DOI: 10.1002/ejoc.200600762

Synthesis of Some Trifluoromethylated Cyclodextrin Derivatives and Analysis of Their Properties as Artificial Glycosidases and Oxidases

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Keywords: Enzyme catalysis / Enzyme models / Supramolecular chemistry / Oxidation / Hydrolysis

Cyclodextrin derivatives containing trifluoromethyl groups at C6 of the A and D rings were synthesized for the purpose of creating artificial enzymes. The compounds were synthesized by perbenzylation of β-cyclodextrin followed by selective A,D-debenzylation according to Sinaÿ. Subsequent oxidation to dialdehyde with Dess–Martin periodinane followed by addition of CF_3 by using Arduengo carbene and $TMSCF_3$ led to the C^6-bistrifluoromethylated alcohols. These were either deprotected by hydrogenolysis or subjected to another round of oxidation to provide the corresponding ketones that were deprotected. The trifluoromethylated alcohols were found to be weak artificial enzymes catalysing hydrolysis of nitrophenyl glycosides at neutral pH with a k_{cat}/k_{uncat} of up to 56. It is proposed that this catalysis is analogues to the catalysis performed by related cyanohydrins. The trifluoro ketones were likewise weak articial enzymes catalysing oxidation of amines to nitro derivatives or alcohols to ketones with a k_{cat}/k_{uncat} of up to 133.

Introduction

Supramolecular chemistry is a science that attempts to understand and use chemistry beyond the molecule.[1] A fascinating research area is aimed at using supramolecular chemistry to achieve catalysis thereby creating what is *defacto* artificial enzymes.[2–26] Cyclodextrins are very attractive supramolecular hosts to be included in artificial enzymes due to their good binding properties in water and water solubility.[4,9]

Our group has recently reported some of the first examples of artificial glycosidases.[27,28] The most effective type discovered was cyclodextrin derivatives, such as **1** (Figure 1), containing a cyanohydrin group at the primary rim.[29] For these catalysts a k_{cat}/k_{uncat} of up to 8000 was obtained for the hydrolysis of aryl glycosides.[30] Based on structure-activity analysis of a series of derivatives it was found that both the cyano group and the cyanohydrin OH were essential for catalysis indicating that the acidity of this group was essential. It is therefore suggested that **1** works by acid catalysis as shown in Figure 1 with the cyano group working as an electron-withdrawing group that increases the alcohol acidity. However, the cyanohydrin moiety can be unstable[31] and substitution of the cyano function with an alternative electron withdrawing groups was potentially desirable. This led to the idea of preparing the trifluoromethyl analogue **2** since the CF_3 group has a σ_I of 0.41 while CN have a σ_I of 0.56.[32]

It has also been found in our group that cyclodextrin ketones catalyse various oxidation reactions such as epoxidation,[33,34] amine[35] and alcohol oxidation.[36] The best catalyst contained a bridged ketone, while diketones, such as **3**, were less effective or non-functional. However, inclusion of a CF_3 group close to the ketone, a modification known to enhance the catalytic efficiency of ketones,[37] could improve these compounds, giving us the idea to prepare **4**.

In this paper we address the synthesis of the two synthetically related targets **2** and **4** and evaluate their catalytic powers in glycoside hydrolysis and oxidation reactions, respectively.

Results and Discussion

Synthesis

The synthesis of **2** and **4** was carried out from the nonadecabenzylated diol **6** readily available from β-cyclodextrin in two steps (Scheme 1):[38–40] The β-cyclodextrin is perbenzylated with NaH and benzyl chloride giving the perbenzylated cyclodextrin **5** in 85% yield. Selective debenzylation with DIBAL (0.2 M) and 4-Å molecular sieves at 25 °C and 18 h gives the diol **6** in 81% yield. Oxidation of this diol with Dess–Martin periodinane gives the dialdehyde **7** in quantitative yield.

There is no doubt that trifluoromethylation of a complex molecule as **7** is no trivial reaction. Though a number of methods for the trifluoromethylation of aldehydes have been reported,[41–43] they have typically been applied to much less complex compounds. These reactions rely on gen-

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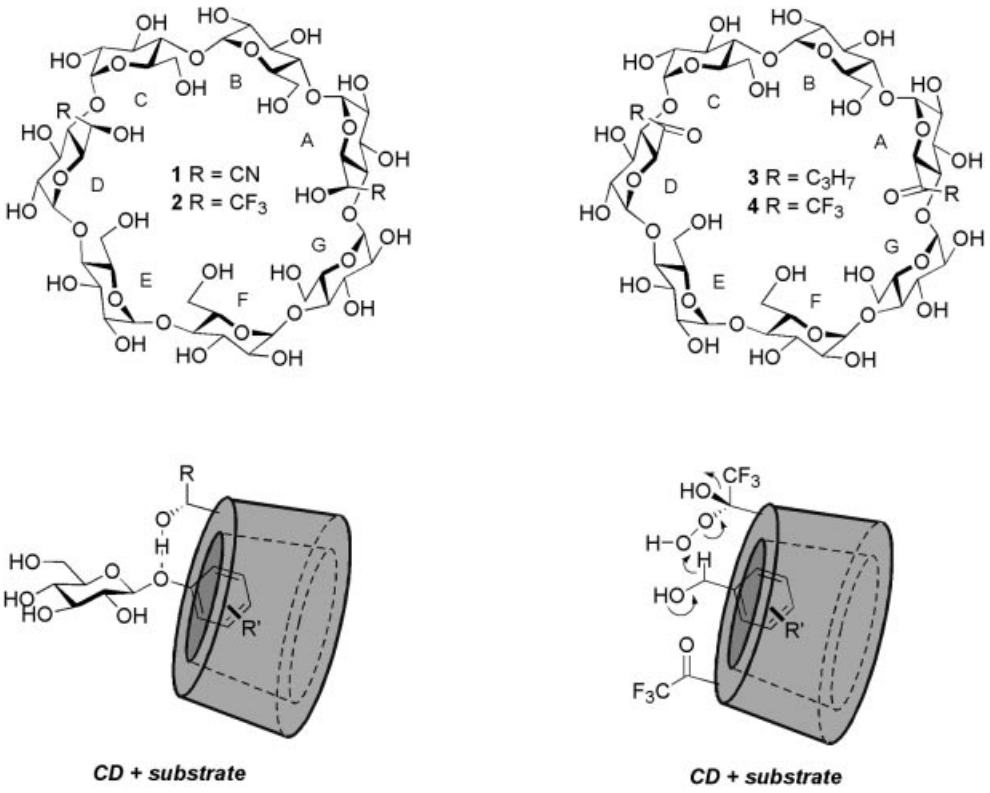
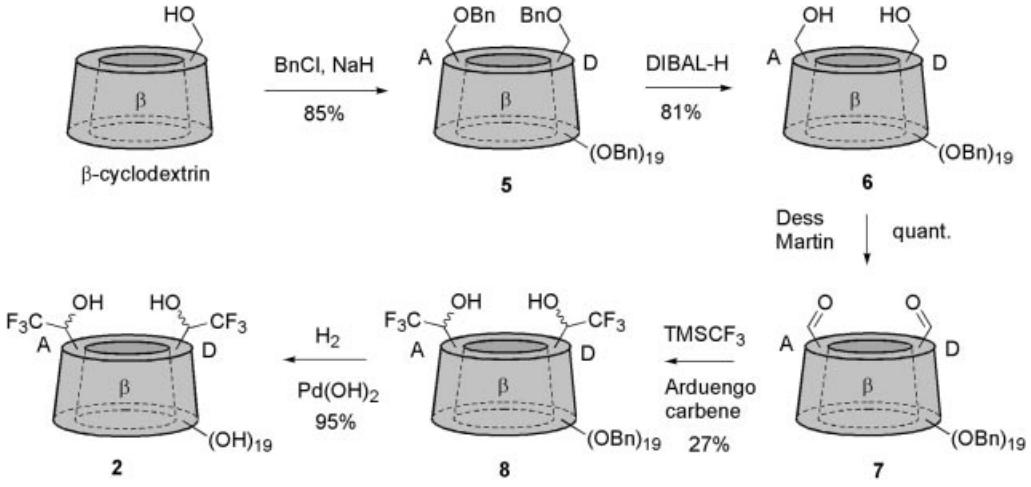


Figure 1. The structure of modified cyclodextrins **1**–**4** and the intended mode of catalysis of **2**, on glycoside hydrolysis and **4** on alcohol oxidation.



Scheme 1. Synthesis of fluorinated derivatives **2** and **8**. The 19 unmodified or benzylated hydroxy groups are distributed on both sides of the cyclodextrin ring.

erating a CF_3 equivalent that adds to the aldehyde and the conditions for generating it may be harsh both for the substrate and the reagent itself. Reaction of **7** with Bu_4NF/$TMSCF_3$ did not give any trifluoromethylated product (Scheme 1). However, reaction of **7** with $TMSCF_3$ and Arduengo carbene[44] (30 mol-%, Figure 2) as a catalyst gave the desired compound **8** in 27% yield. We believe the milder condition of the latter reaction is the basis for its relative success here.

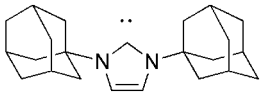
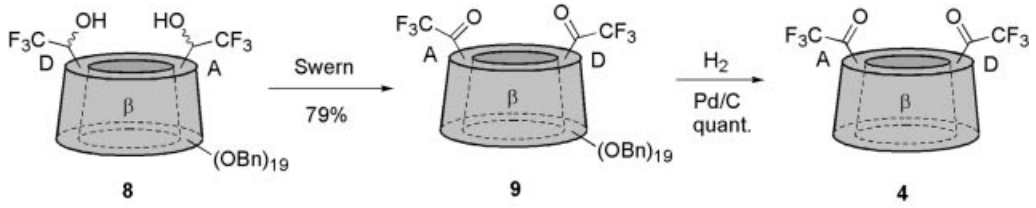


Figure 2. The Arduengo carbene.

Compound **8** is a mixture of diastereoisomers (at C-6A and C-6D) that can be partially separated into isomers by flash chromatography. However due to the low yield of pure



Scheme 2. Synthesis of **4**. The 19 benzylated hydroxy groups are distributed on both sides of the cyclodextrin ring.

isomer and the problem of actually ensuring isomeric purity the combined isomeric fractions were used in the further chemistry. Hydrogenolysis of the compound using Pd-$(OH)_2$/C in EtOAc/MeOH gave the unprotected diol **2** in 95% yield.

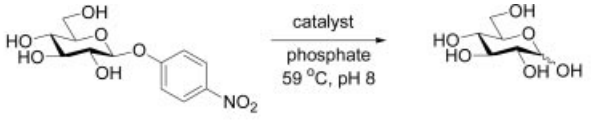
Alternatively, oxidation of **8** to the diketone using Swern oxidation gave **9** in 79% yield (Scheme 2). Again, hydrogenolysis of the benzyl groups with Pd/C in EtOAc/MeOH gave the target **4** in quantitative yield.

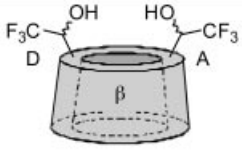
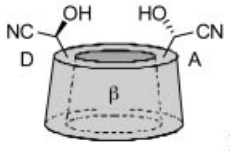
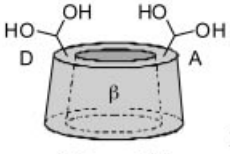
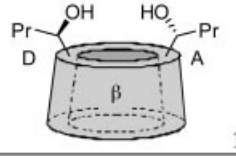
Glycoside Hydrolysis

The glycosidase activity of **2** was investigated by monitoring their influence on the hydrolysis of various 4-nitrophenyl glycopyranosides at pH 8 and 59 °C. These reactions are monitored by following the increase in absorption at 400 nm. In Table 1 is seen the kinetic parameters for the hydrolysis of 4-nitrophenyl-β-D-glucopyranoside as catalyzed by **2** in comparison to analogues **10**–**12** previously made.[30] Compound **2** catalyze the hydrolysis in an enzyme-like manner: The reaction follows Michaelis–Menten kinetics with a K_m of 3–6 mM and give a modest rate increase of up to 56 times at high phosphate concentration. (Table 1)

Since native cyclodextrin or propyl-analogue **12** are not catalysts the electron-withdrawing CF_3 group favors catalysis, and the most likely way this can occur is intuitively by an increase in the acidity of the alcohol group allowing it to act as a better general acid catalyst. However when **2** is compared with dicyano derivative **10** and the dialdehyde dihydrate **11** that both catalyse this reaction (Table 1), we see that while k_{cat} decrease in the order **10** >> **11** > **2** the electron-withdrawing power of the substituents do not fol-

Table 1. Kinetic parameters for hydrolysis of 4-nitrophenyl β-D-glucopyranoside at pH 8.0 and 59 °C as catalysed **2** and other cyclodextrin derivatives.



Catalyst	Phosphate (mM)	k_{cat} ($\times 10^{-7}$ s^{-1})	K_m	k_{cat}/k_{uncat}
 **2**	50	1.98±0.15	2.9±0.8	13
	500	12.1±2.6	5.9±3.0	56
 **10**	50	587±73	10±4	3116
	500	1420±70	6.3±1.3	6396
 **11**	50	13±2	4.5±2.5	55
 **12**	50	no catalysis	-	-

low this order, but rather **10** ($\sigma_I = 0.56$) > **2** ($\sigma_I = 0.41$) > **11** ($\sigma_I = 0.25$). Indeed the aldehyde hydrate **11** is a 6 times better catalyst despite the lower inductive strength of OH than CF_3. This may be partly a consequence of **2** being a mixture of diastereomers where some of the isomers, that has the protonation OH pointing towards the exterior, are inactive.

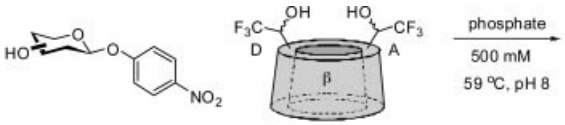
The nitrophenyl α-glucopyranoside, α-galactopyranoside and α-mannopyranoside were also investigated as substrates for **2** (Table 2). The α-substrates were slightly better substrates giving 2 fold higher k_{cat} values and up to 90 fold rate increase.

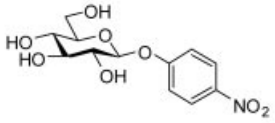
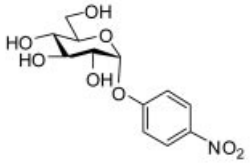
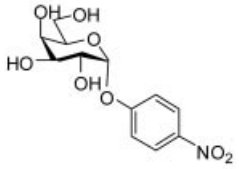
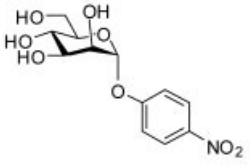
Amine and Alcohol Oxidation

The influence of **4** on the oxidation of amines and alcohols by hydrogen peroxide was investigated by following these reactions by UV at the appropriate wavelength.[35,36] Compound **4** displayed Michaelis–Menten catalysis, which means that catalysis is preceded by binding, and that the cavity must be involved in the process. Therefore the compound is probably functioning as intended as outlined in Figure 1. The compound gives a k_{cat}/k_{uncat} of 89–133 (Table 3), which means that the oxidations catalysed by **4** is about 100 times faster inside the cavity than outside. This is a relative small value compared to the bridged ketones that can afford rate increases over 1000 in these reactions.[35,36] However since **3** displays no catalysis the inductive influence of the CF_3 group does appear to have the intended effect. It also indicate that in **3** and **4**, the ketone's position close to the rim of the cyclodextrin, is far from ideal for interaction with the substrate.

In summary we have prepared two new cyclodextrin derivatives containing the trifluoromethyl group: the diol **2** and diketone **4**. The yield of the trifluoromethylation step is modest but it is doubtful whether it can be improved much since the steric hindrance at the 6-positions is considerable. Both compounds were found to act as artificial enzymes; the diol **2** increased the rate of hydrolysis of nitrophenyl glycosides with 14–90 fold while the diketone **4** increased the rate of hydrogen peroxide oxidation of alcohols and amines up to 89–133 times.

Table 2. Kinetic parameters for the **2** catalysed hydrolysis of various glycosides at 500 mM phosphate, pH 8.0 and 59 °C.

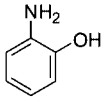
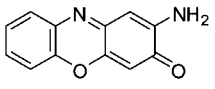
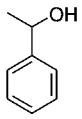
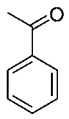


Substrate	k_{cat} ($\times 10^{-7}$ s^{-1})	K_m (mM)	k_{cat}/k_{uncat}
	12.1±2.6	5.9±3.0	56
	22.9±2.1	4.0±1.0	90
	18.4±3.4	8.2±3.2	69
	8.84±1.01	3.3±0.7	14

Experimental Section

All reagents were used as purchased without further purification. TLC was performed on Merck Silica Gel 60 F_{254} plates with detection by charring with cerium sulfate and ammonium heptamolybdate, and by UV light when applicable. Flash column chromatography was performed on Silica Gel Fluka (230–400 mesh) as stationary phase. Optical rotations were recorded on a Perkin–Elmer

Table 3. Kinetic parameters for the **4**-catalysed oxidation of an amine and an alcohol by H_2O_2 at pH 7.0 and 25 °C.

Substrate	k_{cat}/k_{uncat}	k_{cat} ($\times 10^6$ s^{-1})	K_m (mM)	Product
	89	605±145	10.7±1.1	
	133	5.89±0.76	6.6±2.6	

241 polarimeter at room temperature. IR spectra were recorded on a Perkin–Elmer FT-IR PARAGON 1000. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer. Chemical shifts are given in ppm and referenced to internal $SiMe_4$ (δ_H, δ_C = 0.00). *J* values are given in Hz. MALDI-TOF Mass spectra were recorded on a Bruker Daltonics mass spectrometer (Bruker) using a α-cyano-4-hydroxycinnamic acid (HCCA) matrix.

Undodecakis-*O*-benzyl-β-cyclodextrin (5): β-Cyclodextrin (3.76 g, 3.31 mmol) was dissolved in DMSO (100 mL) under N_2. NaH (5.46 g, 55%, 125 mmol) was added and stirred for 30 min. Benzyl chloride (18.7 g, 147.7 mmol) was added at 0 °C and left stirring overnight at room temperature. Water (80 mL) was added slowly, and the mixture was extracted with EtOAc (5 × 100 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (EtOAc/pentane, 1:5) to give 9.59 g of compound **5**[45] (95% yield) as a colorless foam. ^{1}H NMR ($CDCl_3$ 400 MHz): δ_H = 7.30–7.15 (m, 105 H, Ph), 5.32 (d, *J* = 3.2 Hz, 7 H, 1-H), 5.18 (d, *J* = 9.8 Hz, 7 H, CH_2Ph), 4.88 (d, *J* = 9.8 Hz, 7 H, CH_2Ph), 4.62 (d, 7 H, CH_2Ph), 4.58 (d, 7 H, CH_2Ph), 4.52 (d, 7 H, CH_2Ph), 4.46 (d, 7 H, CH_2Ph), 4.20–4.06 (m, 28 H, 3-H, 5-H, 6-H), 3.68 (d, 7 H, *J* = 10.3 Hz, 4-H), 3.60 (dd, 7 H, 2-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 138.17–137.09 (C-*ipso*), 127.07–125.86 (C-Ph), 97.37 (C-1), 79.83, 77.68 (O*C*H_2Ph), 74.37, 72.19 (C-2), 72.19 (C-4), 71.56 (C-3), 70.41 (C-6), 68.21 (C-5).

$2^{A–G}$,$3^{A–G}$,6^B,6^C,6^E,6^F,6^G-Nonadecakis-*O*-benzyl-β-cyclodextrin (6):[38–40] To a solution of compound **5** (7.56 g, 2.50 mmol) and 4-Å molecular sieves (53 g) in toluene (350 mL), stirred under N_2 for 1 h, was added DIBAL-H (1.5 M) (80 mL, 120 mmol) dropwise, and left stirring overnight. The reaction was monitored by TLC (EtOAc/pentane, 1:3) until no starting material (R_f = 0.55) and no monool (R_f = 0.26) were observed, and only the diol occurred (R_f = 0.13). The mixture was cooled to 0 °C before slowly adding water (300 mL), and stirred for 30 min. EtOAc (300 mL) was added and the mixture was filtered through Celite, washed with EtOAc (5 × 50 mL). The combined organic phases were washed with brine (3 × 50 mL), and dried with $MgSO_4$. The residue was concentrated and purified by flash chromatography (EtOAc/pentane, 1:4) to give compound **6** (6.12 g, 86% yield) as a colorless foam. ^{1}H NMR ($CDCl_3$ 400 MHz): δ_H = 7.32–7.00 (m, 95 H, Ph), 5.60 (dd, 2 H), 5.24 (m, 4 H), 5.06 (m, 5 H), 4.95–4.67 (m, 12 H), 4.62–4.43 (m, 23 H), 4.11–3.90 (m, 28 H), 3.83–3.43 (m, 16 H), 2.78 (br. s, 1 H, O*H*), 2.68 (br. s, 1 H, O*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 139.76, 139.62, 139.42, 139.02, 138.85, 138.56, 138.42, 138.35, 138.23, 138.18, 138.06 (C_{ipso}), 128.12, 128.03, 128.01, 127.94, 127.91, 127.87, 127.85, 127.82, 127.80, 127.76, 127.74, 127.55, 127.53, 127.51, 127.49, 127.33, 127.21, 127.09, 127.01, 126.75, 126.63, 126.52 (C_{Ph}), 99.67, 99.63, 98.61, 98.58, 98.53, 98.12, 97.92 (C-1), 82.12, 81.82, 81.75, 81.70, 81.61, 81.49, 81.01, 80.85, 79.76, 76.25, 76.08, 75.81, 73.74, 73.02, 71.88, 69.72 (CH, CH_2), 61.86 (*C*H_2-OH).

$2^{A–G}$,$3^{A–G}$,6^B,6^C,6^E,6,6^G-Nonadecakis-*O*-benzyl-6^A,6^D-dioxo-β-cyclodextrin (7): Dess–Martin reagent was added to a solution of compound **6** (4.42 g, 1.55 mmol) in DCM (200 mL), at 25 °C, under N_2. After 2 h, Et_2O (200 mL), and satd. aqueous $NaHCO_3$ (150 mL) containing $Na_2S_2O_3$ (6.5 g) was added and stirred for 1 h. The residue was diluted with Et_2O (150 mL), and washed with satd. $NaHCO_3$ (4 × 40 mL) and water (3 × 40 mL). The organic phases were dried with $MgSO_4$ and concentrated to give compound **6**,[46] with same R_f as the starting material, as a colorless foam in a quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 9.42 (s, 2 H, C*H*O), 7.22–7.00 (m, 95 H, Ph), 5.18–4.98 (m, 10 H), 4.91–4.80 (m, 2 H), 4.77–4.61 (m, 7 H), 4.58–4.48 (m, 5 H), 4.42–4.21 (m, 24 H), 3.99–3.62 (m, 23 H), 3.56–3.24 (m, 12 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 139.75, 139.68, 139.63, 139.02, 138.81, 138.73, 138.58, 138.46, 138.40, 138.38 (C-*ipso*), 128.38, 128.35, 128.31, 128.29, 128.27, 128.24, 128.21, 128.18, 128.15, 128.03, 127.94, 127.88, 127.36, 127.33, 127.29, 127.24, 127.22, 127.19, 127.14, 127.12, 127.08, 127.05 (C-Ph), 99.12, 99.04, 98.95, 98.90, 98.84, 98.74, 98.42 (C-1), 82.31, 82.12, 81.98, 79.89, 79.76, 79.34, 79.10, 78.84, 78.53, 78.11, 76.53, 75.91, 75.23, 73.87, 73.68, 73.02, 72.83, 71.98, 69.23 (CH, CH_2).

6^A,6^D-Di-*C*-trifluoromethyl-$2^{A–G}$,$3^{A–G}$,6^B,6^C,6^E,6^F,6^G-nonadecakis-*O*-benzyl-β-cyclodextrin (8): Nonadecabenzylated β-cyclodextrindicarbaldehyde **7** (3 g, 1.06 mmol) was dissolved in dry DMF (6 mL) under nitrogen atmosphere. Arduengo carbene (107 mg, 0.317 mmol, 0.3 equiv.) and $TMSCF_3$ (3.12 mL, 21.1 mmol, 20 equiv.) were added, yielding a clear orange solution which was left stirring at room temperature under nitrogen atmosphere for 1.5 hours. The reaction progress was monitored by TLC (silica, eluent EtOAc/pentane, 1:3). Upon completion, water (50 mL) was added and the reaction was extracted with diethyl ether (5 × 40 mL). The combined organic phases were washed with satd. aq. $NaHCO_3$ (3 × 60 mL), brine (4 × 50 mL) and water (9 × 70 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo, yielding 3.38 g crude silylated product as a pale yellow foam. The silyl bonds were hydrolyzed by dissolving the crude product in a mixture of 0.50% TFA in EtOAc/MeOH (2:3, 50 mL). The solution was stirred vigorously at room temperature for 10 min and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent gradient, EtOAc/pentane, 1:7 → 1:0) to afford the desired product (847 mg, 27%) as a colorless solid. Two major product spots were seen on the TLC plate and the shorter-running enantiomer mixture was isolated and analyzed: $[\alpha]_D$ = +35.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3424, 3028, 2925, 2866, 1496, 1453, 1357, 1095, 1040, 733, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz): δ_H = 7.26–6.86 (m, 95 H, H-Ph), 5.64 (d, 0.1 H, $J_{1,2}$ = 3.6 Hz, 1-H), 5.40 (d, 0.1 H, $J_{1,2}$ = 4.0 Hz, 1-H), 5.34 (d, 0.3 H, $J_{1,2}$ = 4.0 Hz, 1-H), 5.26 (m, 0.1 H, 1-H), 5.20–4.75 (m, 9.7 H), 5.12 (d, *J* = 3.6 Hz), 5.08 (d, *J* = 3.6 Hz), 4.86 (d, *J* = 3.6 Hz), 4.78 (dd, *J* = 3.2 Hz, *J* = 7.6 Hz), 4.75–4.09 (m, 40 H), 4.01–3.57 (m, 22.6 H), 3.57–3.27 (m, 11.5 H), 3.24 (dd, 0.7 H, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.6 Hz, 2-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 139.6–137.4 (C-*ipso*), 128.6–126.7 (CH-Ph), 100.1, 99.4, 99.3, 99.1, 98.9, 98.7, 98.4, 98.1, 97.8, 97.5 (10 C1), 83.1, 81.2, 81.1, 80.9, 80.7, 80.4, 80.1, 79.6, 79.4, 79.0, 78.8, 78.6, 78.3, 76.6, 76.5, 76.2, 76.0, 75.7, 75.4, 74.4, 74.0, 73.7, 73.6, 73.5, 73.4, 73.3, 73.2, 7.1, 73.0, 72.9, 72.7, 72.6, 72.5, 72.3, 72.1, 71.7, 71.6, 70.9, 70.4, 69.9, 69.5, 69.3, 69.0, 68.4, 67.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ_F: –71.5 (d, $^3J_{F,H-6}$ = 6.8 Hz), –72.0 (br. s), –72.4 (br. s), –73.9 (d, $^3J_{F,H-6}$ = 6.8 Hz), –74.0 (d, $^3J_{F,H-6}$ = 6.4 Hz), –74.5 (br. s), –74.7 (d, $^3J_{F,H-6}$ = 6.8 Hz), –75.0 (d, $^3J_{F,H-6}$ = 8.3 Hz). MALDI-TOF-MS, *m*/*z* calcd. for $C_{177}H_{182}F_6O_{35}Na$ 3004.2263, found 3004.6748.

6^A,6^D-Di-*C*-trifluoromethyl-β-cyclodextrin (2): Nonadecabenzylated di-trifluoromethylated β-cyclodextrin **8** (216 mg, 0.072 mmol) was dissolved in EtOAc/MeOH (1:1, 15 mL). $Pd(OH)_2$ (20%, 200 mg) and TFA (cat.) were added and the mixture was stirred at room temperature under hydrogen atmosphere until completion of the reaction. Filtration through Celite and evaporation of the solvent gave the desired product **2** (87 mg, 95%) as a colorless powder. $[\alpha]_D$ = +97.6 (*c* = 0.68, D_2O). IR (KBr): $\tilde{\nu}$ = 3404, 2934, 1678, 1426, 1369, 1284, 1156, 1080, 1030, 945, 701, 578 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ_H = 5.00–4.95 (m, 7 H, 1-H), 4.04–4.00 [m, 2 H, 6-H(A,D)], 3.92–3.39 (m, 38 H). ^{19}F NMR (377 MHz, D_2O):

δ_F = –71.9 (d, $^3J_{F,H-6}$ = 6.8 Hz), –75.9 (d, $^3J_{F,H-6}$ = 6.4 Hz), –76.0 (s). MALDI-TOF-MS, *m*/*z* calcd. for $C_{44}H_{68}F_6O_{35}Na$ 1293.3343, found 1292.7385.

6^A,6^D-Di-*C*-trifluoromethyl-6^A,6^D-dioxo-2$^{A–G}$,3$^{A–G}$,6^B,6^C,6^E,6^F,6^G-nonadecakis-*O*-benzyl-β-cyclodextrin (9): A solution of oxalyl chloride (0.015 mL, 0.174 mmol) in DCM (2 mL) was cooled down to –78 °C under N_2. DMSO (0.050 mL, 0.704 mmol) in DCM (1.5 mL) was added dropwise over 5 min; the mixture was stirred for 20 min. Compound **8** (0.222 g, 0.075 mmol) was dissolved in DCM (8 mL) and added dropwise over 15 min. After stirring for 3 h, TEA (0.106 mL, 0.765 mmol) was added and left for 30 min. The reaction mixture was warmed to room temperature and water (10 mL) was added. The water phase was extracted with DCM (4 × 10 mL), the combined organic phases were washed with brine (10 mL), dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (EtOAc/pentane, 1:5) to give 175 mg of compound **9** (79% yield) as a colorless foam. ^{1}H NMR ($CDCl_3$ 400 MHz): δ_H = 7.21–7.00 (m, 95 H), 5.42–4.24 (m, 45 H), 4.21–3.78 (m, 23 H), 3.63–3.22, (m, 13 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 192.26 (C=O), 140.03, 139.98, 139.92, 139.89, 139.86, 138.77, 138.54, 138.42, 138.40, 138.39, 138.37 (C-*ipso*), 129.96, 129.85, 128.10, 128.07, 128.04, 127.99, 127.93, 127.89, 127.85, 127.80, 127.78, 127.75, 127.72, 127.69, 127.66, 127.60, 127.57, 127.54, 127.45, 127.39, 127.36, 127.33, 127.30, 127.27, 127.25, 127.22, 127.19, 127.12, 127.08, 127.01 (C-Ph) 117.58, 114.68 (CF_3), 99.21, 98.46, 98.31, 98.25, 97.78, 97.65, 97.51 (C-1), 81.89, 81.68, 81.61, 81.42, 80.88, 80.75, 80.57, 79.94, 79.85, 76.10, 76.04, 75.92, 75.81, 73.67, 73.62, 73.59, 71.34, 69.68, 68.42 (CH, CH_2). MALDI-TOF, *m*/*z* calcd. for $C_{177}H_{178}F_6O_{35}Na$ 3000.195, found 3000.767.

6^A,6^D-Di-*C*-trifluoromethyl-6^A,6^D-dioxo-β-cyclodextrin (4): Compound **9** (93 mg, 0.031 mmol) was dissolved in MeOH/EtOAc (1:1, 15 mL). TFA (cat) and Pd/C (10%, 51 mg) were added. The mixture was flushed with N_2, then H_2 was introduced; afterwards the solution was left stirring for 28 hours. The reaction mixture was filtered through paper and Millipore filters, and washed with water (3 × 10 mL) and EtOAc (3 × 10 mL). Evaporation and lyophilization gave 40 mg of compound **4** (100% yield) as a colorless fluffy powder. $[\alpha]_D^{23}$ = +80 (*c* = 0.52, H_2O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 5.21 (m, 2 H), 4.98 (m, 7 H), 4.11–4.02 (m, 2 H), 3.96–3.80 (m, 14 H), 3.79–3.63 (m, 15 H), 3.58–3.42 (m, 24 H). ^{13}C NMR (D_2O, 100 MHz): δ_C = 118.01, 115.89 (CF_3), 102.21, 102.19, 102.17, 102.11, 102.05, 101.42, 101.35 (C-1), 81.56, 80.96, 80.88, 80.86, 80.80, 79.96, 79.91, 73.89, 73.81, 73.12, 73.06, 73.04, 73.00, 72.06, 71.98, 60.05, 59.96 (CH, CH_2). ^{19}F NMR (377 MHz, D_2O): δ_F = –74.2 (s). MALDI-TOF, *m*/*z* calcd. for $C_{44}H_{64}F_6O_{35}Na$ 1289.3029, found 1288.5735.

Procedure for Determining the Rate of Hydrolysis: Each assay was performed on 1 mL samples prepared from 0.5 mL aqueous solutions of the appropriate aryl glycoside at different concentrations mixed with 0.5 mL of phosphate containing either cyclodextrin derivative (0.025 mg-5 mg) or nothing as control. The reactions were followed continuously at 59 °C using UV absorption at 400 nm for the nitrophenyl substrates. The reactions were monitored for 3–18 h. Velocities were determined as the slope of the progress curve of each reaction. Uncatalyzed velocities were obtained directly from the control samples. Catalyzed velocities were calculated by subtracting the uncatalyzed velocity from the velocity of the appropriate cyclodextrin-containing sample. The catalyzed velocities were used to determine K_m and V_{max} from non-linear regression of *V* vs. *S* using the program dataplot. k_{cat} was calculated as V_{max}/[cyclodextrin]. k_{uncat} was determined as the slope from a plot of V_{uncat} vs. [*S*].

Procedure for Determining the Rate of Oxidation: Each assay was performed on 4–16 samples (2 mL each) of the appropriate substrate at different concentrations in 190 mM phosphate buffer containing 72 mM H_2O_2, and either **4** or **3** (1 mg) or nothing as control. The reactions were followed at 25 °C using UV absorption at an appropriate wavelength (see below) and typically monitored for 5 h. Velocities were determined as the slope of the progress curve of each reaction. Uncatalyzed velocities were obtained directly from the control samples. Catalyzed velocities were calculated by subtracting the uncatalyzed rate from the total rate of the appropriate cyclodextrin-containing sample. The catalyzed 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: used: 3-aminophenoxazone-2, 0.42 mM^{-1} cm^{-1} at 400 nm, acetophenone, 0.32 mM^{-1} cm^{-1} at 300 nm.

Supporting Information (see also the footnote on the first page of this article): Ion-exchange HPLC chromatograms of **2** and **4** are available.

Acknowledgments

We thank the Lundbeck foundation and Forskningsråd for Natur og Univers (FNU) for financial support.

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Received: August 30, 2006
Published Online: November 27, 2006

