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New cup-shaped α-cyclodextrin derivatives and a study of their catalytic properties in oxidation reactions

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Abstract—A series of new α-cyclodextrin derivatives with a substituted propylene bridge attached to the 6-O's of the A,D-glucose units are reported. The compounds were prepared from the known $6^A,6^D$-di-*O*-(prop-2-methylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin, which was transformed into $6^A,6^D$-di-*O*-(prop-2-methyl-1,3-dienyl)-α-cyclodextrin, $6^A,6^D$-di-*O*-(prop-2-formyl-2-hydroxy-1,3-dienyl)-α-cyclodextrin, $6^A,6^D$-di-*O*-(prop-2-aminomethyl-2-hydroxy-1,3-dienyl)-α-cyclodextrin, $6^A,6^D$-di-*O*-(prop-2-hydroxymethylidene-1,3-dienyl)-α-cyclodextrin, $6^A,6^D$-di-*O*-(prop-2-formyl-1,3-dienyl)-α-cyclodextrin, $6^A,6^D$-di-*O*-(prop-2-carboxy-1,3-dienyl)-α-cyclodextrin and $6^A,6^D$-di-*O*-(prop-2-methoxycarbonyl-1,3-dienyl)-α-cyclodextrin. The new compounds were evaluated for their ability to affect amine and alcohol oxidations in the presence of hydrogen peroxide.

1. Introduction

Supramolecular chemistry refers to the area of chemistry, which focuses on the non-covalent bonding interactions of molecules. In the last decades we have seen an impressive advance in the field and a continuously growing awareness of the importance of this topic. The study of how molecules can organise other molecules in such a way that they are induced to react, when they otherwise would not, is a field that was pioneered by the research groups of Breslow,[1] Bender,[2] Tabushi[3] and others, but nevertheless is still in its infancy.

Cyclodextrins are popular building blocks in supramolecular chemistry and enzyme modelling due to their ready availability, their ability to bind various compounds into their hydrophobic cavities, their low-toxicity and their water solubility.[4,5] The native compounds have major applications in pharmacy, food industry, cosmetics, agrochemistry and analytical chemistry,[6] but when one wishes to use cyclodextrins as building blocks, one encounters the inherent problems of dealing in a specific way with 18 or more hydroxyl groups. While synthetic schemes to solve some of these problems have emerged,[7] generally speaking, synthetic cyclodextrin chemistry is nevertheless a relatively complex and low-yielding endeavour.[8] Furthermore, many modifications are effectively impossible to make. It was therefore very important progress when Sinaÿ et al.[9] discovered that DIBAL can effect regioselective de-O-benzylation of the primary hydroxyls in position 6A and 6D of perbenzylated cyclodextrins, since it makes it possible to work with these molecules in protected form.

One significant problem with many cyclodextrin-based enzyme models may have been too much flexibility. The first attempt to overcome the flexibility problems was made by Tabushi et al.[6] by synthesising a mixture of A,C and A,D capped cyclodextrins on the primary rim. Despite considerable effort and several well-defined protocols,[7] only poor regioselectivities and low yields were reported for the preparation of different bridged cyclodextrins.[8] Using a new methodology, Sinaÿ and collaborators on the other hand made a A,D bridged compound very efficiently. We also reported the synthesis of bridged-cyclodextrin derivatives **1**–**3** (Fig. 1),[10–13] which were found to function as enzyme models.

The bridged ketocyclodextrins **2** and **3** (Fig. 1) were found to catalyse epoxidation through intermediate dioxiranes formed in the presence of persulfates[12,13] and they can increase the oxidation of anilines to nitrobenzenes in the

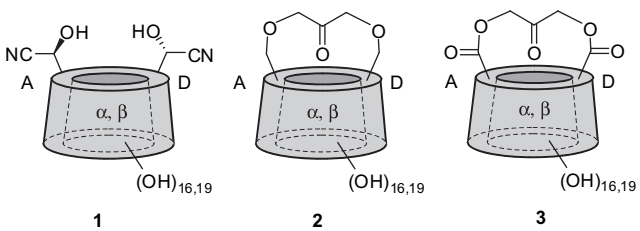

Figure 1. Examples of some cyclodextrin-based artificial enzymes.

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presence of hydrogen peroxide with a k_{cat}/k_{uncat} up to 1070.[14] Our bridged ketoester-cyclodextrins **3** proved to be remarkably good artificial enzymes for benzyl alcohol oxidations into aldehydes or ketones with rate increase of up to 6.3×10^4 in the best case.[15]

In this article we present the synthesis of a series of new capped or bridged cyclodextrins similar to **2** and **3** but with a variety of functional groups in the bridge, and report their ability to catalyse oxidation reactions.

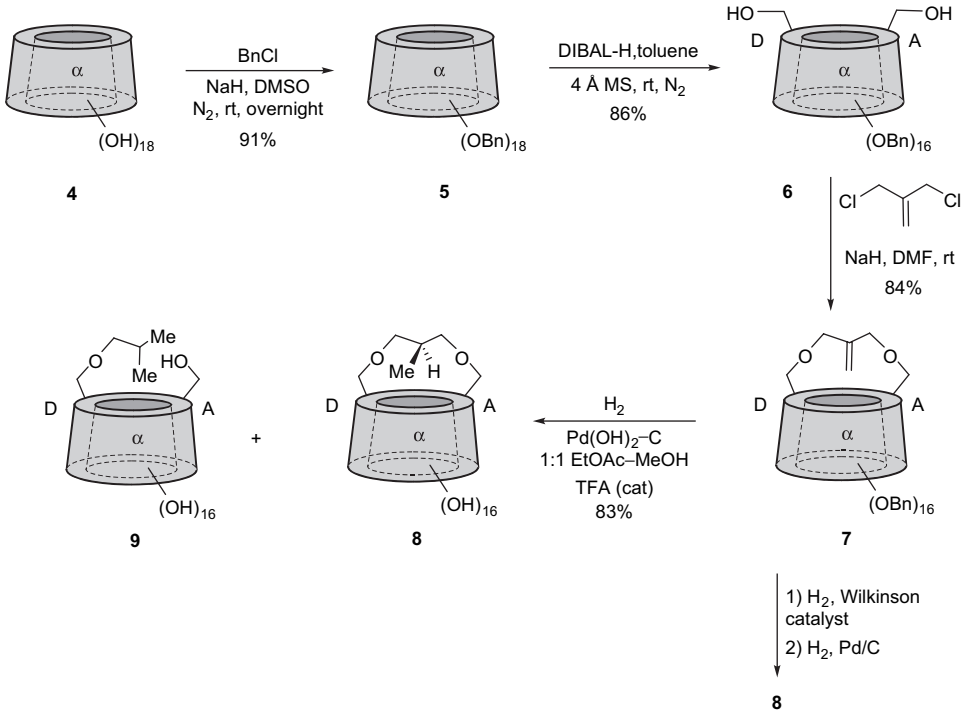
2. Results and discussion

Starting material for all our compounds was commercial α-cyclodextrin **4**. This compound was subjected to per-O-benzylation using BnCl in the presence of NaH and DMSO as solvent (Scheme 1). Original methodology for perbenzylation of α- and β-cyclodextrins was reported by Takahashi[16] and Sato,[17] respectively. Full protection of the cyclomaltohexaose was accomplished[16] using benzyl bromide and DMF as solvent and the product was isolated by column chromatography; on the contrary, per-O-benzylation of cyclomaltoheptaose was carried out[17] with benzyl chloride and DMSO as solvent, and isolation of the final product involved precipitation with a mixture of acetone–MeOH.

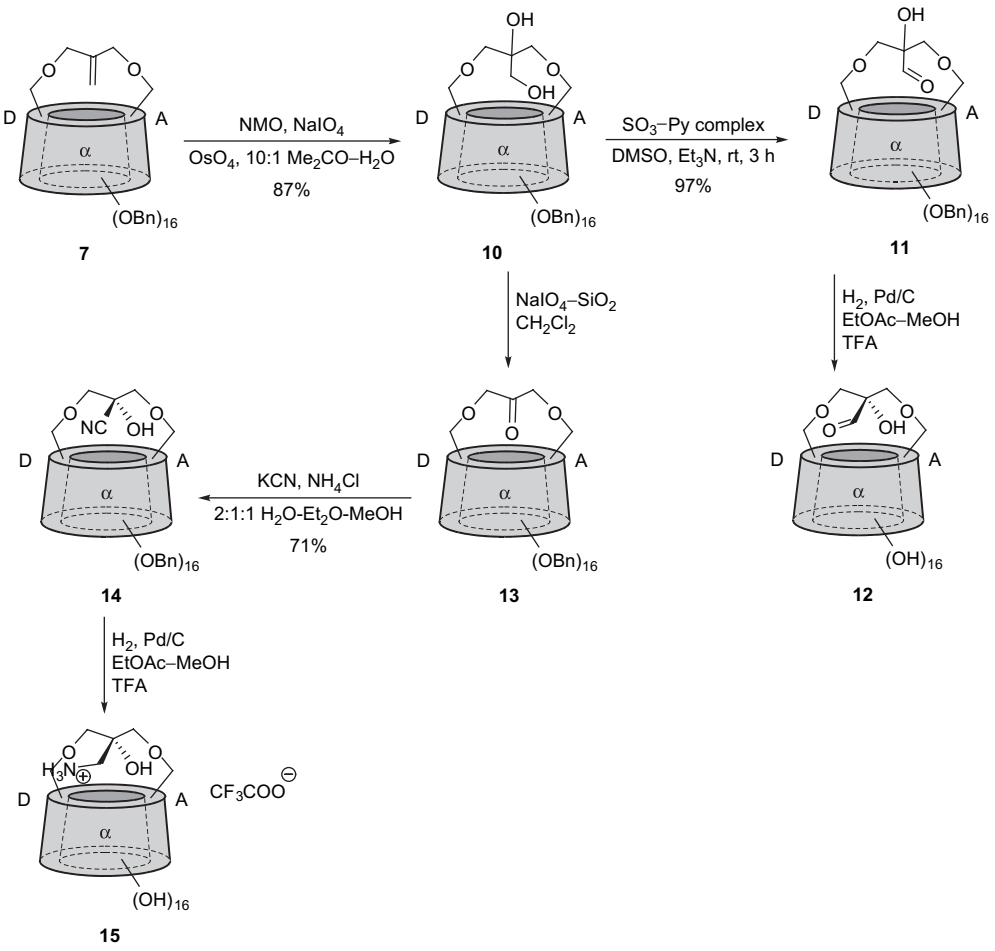
In our hands, full protection of **4** was furnished by using benzyl chloride and DMSO as solvent to give derivative **5** in a 91% yield after column chromatography. Selective A,D di-O-debenzylation of **5** was carried out following the original methodology reported by Sinaÿ,[18,19] including the modifications recently reported by us.[20]

Thus, diol **6** was prepared in an 86% yield after column chromatography upon treatment of **4** with DIBAL-H in anhydrous toluene and inert atmosphere. Coupling of diol **5** with methallyl dichloride (1.1 equiv) in the presence of NaH afforded known bridged-alkene **7**[12] in an 84% yield (Scheme 1). Compound **7** turned out to be a valuable starting material with broad applicability for the preparation of a wide range of bridged-cyclodextrin derivatives. Attempts to carry out standard hydrogenolysis on **7** to afford derivative **8** led to the title compound together with derivative **9**, as a result of the bridge opening; this enhancement of reactivity in this position can be explained by the allylic nature. This problem was overcome by first reducing the double bond using hydrogen and Wilkinson's catalyst, followed by standard hydrogenolysis for the removal of the *O*-benzyl groups (Scheme 1). The presence of the methyl group in the bridge scaffold can increase the hydrophobicity of the cyclodextrin cavity, and thus, might enhance binding affinities of unpolar substrates.

Dihydroxylation of the double bond of **7** was carried out by treatment[12] with NMO and catalytic OsO_4 in aq acetone (Scheme 2), although addition of $NaIO_4$ was found to be important for the reaction to proceed faster. Bridged 1,2-glycol **10** was isolated in an 87% yield after column chromatography, together with a small amount (4%) of **13**; this glycol was previously used by us as a non-isolated intermediate for the synthesis of ketone **13**.[12] Attempts to oxidise **10** to the corresponding α-hydroxy aldehyde **11** using Dess–Martin periodinane failed, and despite the smooth conditions associated with this oxidation, an oxidative cleavage took place, ketone **13** being the major compound detected in MALDI spectrum; only traces of the desired **11** were detected. This sensitivity of 1,2-glycols towards oxidative cleavage was previously reported by Isobe et al.[21] when using different oxidants, rather than Dess–Martin reagent. This problem was overcome by replacing the oxidant with sulfur trioxide–Py complex,[22,23] under conditions similar



Scheme 1. Synthesis of **8**.



Scheme 2. Synthesis of **12** and **15**.

to Swern oxidation, with compound **11** being obtained in almost quantitative yield (Scheme 2). The presence of the α-located hydroxyl group in **11** is expected to enhance electrophilicity of the aldehyde moiety, which might be of interest either in synthesis or in related catalysts. Deprotection under standard hydrogenolysis conditions afforded derivative **12**.

Attempts were also made to oxidise α-hydroxy aldehyde **11** to the corresponding carboxylic acid, which was obtained as the major compound as deduced from MALDI spectrum of the crude reaction; nevertheless, attempts to purify it by column chromatography led to a partial decomposition.

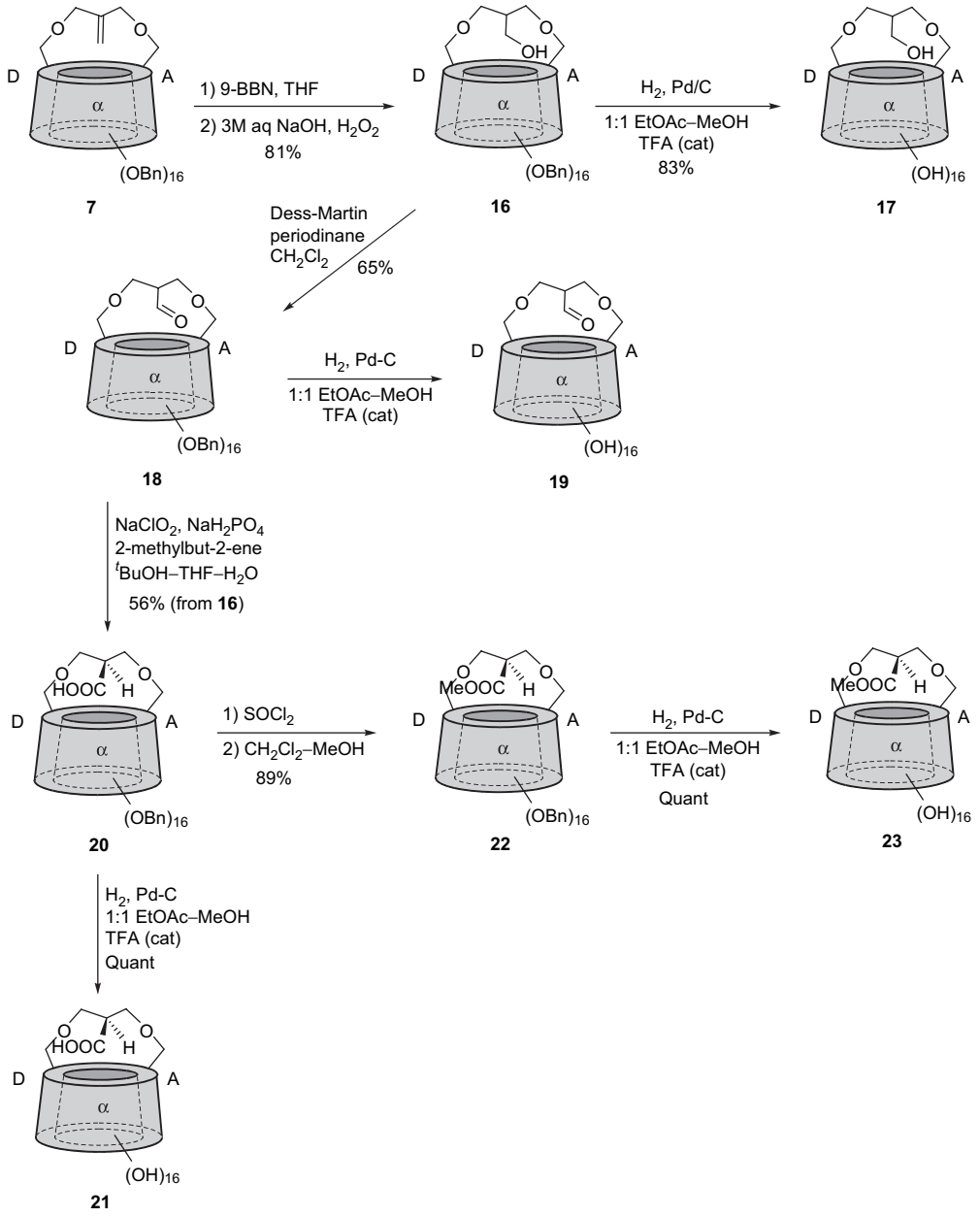
1,2-Glycol **10** was also converted into known ketone **13**[12] by oxidative cleavage induced by silica-supported $NaIO_4$,[24] and the latter was transformed into bridged cyanohydrin **14** in good yield (71%) by treatment with an excess of KCN and NH_4Cl (Scheme 2). The structure was supported by spectroscopic data; thus ^{13}C NMR spectrum showed a signal at 119.0 ppm and the IR data showed a peak at 2250 cm^{-1}, both compatible with the presence of a cyano moiety. Final deprotection of the benzyl groups under standard hydrogenolysis conditions did not afford the expected unprotected cyanohydrin, but reduction of the cyano moiety took place and amino derivative **15** was indeed obtained, probably in equilibrium between the protonated and non-protonated species.

Another synthetic route for derivatisation of this family of cyclodextrins was regioselective hydroxylation of alkene **7**; thus, hydroboration–oxidation process at room temperature employing an excess of 9-BBN[25–27] for the hydroboration step furnished primary alcohol derivative **16** as the only isolated product in an 81% yield; hydrogenolysis afforded fully *O*-unprotected derivative **17** in 83% yield (Scheme 3).

When alcohol **16** was treated with Dess–Martin periodinane, the corresponding aldehyde **18** was obtained in moderate yield (65%) after column chromatography. The presence of the aldehyde moiety was supported by ^1H NMR (broad singlet at 9.24 ppm), ^{13}C NMR (200.9 ppm) and IR (2869, 1726 cm^{-1}). In situ oxidation of the aldehyde with sodium chlorite in a buffered medium[28] gave access carboxylic acid derivative **20**, whose ^{13}C NMR spectrum showed the corresponding peak for the carboxylic residue (177.9 ppm); deprotection under standard conditions gave **21** in a quantitative yield (Scheme 3).

It is noteworthy to mention that fully unprotected aldehydes **12** and **19** present only small signals in NMR spectra corresponding to the aldehyde motif; the reason is that the aldehyde moiety must be in equilibrium with the hemiacetalic form, the equilibrium being shifted to the latter.

Furthermore, treatment of readily-available carboxylic acid derivative **20** with thionyl chloride afforded the



Scheme 3. Synthesis of **17**, **19**, **21** and **23**.

corresponding transient acyl chloride that was in situ coupled with methanol to furnish the corresponding methyl ester **22**, isolated in an 89% yield after purification. Removal of the benzyl groups provided **23** in a quantitative yield (Scheme 3).

Unprotected cyclodextrin derivatives **12**, **15**, **17**, **19**, **21** and **23** were tested for catalysis in the hydrogen peroxide-mediated oxidation of anilines[14] and benzylic alcohols.[15] While no catalysis was found for oxidation of 4-methoxybenzyl alcohol to benzaldehyde by any of the compounds, **12**, **19** and **21** catalysed the oxidation of 2-hydroxyaniline into 2-aminophenoxazin-2-one (Table 1). These oxidations followed the Michaelis–Menten kinetic scheme:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \overset{k_{cat}}{\rightarrow} E + P$$

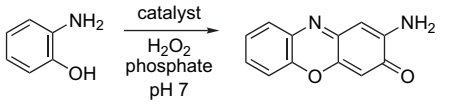
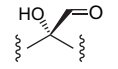
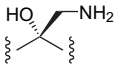
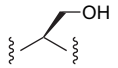
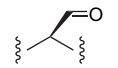
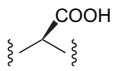
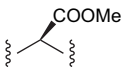
and were analysed using the usual equation:

$$V_{cat} = V_m \frac{S}{S + K_m}$$

where V_{cat} is the initial steady state rate of catalysed reaction, V_m is the maximum rate and K_m is the Michaelis–Menten constant. The fit of the kinetics was found using a Hanes plot shown in Figure 2, and V_m and K_m were obtained using non-linear regression fitting of the data to the Michaelis equation above. From V_m, the value of k_{cat} was calculated by division with the enzyme concentration. The kinetic parameters are shown in Table 1.

Not surprisingly, the aldehyde **19** displayed the best activity giving a k_{cat} of 1.58×10^{-3} s^{-1} and a k_{cat}/k_{uncat} ratio of 410, which represents how much faster the reaction is occurring

Table 1. Kinetic data for the oxidation of 2-hydroxyaniline into 2-aminophenoxazin-2-one catalysed by the new cyclodextrins

Reaction			
Catalyst	k_{cat} ($\times 10^3$ s^{-1})	K_m	k_{cat}/k_{uncat}
12 	0.04±0.004	3.8±1.0	9
15 	—	—	—
17 	—	—	—
19 	1.58±0.08	10.2±1.0	410
21 	0.30±0.05	3.5±1.1	60
23 	—	—	—

— means that no catalysis was observed.

inside the cyclodextrin cavity. It is likely that the aldehyde works similarly to the previously reported ketones, where we proposed that the carbonyl group binds hydrogen peroxide before reacting with bound amine. The corresponding 2-hydroxyaldehyde **12** is somewhat surprisingly about 50 times less efficient. Due to electronic effects it would not be expected to be weaker as the carbonyl group is more electrophilic, but perhaps steric hindrance or conformational differences may be causing decrease in efficiency. The acid **21** also showed some catalysis, which probably is caused by a different mechanism, the nature of which, due to the modest size of the effect, we will not speculate.

3. Conclusions

In summary, we have successfully prepared a series of cup-shaped cyclodextrin derivatives with a considerable variation of substituents on the bridge. A study of these compounds as oxidation catalysts, a reaction where previously reported cyclodextrin ketones have been found efficient, showed that a compound containing an aldehyde substituent displayed catalysis, while the other analogues showed much smaller or no catalysis.

4. Experimental section

4.1. General

Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Evaporation was carried out in a rotatory evaporator. Glassware used for water-free reactions was dried for 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 visualised by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% H_2SO_4 and heating until coloured spots appeared. ^1H, ^{13}C NMR and COSY experiments were carried out with a Varian Mercury 400 instrument. Monoisotopic mass spectra (MALDI-TOF MS) were obtained on a Bruker Daltonics mass spectrometer using an α-cyanohydroxycinnamic acid (α-CHCA) matrix. Spectra were calibrated using a peptide calibration standard solution.

4.1.1. 6^A,6^D-Di-*O*-(prop-2-methyl-1,3-dienyl)-α-cyclodextrin (8). To a solution of 6^A,6^D-di-*O*-(prop-2-methylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**7**) (0.34 g, 0.13 mmol) in EtOAc (20 mL) was added Wilkinson's catalyst (108 mg) and the corresponding mixture was stirred under hydrogen atmosphere (1 atm) for 2 days. Then, it was concentrated to dryness and the residue was purified by column chromatography (pentane → 1:5 EtOAc–pentane). Then, the product was further hydrogenolysed (1 atm) for 2 days in EtOH (20 mL) using Pd–C as catalyst, in the presence of TFA (cat.). Filtration and removal of the solvents gave **8** (65 mg, 50%, two steps). $[\alpha]_D^{21}$ +111 (*c* 0.4, H_2O); IR (ν_{max}): 3406, 2930, 1152, 1033, 951, 721, 707 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.71 (m, 16H, OH), 5.02 (m, 6H, H-1), 4.04 (m, 3H), 3.77–2.89 (m, 39H), 1.70 (m, 1H, C*H*–Me), 0.84 (d, 1H, $J_{H,H}$=6.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.9, 101.8, 101.2, 100.1, 83.1, 82.8, 81.5, 81.4, 80.6, 80.2, 74.2, 73.5, 72.9, 72.8, 72.7, 72.3, 72.2, 72.0, 71.6, 71.3, 71.2, 70.1, 68.4, 59.9, 59.7, 59.3. 34.5 (*C*H–CH_3), 14.5 (CH_3); MS calcd for $C_{40}H_{66}O_{30}Na$: 1049.4, found: 1048.8.

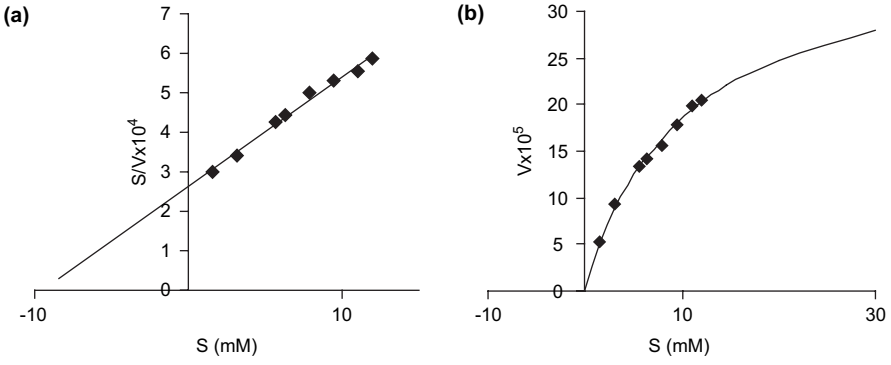


Figure 2. Kinetic plots for the oxidation of 2-hydroxyaniline into 2-aminophenoxazin-2-one catalysed by **19**. (a) Hanes plot of S/V_{cat} vs *S*, where *S* is the concentration of 2-hydroxyaniline and V_{cat} is the catalysed rate of conversion. (b) A plot of V_{cat} vs *S*, which shows the hyperbolic relationship of the saturation kinetics.

4.1.2. $6^A,6^D$-Di-*O*-(prop-2-hydroxy-2-hydroxymethyl-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (10). A mixture of $6^A,6^D$-di-*O*-(prop-2-methylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**7**) (5.0 g, 2.03 mmol), NMO (0.82 g, 6.09 mmol), $NaIO_4$ (1.30 g, 6.09 mmol) and 2.5 wt% OsO_4 (2.0 mL) in 10:1 acetone–H_2O (330 mL) was kept stirring at room temperature overnight. The reaction was quenched by addition of 10% $Na_2S_2O_3$ (300 mL) and the product was extracted with EtOAc (3×100 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane → 1:2 EtOAc–pentane) to afford title compound (4.40 g, 87%), as well as a small amount of $6^A,6^D$-di-*O*-(prop-2-one-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**13**, 216 mg, 4%).

$[\alpha]_D^{23}$ +37 (*c* 1.1, CH_2Cl_2,); IR (ν_{max}): 3484, 3007, 3062, 3029, 2922, 2869, 1605, 1496, 1453, 1353, 1208, 1092, 1026, 909, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–6.90 (m, 80H, Ar–H), 5.49–5.44 (d, 4H, $J_{1,2}$=3.6 Hz, H-1, CH_2), 5.16 (d, 2H, $J_{H,H}$=10.0 Hz, CH_2), 4.90 (d, 2H, $J_{H,H}$=10.4 Hz, CH_2), 4.78–4.59 (dd, 12H, $J_{1,2}$=4.0 Hz, $J_{H,H}$=12.0 Hz, H-1, CH_2), 4.45–4.11 (m, 23H), 4.05–3.74 (m, 16H), 3.65 (d, 2H, $J_{H,H}$=10.0 Hz, CH_2), 3.58–3.55 (m, 5H), 3.41–3.20 (m, 12H), 2.99 (m, 2H, $J_{H,H}$=12.8 Hz, CH_2), 1.94 (br s, 2H, 2OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 139.4, 138.9, 138.5, 138.3, 138.0, 137.9 (C_{ipso}), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 127.0, 126.6, 126.0 (CH_{Ar}), 100.1, 100.0, 97.8 (C-1), 82.4, 82.2, 81.8, 81.2, 80.7, 80.6, 80.2, 79.2, 79.0, 78.9, 78.0, 77.7, 77.4, 76.3, 73.7, 73.6, 73.5, 73.2, 73.0, 72.9, 72.8, 72.4, 72.2, 72.0, 71.9, 71.5, 69.8, 69.5, 69.4, 69.2, 65.3 (CH); MS calcd for $C_{152}H_{162}O_{32}Na$: 2522.1, found: 2522.1.

4.1.3. $6^A,6^D$-Di-*O*-(prop-2-formyl-2-hydroxy-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (11). To a stirred solution of $6^A,6^D$-di-*O*-(prop-2-hydroxy-2-hydroxymethyl-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**10**) (120 mg, 0.048 mmol) and Et_3N (0.1 mL, 0.72 mmol) in dry DMSO (0.8 mL) was dropwise added under N_2 a solution of SO_3–Py complex (78 mg, 0.48 mmol) in dry DMSO (0.5 mL). Reaction mixture was kept stirring at room temperature for 3 h, and after that time, it was quenched by addition of satd aq $NaHCO_3$ (50 mL). Product was extracted with CH_2Cl_2 (50 mL), and the organic layer was separated and washed with brine (3×50 mL), H_2O (50 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness and purified by column chromatography (pentane → 1:3 EtOAc–pentane) to afford **11** as a syrup (116 mg, 97%).

$[\alpha]_D^{23}$ +28 (*c* 0.5, CH_2Cl_2); IR (ν_{max}): 3435, 3006, 3062, 3028, 2923, 2867, 1736, 1496, 1453, 1353, 1208, 1093, 1027, 909, 756, 733, 696, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H, CHO), 7.21–6.92 (m, 80H, Ar–H), 5.45 (2d, 2H, $J_{H,H}$=10.4 Hz, 2CH), 5.38 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.36 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.17 (2d, 2H, $J_{H,H}$=10.4 Hz, 2CH), 4.90 (2d, 2H, $J_{H,H}$=10.2 Hz, 2CH), 4.76–4.57 (m, 12H), 4.45–4.11 (m, 21H), 4.02–4.44 (m, 26H), 3.33–3.22 (m, 9H), 3.06 (d, 2H, $J_{H,H}$=10.0 Hz, 2CH), 3.01 (d, 2H, $J_{H,H}$=9.6 Hz, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0 (CO), 139.8, 139.5, 139.4, 139.0, 138.5, 138.4, 128.2, 138.0, 137.9 (C_{ipso}), 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.3, 127.2, 127.0, 1262.8, 127.7, 126.0 (CH_{Ar}), 100.2, 100.1, 97.9, 97.8 (C-1), 82.6, 81.9, 81.1, 80.7, 80.6, 80.1, 80.0, 79.8, 78.9, 77.9, 77.7, 77.4, 76.5, 76.3, 76.2, 73.8, 73.7, 73.6, 73.5, 73.4, 73.3, 73.1, 73.0, 72.9, 72.6, 72.4, 72.3, 72.1, 72.0, 71.9, 70.9, 70.3, 69.9, 69.4, 69.2, 69.1; MS calcd for $C_{152}H_{160}O_{32}Na$: 2520.1, found: 2520.3.

4.1.4. $6^A,6^D$-Di-*O*-(prop-2-formyl-2-hydroxy-1,3-dienyl)-α-cyclodextrin (12). Compound **11** (250 mg, 0.1 mmol) was dissolved in 1:1 MeOH–EtOAc (20 mL). Then Pd–C (200 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **12** as a foam (98 mg, 93%). $[\alpha]_D^{23}$ +98 (*c* 0.4, H_2O); ^1H NMR (400 MHz, D_2O): δ 5.18, 5.07, 5.03 (m, 6H, H-1), 4.16 (m, 3H), 4.02–3.90 (m, 7H), 3.87–3.41 (m, 32H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.4 102.0, 101.9, 101.4, 100.9, 100.6, 100.1 (C-1, C(OH)OC), 83.0, 82.9, 81.8, 81.7, 80.4, 76.6, 74.5, 74.4, 74.0, 73.8, 73.1, 72.9, 72.8, 73.6, 72.3, 72.2, 72.1, 71.6, 71.4, 71.3, 68.9, 68.6, 65.0, 62.0, 60.5, 60.1, 59.9, 59.5; MS calcd for $C_{40}H_{64}O_{32}Na$: 1079.3, found: 1079.6.

4.1.5. $6^A,6^D$-Di-*O*-(prop-2-cyano-2-hydroxy-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (14). A mixture of KCN (649 mg, 9.96 mmol) and NH_4Cl (802 mg, 15 mmol (14.99 mmol) in H_2O (10 mL) was added to a solution of $6^A,6^D$-di-*O*-(prop-2-oxo-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**13**) (178 mg, 0.072 mmol) in a 1:1 mixture of Et_2O–MeOH (10 mL) at 0 °C. Reaction mixture was kept stirring at room temperature for 40 h. Organic solvents were removed in vacuo and the remaining water was extracted with CH_2Cl_2 (4×20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane → 1:4 EtOAc–pentane) to afford the title compound as a syrup (127 mg, 71%).

$[\alpha]_D^{25}$ +35 (*c* 0.5, CH_2Cl_2); IR (ν_{max}): 3061, 3028, 2922, 2869, 2250, 1496, 1453, 1353, 1207, 1094, 1058, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–6.90 (m, 80H, Ar–H), 5.46 (d, 1H, $J_{H,H}$=12.0 Hz, CH), 5.39 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.38 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.34 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.17 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.15 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 4.93 (d, 1H, $J_{H,H}$=12.0 Hz, CH), 5.86 (d, 1H, $J_{H,H}$=12.0 Hz, CH), 4.78–4.61 (m, 10H), 4.50–4.31 (m, 12H), 4.27–4.13 (m, 8H), 4.10–3.65 (m, 23H), 3.59–3.14 (m, 16H), 3.02 (d, 2H, $J_{H,H}$=8.0 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 139.7, 139.5, 139.4, 139.3, 138.9, 138.5, 138.4, 138.1, 137.9, 137.7 (C_{ipso}), 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.2, 127.1, 127.0, 126.9, 126.7, 126.1, 126.0 (CH_{Ar}), 119.0 (CN), 100.4, 100.3, 100.2, 97.9, 97.7 (C-1), 82.8, 82.6, 82.4, 81.4, 81.1, 81.0, 80.7, 80.4, 80.1, 80.0, 79.8, 78.8, 78.7, 77.9, 77.3, 76.3, 76.1, 74.0, 73.8, 73.6, 73.5, 73.4, 73.2, 73.0, 72.8, 72.5, 72.4, 72.2, 72.0, 71.8, 70.6, 70.0, 69.9, 69.5, 69.2, 68.9, 60.6; MS calcd for $C_{152}H_{159}NO_{31}Na$: 2517.1, found: 2517.1.

4.1.6. $6^A,6^D$-Di-*O*-(prop-2-aminomethyl-2-hydroxy-1,3-dienyl)-α-cyclodextrin (15). Compound **14** (0.14 g, 0.05 mmol) was dissolved in 1:1 MeOH–EtOAc (4 mL).

Then Pd–C (88 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **15** as a foam (50 mg, quant). ^{1}H NMR (400 MHz, D_2O): δ 5.05–4.94 (m, 6H, H-1), 4.11–4.05 (m, 2H), 4.00–3.66 (m, 23H), 3.58–3.48 (m, 12H), 3.46–3.35 (m, 4H), 3.30 (m, 2H), 3.11 (m, 1H); ^{13}C NMR (100 MHz, D_2O): δ 101.6, 100.9, 100.7, 100.5 (C-1), 82.2, 82.0, 81.9, 81.7, 81.5, 81.1, 81.0, 80.7, 74.3, 74.1, 73.5, 73.3, 72.7, 72.5, 72.3, 72.2, 72.1, 72.0, 71.9, 71.8, 7.3, 71.0, 69.7, 69.0, 53.3, 43.3, 43.0; MS calcd for $C_{40}H_{67}NO_{31}Na$: 1080.0, found: 1080.4.

4.1.7. 6^A,6^D-Di-*O*-(prop-2-hydroxymethyl-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (16). A solution of 6^A,6^D-di-*O*-(prop-2-methylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (2.00 g, 0.81 mmol) in dry THF (20 mL) was added to a 0.5 M solution of 9-BBN in THF (27 mL) and the mixture was kept stirring under nitrogen overnight. Then reaction mixture was cooled down to 0 °C and a 3 M solution of NaOH (6.5 mL) and 35% H_2O_2 were slowly added and the corresponding mixture was kept stirring at room temperature overnight. Then, CH_2Cl_2 (150 mL) was added and the organic layer was washed with satd aq NH_4Cl (3×50 mL), satd aq NaCl (1×50 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (pentane → 1:2 EtOAc–pentane) to give compound **16** as a syrup (1.63 g, 81%). $[\alpha]_D^{25}$ +42 (*c* 0.5, CH_2Cl_2); IR (ν_{max}): 3062, 3028, 2922, 2868, 1495, 1453, 1353, 1207, 1092, 1027, 734, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–6.91 (m, 80H, Ar–H), 5.50–5.43 (d, 4H, $J_{H,H}$=10.0 Hz, CH_2, H-1), 5.19–5,14 (d, 2H, $J_{H,H}$=9.4 Hz, CH_2), 4.90 (d, 2H, $J_{H,H}$=9.6 Hz, CH_2), 4.77–4.59 (d, 12H, $J_{H,H}$=10.0 Hz, CH_2, H-1), 4.42–4.12 (m, 26 H), 4.04–3.74 (m, 15H), 3.59 (d, 2H, $J_{H,H}$=9.6 Hz, 2CH), 3.52 (dd, 2H, *J*=4.0 Hz, *J*=10.0 Hz), 3.46 (d, 2H, *J*=11.2 Hz), 3.39–3.22 (m, 11H), 3.01 (m, 2H), 1.70–1.43 (m, 2H, CH, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 139.5, 139.0, 138.9, 138.6, 138.4, 138.3, 138.0, 137.9 (C_{ipso}), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.0, 126.7, 126.0 (CH_{Ar}), 100.0, 99.8, 99.7, 98.1, 97.7 (C-1), 82.4, 82.3, 81.6, 81.2, 80.8, 80.3, 80.2, 79.7, 79.1, 79.0, 77.9, 76.3, 73.6, 73.5, 73.4, 73.2, 73.0, 72.4, 72.2, 72.0, 71.9, 70.0, 69.7, 69.6, 69.2, 68.9, 63.7 (CH_2OH), 41.7 (CH); Anal. Calcd for $C_{152}H_{162}O_{31}$: C 73.47, H 6.57. Found: C 73.30, H 6.59. MS calcd for $C_{152}H_{162}O_{31}Na$: 2506.1, found: 2506.3.

4.1.8. 6^A,6^D-Di-*O*-(prop-2-hydroxymethyl-1,3-dienyl)-α-cyclodextrin (17). Compound **16** (0.60 g, 0.24 mmol) was dissolved in 1:1 MeOH–EtOAc (20 mL). Then Pd–C (241 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **17** as a foam (0.21 g, 83%). $[\alpha]_D^{25}$ +103 (*c* 0.6, H_2O); IR (ν_{max}): 3445, 2931, 1411, 1028, 951, 708 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 5.13 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.12 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.04–5.00 (m, 4H, H-1), 4.17 (m, 3H), 4.10–3.59 (m, 35H), 3.42–3.31 (m, 3H), 3.25 (t, 1H, *J*=9.2 Hz), 1.96 (m, 1H, C*H*–CH_2OH); ^{13}C NMR (100 MHz, D_2O): δ 101.6 (2C, C-1), 101.0 (2C, C-1), 100.3, 100.1 (C-1), 82.0, 81.5, 81.4, 80.3, 80.1, 74.1, 72.7, 72.6, 72.4, 72.3, 72.2, 72.1, 71.9, 71.8, 71.4, 71.2, 70.9, 70.1, 69.5, 68.4, 41.9 (*C*H–CH_2OH); MS calcd for $C_{40}H_{66}O_{31}Na$: 1065.3, found: 1064.5.

4.1.9. 6^A,6^D-Di-*O*-(prop-2-formyl-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (18). To a solution of 6^A,6^D-di-*O*-(prop-2-hydroxymethylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**16**) (857 mg, 0.34 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (440 mg, 1.04 mmol) and the corresponding mixture was kept stirring at room temperature for 4 h. Reaction was quenched by addition of Et_2O (50 mL) and a mixture of satd aq $NaHCO_3$–5% $Na_2S_2O_3$ (75 mL) and the biphasic mixture was kept stirring at room temperature for further 2 h. The organic layer was then separated, dried over Na_2SO_4, filtered and the filtrate was concentrated to dryness and purified by column chromatography (1:5 EtOAc–pentane → 1:3.5 EtOAc–pentane) to afford pure **18** as a white foam (536 mg, 65%).

$[\alpha]_D^{25}$ +46 (*c* 0.8, CH_2Cl_2); IR (ν_{max}): 3061, 3028, 2922, 2869, 1726, 1604, 1495, 1452, 1352, 1207, 1093, 1027, 734, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (br s, 1H, CHO), 7.22–6.91 (m, 80H, Ar–H), 5.45–5.44 (m, 4H, CH_2, H-1), 5.19–5.13 (d, 3H, $J_{H,H}$=11.4 Hz, CH), 4.89–4.86 (m, 3H), 4.78–4.59 (m, 10H), 4.49–3.74 (m, 37H), 3.62–3.12 (m, 21H), 2.08 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9 (CO), 139.8, 139.5, 139.4, 138.9, 138.6, 138.4, 138.0, 137.9 (C_{ipso}), 129.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.2, 127.0, 126.7, 126.6, 126.0 (CH_{Ar}), 100.0, 99.8, 99.7, 98.3, 97.7 (C-1), 82.9, 84.4, 82.2, 81.7, 81.5, 81.4, 81.1, 81.0, 80.7, 80.3, 79.9, 79.7, 79.4, 79.3, 77.8, 76.5, 76.3, 73.7, 73.6, 73.5, 73.1, 73.0, 72.5, 72.4, 72.2, 72.1, 72.0, 71.9, 71.6, 70.2, 69.7, 69.4, 69.3, 69.2, 69.1, 65.9, 65.6, 52.63 (CH); MS calcd for $C_{152}H_{160}O_{31}Na$: 2504.1, found: 2504.4.

4.1.10. 6^A,6^D-Di-*O*-(prop-2-formyl-1,3-dienyl)-α-cyclodextrin (19). Compound **18** (0.48 g, 0.19 mmol) was dissolved in 1:1 MeOH–EtOAc (20 mL). Then Pd–C (345 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **19** as a foam (0.18 g, 90%). $[\alpha]_D^{25}$ +104 (*c* 0.6, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.18–5.15, 5.09–5.08 (m, 6H, H-1$^{A–F}$), 4.03–3.59 (m, 36H, H-2–H6$^{A–F}$), 3.39 (m, 4H, 2CH_2). 2.85 (m, 1H, C*H*–CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.0, 101.8, 101.3, 101.2, 100.7, 100.3 (C-1), 834.0, 82.7, 82.4, 82.3, 82.0, 81.8, 81.6, 81.4, 80.5, 73.9, 73.8, 73.5, 72.7, 72.0, 71.7, 71.4, 70.7, 66.5, 66.3, 66.2, 66.1, 60.6, 60.1, 59.5, 59.2, 59.0 52.9 (*C*H–CHO); MS calcd for $C_{40}H_{64}O_{31}Na$: 1063.3, found: 1062.9.

4.1.11. 6^A,6^D-Di-*O*-(prop-2-carboxy-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (20). A solution of 6^A,6^D-di-*O*-(prop-2-hydroxymethylidene-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin **16** (0.79 g, 0.32 mmol) and Dess–Martin periodinane reagent (0.40 g, 0.95 mmol) in CH_2Cl_2 (35 mL) was kept at room temperature overnight and then quenched by addition of Et_2O (100 mL) and a satd aq $NaHCO_3$ containing 5% of $Na_2S_2O_3$ (75 mL) and kept stirring at room temperature for 2 h. Then, the organic layer was separated, dried over $MgSO_4$ and concentrated to

dryness. To a solution of the residue in 2-methylbut-2-ene (8 mL), ^{t}BuOH (21 mL) and THF (9 mL) was added a solution of $NaClO_2$ (0.65 g, 7.2 mmol) and NaH_2PO_4 (0.60 g, 5.0 mmol) in water (5 mL) and the corresponding mixture was kept stirring at room temperature overnight. The reaction was quenched by addition of 1 M HCl (24 mL) and the product was extracted with EtOAc (3×50 mL). The organic phase was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness and purified by flash chromatography (1:4 EtOAc–pentane → 1:2 EtOAc–pentane containing 1% HCOOH) to give compound **20** as a syrup (0.45 g, 56%, two steps). $[\alpha]_D^{25}$ +41 (*c* 0.5, CH_2Cl_2); IR (ν_{max}): 3061, 3028, 2923, 1774, 1495, 1452, 1352, 1027, 734, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–6.91 (m, 80H, Ar–H), 5.48–5.41 (d, 4H, $J_{H,H}$=10.0 Hz, CH), 5.16 (d, 1H, $J_{H,H}$=10.0 Hz, CH), 5.14 (d, 1H, $J_{H,H}$=10.0 Hz, CH) 4.88 (d, 1H, $J_{H,H}$=10.4 Hz, CH), 4.77–4.58 (m, 13H), 4.45–4.12 (m, 21H), 4.07–3.73 (m, 17H), 3.62–3.17 (m, 19H), 2.38 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (CO), 139.7, 139.4, 138.9, 138.7, 138.8, 138.5, 138.3, 138.2, 138.1, 137.9, 137.8 (C_{ipso}), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 126.9, 126.6, 126.5, 126.0 (C_{Ar}), 99.9, 99.8, 99.7, 99.6, 98.1, 97.6 (C-1), 82.1, 82.0, 81.7, 81.3, 81.2, 81.0, 80.7, 80.3, 79.9, 79.5, 79.3, 79.0, 78.9, 77.8, 77.4, 76.7, 76.2, 73.6, 73.5, 73.4, 73.2, 72.9, 72.3, 72.2, 72.0, 71.9, 71.5, 69.8, 69.5, 69.4, 69.3, 69.0. 68.9, 68.5, 67.3, 66.5, 45.6 (*C*H–COOH); MS calcd for $C_{152}H_{160}O_{32}Na$: 2520.1, found: 2520.1.

4.1.12. 6^A,6^D-Di-*O*-(prop-2-carboxy-1,3-dienyl)-α-cyclodextrin (21). Compound **20** (0.43 g, 0.17 mmol) was dissolved in 1:1 MeOH–EtOAc (60 mL). Then Pd–C (144 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **21** as a foam (0.16 g, 90%). $[\alpha]_D^{25}$ +109 (*c* 0.4, H_2O); IR (ν_{max}): 3376, 2929, 1724, 1374, 1037, 950, 708 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 5.13–4.99 (m, 6H, H-1$^{A–F}$, 4.19–3.59 (m, 36H, H-2–H6$^{A–F}$), 3.35 (m, 4H, 2CH_2), 2.84 (m, 1H, C*H*–COOH); ^{13}C NMR (100 MHz, D_2O): δ 175.7 (COOH), 101.7, 101.5, 101.1, 101.0, 100.0 (C-1), 82.0, 81.8, 81.4, 81.0, 80.3, 80.0, 74.3, 74.2, 72.7, 72.5, 72.4, 72.3, 72.0, 71.9, 71.8, 71.7, 71.6, 71.2, 70.8, 70.0, 69.4, 68.1. 60.8, 60.6, 60.1 (C2–C6$^{A–F}$), 46.6 (*C*H–COOH); MS calcd for $C_{40}H_{64}O_{32}Na$: 1079.3, found: 1078.5.

4.1.13. 6^A,6^D-Di-*O*-(prop-2-methoxycarbonyl-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (22). A solution of 6^A,6^D-di-*O*-(prop-2-carboxylic acid-1,3-dienyl)-hexadeca-*O*-benzyl-α-cyclodextrin (**20**) (0.8 g, 0.32 mmol) in $SOCl_2$ was kept at room temperature for 1 h. Then $SOCl_2$ was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (4 mL). Triethylamine (0.1 mL) was added and the solution was cooled down to 0 °C, when MeOH (4 mL) was added dropwise. After warming up to room temperature, the solution was kept at that temperature for 3 h. Removal of the solvents and column chromatography (pentane → 1:3 EtOAc–pentane) afforded **22** as a white foam (0.72 g, 89%). $[\alpha]_D^{25}$ +42 (*c* 0.6, CH_2Cl_2); IR (ν_{max}): 3062, 3028, 2922, 2869, 1739, 1605, 1496, 1453, 1352, 1039, 1027, 909, 755, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$): δ 7.23–6.89 (m, 80H, Ar–H), 5.50–5.43 (dd, 4H, $J_{1,2}$=3.6 Hz, $J_{H,H}$=10.8 Hz, H-1, CH), 5.18 (d, 1H, $J_{H,H}$=9.8 Hz, CH), 5.15 (d, 1H, $J_{H,H}$=9.8 Hz, CH), 4.89 (d, 1H, $J_{H,H}$=10.0 Hz, CH), 4.88 (d, 1H, $J_{H,H}$=10.4 Hz, CH), 4.77–4.59 (m, 12 H), 4.52–4.15 (m, 22H), 4.12–3.72 (m, 18 H), 3.66–3.18 (m, 18H), 3.51 (s, 3H, OMe), 2.38 (m, 1H, CH); ^{13}C NMR (100 MHz, $CHCl_3$): δ 171.9 (CO), 139.8, 139.4, 138.9, 138.8, 138.6, 138.l4, 138.3, 138.2, 138.0, 137.8 (C_{ipso}), 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.2, 126.8, 126.3 (CH_{Ar}), 100.0, 99.9, 99.7, 99.6, 98.1, 97.6 (C-1), 82.1, 82.0, 81.7, 81.3, 81.2, 81.1, 80.8, 80.7, 80.3, 79.9, 79.6, 79.4, 79.1, 78.9, 77.9, 77.8, 76.8, 76.3, 73.7, 73.5, 73.4, 73.1, 72.9, 72.4, 72.3, 72.2, 72.0, 71.5, 69.9, 69.6, 69.5, 69.4, 69.1, 68.9, 67.8, 67.0, 51.7 (OMe), 45.6 (CH); MS calcd for $C_{153}H_{162}O_{32}Na$: 2534.1, found: 2533.8.

4.1.14. 6^A,6^D-Di-*O*-(prop-2-methoxycarbonyl-1,3-dienyl)-α-cyclodextrin (23). Compound **22** (0.52 g, 0.21 mmol) was dissolved in 1:1 MeOH–EtOAc (50 mL). Then $Pd(OH)_2$ (150 mg) and TFA (cat.) were added and the mixture was kept stirring overnight under hydrogen atmosphere. Filtration and removal of the solvents gave **23** as a foam (0.22 g, quant). $[\alpha]_D^{25}$ +98 (*c* 0.7, H_2O); IR (ν_{max}): 3366, 2928, 1728, 1677, 950 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.89–5.0 (m, 11H, OH), 4.88, 4.78–4.76 (m, 6H, H-1), 4.64–4.10 (m, 5H, OH), 3.96–3.89 (m, 4H), 3.81–3.23 (m, 34H), 3.61 (s, 3H; OMe), 3.07–3.01 (m, 2H), 2.63 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2 (CO), 102.1, 101.9, 101.4, 101.2, 100.6, 100.2 (C-1), 83.0, 82.9, 81.8, 81.3, 81.2, 80.3, 74.5, 74.4, 74.5, 74.4, 73.0, 72.8, 72.4, 72.2, 72.0, 71.6, 71.4, 71.3, 71.2, 70.1, 69.1, 68.4, 67.8, 60.3, 59.8, 59.5, 59.4, 59.2, 51.6 (OMe), 46.5 (CH); MS calcd for $C_{41}H_{66}O_{32}Na$: 1093.3, found: 1092.7.

4.2. Procedure for determining the rate of oxidation

Each assay was performed on 8–16 samples (2 mL each) of the appropriate substrate at different concentrations in 0.1 M phosphate buffer. To each sample was added 1 mg of the corresponding cyclodextrin or nothing (as control) and 64 mM H_2O_2. The reactions were followed at 25 °C using UV absorption at 400 nm and typically monitored for 3 h. Velocities were determined as the slope of the progress curve of each reaction. Uncatalysed velocities were obtained directly from the control samples. Catalysed velocities were calculated by subtracting the uncatalysed rate from the total rate of the appropriate cyclodextrin containing sample. The catalysed velocities were used to construct Hanes plots ([*S*]/*V* vs [*S*]) to ensure that the reaction followed Michaelis–Menten kinetics. In that case K_m and V_{max} were determined using least square non-linear regression fitting to the V_{max} vs *S* curve. k_{cat} was calculated as V_{max}/[cyclodextrin]. k_{uncat} was determined as the slope from a plot of V_{uncat} vs [*S*]. The following extinction coefficients (25 °C, pH 7) and wavelengths were determined and used: 3-aminophenoxaz-2-one, 0.42 mM^{-1} cm^{-1} at 400 nm.

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