMS (ESI): Calcd. For $C_{180}H_{204}O_{30}$ [M+2Na]: 1446.2134 (2+); Found: 1446.2189

Octadeca-*O*-(4-chlorobenzyl)-α-cyclodextrin (10): Was performed as the synthesis of 9 using α-cyclodextrin (1.0 g, 1.03 mmol), DMSO (20 mL), NaH (1.5 g, 60%, 36 equiv., 37 mmol) and 4-chlorobenzyl-chloride (4.5 g, 27 equiv., 28 mmol). Silica gel flash chromatography in a solvent gradient of heptane-EtOAc 1:0→0:1 gave octadeca-O-(4-chlorobenzyl)- α-cyclodextrin **10** (2.57 g, 78%) as a clear syrup. $R_f=0.5$ (p-ether/EtOAc: 3/1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.93–7.30 (m, 72H, ArH), 5.04 (d, $J=11.5$ Hz, 6H, BnH), 4.99 (d, $J=3.4$ Hz, 6H, H1), 4.71 (d, $J=11.5$ Hz, 6H, BnH), 4.24–4.47 (m, 24H, BnH), 4.01 (dd, $J=9.9$, 7.3 Hz, 6H, H3), 3.87 (m, 18H, H4,H5,H6a), 3.50 (d, $J=10.3$ Hz, 6H, H6b), 3.40 (dd, $J=9.9$, 3.3 Hz, 6H, H2). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 137.46, 136.39, 136.33, 133.78, 133.71, 133.09 (Ar-ipso), 129.00, 128.95, 128.85, 128.75, 128.53, 128.52, 128.39, 128.02 (ArH), 99.77 (C1), 80.87, 80.55, 79.52 (C2,C3,C4), 74.87(Bn), 72.72 (Bn), 72.34 (Bn), 71.77 (C5), 69.22 (C6). HRMS (MALDI): Calcd. For $C_{162}H_{150}Cl_{18}O_{30}$ [M+Na]: 3238.4389 (89.5%); Found: 3238.6155

Octadeca-*O*-(2,4-dichlorobenzyl)-α-cyclodextrin (11): Was performed as the synthesis of **9** using α-cyclodextrin (1.0 g, 1.03 mmol), DMSO (20 mL), NaH (1.5 g, 60%, 36 equiv., 37 mmol) and 2,4-dichlorobenzyl chloride (5.1 ml, 7.2 g, 36 equiv., 37 mmol). Silica gel flash chromatography in a solvent gradient of p-ether-toluene 1:4→0:1 gave octadeca-O-(2,4-dichlorobenzyl)- α-cyclodextrin **11** (2.68 g, 68%) as a clear syrup. $R_f=0.63$ (p-ether/EtOAc: 3/1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, $J=8.3$, 6H, H6′a), 7.33 (d, $J=2.1$, 6H, H3′a), 7.17 (dd, $J=8.3$, 2.1 Hz, 6H, H5′a), 7.12 (d, $J=8.3$ Hz, 6H, H6′b), 7.01 (d, 6H, H3′b), 7.00 (d, 6H, H3′c), 6.81 (dd, $J=8.4$, 2.1 Hz, 6H, H5′b), 6.70 (d, $J=8.3$ Hz, 6H, H6′c), 6.56 (dd, $J=8.3$, 2.1 Hz, 6H, H5′c), 5.18 (d, 6H, H1), 5.17 ((d, 6H, BnH), m, 2H), 4.73 (d, $J=13.8$ Hz, 6H, BnH), 4.58 (d, 6H, BnH), 4.55 (d, 6H, BnH), 4.48 (d, $J=13.9$ Hz, 6H, BnH), 4.07–4.19 (m, 18H, H3, H6a, BnH), 4.03 (dd, 6H, H5), 3.95 (t, $J=9.1$ Hz, 6H, H4), 3.76 (d, $J=10.4$ Hz, 6H, H6b), 3.44 (dd, $J=9.9$, 3.3 Hz, 6H, H2). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 135.16, 134.36, 134.25, 133.73, 133.48, 133.44, 132.73, 131.84, 131.03, 129.83, 129.34, 128.50, 128.29, 128.09, 127.33, 127.04, 126.62(2 C, Ar), 100.59 (C1), 82.27, 81.21, 80.38 (C2,C3,C4), 72.45, 72.04, 70.19, 69.98, 69.48 (3xBn,C5,C6). HRMS (MALDI): Calcd. For $C_{162}H_{132}Cl_{36}O_{30}$ [M+Na]: 3857.7251 (99.4%); Found: 3857.7397

2^{A-F},3^{A-F},6^{B-F}-heptadeca-O-(4-methylbenzyl)-α-cyclodextrin (12) and 2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(4-methylbenzyl)-α-cyclodextrin (13): Octadeca-O-(4-methylbenzyl)-α-cyclodextrin (**9**, 0.42 g, 0.147 mmol) was dissolved in dry toluene (5 mL) in a dry flask under nitrogen and DIBAL (1 mL, 1.5 M, 10 equiv.) was added. The reaction mixture was stirred at 30 C for 8 h. Then EtOAc (50 mL) was added and the organic layer was washed with 1 M H_2SO_4 (20 ml) and $NaHCO_3$ (20 ml), dried and evaporated to give an oily residue (407 mg). Flash chromatography in heptane-EtOAc 1:0→3:1→0:1 afforded monool **12** (60 mg, 15%) and diol **13** (329 mg, 85%) as white foams. **12**: $R_f=0.57$ (p-ether:EtOAc 3:1), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.9–7.25 (m, 68H, ArH), 5.49 (2d, $J=3.5$ Hz, 2H), 5.33 (d, $J=10.2$ Hz, 1H), 5.29 (d, $J=10.2$ Hz, 1H), 5.14 (d, $J=10.4$ Hz, 1H), 5.12 (d, $J=10.4$ Hz, 1H), 4.95 (d, $J=3.4$ Hz, 1H), 4.89–4.67 (m, 16H), 4.61–3.79 (m, 44H), 3.76–3.61 (m, 2H), 3.53 (m, 2H), 3.41 (m, 4H), 2.35–2.25 (m 45H), 2.16 (s, 3H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 137.5–135.0 (m, ArC), 129.2–116.9 (m, ArH), 98.61, 98.05, 97.92, 97.87, 97.84, 97.82 (6 C-1), 81.54 (CH), 81.51 (CH), 81.34 (CH), 80.99 (CH), 80.90 (CH), 80.87 (CH), 80.28 (CH), 79.99 (CH), 79.68 (CH), 79.56 (CH), 79.22 (CH), 79.05 (CH), 78.96 (CH), 78.44 (CH), 78.08 (CH), 76.17 (Bn), 76.13 (Bn), 76.0 (CH), 75.86 (Bn), 75.80 (Bn), 75.26 (CH), 74.65 (Bn), 73.71, 73.28, 73.21, 73.16, 73.07, 72.88, 72.78, 72.31 (Bn), 72.27 (Bn), 71.98 (CH), 71.82 (CH), 71.77 (CH), 71.41 (2 C, CH), 71.38 (2 C, CH), 69.44 (C-6), 69.37 (C-6), 69.22 (2 C, C-6), 68.95 (C-6), 61.49 (C-6^A), 21.25 (8 C, Me), 21.22 (7 C, Me), 21.08 (Me), 21.05 (Me). HRMS(MALDI) Calc for $C_{172}H_{196}O_{30}+H^+$: 2743.3923. Found: 2743.3839. 13: $R_f=0.57$ (p-ether:EtOAc 3:1), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–6.77 (m, 64H), 5.68 (d, $J=3.7$ Hz, 2H), 5.38 (d, $J=10.0$ Hz, 2H), 5.10 (d, $J=10.3$ Hz, 2H), 4.90–4.60 (m, 14H), 4.58–4.42 (m, 10H), 4.40–4.26 (m, 6H), 4.20–4.11 (m, 2H), 4.10–3.95 (m, 4H), 3.95–3.80 (m, 14H), 3.72 (m, 8H), 3.60 (d, $J=11.7$ Hz, 2H), 3.55 (s, 2H), 3.37 (m, 4H), 3.27 (m, 2H), 3.13 (bd, 2H), 2.44–2.15 (m, 48H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.45, 137.34, 137.31, 137.24, 136.71, 136.66, 136.54, 136.43, 136.40, 135.85, 135.47, 135.22, 135.08, 134.96, 129.80, 129.16, 129.11, 129.06, 128.89, 128.82, 128.80, 128.77, 128.47, 128.44, 128.26, 128.23, 128.19, 128.17, 128.02, 127.42, 126.87, 98.40 (2 C), 97.65 (4 C), 81.78, 81.07, 80.75, 79.62, 79.02, 76.52, 76.09, 74.06, 73.62, 73.39, 73.26, 72.95, 72.18, 71.76, 71.24, 69.57, 61.55, 21.32, 21.27, 21.24, 21.03. MS(MALDI) Calc for $C_{162}H_{188}O_{30}+H^+$: 2639.3297. Found: 2639.3330.

2^{A-F},3^{A-F},6^{B-F}-heptadeca-O-(4-chlorobenzyl)-α-cyclodextrin (14): Octadeca-O-(4-chlorobenzyl)-α-cyclodextrin (**10**, 358 mg) was placed in a dry flask under nitrogen and DIBAL (5 mL, 1.5 M) was added. The reaction mixture was stirred at 50 °C for 24 h. Then toluene (50 mL) was added and the organic layer was washed with 1 M H_2SO_4 (20 ml) and $NaHCO_3$ (20 ml), dried and evaporated to give an oily residue (329 mg). Flash chromatography in heptane-EtOAc 1:0→1:1 afforded **10** (138 mg) and monool **14** (65 mg, 19%) as a clear syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–6.88 (m, 68H), 5.36 (d, $J=3.7$ Hz, 1H), 5.27 (d, $J=3.6$ Hz, 1H), 5.16 (2d, $J=10.6$ Hz, 2H), 5.06 (d, $J=11.2$ Hz, 1H), 5.01 (d, $J=11.4$ Hz, 1H), 4.90 (d, $J=3.3$ Hz, 1H), 4.86 (d, $J=3.3$ Hz, 1H), 4.85–4.60 (m, 12H), 4.56–4.20 (m, 27H), 4.08–3.68 (m, 18H), 3.64–3.58 (m, 1H), 3.57–3.35 (m, 10H), 2.67 (bs, 1H, OH). HRMS(MALDI) calc. for $C_{155}H_{145}Cl_{17}O_{30}+Na$ m/z: 3113.4372 (83.3%), 3113.4276 (49.6%). Found: 3113.4232

2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(4-chlorobenzyl)-α-cyclodextrin (15): Octadeca-O-(4-chlorobenzyl)-α-cyclodextrin (**10**, 138 mg) was placed in a dry flask under nitrogen and DIBAL (3 mL, 1.5 M) was added. The reaction mixture was stirred at 50 °C for 6 days. Then toluene (50 mL) was added and the organic layer was washed with 1 M H_2SO_4 (20 ml) and $NaHCO_3$ (20 ml), dried and evaporated to give an oily residue (117 mg). Flash chromatography in heptane-EtOAc 1:0→1:1 afforded monool **14** (24 mg) and diol **15** (18 mg,

14%) as a clear syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–6.59 (m, 64H), 5.48 (d, J=3.9 Hz, 2H), 5.18 (d, J=10.9 Hz, 2H), 4.91 (d, J=11.2 Hz, 2H), 4.65–4.57 (m, 10H), 4.49–4.10 (m, 22H), 3.98 (m, 2H), 3.92–3.62 (m, 18H), 3.61–3.49 (m, 8H), 3.39 (dd, J=9.8, 4.0 Hz, 2H), 3.33–3.19 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.36, 137.32, 136.55, 136.48, 136.31, 136.14, 135.98, 134.01, 133.94, 133.82, 133.39, 133.33, 133.24, 133.00, 129.38, 129.35, 129.29, 129.25, 129.06, 128.77, 128.75, 128.70, 128.57, 128.54, 128.52, 128.48, 128.44, 128.42, 128.34, 128.22, 128.17, 127.18, 98.33, 98.18, 97.98, 82.01, 81.52, 81.38, 81.01, 80.54 (4 C), 79.40, 77.90, 75.58 (4 C), 75.32, 73.28, 73.02, 72.83, 72.81 (4 C), 72.63, 72.23, 72.15, 71.85, 71.79, 70.25, 69.56, 62.35. HRMS(MALDI) calc. for $C_{155}H_{145}Cl_{17}O_{30}$+Na: m/z: 2988.4376, 2989.4354. Found: 2988.4356 (40.3%), 2989.4365 (4.7%)

2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(2,4-dichlorobenzyl)-α-cyclodextrin (16): Octadeca-O-(2,4-dichlorobenzyl)-α-cyclodextrin (**11**, 1.37 g) was placed in a dry flask under nitrogen, DIBAL in toluene (10 mL, 1.5 M) and trimethyl aluminum in toluene (1 mL, 2.0 M) was added. The reaction mixture was stirred at 70 C for 48 h. The mixture was poured into 120 ml EtOAc and 10 ml isopropanol and the organic layer was washed with 50 ml 1 M H_2SO_4 and 50 ml sat $NaHCO_3$, dried and evaporated to give an oily residue (1.14 g). Flash chromatography in p-ether-EtOAc 3:1→3:2→0:1 afforded diol **16** (0.75 g, 60%) as a clear syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.33 (m, 8H), 7.30–7.20 (m, 7H), 7.18 (dd, J=8.4, 1.1 Hz, 3H), 7.13–6.95 (m, 17H), 6.88 (dd, J=8.3, 2.1 Hz, 2H), 6.84 (dd, J=8.3, 2.1 Hz, 2H), 6.79 (dd, J=8.3, 2.1 Hz, 2H), 6.71 (d, J=8.3 Hz, 2H), 6.66 (d, J=8.3 Hz, 2H), 6.60 (ddd, J=8.3, 5.3, 2.1 Hz, 3H), 5.53 (d, J=3.9 Hz, 2H), 5.29 (d, J=13.7 Hz, 2H), 5.22 (d, J=13.9 Hz, 2H), 5.08 (2d, J=3.6 Hz, 4H), 4.83–3.74 (m, 60H), 3.57 (dd, J=9.9, 3.8 Hz, 2H), 3.45 (m, 4H), 3.07 (bs, 2H, OH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.34, 135.28, 135.16, 134.48, 134.31, 134.24, 134.16, 134.08, 133.94, 133.80, 133.70, 133.67, 133.61, 133.35, 133.29, 132.94, 132.82, 132.62, 132.45, 132.28, 131.78, 131.36, 131.27, 130.93, 130.35, 130.20, 129.45, 129.35, 128.87, 128.69, 128.61, 128.59, 128.53, 128.39, 128.16, 127.68, 127.33, 127.29, 127.01, 126.91, 126.83, 126.78, 126.66, 126.58, 99.78, 99.05, 98.53, 82.25 (4 C), 81.46, 81.23, 81.14, 80.73, 80.28, 79.72, 78.78, 72.55, 72.51, 72.25, 72.18 (2 C), 71.94, 71.40, 70.76, 70.63, 70.28, 70.21, 69.98, 69.33, 68.98, 62.80. HRMS (MALDI). Calc for $C_{148}H_{124}Cl_{32}O_{30}+Na^+$: 3537.7935 (100%). Found: 3237.8176.

2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(2,4-dichlorobenzyl)−6^A,6^D-O-(2-metha-1,3-diyl)-α-cyclodextrin (17): 2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(2,4-dichlorobenzyl)-α-cyclodextrin (**16**, 690 mg) was dissolved in 5 ml dry DMF & NaH (58 mg, 60% suspension) was added under nitrogen – after 20 min. methallyl dichloride (25 µl; 26.2 mg) was added, and the mixture was stirred for 18 h. Toluene (50 ml) and 0.1 M HCl (20 ml) were added, separated, and the toluene phase was further washed 3 times with brine (20 ml). Drying and evaporation gave a syrup (724 mg). Flash chromatography (Büchi 24 g silica clm) in heptane-EtOAc 1:0→7:3 gave **17** (428 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J=8.3 Hz, 2H), 7.42 (d, J=2.1 Hz, 2H), 7.37 (d, J=2.1 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 7.33–7.29 (m, 2H), 7.19 (dt, J=8.4, 2.2 Hz, 4H), 7.14 (m, 8H), 7.00 (dt, J=15.6, 2.5 Hz, 6H), 6.92 (td, J=8.5, 4.0 Hz, 8H), 6.79 (dd, J=8.3, 2.2 Hz, 2H), 6.73 (dd, J=8.3, 2.2 Hz, 2H), 6.61 (d, J=8.4 Hz, 2H), 6.57–6.48 (m, 6H), 5.43 (d, J=3.9 Hz, 2H), 5.36 (d, J=13.5 Hz, 2H), 5.29 (d, J=13.7 Hz, 2H), 5.24–5.15 (m, 2H), 5.11–5.06 (m, 4H), 5.01 (d, J=3.3 Hz, 2H), 4.81–4.43 (m, 22H), 4.31 (ddt, J=16.5, 10.8, 6.2 Hz, 4H), 4.22–3.91 (m, 24H), 3.72 (dd, J=10.8, 7.8 Hz, 4H), 3.63–3.49 (m, 4H), 3.48–3.33 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.47, 135.52, 135.34, 134.89, 134.48, 134.39, 134.33, 134.23, 134.13, 134.06, 133.69, 133.67, 133.60, 133.53, 133.21, 133.01, 132.78, 132.69, 132.39, 132.36, 132.32, 131.29, 131.25, 131.13, 130.77, 130.47, 130.22, 129.38, 129.31, 128.84, 128.73, 128.58, 128.55, 128.29, 128.24, 127.85, 127.38, 127.11, 127.04, 126.93, 126.85, 126.75, 126.71, 126.68, 126.57, 126.50, 126.30, 114.24, 100.75, 99.38, 98.02, 82.52, 81.83, 81.79, 81.56, 81.02, 80.77, 80.65, 80.08, 79.59, 72.91, 72.80, 72.24, 72.06, 71.96, 71.25, 70.92, 70.23, 70.19, 69.85, 69.33, 69.25, 69.20, 68.38. HRMS (MALDI) Calc. for $C_{152}H_{128}Cl_{32}O_{32}+H^+$: 3592.8252 (81.6%), 3592.8155 (51.8%), 3592.8349 (17.8%), 3592.8324 (5.0%), 3592.8227 (3.7%); Found: 3592.82922 (highest peak)

6^A,6^D-O-(2-methylpropan-1,3-diyl)-α-cyclodextrin (18): 2^{A-F},3^{A-F},$6^{B-C,E-F}$-hexadeca-O-(2,4-dichlorobenzyl)-6^A,6^D-O-(2-metha-1,3-diyl)-α-cyclodextrin (**17**, 335 mg) was dissolved in 50 ml methoxyethanol, 50 ml EtOAc, 1 drop of TFA and 200 mg $Pd(OH)_2$ was added – the mixture was stirred under 33 atm hydrogen for 48 h. Filtration and washing of the filter with ethanol and concentration gave **18** (96 mg, 100%). ^{1}H NMR (500 MHz, CD_3OD) δ 4.24–4.15 (m, 2H), 4.04–3.35 (m, 42H), 3.01 (m, 2H), 1.87 (m, 1H), 0.92 (d, J=9.3 Hz, 3H). HRMS (ESI) for $C_{40}H_{66}O_{30}+H^+$: 1027.37174; Found: 1027.37216

Supporting Information

Copies of NMR spectra of compounds **3**–**5** & **7**–**18** are available.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: aluminium hydrides · benzyl groups · cyclodextrin · kinetics · substituent effects

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