Artificial Epoxidase II. Synthesis of Cyclodextrin Ketoesters and Epoxidation of Alkenes

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Four cyclodextrin ketones were synthesised and investigated as epoxidation catalysts. In the presence of oxone they catalysed the epoxidation of mono-, di- and trisubstituted alkenes in 17–100 % yield and 0–45 % *ee*.

Introduction

Cyclodextrins are highly attractive components of artificial enzymes[1] because of their water solubility, tight, but not too tight, binding of simple aromatic or aliphatic substrates,[2] their ready availability and, with the progress of synthetic methods,[3,4] the many possibilities of modifying them. We have recently focussed on creating cyclodextrin derivatives that could be useful as epoxidation catalysts.[5] We reported that ketone **1** (Figure 1) could be used to catalyse the epoxidation of a number of alkenes in water with oxone as stoichiometric oxidant.

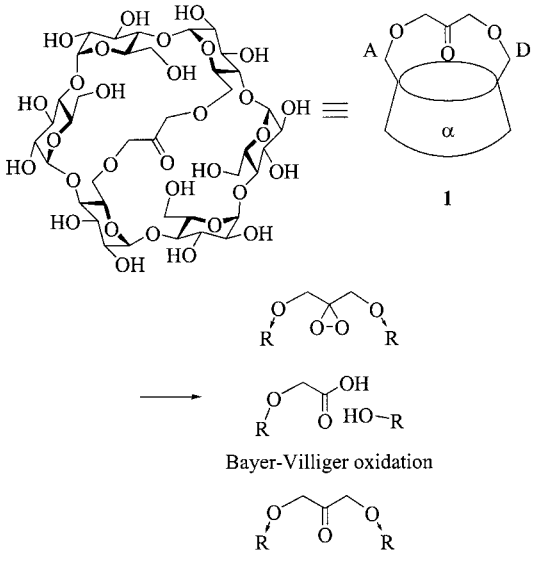

Figure 1. Bridged epoxidation catalyst **1** and its oxidation products.

The idea behind this epoxidation method is (Figure 2) that ketone **1** (E) is activated by reaction with oxone and conversion to dioxirane (E*). Complexation with substrate (E*S) and subsequent reaction gives a product–enzyme complex that dissociates to epoxide and ketone. Ketone **1** and its β-cyclodextrin analogue **2** displayed enzymelike properties, such as substrate recognition and inhibition.[5] However, usually 30 mol percent of the catalyst was required to obtain full conversion; epoxidation was in some cases accompanied by dihydroxylation, and the enantioselectivity was low. It was suggested that some of these deficiencies could be associated with the decomposition of the catalyst by Bayer–Villiger oxidation (Figure 1).[6] It has been reported that electron-withdrawing groups close to the ketone improve its stability towards Bayer–Villiger oxidation and increase its reactivity as a catalyst.

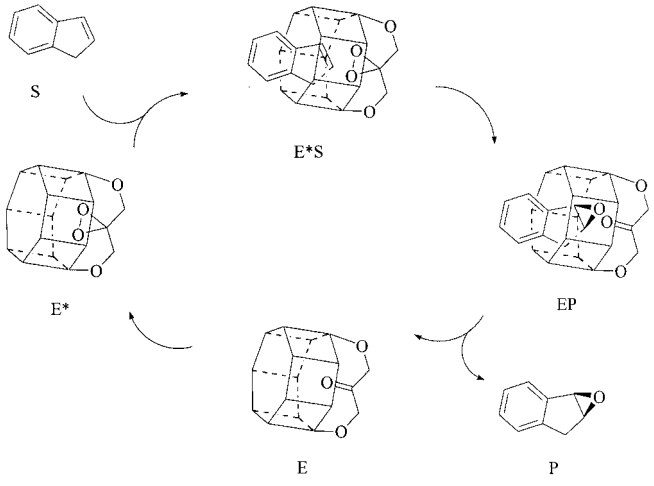

Figure 2. Epoxidation of indene with a capped cyclodextrin ketone in the presence of oxone.

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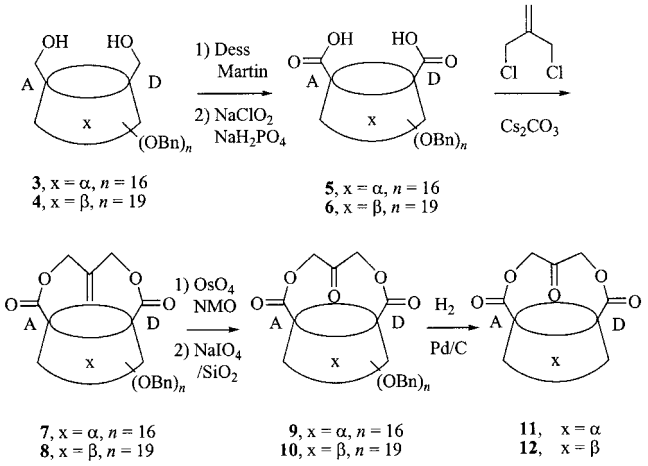
This led us to address the attachment of the ketone bridge to the cyclodextrin moiety. In this paper we report the synthesis of new cyclodextrin ketones having acetone bridges attached by ester groups. This gives a more reactive catalyst that displays higher enantioselectivity in epoxidation.

Results and Discussion

The synthesis of ester analogues of **1** and **2** was carried out by the preparation of cyclodextrin diacids. To this end, diol **3**[4] was oxidised to diacid **5** in two steps, oxidation with Dess–Martin's reagent to the dialdehyde followed by chlorate oxidation,[7] with 86% yield (Scheme 1).

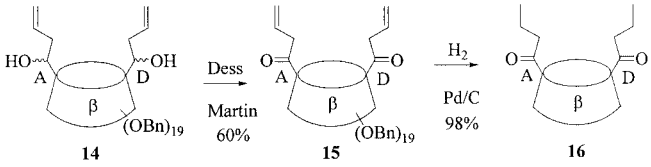


Scheme 1.

This diacid was reacted with methallyl dichloride and cesium carbonate in DMF, affording smooth dialkylation resulting in diester **7** in 80% yield. Osmium-catalysed dihydroxylation of the double bond followed by periodate cleavage with periodate on silica[8] gave the bridged ketone **9** in 82% yield. Hydrogenolysis of the benzyl groups with palladium catalysis in MeOH/EtOAc afforded **11** in quantitative yield.

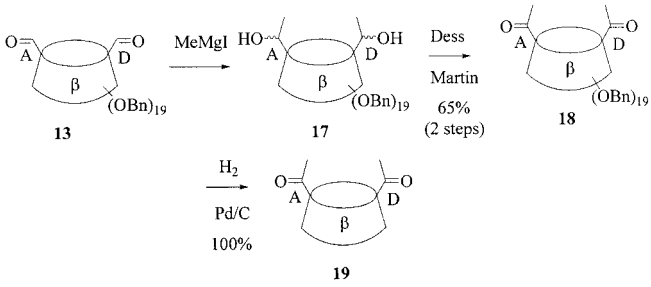
A similar sequence was used to obtain the β-cyclodextrin analogue **12** (Scheme 1). Diol **4**[4] was oxidised with Dess–Martin/$NaClO_2$ giving 84% of **6**. Alkylation with methallyl dichloride/Cs_2CO_3 gave the bridged ester **8** in 69% yield. As the yield indicates, this reaction works less well in the β-cyclodextrin than in the α-cyclodextrin case. Dihydroxylation/diol cleavage with OsO_4/NMO and $NaIO_4/SiO_2$ afforded 79% of ketone **10**. Deprotection with Pd/C and hydrogen (1 atm) gave **12** in quantitative yield.

Work in our group has shown that position 6 of cyclodextrins is hindered and conformationally restricted.[9] We therefore speculated that $6^A,6^D$ diketones might be efficient. Therefore, the known[9] diastereomeric mixture of diols **14** was oxidised with the Dess–Martin reagent to produce the diketone **15** in 60% yield (Scheme 2). Hydrogenolysis and hydrogenation gave diketone **16** in 98% yield.



Scheme 2.

As the solubility of **16** in water was poor, we also prepared the methyl analogue **19** (Scheme 3). The dialdehyde **13**[9] reacted with MeMgI to give a diastereomeric mixture of diols **17**. This mixture was directly oxidised to afford the diketone **18** in 65% yield from **13**. Deprotection by hydrogenolysis gave **19** in quantitative yield.



Scheme 3.

Epoxidation experiments were carried out by the method previously established:[5] The reaction is done in water with 30 mol percent of cyclodextrin ketone present, alkene and oxone being added slowly over one hour. Under these conditions, there is no reaction between oxone and alkene, and the entire reaction is catalytic. Furthermore, the reaction could be inhibited by 2-naphtalenesulfonic acid.[5] The results of epoxidation of six alkenes in the presence of **11** and **12** are shown in Table 1 and compared to **1**, **2** and dichloroacetone. First, it is seen that there is no dihydroxylation occurring with **11** and **12**, but only epoxidation. Also **11** and **12** are better catalysts, giving higher conversion in almost all cases. The exception is indene (**22**) for which the α-CD ester **11** is a poor catalyst. Particularly the β-CD ester **12** is an efficient catalyst, giving high yields of epoxide. The enantioselectivities of the epoxidations were determined by HPLC and compared with those of **1** and **2**. While **11** gives essentially no enantioselectivity, which is similar to **1** and **2**, the β-CD ester **12** gave enantioselectivies up to 45%. This makes sense, because **11** has a high degree of symmetry, whereas **12** is more asymmetric. It is also noteworthy that **11** and **12** are able to catalyse the epoxidation of trisubstituted alkenes **24** and **25** (Table 1).

The diketones **16** and **19** were comparatively poor catalysts (Table 2). Poor solubility and possibly formation of self-inclusion complexes of the propyl groups into the cavity of the catalyst is undoubtedly the reason why **16** is the worse catalyst of the two. Another reason for the lower activity of these ketones is electronic effects: **16** and **19** have less electron-withdrawing α-substituents than **11** and **12**.

In summary, we have synthesised the new bridged keto esters **11** and **12** and shown that they are better epoxidation

Table 1. Yields of epoxide on epoxidation for 1 h in water with oxone and $NaHCO_3$. Yields in parentheses are those of diol. The enantiomeric excess is shown in square brackets.

Catalyst / Substrate	1	2	11	12	
20	50 % (+50 %) [12 % *ee*]	19 % (+44 %) [0 % *ee*]	70 % [< 5 % *ee*]	100 % [45 % *ee*]	70 % –
21	35 %	19 % (+21 %)	70 % [< 5 % *ee*]	90 % [25 % *ee*]	35 %
22	80 % (+20 %) [1 % *ee*]	50 % (+20 %)	35 % [< 5 % *ee*]	82 % [35 % *ee*]	86 %
23	30 %	40 % (+20 %)	55 % [< 5 % *ee*]	86 % [40 % *ee*]	40 %
24	–	–	60 %	44 %	–
25	–	–	71 %	35 %	–

Table 2. Yields of epoxide on epoxidation for 1 h in water with oxone and $NaHCO_3$.

Alkene	16	19	
20	25 %	46 %	–
22	17 %	33 %	<10 %

catalysts than the corresponding ethers **1** and **2**. They also give better enantioselectivity. The diketones **16** and **19** were also made, but they were comparatively poor catalysts.

Experimental Section

General: Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Evaporation was carried out in a rotary evaporator with the temperature being kept below 40 °C. Glassware used for water-free reactions was dried at least 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. ^1H NMR, ^{13}C NMR and COSY were carried out with a Varian Mercury 400 instrument. Monoisotopic mass spectra (MALDI-TOF 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.

Hexadeca-*O*-benzyl-α-cyclodextrin-6^A,6^D-dicarboxylic Acid (5): To a solution of diol **3** (1.1 g, 0.46 mmol) in CH_2Cl_2 (50 mL) was added the Dess–Martin periodinane reagent (0.97 g, 5 equiv.). The reaction mixture was stirred at room temperature for 4 hours and then quenched by the addition of Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (75 mL, containing 3 g $Na_2S_2O_3$). After being stirred for an additional 2 h, the solution was diluted with Et_2O (100 mL) and washed successively with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried and concentrated. To a solution of the residue in *t*BuOH (27 mL), THF (11 mL) and 2-methylbut-2-ene (11 mL) were added $NaClO_2$ (0.78 g, 15 equiv.) and NaH_2PO_4 (0.36 g) in water (11 mL). The reaction mixture was stirred overnight and then quenched with aqueous HCl (75 mL, 1 M) and extracted with EtOAc (4×20 mL). The organic extracts were dried and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt, 5:1, with HCOOH 1%), which resulted in 0.92 g (86%) of compound **5** as a white foam. $[\alpha]_D$ +21.5 (*c* = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–6.68 (m, 80 H, CH_{Ph}), 5.64 (d, 2 H, *J* = 3.6 Hz, 1-H), 5.48 (d, 2 H, J_{gem} = 10.4 Hz, *H*-CHPh), 5.06 (d, 2 H, J_{gem} = 10.4 Hz, *H*-CHPh), 4.90 (d, 2 H, J_{gem} = 10.4 Hz, *H*-CHPh), 4.83–4.50 (m, 21 H), 4.48–4.33 (m, 8 H), 4.30–3.86 (m, 28 H), 3.57 (d, 2 H, *J* = 11.6 Hz), 3.52 (dd, 2 H, *J* = 3.4 Hz, *J* = 9.8 Hz), 3.43 (dd, 2 H, *J* = 2.8 Hz, *J* = 8.8 Hz), 3.23–3.03 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.31 (C=O), 139.46, 139.18, 139.06, 138.41, 138.32, 138.28, 137.72, 136.29 (C_{ipso}), 128.63, 128.44, 128.43, 128.37, 128.34, 128.31, 128.16, 128.14, 128.08, 128.06, 127.95, 127.88, 127.71, 127.64, 127.28, 127.19, 127.07, 126.96, 126.28 (CH_{ph}), 99.66, 98.22, 96.17 (C-1), 84.17, 81.16, 81.12, 80.49, 80.42, 79.25, 79.20, 77.91, 76.77, 76.34, 75.95, 74.16, 73.66, 73.37, 72.83, 72.56, 71.38, 70.63, 70.03, 68.73 (CH_2, CH) ppm. MS: calcd. for $C_{148}H_{152}NaO_{32}$ 2464.0164, found 2464.0820.

Nonadeca-*O*-benzyl-β-cyclodextrin-6^A,6^D-dicarboxylic Acid (6): To a solution of diol **4** (2.6 g, 0.92 mmol) in CH_2Cl_2 (100 mL) was added the Dess–Martin periodinane reagent (1.95 g, 5 equiv.). The reaction mixture was stirred at room temperature for 4 h and then quenched by the addition of Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL, containing 3 g $Na_2S_2O_3$). After being stirred for an additional 2 h, the solution was diluted with Et_2O (150 mL) and washed successively with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried and concentrated. To a solution of the residue in *t*BuOH (53 mL), THF (22 mL) and 2-methylbut-2-ene (22 mL) were added $NaClO_2$ (1.39 g, 15 equiv.) and NaH_2PO_4 (0.8 g) in water (22 mL). The reaction mixture was stirred for ca. 12 h and then quenched with 1 M aqueous HCl (100 mL) and extracted with EtOAc (4×20 mL). The organic extracts were dried and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt/HCOOH, 5:1.5:1%), which resulted in 2.2 g (84%) of compound **6** as a white foam. $[\alpha]_D$ +30.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–6.88 (m, 95 H, CH_{Ph}), 5.78 (d, 1 H, *J* = 4.0 Hz, 1-H), 5.68 (d, 1 H, *J* = 3.2 Hz, 1-H), 5.43 (d, 1 H, J_{gem} = 10.4 Hz, *H*-CHPh), 5.37 (d, 1 H, J_{gem} = 10.0 Hz, *H*-CHPh), 5.16 (d, 1 H, J_{gem} = 11.2 Hz, *H*-CHPh), 5.12 (d, 1 H, J_{gem} = 10.8 Hz, *H*-CHPh), 5.02 (d, 2 H, J_{gem} = 11.2 Hz, *H*-CHPh), 4.92–4.80 (m, 6 H), 4.78–4.46 (m, 20 H), 4.43–4.26 (m, 14 H), 4.22–3.78 (m, 22 H), 3.73 (d, 1 H, *J* = 11.6 Hz), 3.67 (d, 1 H, *J* = 11.2 Hz), 3.60–3.47 (m, 4 H), 3.43–3.15 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.96,

171.89 (C=O), 139.66, 139.34, 139.28, 139.21, 139.15, 138.86, 138.65, 138.56, 138.47, 138.31, 138.28, 138.20, 138.13, 137.79, 137.73, 136.90, 136.67 (C_{ipso}), 128.69, 128.47, 128.40, 128.37, 128.33, 128.28, 128.22, 128.18, 128.08, 128.05, 127.98, 127.93, 127.86, 127.76, 127.69, 127.65, 127.60, 127.57, 127.37, 127.25, 127.10, 127.02, 127.00, 126.95, 126.81, 126.53, 126.47 (CH_{Ph}), 100.79, 100.18, 98.84, 97.90, 97.24, 96.17, 95.76 (C-1), 83.23, 82.37, 81.07, 80.44, 80.24, 79.74, 79.22, 78.16, 77.73, 76.53, 76.25, 75.61, 74.55, 74.15, 73.37, 73.13, 72.93, 72.73, 72.66, 72.59, 71.29, 70.74, 70.57, 70.44, 69.38, 68.95, 60.46 (CH_2, CH) ppm. MS: calcd. for $C_{175}H_{180}KO_{37}$ 2912.1840, found 2912.9507.

6^A,6^D-Di-*O*-prop(2-methylene)-1,3-diyl Hexadeca-*O*-benzyl-α-cyclodextrin-6^A,6^D-dicarboxylate (7): To a solution of diacid **5** (1.11 g, 0.45 mmol) in dry DMF (30 mL) was added Cs_2CO_3 (592 mg, 4 equiv.). After stirring for 30 min at room temperature, 3-chloro-2-chloromethylpropene (58 μL, 1.1 equiv.) was added, and the reaction mixture was stirred for ca. 12 h at room temperature. The reaction was quenched by the addition of water (30 mL) and AcOEt (50 mL), and then the organic phase was washed with water (4 × 30 mL), dried with $MgSO_4$ and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt, 5:1.5), which resulted in 0.91 g (80%) of compound **7** as a white foam. $[\alpha]_D$ +30.0 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–6.90 (m, 80 H, CH_{Ph}), 5.73 (d, 2 H, J = 4.0 Hz, 1-H), 5.61 (d, 2 H, J = 10.8 Hz, *H*-CHPh), 5.22 (d, 2 H, J = 10.4 Hz, *H*-CHPh), 5.04 (d, 4 H, J = 11.2 Hz, CH_2), 4.96–4.71 (m, 13 H), 4.69–4.05 (m, 43 H), 4.02–3.94 (m, 5 H), 3.90–3.77 (m, 5 H), 3.72–3.63 (m, 5 H), 3.49 (d, 3 H, J = 9.2 Hz), 3.26 (td, 3 H, J = 3.1 Hz, J = 9.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.11 (C=O), 139.62, 139.41, 139.34, 138.87, 138.65, 138.48, 137.85, 137.79 (C=, C_{ipso}), 128.43, 128.38, 128.36, 128.13, 128.10, 128.02, 127.97, 127.90, 127.84, 127.79, 127.66, 127.53, 127.34, 127.02, 126.89, 126.79, 126.12 (CH_{Ph}), 121.53 (CH_2=), 99.11, 98.88, 98.28 (C-1), 81.85, 81.50, 81.27, 80.51, 79.73, 78.80, 78.35, 76.75, 76.53, 76.04, 73.83, 73.68, 73.48, 73.45, 72.75, 72.50, 71.79, 71.31, 69.81, 69.62, 69.05, 64.22 (CH, CH_2) ppm. MS: calcd. for $C_{152}H_{156}NaO_{32}$ 2516.0477, found 2516.0084.

6^A,6^D-Di-*O*-prop(2-methylene)-1,3-diyl Nonadeca-*O*-benzyl-β-cyclodextrin-6^A,6^D-dicarboxylate (8): To a solution of diacid **6** (900 mg, 0.31 mmol) in dry DMF (20 mL) was added Cs_2CO_3 (410 mg, 4 equiv.). After stirring for 30 min at room temperature, 3-chloro-2-chloromethyl propene (40 μL, 1.1 equiv.) was added, and the reaction mixture was stirred for ca. 12 h at room temperature. The reaction was quenched by the addition of water (30 mL) and AcOEt (50 mL), and then the organic phase was washed with water (4 × 30 mL), dried with $MgSO_4$ and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt, 5:1), which resulted in 0.63 g (69%) of compound **8** as a white foam. $[\alpha]_D$ +37.6 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–6.82 (m, 95 H, CH_{Ph}), 5.83 (d, 1 H, J = 4.0 Hz, 1-H), 5.63 (d, 1 H, J = 4.0 Hz, 1-H), 5.41 (t, 2 H, J = 9.8 Hz), 5.25–5.16 (m, 3 H), 5.01 (d, 2 H, J = 10.8 Hz, *H*-CHPh), 4.97 (d, 1 H, J = 3.2 Hz, 1-H), 4.91–4.76 (m, 6 H), 4.74–4.09 (m, 40 H), 4.09–3.99 (m, 5 H), 3.98–3.66 (m, 33 H), 3.62 (d, 1 H, J = 10.4 Hz), 3.58–3.41 (m, 6 H), 3.40–3.30 (m, 6 H), 3.26 (dd, 1 H, J = 3.4 Hz, J = 9.8 Hz), 3.19 (d, 1 H, J = 10.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.70, 168.25 (C=O), 139.75, 139.71, 139.46, 139.33, 139.27, 138.99, 138.71, 138.65, 138.60, 138.54, 138.37, 138.20, 138.17, 138.01, 137.95, 137.75, 137.72, 137.66, 137.03 (C=, C_{ipso}), 128.51, 128.44, 128.40, 128.35, 128.29, 128.25, 128.22, 128.11, 128.05, 128.00, 127.96, 127.89, 127.83, 127.80, 127.76, 127.69, 127.60, 127.57, 127.44, 127.37, 127.18, 127.11, 127.05, 126.95, 126.89, 126.61, 126.53, 126.37 (CH_{Ph}), 121.43 (CH_2=), 100.79, 99.88, 98.17, 98.01, 97.63, 97.25, 97.08 (C-1), 83.53, 81.88, 81.50, 81.36, 81.17, 81.03, 80.93, 80.80, 80.53, 80.37, 80.12, 79.43, 79.27, 79.09, 78.95, 78.40, 78.37, 78.06, 77.37, 76.63, 76.59, 76.56, 76.20, 76.04, 74.29, 74.19, 74.00, 73.44, 73.41, 73.37, 73.28, 72.83, 72.80, 72.63, 72.57, 72.45, 72.23, 71.75, 71.58, 71.45, 70.92, 70.59, 70.09, 69.66, 69.38, 68.92, 68.62, 68.45, 64.26, 63.50 (CH, CH_2) ppm. MS: calcd. for $C_{179}H_{184}NaO_{37}$ 2948.2413, found 2948.5800.

6^A,6^D-Di-*O*-propan-2-on-1,3-diyl Hexadeca-*O*-benzyl-α-cyclodextrin-6^A,6^D-dicarboxylate (9): To a solution of compound **7** (820 mg, 0.33 mmol) in a mixture of acetone/water (9:1, 50 mL) was added NMO (*N*-methylmorpholine *N*-oxide) (133 mg, 3 equiv.) and a solution of osmium tetroxide 2.5% in butanol (412 μL). The reaction mixture was stirred for ca. 12 h 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 with $MgSO_4$. Evaporation of the solvent gave the corresponding diol as a white foam. The diol was dissolved in CH_2Cl_2 (5 mL), and 1.5 g of $NaIO_4/SiO_2$ (2.54 g $NaIO_4$/10 g SiO_2, 5 equiv.) was added. After stirring for 3 h, the suspension was filtered through Celite. Evaporation of the solvent and flash chromatography (eluent: pentane/AcOEt, 5:2) gave 0.67 g (82%, 2 steps) of compound **9** as a white foam. $[\alpha]_D$ +36.2 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–6.80 (m, 80 H, CH_{Ph}), 5.61 (d, 2 H, J = 4.0 Hz, 1-H), 5.45 (d, 2 H, J = 10.4 Hz, *H*-CHPh), 5.07 (d, 2 H, J = 10.4 Hz, *H*-CHPh), 4.89 (d, 2 H, J = 10.4 Hz, *H*-CHPh), 4.77–4.59 (m, 13 H), 4.53–3.94 (m, 50 H), 3.79 (dd, 3 H, J = 4.4 Hz, J = 9.2 Hz), 3.72–3.59 (m, 6 H), 3.54 (dd, 3 H, J = 4.0 Hz, J = 9.6 Hz), 3.43 (t, 5 H, J = 10.0 Hz), 3.32–3.24 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.48, 167.72 (C=O), 139.53, 139.31, 139.80, 138.60, 138.42, 137.75, 137.59 (C_{ipso}), 128.50, 128.41, 128.18, 128.12, 128.08, 128.07, 128.02, 127.80, 127.73, 127.60, 127.37, 127.31, 127.11, 126.96, 126.87, 126.14 (CH_{Ph}), 98.89, 98.49 (C-1), 82.22, 81.24, 80.95, 80.50, 79.65, 78.85, 78.21, 76.72, 76.38, 76.01, 73.88, 73.66, 73.46, 72.80, 72.65, 71.90, 71.48, 69.83, 69.72, 68.89, 66.59 (CH, CH_2) ppm. MS: calcd. for $C_{151}H_{154}NaO_{33}$ 2518.0269, found 2518.0715.

6^A,6^D-Di-*O*-propan-2-on-1,3-diyl Nonadeca-*O*-benzyl-β-cyclodextrin-6^A,6^D-dicarboxylate (10): To a solution of compound **8** (763 mg, 0.26 mmol) in a mixture of acetone/water (9:1, 40 mL) was added NMO (106 mg, 3 equiv.) and a solution of osmium tetroxide 2.5% in butanol (327 μL). The reaction mixture was stirred for ca. 12 h, 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 with $MgSO_4$. Evaporation of the solvent gave the corresponding diol as a white foam. The diol was dissolved in CH_2Cl_2 (5 mL), and 1.3 g of $NaIO_4/SiO_2$ (2.54 g $NaIO_4$/10 g SiO_2, 5 equiv.) was added. After stirring for 3 h, the suspension was filtered through Celite. Evaporation of the solvent and flash chromatography (eluent: pentane/AcOEt, 5:2) gave 0.60 g (79%, 2 steps) of compound **10** as a white foam. $[\alpha]_D$ +41.1 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–6.70 (m, 95 H, CH_{Ph}), 5.73 (d, 1 H, J = 4.0 Hz, 1-H), 5.43 (d, 1 H, J = 11.2 Hz, *H*-CHPh), 5.39 (d, 1 H, J = 3.6 Hz, 1-H), 5.27 (d, 1 H, J = 10.0 Hz, CH_2), 5.17–4.95 (m, 7 H), 4.90–4.34 (m, 62 H), 4.32–3.65 (m, 27 H), 3.63–3.19 (m, 21 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.95, 168.46, 166.98 (C=O), 139.62, 139.43, 139.31, 138.95, 138.85, 138.71, 138.63, 138.37, 138.28, 138.23, 137.90, 137.86, 137.73, 137.70, 137.52 (C_{ipso}), 128.66, 128.43, 128.40, 128.36, 128.29, 128.22, 128.20, 128.17, 128.11, 127.99, 127.94, 127.92, 127.88, 127.85, 127.81, 127.73, 127.69, 127.63, 127.50, 127.47, 127.28, 127.25, 127.18, 126.93, 126.44 (CH_{Ph}), 99.58, 99.24, 99.14, 98.40, 97.68, 97.59, 97.05 (C-1), 83.01, 82.18, 81.92, 81.37, 81.15,

80.75, 80.69, 80.57, 80.27, 80.22, 79.29, 78.53, 78.11, 76.41, 76.28, 76.20, 75.59, 75.16, 74.48, 74.28, 73.69, 73.59, 73.54, 73.43, 73.36, 73.20, 73.15, 72.94, 72.78, 72.67, 72.55, 72.43, 72.22, 71.43, 71.33, 71.16, 70.92, 70.50, 69.97, 69.81, 69.41, 68.56, 67.99, 65.39 (CH, CH_2) ppm. MS: calcd. for $C_{178}H_{182}NaO_{38}$ 2950.2206, found 2950.2357.

6^A,6^D-Di-*O*-propan-2-on-1,3-diyl α-Cyclodextrin-6^A,6^D-dicarboxylate (11): Compound **9** (1 g, 0.40 mmol) was dissolved in a mixture of MeOH/AcOEt (1:1, 100 mL). Then Pd/C (200 mg) and TFA (cat) were added and the mixture was stirred for ca. 12 h under hydrogen. Filtration through Celite (eluent: H_2O) and evaporation of the solvent gave 0.42 g (100%) of compound **11** as a white foam. $[\alpha]_D$ +97.2 (c = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 5.30 (d, 2 H, J = 3.6 Hz, 1-H), 5.14 (d, 2 H, J = 3.6 Hz, 1-H), 5.08 (d, 2 H, J = 3.2 Hz, 1-H), 4.85 (d, 2 H, J = 10.8 Hz, CH_2), 4.62 (d, 2 H, J = 10.0 Hz, CH_2), 4.12–3.58 (m, 38 H), 3.33 (bd, 2 H, J = 9.2 Hz) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 169.41 (C=O), 100.91, 100.75, 99.60 (C-1), 93.31, 80.37, 79.98, 79.48, 73.43, 72.68, 72.37, 72.09, 71.71, 71.61, 71.43, 71.07, 70.08, 64.94, 60.81, 59.60 (CH, CH_2) ppm. MS: calcd. for $C_{39}H_{58}NaO_{33}$ 1077.2758, found 1077.2463.

6^A,6^D-Di-*O*-propan-2-on-1,3-diyl β-Cyclodextrin-6^A,6^D-dicarboxylate (12): Compound **10** (800 mg, 0.27 mmol) was dissolved in a mixture of MeOH/AcOEt (1:1, 100 mL). Then Pd/C (200 mg) and TFA (cat) were added, and the mixture was stirred for ca. 12 h under hydrogen. Filtration through Celite (eluent: H_2O) and evaporation of the solvent gave 0.327 g (100%) of compound **12** as a white foam. $[\alpha]_D$ +82.5 (c = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 5.31 (d, 1 H, J = 4.0 Hz, 1-H), 5.26 (d, 1 H, J = 4.0 Hz, 1-H), 5.05–5.89 (m, 5 H, 1-H), 4.44–3.36 (m, 4 H, CH_2), 3.96–3.38 (m, 50 H), 3.26 (d, 2 H, J = 9.2 Hz), 3.12 (d, 2 H, J = 9.6 Hz) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 170.24, 169.28 (C=O), 101.98, 100.65, 100.46, 99.84, 98.46 (C-1), 80.79, 80.53, 79.95, 79.49, 78.66, 77.04, 73.96, 73.50, 72.94, 72.68, 72.50, 72.42, 72.32, 72.26, 72.02, 71.98, 71.91, 71.68, 71.26, 71.16, 70.99, 70.30, 70.01, 64.37, 64.12, 60.90, 60.67, 60.24, 59.67, 59.46 (CH, CH_2) ppm. MS: calcd. for $C_{45}H_{68}NaO_{38}$ 1239.3286, found 1239.3023.

6^A,6^D-Di-*C*-prop-2-enyl-6^A,6^D-dioxononadeca-*O*-benzyl-β-cyclodextrin (15): To a solution of diol **14** (1.0 g, 0.34 mmol) in CH_2Cl_2 (60 mL) was added the Dess–Martin periodinane reagent (868 mg, 6 equiv.). The reaction mixture was stirred at room temperature for ca. 12 h and quenched by the addition of Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL, containing 3 g $Na_2S_2O_3$). After being stirred for an additional 2 h, the solution was diluted with Et_2O (100 mL) and washed successively with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried with $MgSO_4$ and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt, 5:2) which resulted in 0.59 g (60%) of compound **15** as a white foam. $[\alpha]_D$ +19.9 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–6.95 (m, 95 H, CH_{Ph}), 5.88–5.71 (m, 2 H, $=CH_{All}$), 5.49 (d, 1 H, J = 3.6 Hz, 1-H), 5.42 (d, 1 H, J = 4.0 Hz, 1-H), 5.36 (d, 1 H, J = 3.6 Hz, 1-H), 5.33 (d, 1 H, J = 4.0 Hz, 1-H), 5.18 (d, 1 H, J = 3.2 Hz, 1-H), 5.17–4.66 (m, 28 H), 4.61–4.25 (m, 31 H), 4.20–3.85 (m, 28 H), 3.76–3.40 (m, 18 H), 3.35 (d, 2 H, J = 6.8 Hz), 3.25 (t, 2 H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.21, 203.50 (C=O), 139.77, 139.69, 139.54, 139.51, 139.26, 139.15, 138.75, 138.69, 138.63, 138.49, 138.34, 138.30, 138.16, 138.08 (C_{ipso}), 130.46, 130.19 (CH_{All}), 128.63, 128.60, 128.53, 128.47, 128.44, 128.40, 128.35, 128.29, 128.24, 128.18, 128.14, 128.06, 128.03, 127.98, 127.90, 127.83, 127.75, 127.71, 127.66, 127.60, 127.56, 127.46, 127.31, 127.23, 127.17, 127.10 (CH_{Ph}), 119.09, 118.86 (= CH_{2All}), 99.52, 98.86, 98.63, 98.57, 98.39, 98.30, 98.17 (C-1), 81.17, 81.04, 80.91, 80.86, 80.79, 79.98, 79.83, 79.72, 79.54, 79.33, 79.27, 79.12, 78.99, 78.69, 78.63, 77.12, 76.30, 76.12, 75.97, 75.26, 74.87, 74.69, 73.86, 73.80, 73.59, 73.37, 73.09, 72.99, 72.89, 71.86, 71.67, 71.49, 69.63, 69.34, 69.11, 68.95 (CH, CH_2), 44.85, 42.86 (CH_{2All}) ppm. MS: calcd. for $C_{181}H_{188}NaO_{35}$ 2944.2828, found 2944.3350.

6^A,6^D-Di-*C*-propyl-6^A,6^D-dioxo-β-cyclodextrin (16): Compound **15** (450 mg, 0.15 mmol) was dissolved in a mixture of MeOH/AcOEt (1:1, 50 mL). Then Pd/C (100 mg) and TFA (cat) were added, and the mixture was stirred for ca. 12 h under hydrogen. Filtration through Celite (eluent: H_2O) and evaporation of the solvent gave 0.183 g (98%) of compound **16** as a white foam. $[\alpha]_D$ +94.6 (c = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 5.02–4.84 (m, 7 H, 1-H), 4.14 (t, 2 H, J = 10.0 Hz), 3.82–3.32 (m, 40 H), 2.67–2.48 (m, 4 H, CH_2), 1.48–1.36 (m, 4 H, CH_2), 0.80–0.69 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 208.98 (C=O), 101.87, 101.69, 101.59, 100.67 (C-1), 80.79, 80.37, 79.79, 74.66, 73.30, 73.10, 72.91, 72.73, 72.10, 71.78, 71.60, 60.42, 60.18, 59.83 (CH, CH_2), 42.30, 16.36 (CH_2), 13.09 (CH_3) ppm. MS: calcd. for $C_{48}H_{78}NaO_{35}$ 1237.4221, found 1237.4830.

6^A,6^D-Di-*C*-methyl-6^A,6^D-dioxononadeca-*O*-benzyl-β-cyclodextrin (18): Methyl iodide (430 μL, 20 equiv.) was slowly added to a stirred suspension of magnesium turnings (170 mg, 20 equiv.) in diethyl ether (6 mL) under an inert atmosphere. After 2 h, the solution containing the Grignard reagent was added dropwise at room temperature to a stirred solution of dialdehyde **13** (1.0 g, 0.35 mmol) in diethyl ether (20 mL). The reaction mixture was stirred for 1 h and quenched by the addition of saturated aqueous NH_4Cl (20 mL) at 0°C. The mixture was extracted with Et_2O (3 × 20 mL), and the organic layer was dried with $MgSO_4$. Evaporation of the solvent gave the corresponding diol **17** as a white foam. To a solution of crude diol **17** (0.90 g, 0.31 mmol) in CH_2Cl_2 (50 mL) was added the Dess–Martin periodinane reagent (795 mg, 6 equiv.). The reaction mixture was stirred at room temperature for ca. 12 h and quenched by the addition of Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL, containing 3 g $Na_2S_2O_3$). After being stirred for an additional 2 h, the solution was diluted with Et_2O (100 mL) and washed successively with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried with $MgSO_4$ and concentrated. The remaining oil was purified by column chromatography on silica gel (eluent: pentane/AcOEt, 5:1.5), which resulted in 0.65 g (65%) of compound **18** as a white foam. $[\alpha]_D$ +24.5 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–6.90 (m, 95 H, CH_{Ph}), 5.35 (d, 1 H, J = 4.0 Hz, 1-H), 5.28 (d, 1 H, J = 3.6 Hz, 1-H), 5.26–17 (m, 3 H), 5.15 (d, 1 H, J = 3.6 Hz, 1-H), 5.13–4.98 (m, 5 H), 4.93–4.56 (m, 10 H), 4.54–4.16 (m, 24 H), 4.14–3.76 (m, 24 H), 3.68–3.30 (m, 15 H), 2.05 (s, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.93, 203.68 (C=O), 139.39, 139.28, 139.21, 138.95, 138.90, 138.47, 138.41, 138.37, 138.27, 138.22, 138.13, 138.07, 137.90, 137.83 (C_{ipso}), 128.38, 128.34, 128.32, 128.21, 128.18, 128.13, 128.08, 128.02, 127.97, 127.90, 127.78, 127.67, 127.62, 127.60, 127.53, 127.48, 127.43, 127.36, 127.25, 127.15, 127.09, 127.01 (CH_{Ph}), 98.64, 98.39, 98.31, 98.22, 97.89 (C-1), 81.10, 80.74, 80.53, 80.48, 79.78, 79.68, 79.31, 79.21, 78.78, 78.55, 78.23, 77.00, 75.87, 75.77, 75.40, 75.27, 74.93, 74.50, 73.44, 73.34, 73.31, 73.19, 73.15, 73.11, 72.86, 72.79, 72.64, 71.50, 71.40, 71.24, 71.15, 69.21, 68.82, 68.69 (CH, CH_2), 27.11, 26.67 (CH_3) ppm. MS: calcd. for $C_{177}H_{184}NaO_{35}$ 2892.2515, found 2892.3079.

6^A,6^D-Di-*C*-methyl-6^A,6^D-dioxo-β-cyclodextrin (19): Compound **18** (400 mg, 0.14 mmol) was dissolved in a mixture of MeOH/AcOEt

(1:1, 50 mL). Then Pd/C (100 mg) and TFA (cat) were added, and the mixture was stirred for ca. 12 h under hydrogen. Filtration through Celite (eluent: H_2O) and evaporation of the solvent gave 0.16 g (100%) of compound **19** as a white foam. $[\alpha]_D$ +78.2 (c = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 4.99 (d, 1 H, J = 3.6 Hz, 1-H), 4.97 (d, 1 H, J = 4.0 Hz, 1-H), 4.92–4.83 (m, 5 H, 1-H), 4.08 (dd, 2 H, J = 2.8 Hz, J = 9.2 Hz, CH_2), 3.82–3.34 (m, 40 H), 2.19, 2.18 (2s, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 207.82, 207.70 (C=O), 101.84, 101.69, 101.11, 100.95 (C-1), 81.08, 80.84, 80.77, 80.47, 75.59, 75.48, 73.11, 72.75, 72.33, 72.13, 71.76, 71.64, 71.52, 60.20, 59.65 (CH, CH_2), 26.88, 26.77 (CH_3) ppm. MS: calcd. for $C_{44}H_{70}NaO_{35}$ 1181.3595, found 1181.3409.

General Procedure for Epoxidation: To a solution of alkene (0.5 mmol) and ketone (0.15 mmol) in H_2O (5 mL) at 0 °C were added oxone (153 mg) and $NaHCO_3$ (84 mg) every 10 min over a 1-h period. In total, 3 equiv. of oxone and 12 equiv. of $NaHCO_3$ were added. Water was added, the aqueous layer was extracted with CH_2Cl_2 and dried ($MgSO_4$), and the solvents were evaporated.

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