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Cyclodextrins containing an acetone bridge. Synthesis and study as epoxidation catalysts†

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Three cyclodextrine derivatives (6^A,6^D-di-*O*-(prop-2-one-1,3-dienyl)-α-cyclodextrin (**1**), 6-*O*-(prop-2-one-1-yl)-α-cyclodextrin (**2**) and 6^A,6^D-di-*O*-(prop-2-one-1,3-dienyl)-β-cyclodextrin (**3**)) were synthesised and investigated as epoxidation catalysts. The three compounds were synthesised from the corresponding perbenzylated cyclodextrins which were mono- or didebenzylated in the 6-position using Sinaÿ's method. Reaction with NaH and methallyl chloride in the case of **2**, or methallyl dichloride in the case of **1** and **3**, followed by dihydroxylation, periodate cleavage and protection group removal gave the target compounds. All three compounds catalysed, in the presence of oxone, the epoxidation of a series of alkenes. Epoxidation was compared to the reaction catalysed by simple ketones and inhibition was studied.

Introduction

Mimicking Nature's complex syntheses has long been an outstanding challenge for organic chemists. The very specific transformations during biosynthesis rely on highly developed molecular recognition performed by enzymes. While recent years have shown many wonderful applications of enzymes in organic synthesis,[1] their use is nevertheless subject to inherent limitations in terms of substrate, reaction and solvent. Designed intelligent catalysts that, like enzymes, can recognise substrates,[2] can on the other hand potentially be engineered to any reaction and medium. The present work aimed at developing such artificial enzymes for the epoxidation reaction. Several oxidising artificial enzymes have been reported[2,3] including an elegant epoxidising metalloenzyme.[3a] In the present work we have explored the combination of dioxirane chemistry with cyclodextrins as complexing agents.

In the presence of oxone, ketones are known to act as epoxidation catalysts through the intermediacy of dioxiranes.[4] A wide variety of ketones have in recent years been investigated as epoxidation catalysts particularly with the aim of obtaining enantioselective epoxidations under a variation of conditions.[5] The catalytic efficiency of these ketones vary somewhat unpredictably, but it has generally been found that electron-withdrawing groups, such as oxygen and fluorine, in the vicinity of the ketone is favourable for its catalytic efficiency. Often stoichiometric amounts of ketone have been necessary, but epoxidation of trans-stilbene with as little as 1 mol% ketone has been reported.[5b]

Our molecules were designed based on the idea to employ the cyclodextrin as a bucket-like complexing agent with an epoxidising entity in the bottom. The epoxidation catalysts made were the cyclodextrin derivatives **1**, **2** and **3** (Fig. 1). Compounds **1** and **3** contain a 1,3-dialkoxyacetone bridge between the 6-oxygen atoms of the A and D sugar units of an α- or β-cyclodextrin moiety, respectively. Inspection of computer models suggested that in **4** (Fig. 1) the dioxirane group would be situated to interact with a cyclic alkene bound in the cyclodextrin cavity. Dioxirane epoxidation with other 1,3-alkoxyacetone derivatives have previously been investigated. A BINOL derivative was found to be a comparative poor epoxidation catalyst[5i,5g] while 1,3-alkoxyacetone derivatives of other diols appeared better catalysts.[5j] A related work on an epoxidising β-cyclodextrin ketoester has recently been reported.[3e] In this work a pyruvic acid was attached to the primary rim of the cyclodextrin. This catalyst was used in stoichiometric amounts to epoxidise various alkenes with moderate enantioselectivity.

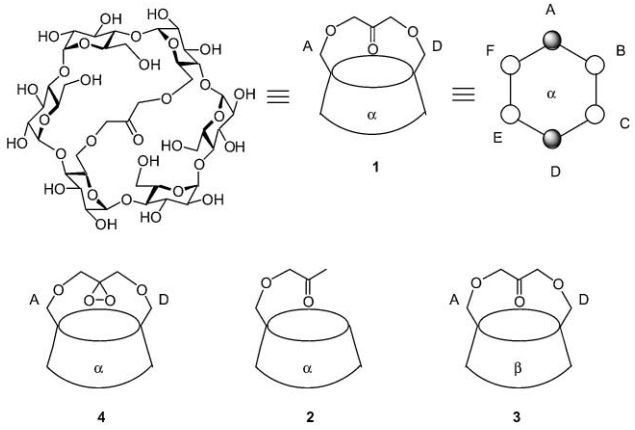

Fig. 1 Catalysts **1**, **2** and **3** and the dioxirane **4** formed when **1** is treated by oxone.

Results and discussion

The synthesis of **1** was carried out as depicted in Scheme 1. From perbenzylated α-cyclodextrin[6] the Pearce–Sinaÿ procedure[7] was used to obtain the diol **5** in high yield. Reaction of **5** with methalyl dichloride (1.1 equiv.) and NaH (4 equiv.) in DMF gave a high yield of **6**. Through the sequence of dihydroxylation and treatment with $NaIO_4$–SiO_2 in CH_2Cl_2[8] the ketone **7** was obtained, that was deprotected to give **1**.

Analogues **2** and **3** were made in a similar manner (Schemes 2 and 3). Compound **2** is a mimic that does not contain the bridge. It was made from **8**[7] by alkylation with methallylchloride/NaH in DMF to give the alkene **9** (Scheme 2). Dihydroxylation of **9** with OsO_4/NMO to the diol followed by periodate cleavage with $NaIO_4$ on silica gave the protected ketone **10**, that was

† Electronic supplementary information (ESI) available: ^1H and ^{13}C nmr spectra for selected compounds. See http://www.rsc.org/suppdata/ob/b4/b410098k/

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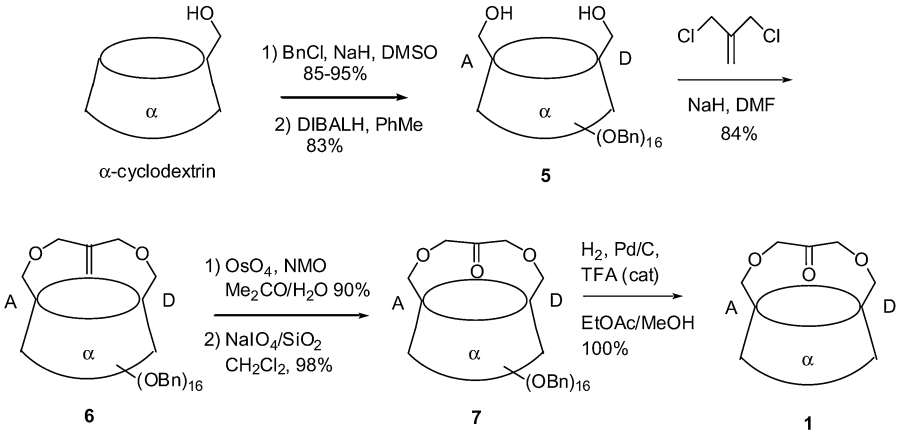
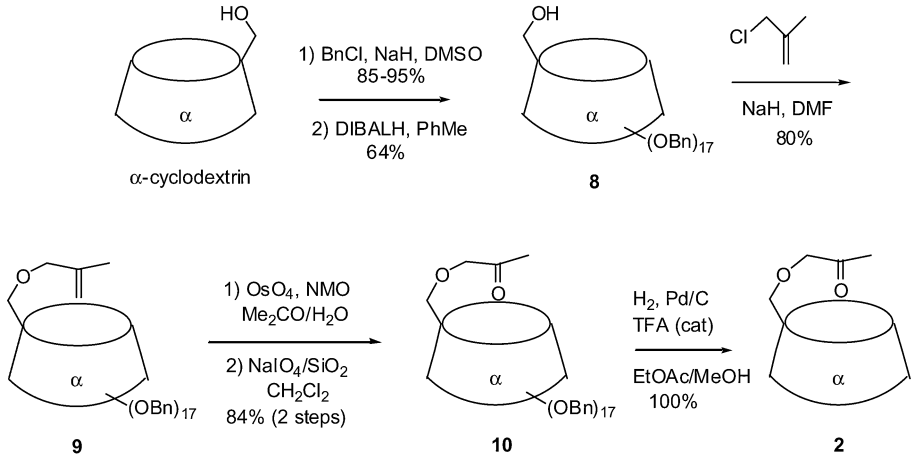
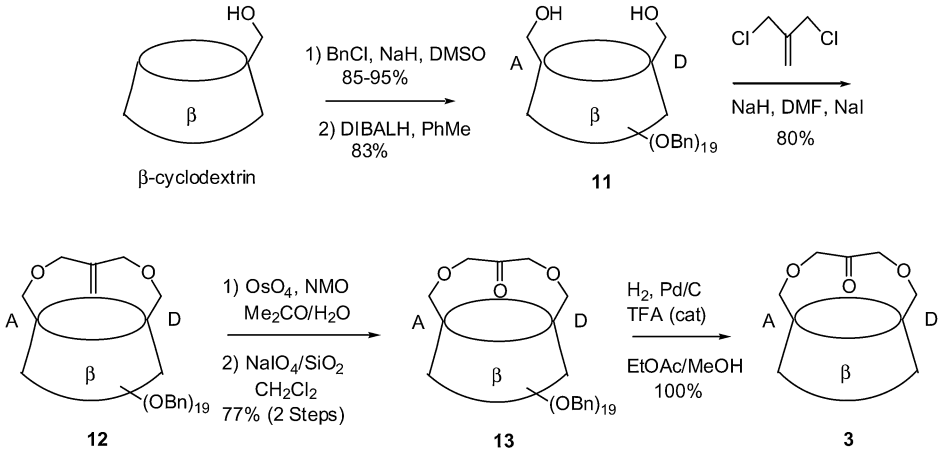


Scheme 1 Synthesis of catalyst **1**.



Scheme 2 Synthesis of catalyst **2**.



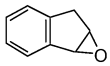
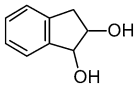
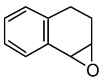
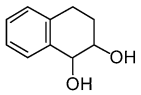
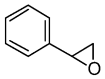
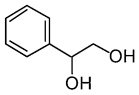
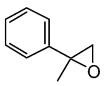
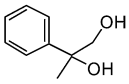
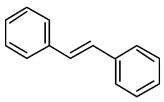
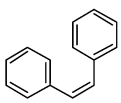
Scheme 3 Synthesis of catalyst **3**.

deprotected to **2** by hydrogenolysis with Pd/C in EtOAc–MeOH–TFA.

In a similar set of reactions the A,D-diol of partially benzylated β-cyclodextrin **11**[7] was converted, by the intemediacy of alkene **12**, to bridged ketone **13** that was hydrogenolysed to **3** (Scheme 3). Noteworthy in this case was that the alkylation of diol **11** with methylenedichloride appeared less facile than the reaction of diol **5**, but with the addition of NaI as nucleophilic catalyst the reaction gave a good yield.

Epoxidation experiments were carried out with the ketone **1**–**3** (30 mol%), oxone (3 equiv.), $NaHCO_3$ (12 equiv.) and different alkenes (Table 1). Some general comments can be made. In all cases oxone and $NaHCO_3$ was slowly added over the time period, but two different solvent systems were used: Either MeCN–water (3 : 2), which are classical dioxirane epoxidation conditions (condition A),[5d,9] or pure water (condition B) which was used to favor host–guest complexation. In water the reaction is faster, but quite surprisingly epoxidation by oxone itself (background reaction) occurs quite fast as well and is a greater problem. Therefore simultaneous control experiments without ketone were necessary in each case. These controls (not shown) give negligible formation of epoxide (<10%) when the reaction time is 1 h. It should be noted that in most cases not only epoxide but also the corresponding diol was obtained. The efficacy

Table 1 Epoxidation of alkenes at 0 °C in the presence of **1** (0.3 equiv.) and oxone (3 equiv.) under condition A or condition B. ACE = acetone, DCA = 1,3-dichloroacetone.

Entry	Alkene	Catalyst	Conditions	Time	Epoxide	Diol	Alkene
							
1	**14**	**1**	A	6 h	30%	10%	60%
2		**1**	A	8 h	30%	60%	10%
3		ACE	A	8 h	<10%	—	>90%
4		**1**	B	1 h	80% (1% ee)	20%	—
5		**2**	B	1 h	35%	—	65%
6		**3**	B	1 h	50%	20%	30%
7		DCA	B	1 h	86%	—	14%
							
8	**15**	**1**	A	8 h	30%	—	70%
9		**1**	B	1 h	30%	—	70%
10		**2**	B	1 h	25%	—	75%
11		**3**	B	1 h	40%	20%	40%
12		DCA	B	1 h	40%	—	60%
					 **21**		
13	**16**	**1**	A	8 h	30%	50%	20%
14		**1**	B	1 h	50% (12% ee)	50%	—
15		**1**[a]	B	1 h	18%	28%	54%
16		**2**	B	1 h	50% (0% ee)	—	50%
17		**2**[a]	B	1 h	13%	13%	74%
18		**3**	B	1 h	19% (0% ee)	44%	36%
19		**3**	B	20 min	5%	22%	73%
20		**3**[a]	B	1 h	12%	77%	10%
21		**3**[b]	B	1 h	18%	82%	—
22		DCA	B	1 h	70%	—	30%
23		DCA[a]	B	1 h	59%	23%	17%
							
24	**17**	**1**	A	8 h	—	—	100%
25		**1**	B	1 h	35%	—	65%
26		**2**	B	1 h	10%	—	90%
27		**3**	B	1 h	19%	21%	60%
28		DCA	B	1 h	35%	—	65%
							
29	**18**	**1**	A	8 h	—	—	100%
30		**1**	B	1 h	—	—	100%
31		**2**	B	1 h	—	—	100%
32		**3**	B	1 h	—	—	100%
33		DCA	B	1 h	—	—	100%
							
34	**19**	**1**	A	8 h	—	—	100%

[a] 2 equiv. of sodium benzene 2-naphtalenesulfonate was added. [b] $NaHCO_3$ (20 equiv.) added.

of the oxidation is therefore based on the formation of both these oxidation products. For comparison to control ketones, acetone (ACE) and 1,3-dichloroacetone (DCA), were also tested as catalysts on the various substrates.

All ketones **1–3** and DCA catalyse oxidation of indene (**14**), dihydronaphthalene (**15**), styrene (**16**) and α-methylstyrene (**17**), while none of them touch either *cis* or *trans* stilbene (**18**). Acetone was found to be an extremely poor catalyst compared to the other ketones presumably due to unfavourable electronic effects. In water the oxidation of indene (**14**) occurs with an order of catalyst reactivity that is **1** > DCA > **3** > **2** (entries 4–7). The lower reactivity of **2** can be explained by electronic effects as electron deficient ketones are known to be more reactive and **2** only has one electron-withdrawing α-alkoxy group. Also for electronic reasons DCA is intrinsically the most reactive ketone because of the larger electron-withdrawing effect of chlorine ($\sigma_I = 0.47$) compared to alkoxy ($\sigma_I = 0.25$). Therefore the higher catalyst activity of **1** must be attributed to an inclusion effect that is expected to be better in **1** than in **3** due to the snugger fit of **14** into the α-cyclodextrin. A similar pattern is seen for the oxidation of styrene (**16**) where the efficiency order was **1** > DCA > **3** > **2** (entries 14, 16, 18 and 22). Again this can be explained with **16** fitting better into α-cyclodextrin.

With the more bulky alkenes **15** and **17** the catalyst efficiency in water changed to **3** > DCA > **1** > **2** (entries 9–12 and 25–28), which is in accordance with these alkenes fitting better into β-cyclodextrin.

To explore the effect of the binding cavity experiments were carried out where 2 equiv. of sodium naphthalene-2-sulfonate (**20**) was added to the oxidation of **16** (entries 15, 17, 20 and 23). Compound **20** binds to α-cyclodextrin and β-cyclodextrin with binding constants of 3.6×10^2 and 2.3×10^5 M,[10] respectively and should therefore be an effective inhibitor. The catalytic effect of the α-cyclodextrin derivatives **1** and **2** was significantly inhibited (entries 15 and 17), while no inhibition, rather a slight rate increase, was observed with **3** and DCA as catalysts (entries 20 and 23). This is in accordance with observations above that suggested that inclusion increased the rate of styrene (**16**) catalysed by **1** because of a better fit of this alkene into the α-cyclodextrin.

The enantioselectivity of the oxidation of **14** by **1** under condition B was also determined (HPLC, chiralcel OD column, hexane–isopropanol 9 : 1), and indene oxide obtained was found to be essentially racemic (1% ee). This is not entirely surprising given the highly symmetric nature of the catalyst. For the oxidation of styrene (**16**) catalysed by **1** the ee increased to 12% while the similar oxidation catalysed by **2** and and **3** gave no enantioselectivity (Table 1). Nevertheless it is remarkable that Chan *et al.* obtain enantioselectivities up to 40% ee in epoxidation with a cyclodextrin ketoester being very similar to **2**.[3e] They use stoichiometric amounts of ketoester, however.

The effectiveness of host–guest binding was determined for binding of **16** to **2** using NMR as previously described (Fig. 2), using the change in chemical shift of H-3 protons in **2** to monitor the binding process. A dissociation constant (K_d) of 3.0 mM was found for this binding process, which is quite similar to the binding many enzymes have with their substrates. Similar measurements for **1** and **3** were not possible because the H-3 NMR signals were not clearly resolved in these.

The diol formation that was observed in almost all the reactions was puzzling because diol formation has rarely if ever been reported in dioxirane epoxidations. Initially we attributed the presence of diol products to the spontaneous hydrolysis of the epoxides occurring more readily in water. However, the observation that no diol was formed when DCA (or **2**) were used as catalysts suggested that the formation of diol was related to the catalyst. Experiments were therefore carried out to see if the cyclodextrin catalyst also catalysed epoxide hydrolysis. However, when **3** and styrene oxide (**21**) was incubated in D_2O and monitored by NMR no hydrolysis was apparent. To see if

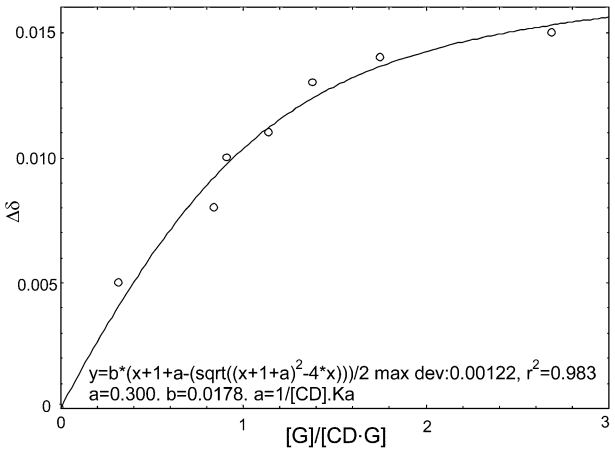


Fig. 2 Plot of the change in chemical shift $\Delta\delta$ of H-3 in compound **2** versus the ratio of [**16**] to $[\mathbf{2}]_{tot}$ ([G]/[CD.G]).

the presence of oxone and $NaHCO_3$ was necessary to induce the hydrolysis, a full oxidation experiment, similar to entry 18 (Table 1), was carried out but substituting the alkene **16** with the product **21**. Also here the styrene oxide (**21**) was recovered unchanged. Since this suggested, quite surprisingly, that the diol was formed from the alkene the epoxidation of **16** catalysed by **3** was stopped after 20 min (entry 19), which showed that the ratio between diol and epoxide was the same as after 1 h, and thus remained constant over time. The epoxide and diol must therefore be formed by two parallel reactions.

The catalysts **1**–**3** reported here display some the basic characteristics of an enzyme such as substrate recognition and inhibition. While the binding strength between cyclodextrin and substrate is within the normal range for natural enzyme–substrate pairs, at least for **2** and **16**, the catalysis found is very far from showing enzymatic catalysis rate. Therefore the catalytic step needs to be improved and therefore work is required to optimise the structure of these catalytic groups either through variation in its position or modulating its electronic surroundings. Such work is underway.

Experimental

General

Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Evaporation was carried out on a rotatory evaporator with the temperature kept below 40 °C. Glassware used for waterfree reactions was dried for a minimum 2 h 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 were carried out on a Varian Mercury 400 instrument. Mass spectra (MALDI MS) were obtained on a Voyager DE PRO mass spectrometer (Applied Biosystems) using an α-cyanohydroxycinnamic acid (α-CHCA) matrix. Spectra were calibrated with angiotensin I *m/z* 1296.69, adrenocorticotropic hormone (ACTH) (clip 1–17) *m/z* 2093.09, ACTH (clip 18–39) *m/z* 2465.20, and ACTH (clip 7–38) *m/z* 3657.93.

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (6)

To a solution of compound **5**[7] (800 mg, 0.33 mmol) in dry DMF (50 ml) was added NaH (58 mg, 4 equiv.). After stirring for 30 min at room temperature, 3-chloro-2-chloromethyl propene (42 μl, 1.1 equiv.) was added and the reaction mixture was stirred over night. The reaction was quenched by addition

of water (30 ml) and AcOEt (50 ml) and then the organic phase was washed with water (4 × 30 ml), dried over $MgSO_4$, and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane–AcOEt 5 : 1.5), which resulted in 690 mg (84%) of compound **6** as a white foam. $[\alpha]_D$ +31.4 (*c* 1.1, $CHCl_3$); MS: calcd for $C_{152}H_{160}O_{30}Na$ 2488.0892, found 2488.1388; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–6.88 (m, 80H, CH_{Ph}), 5.55–5.45 (m, 4H, CH_2, H-1), 5.16 (d, 2H, J_{gem} 10.8 Hz, *H*-CHPh), 4.88 (d, 2H, J_{gem} 10.4 Hz, *H*-CHPh), 4.84 (bs, 2H, CH_2), 4.78–4.68 (m, 6H), 4.67–4.61 (m, 3H), 4.59 (d, 2H, *J* 3.2 Hz, H-1), 4.40–4.10 (m, 23H), 4.05–3.95 (m, 8H), 3.89–3.68 (m, 12H), 3.59 (d, 2H, *J* 9.2 Hz), 3.52 (dd, 2H, *J* 3.8 Hz, *J* 9.8 Hz), 3.45 (d, 2H, *J* 11.2 Hz), 3.40–3.30 (m, 8H), 3.24 (dd, 2H, *J* 3.2 Hz, *J* 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.09 (C=), 139.77, 139.50, 139.45, 138.88, 138.57, 138.39, 138.25, 137.99 (C_{ipso}), 129.19, 128.41, 128.36, 128.25, 128.22, 128.20, 128.06, 127.99, 127.85, 127.77, 127.73, 127.61, 127.55, 127.18, 127.00, 126.72, 126.07 (CH_{Ph}), 114.04 (CH_2=), 99.75, 99.46, 98.04 (C-1), 82.11, 81.67, 81.27, 80.76, 80.22, 79.30, 78.97, 77.88 (CH), 76.69, 76.22, 73.62, 73.55, 73.41, 73.27, 72.92, 72.00 (CH_2), 72.08, 71.91, 71.85 (CH), 69.16 (CH_2).

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (7)

To a solution of compound **6** (1.53 g, 0.62 mmol) in a mixture of acetone–water 9 : 1 (90 ml) was added *N*-methyl morpholine *N*-oxide NMO, (252 mg, 3 equiv.) and a solution of osmium tetroxide 2.5% in butanol (743 µl, 10%). The reaction mixture was stirred overnight and a solution of sodium thiosulfate 10% in water was added. The mixture was extracted with AcOEt (3 × 50 ml) and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave the corresponding diol as a white foam. The diol was dissolved in CH_2Cl_2 (10 ml) and 4.16 g of $NaIO_4$–SiO_2 (1.60 g $NaIO_4$/10 g SiO_2, 5 equiv.) was added. After 2 h of stirring, the suspension was filtered through Celite. Evaporation of the solvent and flash chromatography (eluent: pentane–AcOEt 5 : 1.5) gave 1.35 g (88%, 2 steps) of compound **7** as a white foam. $[\alpha]_D$ +32.5 (*c* 1.0, $CHCl_3$); MS: calcd for $C_{151}H_{158}O_{31}Na$ 2490.0684, found 2490.0571; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−6.90 (m, 80H, CH_{Ph}), 5.43 (d, 2H, J_{gem} 10.4 Hz, *H*-CHPh), 5.30 (d, 2H, *J* 4.0 Hz, H-1), 5.17 (d, 2H, J_{gem} 10.4 Hz, *H*-CHPh), 4.89 (d, 2H, J_{gem} 10.4 Hz, *H*-CHPh), 4.80–4.62 (m, 6H, CH_2Ph), 4.63 (d, 2H, *J* 3.2 Hz, H-1), 4.58 (d, 2H, *J* 3.2 Hz, H-1), 4.38–4.07 (m, 23H), 4.04–3.85 (m, 12H), 3.81–3.65 (m, 14H), 3.51–3.20 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.53 (C=O), 139.94, 139.65, 139.58, 138.97, 138.66, 138.36, 138.25, 138.10 (C_{ipso}), 128.63, 128.60, 128.55, 128.50, 128.42, 128.40, 128.23, 128.19, 128.16, 128.12, 127.99, 127.95, 127.90, 127.87, 127.84, 127.58, 127.33, 127.19, 127.00, 126.22 (CH_{Ph}), 100.64, 100.00, 98.64 (C-1), 82.57, 82.24, 81.14, 80.97, 80.80, 80.15, 79.05, 77.91 (CH), 76.86, 76.35, 74.05, 74.01, 73.62, 73.54, 73.11, 73.02 (CH_2), 72.44 (CH), 72.22 (CH, CH_2), 69.86, 68.91 (CH_2), 68.87 (CH).

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-α-cyclodextrin (1)

Compound **7** (3 g, 1.2 mmol) was dissolved in a mixture of MeOH–AcOEt (1 : 1) (150 ml). Then Pd/C (300 mg) and TFA (cat.) were added and the mixture was stirred over night under hydrogen atmosphere. Filtration through silica gel (eluent: *n*-BuOH–EtOH–H_2O 5 : 4 : 3) and evaporation of the solvent gave 1.2 g (100%) of compound **1** as a white foam. MS: calcd for $C_{39}H_{62}O_{31}Na$ 1049.3173, found 1049.3522; $[\alpha]_D$ +83.6 (*c* 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.00–4.88 (m, 6H, H-1), 4.35 (d, 2H, J_{gem} 18.8 Hz, *H*-CHCO), 4.29 (bt, 2H, H-3), 4.16 (d, 2H, *H*-CHCO, J_{gem} 18.8 Hz), 4.00–3.70 (m), 3.62–3.47 (m), 3.34 (m, 2H, H-4), 3.22 (m, 2H, H-4). ^{13}C NMR (100 MHz, D_2O): δ 208.84 (C=O), 102.02 (2C, C-1), 101.98 (2C, C-1), 98.16 (2C, C-1), 82.49 (4C, CH), 79.71 (2C, CH), 73.63 (2C, CH), 73.08 (2C, CH), 72.85 (2C, CH), 72.49 (2C, CH), 72.41 (2C, CH_2), 71.50 (4C, CH), 71.33 (4C, CH), 71.27 (2C, CH_2), 70.55 (2C, CH), 62.01 (2C, CH_2), 61.06 (2C, CH_2). IR (KBr): 1683 (s, C=O).

6-*O*-(Methall-1-yl)-hexadeca-*O*-benzyl-α-cyclodextrin (9)

To a solution of compound **8**[7] (1.3 g, 0.52 mmol) in dry DMF (50 ml) was added NaH (50 mg, 4 equiv.). After stirring for 30 min at room temperature, methallyl chloride (256 µl, 5 equiv.) was added and the reaction mixture was stirred over night. The reaction was quenched by addition of water (50 ml) and AcOEt (50 ml), and then the organic phase was washed with water (4 × 50 ml), dried over $MgSO_4$, and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane–AcOEt 5 : 1), which resulted in 1.06 g (80%) of compound **9** as a white foam. $[\alpha]_D$ +33.3 (*c* 1.2, $CHCl_3$); MS: calcd for $C_{159}H_{168}O_{30}Na$ 2580.1518, found 2580.2033; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.00 (m, 85H, CH_{Ph}), 5.10 (d, 1H, J_{gem} 11.2 Hz, *H*-CHPh), 5.09 (d, 1H, J_{gem} 10.8 Hz, *H*-CHPh), 5.04 (d, 1H, *J* 3.2 Hz, H-1), 5.02–4.97 (m, 5H, H-1), 4.82–4.70 (m, 8H), 4.44–4.20 (m, 24H), 4.10–4.01 (m, 6H), 3.99–3.88 (m, 12H), 3.86–3.77 (m, 8H), 3.64 (s, 2H, CH_2), 3.52–3.32 (m, 12H), 1.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.11, 139.55, 139.51, 138.51, 138.33, 138.28 (C_{ipso}), 128.41, 128.27, 128.09, 127.85, 127.72, 127.68, 127.51, 127.41, 127.39, 127.35, 127.03 (CH_{Ph}), 112.04 (CH_2=), 98.93, 98.82, 98.76, 98.68 (C-1), 81.14, 79.69, 79.46, 79.37, 79.35, 79.16 (CH), 75.69, 75.30, 73.52, 72.86 (CH_2), 71.67 (CH), 69.19 (CH_2), 19.68 (CH_3).

6-*O*-(Prop-2-one-1-yl)-hexadeca-*O*-benzyl-α-cyclodextrin (10)

To a solution of compound **9** (1.05 g, 0.41 mmol) in a mixture of acetone–water 9 : 1 (80 ml) was added NMO (166 mg, 3 equiv.) and a solution of osmium tetroxide 2.5% in butanol (514 µl, 10%). The reaction mixture was stirred over night and a solution of sodium thiosulfate 10% in water was added. The mixture was extracted with AcOEt (3 × 50 ml) and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave the corresponding diol as a white foam. The diol was dissolved in CH_2Cl_2 (8 ml) and 1.7 g of $NaIO_4$–SiO_2 (2.54 g $NaIO_4$/10 g SiO_2, 5 equiv.) was added. After 2 h of stirring, the suspension was filtered through Celite. Evaporation of the solvent and flash chromatography (eluent: pentane–AcOEt 5 : 1.5) gave 0.89 g (84%, 2 steps) of compound **10** as a white foam. $[\alpha]_D$ +35.0 (*c* 1.1, $CHCl_3$); MS: calcd for $C_{158}H_{166}O_{31}Na$ 2582.1310, found 2582.1347; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.00 (m, 85H, CH_{Ph}), 5.15 (d, 2H, J_{gem} 10.5 Hz, *H*-CHPh), 5.12–5.02 (m, 6H), 5.00–4.90 (m, 4H), 4.82–4.74 (m, 6H), 4.46–4.18 (m, 22H), 4.10–3.74 (m, 24H), 3.72 (s, 2H, CH_2), 3.50–3.32 (m, 12H), 1.87 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.48 (C=O), 139.51, 139.48, 138.56, 138.51, 138.48, 138.43, 138.34, 138.29, 138.18 (C_{ipso}), 128.46, 128.42, 128.27, 128.10, 128.00, 127.89, 127.87, 127.83, 127.81, 127.75, 127.71, 127.54, 127.48, 127.43, 127.32, 127.30, 127.05 (CH_{Ph}), 99.13, 99.04, 98.83, 98.76, 98.67 (C-1), 81.16, 81.10, 80.97, 80.92, 80.04, 79.88, 79.53, 79.24, 78.98, 78.85, 76.92, 75.79, 75.53, 73.57, 73.52, 73.49, 73.45, 72.96, 72.86, 72.80, 71.77, 71.61, 71.53, 70.55, 69.21 (CH, CH_2), 26.46 (CH_3).

6-*O*-(Prop-2-one-1-yl)-α-cyclodextrin (2)

Compound **2** was obtained from the compound **10** (0.98 g, 0.38 mmol) and Pd/C (100 mg) in a mixture of MeOH–AcOEt (1 : 1) (70 ml) following the same procedure given above for the preparation of the compound **1**. Gave 390 mg (100%) of compound **2** as a white foam. $[\alpha]_D$ +57.8 (*c* 1.2, H_2O); MS: calcd for $C_{39}H_{64}O_{31}Na$ 1051.3329, found 1051.3799; ^{1}H NMR (400 MHz, D_2O): δ 4.89 (d, 6H, *J* 2.8 Hz, H-1), 4.26 (d, 1H, J_{gem} 18.6 Hz, *H*-CH), 4.21 (d, 1H, J_{gem} 18.6 Hz, *H*-CH), 3.92–3.80 (m, 8H), 3.78–3.60 (m, 20H), 3.56–3.38 (m, 14H), 2.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, D_2O): δ 211.05 (C=O), 101,80

(C-1), 81.13, 76.12, 73.24, 72.16, 71.76, 70.72, 69.45, 60.10 (CH_2, CH), 25.68 (CH_3). IR (KBr): 1683 (s, C=O).

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-heptadeca-*O*-benzyl-β-cyclodextrin (12)

To a solution of compound **11**[7] (1.7 g, 0.60 mmol) in dry DMF (60 ml) was added NaH (117 mg, 4 equiv.). After stirring 30 minutes a room temperature, 3-chloro-2-chloromethyl propene (76 µl, 1.1 equiv.) and NaI (360 mg, 4 equiv.) were added to the solution and the reaction mixture was stirred over night. The reaction was quenched by addition of water (50 ml) and AcOEt (100 ml) and then the organic phase was washed with water (4 × 50 ml), dried over $MgSO_4$, and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane–AcOEt 5 : 1 to 5 : 1.5), to give 1.38 g (80%) of compound **12** as a white foam. $[\alpha]_D$ +37.4 (*c* 1.0, $CHCl_3$); MS: calcd for $C_{179}H_{188}O_{35}Na$ 2920.2828, found 2920.3506; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–6.98 (m, 95H, CH_{Ph}), 5.89 (d, 1H, *J* 4.4 Hz, H-1), 5.65 (d, 1H, *J* 4.4 Hz, H-1), 5.47 (d, 1H, J_{gem} 10.4 Hz, *H*-CHPh), 5.32–5.25 (m, 3H, CH_2Ph), 5.17 (d, 1H, J_{gem} 10.8 Hz, *H*-CHPh), 5.00 (bs, 2H, CH_2=), 4.92 (d, 2H, *J* 3.2 Hz, H-1), 4.91 (d, 2H, *J* 3.6 Hz, H-1), 4.88–4.16 (m, 40H), 4.10–3.24 (m, 40H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.55 (C=), 139.74, 139.69, 139.61, 139.48, 139.37, 139.30, 139.15, 138.86, 138.76, 138.74, 138.63, 138.42, 138.40, 138.34, 138.30, 138.09, 138.05 (C_{ipso}), 128.41, 128.36, 128.28, 128.23, 128.20, 128.16, 128.10, 128.03, 128.02, 128.00, 127.98, 127.87, 127.82, 127.81, 127.78, 127.69, 127.65, 127.58, 127.21, 127.17, 127.09, 127.04, 126.97, 126.94, 126.51, 126.45 (CH_{Ph}), 114.47 (CH_2=), 100.47, 99.89, 98.51, 98.27, 98.06, 98.05, 97.37 (C-1), 82.66, 82.17, 81.63, 81.41, 81.35, 81.04, 80.96, 80.84, 80.72, 80.64, 80.46, 80.11, 80.01, 79.17, 79.07, 78.63, 77.85, 77.77, 77.28 (CH), 76.67, 76.58, 76.48, 76.28, 75.40, 74.06, 73.61, 73.46, 73.42, 73.30, 73.21, 73.06, 72.97, 72.63, 72.24, 72.20, 71.98, 71.84, 70.82 (CH, CH_2), 69.89 (CH), 69.58, 69.21, 68.93 (CH_2), 68.70 (CH).

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-heptadeca-*O*-benzyl-β-cyclodextrin (13)

Compound **13** was obtained from the compound **12** (1.29 g, 0.44 mmol) and NMO (178 mg, 3 equiv.), OsO_4 (560 µl, 10%), 1,4 g of $NaIO_4$–SiO_2 (2.54 g $NaIO_4$/10 g SiO_2, 5 equiv.) following the same procedure given above for the preparation of the compound **7**. Flash chromatography (eluent: pentane–AcOEt 5 : 1.5). Gave 1.0 g (77%) of compound **13** as a white foam. $[\alpha]_D$ +37.0 (*c* 1.8, $CHCl_3$); MS: calcd for $C_{178}H_{186}O_{36}Na$ 2922.2621, found 2922.2444; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–6.80 (m, 95H, CH_{Ph}), 5.74 (d, 1H, *J* 4.0 Hz, H-1), 5.35 (d, 1H, J_{gem} 10.4 Hz, *H*-CHPh), 5.28 (d, 1H, *J* 4.4 Hz, H-1), 5.24 (d, 1H, J_{gem} 9.6 Hz, *H*-CHPh), 5.13 (d, 1H, J_{gem} 10.8 Hz, *H*-CHPh), 5.12 (d, 1H, J_{gem} 11.2 Hz, *H*-CHPh), 5.05 (d, 1H, *J* 3.2 Hz, H-1), 5.01 (d, 1H, J_{gem} 10.8 Hz, *H*-CHPh), 4.82–4.54 (m, 15H), 4.49–4.03 (m, 30H), 4.01–3.42 (m, 31H), 3.39–3.20 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.04 (C=O), 139.61, 139.35, 139.15, 138.78, 138.59, 138.52, 138.28, 138.10, 138.03 (C_{ipso}), 128.34, 128.21, 128.15, 128.07, 127.95, 127.82, 127.66, 127.55, 127.34, 127.10, 126.86, 126.66, 126.41 (CH_{Ph}), 99.72, 98.84, 98.73, 98.25, 98.10, 97.50 (C-1), 81.88, 81.77, 81.59, 81.33, 81.09, 80.90, 80.63, 79.93, 79.69, 78.99, 78.68, 78.31, 78.21, 77.98, 77.77, 77.40, 76.80, 76.37, 76.14, 75.01, 74.79, 74.36, 73.87, 73.60, 73.43, 73.35, 73.26, 73.14, 72.93, 72.72, 72.56, 72.33, 72.22, 72.03, 71.93, 70.31, 69.78, 69.25, 68.84, 68.60 (CH, CH_2).

6^A,6^D-Di-*O*-(prop-2-one-1,3-dienyl)-β-cyclodextrin (3)

Compound **3** was obtained from the compound **13** (1 g, 0.34 mmol) and Pd/C (100 mg) in a mixture of MeOH–AcOEt (1 : 1) (70 ml) following the same procedure given above for the preparation of the compound **1**. Gave 408 mg (100%) of compound **3** as a white foam. $[\alpha]_D$ +37.2 (*c* 1.1, H_2O); MS: calcd for $C_{45}H_{72}O_{36}$ 1211.3701, found 1211.3876; ^{1}H NMR (400 MHz, D_2O): δ 5.11–5.04 (m, 2H, H-1), 5.00 (d, 1H, *J* 3.6 Hz, H-1), 4.96–4.84 (m, 4H, H-1), 4.28–3.94 (m, 5H), 3.88–3.14 (m, 38H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.83 (C=O), 101.68, 101.19, 101.01, 100.79, 99.99, 98.50 C-1), 94.05, 81.33, 80.70, 80.52, 80.38, 80.22, 80.08, 79.52, 78.82, 74.41, 74.27, 74.13, 73.31, 73.11, 72.85, 72.74, 72.61, 72.42, 72.27, 71.98, 71.93, 71.81, 71.51, 71.18, 70.86, 69.33, 68.75, 68.15, 60.64, 60.58, 60.14 (CH, CH_2). IR (KBr): 1679 (s, C=O).

Epoxidation procedure A

To a solution of alkene (0.5 mmol) and **1** (0.15 mmol, 153 mg) in MeCN–H_2O (3/2, 25 ml) at 0 °C were added oxone (115 mg) and $NaHCO_3$ (63 mg) at the beginning of each hour over a 8 h period. In total three equivalents of oxone and 12 equivalents of $NaHCO_3$ were added. Water was added and the aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated.

Epoxidation procedure B

To a solution of alkene (0.5 mmol) and **1** (0.15 mmol, 153 mg) in H_2O (5 ml) at 0 °C were added oxone (153 mg) and $NaHCO_3$ (84 mg) at the beginning of each 10 min over a 1 h period. In total three equivalents of oxone and 12 equivalents of $NaHCO_3$ were added. Water was added and the aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated.

Experimental procedure for NMR titration experiment[3e,11]

To a solution of **2** in D_2O (1.5 ml, 0.89 mM) in a NMR tube at ambient temperature was added styrene in portion (0.2–2.7 equiv.) until the change in chemical shift ($\Delta\delta$H-3) of **2** was negligible. The exact mole ratio of **2** to styrene were determined from the integration ratios of their ^{1}H NMR signal (CH_3 of **2** and olefinic proton of styrene). The chemical shift (CH_3) of **2** was used as an internal reference. A ^{1}H NMR titration curve was obtained by plotting $\Delta\delta$H-3 of **2** against the mole ration of **2** and styrene.

Calculation of association constant in D_2O[11,12]

For 1 : 1 complex formation between a cyclodextrin (CD) and a guest (G) in solution the amount of bound host compared to the total amound of host (percent complex), P, can be calculated from the total concentration and the equilibrium constant. The following equations can be written:

$$CD + G \rightleftharpoons CD \cdot G$$

$$K_a = \frac{[CD \cdot G]}{[CD][G]},\ C_{CD} = [CD \cdot G] + [CD]$$

$$C_G = [CD \cdot G] + [G],\ P = \frac{[CD \cdot G]}{[CD \cdot G] + [CD]}$$

$$\alpha_0 = \frac{[CD]}{C_{CD}},\ \alpha_1 = \frac{[CD \cdot G]}{C_{CD}},\ \alpha_0 + \alpha_1 = 1$$

C_{CD} and C_G being the total concentration of cyclodextrin and guest, respectively. A combination of the above results give:

$$P = \frac{E + 1 + \frac{1}{S}\sqrt{\left(E + 1 + \frac{1}{S}\right)^2 - 4E}}{2}$$

$$\text{where } E = \frac{[G]}{[CD]} \text{ and } S = [CD]K_a$$

If δ_{CD} and $\delta_{CD \cdot G}$ are the chemical shift of the observed nucleus in sites CD and CD·G, then, under fast exchange in the NMR time scale,

$$\delta = \alpha_0\delta_{CD} + \alpha_1\delta_{CD \cdot G} \text{ or } \Delta\delta = \alpha_1\Delta\delta_0$$

$\Delta\delta$ being the observed chemical shift displacement of the signal of CD and $\Delta\delta_0$ being the corresponding difference between

pure CD and pure complex CD·G. A combination of the above result in:

$$[\mathrm{CD}\cdot\mathrm{G}] = \frac{\Delta\delta}{\Delta\delta_0}C_{\mathrm{CD}} \text{ and } [\mathrm{CD}] = C_{\mathrm{CD}} - \frac{\Delta\delta}{\Delta\delta_0}C_{\mathrm{CD}}$$

$$\Rightarrow P = \frac{\Delta\delta}{\Delta\delta_0}$$

$$\Rightarrow \frac{\Delta\delta}{\Delta\delta_0} = \frac{E + 1 + \frac{1}{S} - \sqrt{\left(E + 1 + \frac{1}{S}\right)^2 - 4E}}{2}$$

If $\Delta\delta_0$ is unknown, the equation becomes nonlinear and is solved with the aid of a computer program. The fitting program EASYPLOT was used.

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