DOI: 10.1002/ejoc.200901099

Amino–Acetone-Bridged Cyclodextrins – Artificial Alcohol Oxidases

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Keywords: Amines / Enzyme catalysis / Alcohols / Oxidation / Cyclodextrins

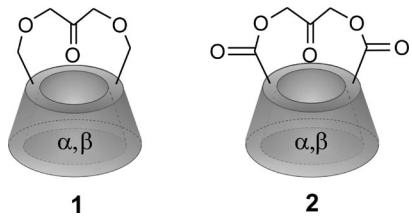
A new series of α- and β-cyclodextrin derivatives containing a substituted amino–acetone bridge attached to the 6A and 6D positions of the cyclodextrin are reported. The synthesis starts from the known α- or β-cyclodextrin A,D-diols, which were either oxidized to α- or β-cyclodextrin A,D-dicarbaldehydes and then coupled with 1,3-diamino-2-propanol by a reductive amination reaction and further modified to give the final 6^A,6^D-diamino-6^A,6^D-dideoxy-*N*,*N*′-(2-oxopropa-1,3-dienyl)-*N*,*N*′-acetyl-α- or -β-cyclodextrin or the cyclodextrin-diol was substituted with azide then reduced and after a few alkylation steps the final 6^A,6^D-dideoxy-*N*,*N*′-(2-oxopropa-1,3-dienyl)-6^A,6^D-(*N*,*N*,*N*′*N*′-tetramethyldiammonio)-α-cyclodextrin dibromide was obtained. The new compounds display very good enzymatic catalytic properties in the oxidation of benzyl alcohols with a rate increase of up to 18500 but only appreciable catalysis for aniline oxidations. Thus, unlike previously studied cyclodextrin ketones, these new amino–acetone-bridged cyclodextrins have high substrate selectivity and also exhibit stereoselectivity in the oxidation of different enantiomers.

Introduction

In recent years many chemists have devoted themselves to creating small molecules that mimic complex enzymes and to designing intelligent artificial catalysts that recognize substrates and can be engineered to suit any reaction and medium.[1] Enzymes catalyse reactions with a remarkable rate and selectivity.[2] The basic principles behind their activity are the molecular recognition and stabilization of the transition state of the reaction. However, despite some impressive advances in the field, the activity of natural enzymes is still not fully understood. Native[3] and modified[4] cyclodextrins have been extensively studied as potential enzyme mimics and have proved to be valuable candidates mostly due to their binding properties and their water solubility. A big challenge for chemists is to produce a small synthetic equivalent to the active site that can rival enzymes in rate acceleration, turnover and specificity.

We report herein artificial alcohol dehydrogenases that have an efficiency comparable per molecular weight to a real enzyme. The oxidation of several benzyl alcohols to aldehydes was performed with the catalysts in the presence of a stoichiometric amount of hydrogen peroxide. A study was performed of the substituent effect on the efficiency of several artificial enzymes by functional modification of the amino moiety in the β position next to the acetone. It was interesting to explore the effect of different substrates on binding properties, including a more polar environment, and to compare them with previous reported catalysts.[5]

Cyclodextrins are frequently used as host molecules because they can be synthetically modified with different functional groups to create new artificial enzymes. Reactions like alkene epoxidation[6] and aniline oxidation have been catalysed by the bridged acetone-cyclodextrins **1** and **2** (Figure 1). The oxidation reactions were performed with hydrogen peroxide and exhibited a k_{cat}/k_{uncat} value of up to 1070.[5] The oxidation reactions of different benzyl alcohols to aldehydes were carried out by using the bridged acetone-ester-cyclodextrin **2**, which proved to be a remarkably good artificial enzyme with a rate increase of up to 6.3×10^4 in the best case.[7]



1 **2**

Figure 1. Catalysts **1** and **2** consisting of a core of either α- or β-cyclodextrin with dihydroxyacetone attached to the primary rim through an ether or ester connection.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901099.

The cup-shaped **1** and **2** bind the aromatic substrate into their hydrophobic cavity ($K_m \approx 1$–5 mM) and the acetone is believed to react with H_2O_2 to form a hydroperoxide adduct which is responsible for the oxidation of the bound amine or alcohol group.

Our promising results with **1** and **2** encouraged us to study further structural modifications of the β position with respect to the reactive acetone. We were particularly interested in the incorporation of quaternary ammonium which previously has been successfully used in ketone epoxidation catalysts.[8] Thus, we describe herein the synthesis of new bridged amino–acetone-cyclodextrin derivatives and a study of their activity when having different electron-withdrawing amino-protecting groups close to the functional acetone moiety.

Results and Discussion

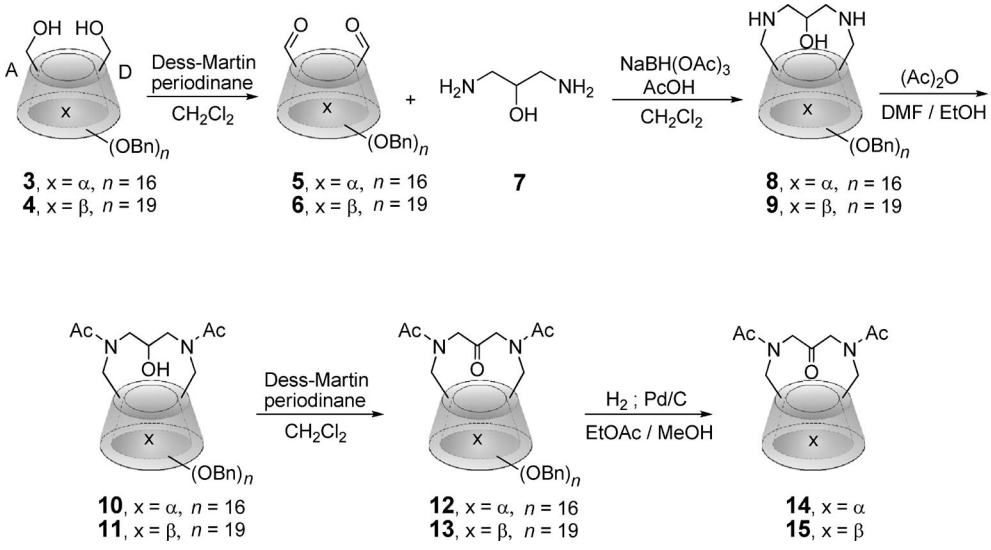
Synthesis

Amino-cyclodextrins are interesting compounds mainly due to their ability to form strong guest–host complexes through van der Waals forces, hydrogen-bonding and hydrophobic interactions with the cyclodextrin moiety but also through molecular recognition by electrostatic interactions between the substrate and the amino group at different pHs. Therefore several strategies for the synthesis of amino-modified cyclodextrins have been reported using different methods for the selective modification of one, two or the entire face of the cyclodextrin.[9] In general these strategies present many problems concerning poor regioselectivity and the tedious separation of the mixtures, and so the preparation of regioselectively modified amino-cyclodextrins is a difficult low-yielding task.[10] The general method for the synthesis of amino-cyclodextrins involves the regioselective preparation of different sulfonyl esters followed by substitution with sodium azide and subsequent reduction to the final amino compound, but it seemed almost impossible to obtain pure sulfonyl esters even if many highly selective sulfonylation reagents have been reported so far.[11] It was therefore a very important development when Sinaÿ and co-workers[12] discovered that DIBAL-H could effect the regioselective de-*O*-benzylation of the primary hydroxy groups in positions 6A and 6D of perbenzylated cyclodextrins as it allowed the use of these molecules in a protected form to ease the purification after each step.

By using this strategy, we prepared the A,D-bridged amino-cyclodextrin derivatives **14**, **15** and **21** (Scheme 1 and Scheme 2) very efficiently starting from commercially available α- and β-cyclodextrins, which were, in the first step, subjected to per-*O*-benzylation using BnCl and NaH in DMSO as solvent. The per-*O*-benzylated cyclodextrins were treated with DIBAL-H in anhydrous toluene under an inert atmosphere to afford the cyclodextrin-diols **3** and **4** in 90 and 86% yields, respectively, as previously described.[13] Oxidation of these diols with Dess–Martin periodinane in dichloromethane gave the α- and β-cyclodextrin dialdehydes **5** and **6** in quantitative yields.[12] Although a number of methods for the preparation of amino-cyclodextrins have been reported, they have typically been applied to more simple compounds[14] and because cyclodextrin-dialdehydes are readily available, a reductive amination reaction was the obvious starting point for secondary amine synthesis.

The reductive amination approach has been used on cyclodextrins several times before for linking chitosan derivatives,[15] hyaluronic acid derivatives[16] and porphyrins[17] or for the *N*-glycosidation of 6-amino-6-deoxy-cyclodextrin with various 6-oxogalactosides[18] with reaction yields of 15–70%.

Herein we present the synthesis of different 6A,6D-modified cyclodextrin derivatives with an acetone bridge attached to the amino groups (**14** and **15**) by a reductive amination reaction of α- and β-cyclodextrin dialdehydes **5** and **6** with 1 equiv. of 1,3-diamino-2-propanol (**7**) in the presence of sodium triacetoxyborohydride in dichloromethane at room temperature. Bridged amino compound **8** was ob-



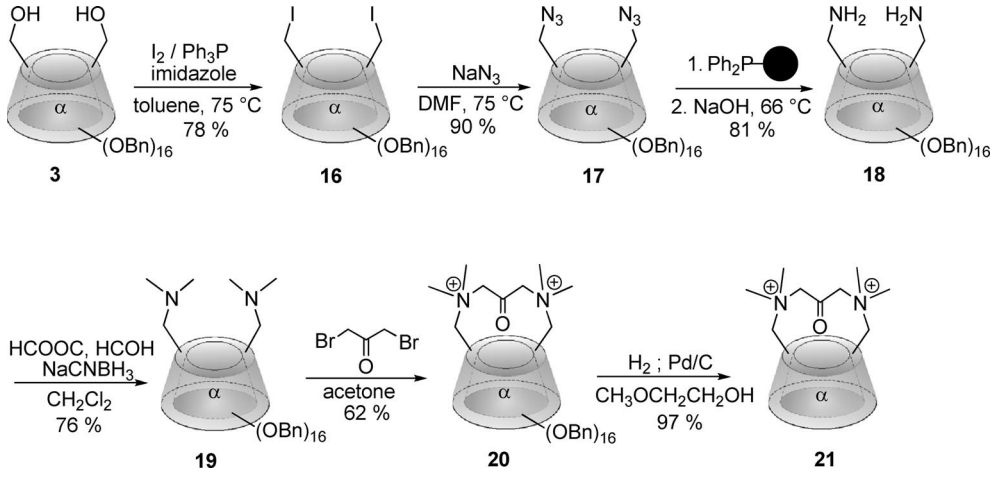
Scheme 1. Synthesis of amino–acetone-cyclodextrins **13** and **14**.

tained in 42% yield starting from α-cyclodextrin-dialdehyde **5** and compound **9** in 50% yield starting with the β-cyclodextrin-dialdehyde **6** (Scheme 1). No dimer formation was observed in this step by MALDI-TOF MS or TLC, but imine intermediates were isolated after column chromatography.

Further acetylation of the secondary amino group using acetic anhydride in DMF/ethanol (1:1) afforded amide derivatives **10** and **11** in 94 and 89% yield, respectively, after column chromatography. When the secondary alcohol moiety was treated with Dess–Martin periodinane, the corresponding acetones **12** and **13** were obtained in 86 and 88% yields. The presence of the ketone moiety was supported by ^{13}C NMR (200.9 ppm) and IR (1728 cm^{-1}) spectroscopy. The somewhat low yields in the reductive amination steps are due to problems arising during purification. When compound **13** was prepared without purifying the intermediates **9** and **11** an overall yield of 80% was obtained after three steps. A final hydrogenolysis with H_2 and 10% Pd/C as catalyst in methanol/ethyl acetate (1:1) provided the final amino–acetone-cyclodextrin derivatives **14** and **15** in 80% and quantitative yields, respectively.

An enzyme mimic thought interesting to study was a compound bearing positive charges next to the ketone moiety to induce a better electronic activation of the ketone functionality.[8] Therefore a bis(dimethylammonium salt), with the derivatizations at the β positions with respect to the ketone, was prepared. The synthesis of the bis(dimethylamino)acetone-bridged cyclodextrin **21** proved not to be trivial. Attempts to follow the conventional route, a reductive amination reaction to compound **8** followed by full methylation of the secondary amino groups, were not successful due to problems during the purification of the final product. Methylation of the diamino-bridged compound **8** with MeI/K_2CO_3 or, alternatively, with MeOTf/2,6-di-*tert*-butylpyridine gave mixtures in which the main product was the trimethylated compound. The following oxidation step, using either Dess–Martin periodinane or the Swern oxidation approach, failed to afford the ketone. A very polar product was detected by TLC using EtOAc as eluent, probably a result of further oxidations of the amino functionality. The synthesis was finally achieved by the alternative route shown in Scheme 2.

Conversion of the 6A,6D-alcohols in compound **3** to iodides (Scheme 2) proceeded smoothly if care was taken when adding the iodine. The use of triphenylphosphane and iodine can lead to the formation of insoluble adducts, which can be prevented by the addition of imidazole.[19] Diol **3** was dissolved in toluene, triphenylphosphane and imidazole were added and the resulting mixture was warmed to 75 °C before adding the iodine in one portion to afford compound **16** in 78% yield. Nucleophilic substitution of the 6A,6D-diiodide **16** to the diazide proceeded in excellent yield (Scheme 2). The substitution took place at 75 °C in DMF overnight to afford the 6A,6D-diazide **17** in 90% yield after flash chromatography. The reaction could in this case not be monitored by TLC because compounds **16** and **17** exhibited identical R_f values. Reduction to the diamino compound **18** was achieved by using styrene-supported triphenylphosphane in THF with further hydrolysis of the iminophosphorane intermediate using a 1 M NaOH solution at 66 °C to give an 81% yield. The α-cyclodextrin-diamine **18** was bis-dimethylated in 76% yield by a reductive-amination-type reaction using a mixture of formic acid/formaldehyde in dichloromethane and sodium cyanoborohydride as a reducing reagent. Compound **19** was further alkylated with 1,3-dibromoacetone to the bridged compound **20**, which was recrystallized from acetone/water to give the final bis-ammonium compound in 62% yield. The presence of the ketone moiety was supported by ^{13}C NMR (194.1 ppm) and IR (1729 cm^{-1}) spectroscopy and the ammonium salts were indicated by the shift of the methyl signals in the ^1H NMR spectra from 2.12 ppm in compound **19** to 3.05 ppm in compound **20**. Hydrogenolysis of the benzyl groups with H_2 and 10% Pd/C as catalyst in 2-methoxyethanol as solvent afforded the final bis-ammonium-bridge acetone compound **21** in 97%, which was fully characterized by IR, NMR and MS (see the Exp. Sect.).



Scheme 2. Synthesis of the 1,3-bis(dimethylamino)acetone-bridged cyclodextrin **21**.

Catalysis

Oxidation experiments were carried out with the final compounds **14**, **15** and **21** to test their activity as catalysts in hydrogen peroxide mediated oxidation of differently substituted anilines and benzylic alcohols. The kinetics experiments were performed under enzymatic conditions (i.e., water, pH 7, ambient temperature) using a dilute solution of hydrogen peroxide. The catalytic activity was quantified by following the product formation at the appropriate wavelength versus time with and without small concentrations of catalyst (ca. 0.5 mM). The reaction rate increases with an increasing amount of catalyst (Figure 4) and follows Michaelis–Menten-type kinetics, which means that the substrate binds to the catalyst cavity where the reaction takes place faster than outside. The entire process was analysed by using the Michaelis–Menten equation (1), in which V_{cat} is the initial steady-state rate of the catalysed reaction, V_m is the maximum rate, K_m is the Michaelis–Menten constant and S is the substrate concentration. The fit of the kinetics was revealed by a Hanes plot, as shown in Figure 2, and V_m and K_m were obtained by a non-linear regression fit of the data to the Michaelis–Menten equation. The value of k_{cat} was calculated from V_m/[enzyme] and the effect of the catalyst is expressed as k_{cat}/k_{uncat}. Several substrates were investigated and the kinetic parameters are summarized in Tables 1 and 2.

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

$$V_{cat} = V_m \frac{S}{S + K_m} \quad (1)$$

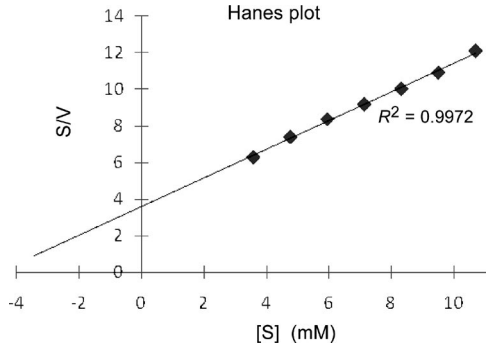


Figure 2. Enzyme kinetic model, Michaelis–Menten equation and an example of the Hanes plot for the oxidation of *o*-aminophenol with 64 mM H_2O_2 in phosphate buffer pH 7 and 25°C.

Not surprisingly, the amino–acetone-bridged cyclodextrins **14**, **15** and **21** displayed medium activity in aniline oxidations giving a k_{cat}/k_{uncat} ratio of up to 160, which shows the improvement in the reaction when it takes place inside the functionalized cavity. The β-derivative **15** exhibited somewhat better activity with most of the substrates, probably due to the size of the β-cyclodextrin cavity, which can accommodate bigger molecules. However, none of the catalysts was as efficient in the aniline oxidation as the previously reported catalysts **1** and **2**.[5,20] Interestingly, both **14** and **15** displayed better reactivity with *o*-substituted anilines than with *p*-substituted derivatives, possibly due to the formation of a hydrogen bond between the amino moiety of the catalyst and the *o*-hydroxy group of the substrates, which could influence the reaction path. This interaction is not possible with the *p*-hydroxy group and therefore it has a larger K_m value compared with the *ortho* derivative (see Table 1). The compound bearing the ammonium in close proximity to the ketone is somewhat more efficient for aniline oxidation but showed no activity in benzyl alcohol oxidation. This is probably due to two antagonistic effects: the increase in the ketone reactivity towards nucleophilic attack by hydrogen peroxide to form the active hydroperoxide intermediate and the electrostatic stabilization of the lone pair from the amines and alcohols (Figure 3).

The kinetic data (K_m and k_{cat}) for the oxidation of a range of benzyl alcohols were obtained from V_{cat} versus S in the usual manner using non-linear least-squares fitting and are shown in Table 2. The k_{cat} values range from 10^{-4} to 2×10^{-3} min^{-1} and the effect of the reaction taking place inside the cavity was as high as 18450 under neutral conditions at ambient temperature and with dilute hydrogen peroxide solutions. The K_m values range from 0.2–3.4 mM, which are typical values for the binding of cyclodextrins to small aromatics (see Table 2).

Note that both α- and β-amino–acetone-cyclodextrin derivatives **14** and **15** displayed good substrate selectivity, exhibiting a very poor activity towards aniline oxidation but a much better activity towards benzyl alcohol oxidation (see Tables 1 and 2). This tendency could be an indication that, in the case of benzyl alcohol, the reaction is facilitated by hydrogen-bonding between the benzylic proton and the amido groups of the bridged cyclodextrins. Compounds **14** and **15** exhibit good activity towards the oxidation of 1-phenylethanol to acetophenone and notable enantiomer selectivity (Table 2). The α-amino–acetone-bridged cyclodextrin **14** is 1.4 times more reactive with the (*R*)-1-phenylethanol enantiomer, whereas the β-amino–acetone-bridged cyclodextrin **15** was more than three times more reactive with the (*S*) enantiomer, although the binding properties of both enantiomers are very similar.

The mechanisms, as they have been discussed before,[7,20] show that the bridged ketone plays an essential role both in amine and alcohol oxidation, and reacts initially with hydrogen peroxide to form a hydroperoxide adduct which is responsible for the oxidation of the bound substrate (Figure 3). The amine oxidation is a complex reaction that results in the formation of hydroxylamine and nitroso derivatives in the initial step, which can be oxidized further to nitro compounds and also react further to give mixtures of dimers. The bridged amino–acetone-cyclodextrins catalyse the oxidation of primary alcohols to aldehydes as well as secondary alcohols to ketones. Substitution of the aromatic ring is accepted with certain differences in the rate of catalysis (see Table 2).

Table 1. Kinetic data for the oxidation of several anilines catalysed by **14**, **15** or **21**. Unless otherwise noted the experiments were performed in phosphate buffer pH 7 at 25 °C with a H_2O_2 concentration of 64 mM and a catalyst concentration of ca. 0.5 mM.

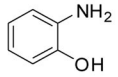
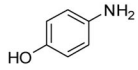
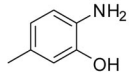
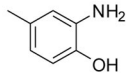
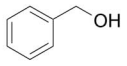
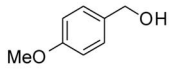
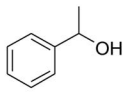
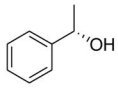
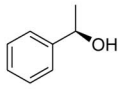
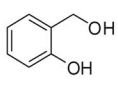
Substrate	Catalyst	k_{cat} ($\times 10^{-3}$min^{-1})	K_m (mM)	k_{cat}/k_{uncat}
	**14**	11.06±0.05	7.5±0.03	44
	15	33.48±0.81	4.6±0.17	133
	21	39.71±0.72	8.1±0.14	158
	α-**CD**	no catalysis	–	–
	β-**CD**	no catalysis	–	–
	$(CH_3)_2C=O$	no catalysis	–	–
	**14**	no catalysis	–	–
	15	8.49±0.44	9.9±0.7	20
	**14**	5.24±0.06	3.7±0.08	3
	15	76.65±0.11	33±3.4	46
	**14**	8.63±0.001	4.86±0.06	56
	15	22.38±0.33	3.17±0.75	146

Table 2. Kinetic data for the oxidation of various benzylic alcohols catalysed by **14**, **15** or **21**. Experiments were performed in phosphate buffer pH 7 at 25 °C with a H_2O_2 concentration of 64 mM and a catalyst concentration of ca. 0.5 mM.

Substrate	Catalyst	k_{cat} ($\times 10^{-3}$min^{-1})	K_m (mM)	k_{cat}/k_{uncat}
	**14**	0.55±0.01	0.51±0.08	576
	15	1.12±0.1	0.9±0.3	1171
	**14**	0.182±0.07	1.05±0.2	2133
	15	0.291±0.03	3.34±0.5	3404
	**14**	1.66±0.04	0.18±0.01	6700
	15	0.58±0.04	0.33±0.03	2350
	21	no catalysis	–	1
	**14**	1.88±0.01	0.62±0.03	7596
	15	1.59±0.09	3.24±0.2	6447
	**14**	2.64±0.01	0.73±0.03	10660
	15	0.51±0.05	0.46±0.04	2069
	**14**	0.242±0.03	0.31±0.07	18446
	15	0.107±0.03	0.38±0.1	8194
	21	no catalysis	–	1
	β-**CD**	no catalysis	–	1
	$(ClCH_2)_2C=O$	no catalysis	–	1

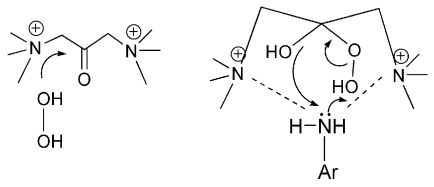


Figure 3. Mechanism for the formation of the hydroperoxide intermediate in aniline oxidation.

All these experiments followed Michaelis–Menten kinetics and the reactions could be inhibited by the addition of the 2-naphthalenesulfonic acid sodium salt, which confirms again that the cyclodextrin cavity is involved in the process. Neither acetone nor α- or β-cyclodextrin exhibited catalytic behaviour under the same reaction conditions. The rate increases with increasing enzyme concentration and can be observed even with a concentration of less than 10 μM of modified cyclodextrin (see Figure 4).

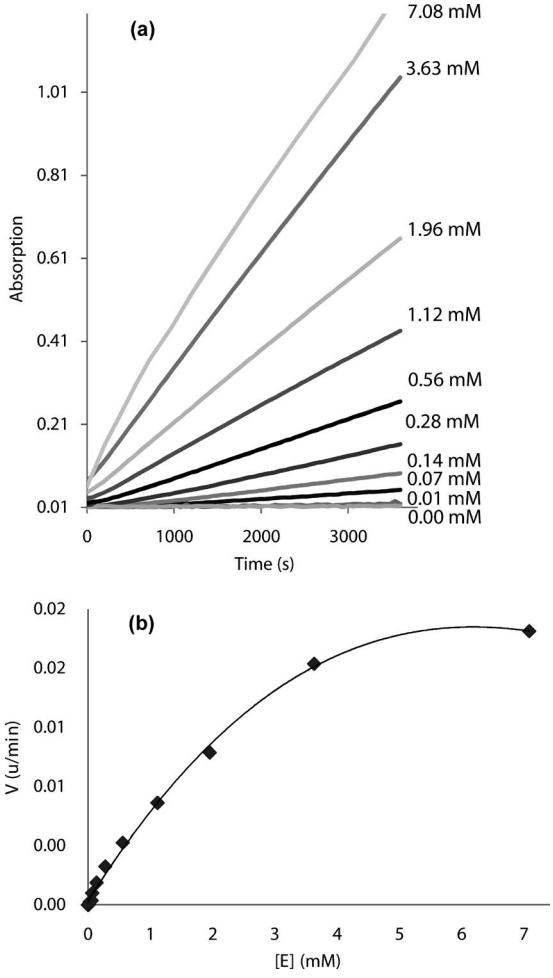


Figure 4. 2-Aminophenol oxidation with different concentrations of catalyst **15** in phosphate buffer pH 7 with 64 mM H_2O_2 at 25 °C.

Inhibition studies were carried out for the oxidation of 4-aminophenol using the 2-naphthalenesulfonic acid sodium salt as the inhibitor. A Dixon plot was used as a graphical method to determine the dissociation constant K_i of the enzyme–inhibitor complex (Figure 5). The reaction velocity was measured at three fixed substrate concentrations with varying concentrations of inhibitor. A graph of the reciprocal of the velocity against inhibitor concentration was plotted for each of the substrate concentrations. The lines corresponding to each substrate concentration intersected to give a K_i value of 63.6 mM and showed a good competitive inhibition of the reaction (Figure 5).

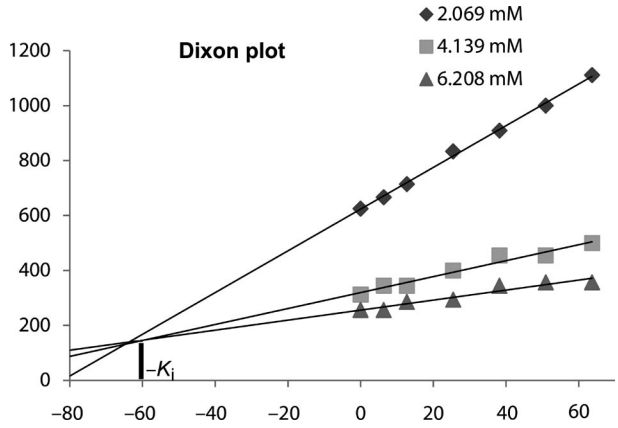


Figure 5. Dixon plot for the inhibition of 4-aminophenol oxidation using 64 mM H_2O_2 in phosphate buffer pH 7 at 25°C with different concentrations of 2-naphthalenesulfonic acid sodium salt as inhibitor.

The equilibrium constant for the addition of hydrogen peroxide to the carbonyl moiety of the catalyst **15** was measured to be 2.9 mM (Figure 6), which reveals a very good affinity of the ketone in nucleophilic reactions in agreement with previously reported studies of nucleophilic addition to carbonyl compounds.[21] The experiments were carried out with increasing hydrogen peroxide concentrations at fixed enzyme and substrate concentrations and the binding constants were calculated using non-linear least-squares regression fitting to the V versus $[H_2O_2]$ curve (Figure 6) for two different substrates.

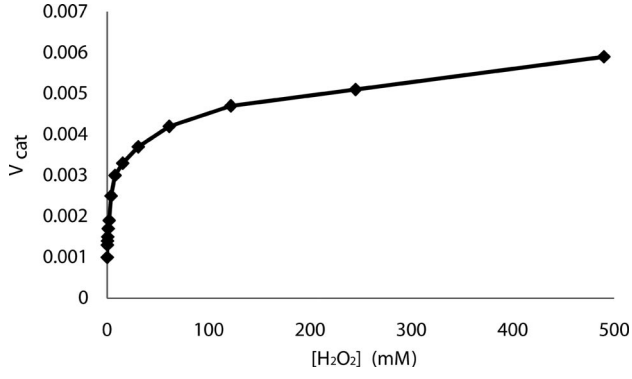


Figure 6. Effect of hydrogen peroxide concentration on the rate of 2-aminophenol oxidation in phosphate buffer pH 7 at 25 °C.

Conclusions

We have prepared three new cyclodextrin catalysts bearing an active ketone site linked by two amine functionalities.

The amine was protected either by acetylation to give compounds **14** and **15** or by full methylation to give the quaternary derivative **21**. Their syntheses involve a facile reductive amination followed by amine protection for derivatives **14** and **15** or a final alkylation of the bis-dimethylated-amino-cyclodextrin derivative for compound **21**. This last reaction is a slow, low-yielding step that will need to be optimized in the future. It may be anticipated that all amino-ketone-bridged cyclodextrins may have a certain activity towards aniline oxidation, but to our surprise they displayed impressive substrate selectivity towards alcohols, probably due to guest–host electrostatic interactions. Compounds **14** and **15** displayed enzyme activity in benzyl alcohol oxidation with hydrogen peroxide with rate increases of up to 18500 under neutral conditions, but increases of only up to 158 in aniline oxidation. This feature of the catalysts will open the way to new applications in asymmetric synthesis and in molecular recognition studies in aqueous media for functional chemical sensors and molecular devices.

Experimental Section

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 visualized 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 and COSY NMR experiments were carried out with a Varian Mercury 300 instrument. Monoisotopic mass spectra (MALDI-TOF MS) were obtained with a Bruker Daltonics mass spectrometer using ditranol (1,8-dihydroxyanthron) as the matrix. Spectra were calibrated with a standard peptide calibration solution.

***O*-Benzyl-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-α-cyclodextrin-6^A,6^D-dicarbaldehyde (5):** Dess–Martin reagent (5 equiv., 6.21 mmol, 2.634 g) was added to a solution of diol **3** (3 g, 1.242 mmol) in dry CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temp. for 2.5 h and then was quenched with Et_2O (25 mL) and a solution of satd. $NaHCO_3$ (825 mL) containing $Na_2S_2O_3$ (1.5 g) and was stirred for a further 1 h. The organic phase was washed with $NaHCO_3$ (6 × 25 mL) and water (6 × 25 mL), dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (4:1 mixture of pentane/EtOAc) to give the product as a white foam (2.591 g, 87%). R_f (EtOAc/pentane, 1:3) = 0.75. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.41 (d, J = 2.6 Hz, 2 H, aldehyde-H), 7.27–7.11 (m, 80 H, Ar-H), 5.38 (d, J = 3.5 Hz, 1 H, 1-H), 5.31 (d, J = 10.8 Hz, 1 H, CHPh-H), 5.10 (d, J = 10.8 Hz, 1 H, CHPh-H), 4.98 (d, J = 3.2 Hz, 1 H, 1-H), 4.89–4.82 (m, 4 H), 4.79–4.70 (m, 6 H), 4.52–4.26 (m, 18 H), 4.18–3.9 (m, 20 H), 3.74–3.63 (m, 4 H), 3.59–3.35 (m, 14 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 196.86 (C=O), 139.51, 139.45, 139.04, 138.68, 138.52, 138.42, 138.33, 138.14 (C_{ipso}), 128.64, 128.53, 128.37, 128.28, 128.17, 128.14, 128.12, 127.83, 127.80, 127.60, 127.35, 127.27, 127.19 (CH_{Ph}), 98.44, 98.17 (C-1), 81.05, 80.95, 80.69, 80.33 (C-3), 79.97, 79.42, 78.83, 78.50, 76.47, 76.27, 76.08, 75.77, 75.00, 74.18, 73.60, 73.52, 73.17, 72.72, 71.69, 71.41, 69.28 (CH_2, CH) ppm. MS (MALDI-TOF): calcd. for $C_{148}H_{152}O_{30}Na^+$ 2433.76; found 2434.8.

***O*-Benzyl-2$^{A–G}$,3$^{A–G}$,6^B,6^C,6^E,6^F,6^G-nonadecyl-β-cyclodextrin-6^A,6^D-dicarbaldehyde (6):** See ref.[22]

6^A,6^D-Diamino-*O*-benzyl-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-6^A,6^D-dideoxy-*N*,*N*′-(2-hydroxypropa-1,3-dienyl)-α-cyclodextrin (8): 1,3-Diamino-2-propanol (95.13 mg, 1.057 mmol) dissolved in DMF (4 mL), $NaBH(OAc)_3$ (10.57 mmol, 10 equiv.) and glacial AcOH (80.61 μL, 0.528 mmol) were added to a solution of the aldehyde **5** (2.549 g, 1.057 mmol) in CH_2Cl_2 (42 mL) . The reaction mixture was stirred at room temp. overnight. Then, the mixture was washed with satd. $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL) and the organic phases were separated, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (3:1 mixture of EtOAc/pentane) to give the product as a white foam in 42% yield. R_f (EtOAc) = 0.62. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35–6.91 (m, 80 H, Ar-H), 5.55 (dd, J = 3.5, 10.5 Hz, 2 H), 5.39 (t, J = 5.2 Hz, 2 H, CHPh-H), 5.26 (d, J = 10.5 Hz, 2 H, CHPh-H), 5.03 (dd, J = 5.5, 10.5 Hz, 2 H), 4.83–4.69 (m, 8 H), 4.57 (d, J = 3.2 Hz, 1 H, 1-H), 4.54 (d, J = 3.2 Hz, 1 H, 1-H), 4.51 (d, J = 2.9 Hz, 1 H, 1-H), 4.46–4.26 (m, 18 H), 4.18–3.70 (m, 20 H), 3.59–3.49 (m, 4 H), 3.40–3.21 (m, 8 H), 2.93 (d, J = 13.5 Hz, 1 H), 2.75 (d, J = 12.3 Hz, 1 H), 2.67–2.51 (m, 4 H), 2.46–2.33 (m, 3 H), 2.26–2.22 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 140.04, 139.74, 139.68, 139.12, 138.69, 138.57, 138.51, 138.39, 138.31, 137.97, 137.74 (C_{ipso}), 128.71, 128.64, 128.60, 128.52, 128.49, 128.42, 128.35, 128.25, 128.15, 128.06, 127.99, 127.93, 127.89, 127.79, 127.71, 127.37, 127.32, 127.26, 127.10, 127.02 126.94, 126.84, 126.79, 126.17 (CH_{Ph}), 100.52, 100.36, 98.60, 98.19 (C-1), 82.74, 82.67, 81.89, 81.68, 81.22, 81.08, 80.97, 80.77, 80.65, 80.47, 78.78, 78.30, 76.86, 76.34, 73.95, 73.74, 73.65, 73.56, 72.90, 72.59, 72.29, 72.16, 72.04, 71.08, 70.62, 69.52, 69.21 (CH, CH_2), 53.57, 53.35, 52.69, 52.52 (C-6) ppm. MS (MALDI-TOF): calcd. for $C_{151}H_{162}N_2O_{29}H^+$ 2469.14; found 2469.9.

6^A,6^D-Diamino-*O*-benzyl-2$^{A–G}$,3$^{A–G}$,6^B,6^C,6^E,6^F,6^G-nonadecyl-6^A,6^D-dideoxy-*N*,*N*′-(2-hydroxypropa-1,3-dienyl)-β-cyclodextrin (9): 1,3-Diamino-2-propanol (184.5 mg, 2.05 mmol) dissolved in DMF (8 mL), $NaBH(OAc)_3$ (4.34 g, 10 equiv.) and glacial AcOH (180 μL) were added to a solution of the aldehyde **6** (5.83 g, 2.05 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred at room temp. overnight. Then the mixture was washed with satd. $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL) and the organic phases were separated, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (3:1 to 1:1 mixture of EtOAc/pentane) to give the product as a mixture of diastereoisomers in 50% yield. R_f (EtOAc/pentane, 1:1, + Et_3N) = 0.25. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40–7.26 (m, 95 H, Ar-H), 5.89 (d, J = 3.5 Hz, 1 H, 1-H), 5.82 (d, J = 3.7 Hz, 1 H, 1-H), 5.61 (d, J = 9.9 Hz, 1 H, CH_2), 5.51 (d, J = 10.6 Hz, 1 H, CH_2), 5.39 (d, J = 10.5 Hz, 2 H, CH_2), 5.31 (d, J = 10.4 Hz, 2 H, CH_2), 5.01 (m, 6 H), 4.82 (m, 6 H), 4.73 (d, J = 10.1 Hz, 4 H, CH_2), 4.53 (m, 20 H), 4.04 (m, 25 H), 3.52 (m, 16 H), 3.04 (m, 2 H), 2.54 (m, 6 H), 2.00 (br. s, 2 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 140.18, 139.73, 139.55, 139.13, 139.06, 138.76, 138.59, 138.54, 138.44, 138.25, 137.99, 137.64 (C_{ipso}), 128.71, 128.70, 128.64, 128.59, 128.50, 128.47, 128.43, 128.37, 128.25, 128.19, 127.94, 127.89, 127.74, 127.79, 127.62, 127.53, 127.39, 127.30, 127.25, 126.93, 126.86, 126.78, 126.58, 126.50, 126.45 (CH_{Ph}), 99.27, 99.19, 99.08, 98.84, 98.59, 98.32, 97.72, 97.65 (C-1), 81.40, 81.21, 80.92, 80.47, 80.02, 79.18, 78.17, 77.95, 77.73, 77.53, 77.11, 76.85, 76.56, 76.31, 76.06, 73.92, 73.63, 73.19, 73.06, 72.86, 72.65, 72.19, 71.87, 70.25, 69.88, 69.49, 69.25, 68.54 (CH, CH_2), 53.78, 52.61, 52.41, 52.21, 51.98, 51.76 (C-6) ppm. MS (ES): calcd. for $C_{178}H_{190}O_{34}N_2$ 2899.32; found 2899.67.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-*O*-benzyl-2$^{A–F}$,3$^{A–F}$,6^{B},6^{C},6^{E},6^{F}-hexadecyl-6^{A},6^{D}-dideoxy-*N,N′*-(2-hydroxypropa-1,3-dienyl)-α-cyclodextrin (10):** $(Ac)_2O$ (170.75 mg, 1.672 mmol) was gradually added to a cooled solution of compound **8** (688.5 mg; 0.278 mmol) in DMF/EtOH (1:1, 80 mL) and the mixture was stirred at room temp. under nitrogen overnight. Then, the solvent was evaporated and the residue was dissolved in ethyl acetate and washed with water (50 mL × 4). The organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (EtOAc/pentane, 2:1) to give the product as a white foam (667 mg, 94%). R_f (EtOAc/pentane, 1:1) = 0.47. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.33–6.95 (m, 80 H, Ar-H), 5.38–5.09 (m, 4 H), 5.09–4.21 (m, 37 H), 4.21–3.07 (m, 38 H), 2.06 (s, 3 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.33 (C=O, Ac), 139.92, 139.79, 139.40, 139.11, 138.68, 138.54, 138.22, 138.02 (C_{ipso}), 128.76, 128.61, 128.56, 128.46, 128.32, 128.23, 128.05, 127.97, 127.91, 127.86, 127.78, 127.67, 127.47, 127.29, 126.94, 126.82, 126.46, 126.31, 126.19, 126.05 (CH_{Ph}), 101.46, 101.05, 97.60 (C-1), 83.79, 83.08, 81.96, 81.52, 81.20, 80.91, 78.48, 78.19, 77.65, 75.50, 74.47, 73.19, 73.05, 72.90, 72.60, 72.28, 72.14, 71.87, 70.55, 69.78, 69.01, 67.99 (CH, CH_2), 54.39, 52.85 (C-6), 31.67, 29.97, 22.86, 22.57 (CH_3) ppm. MS (MALDI-TOF): calcd. for $C_{155}H_{166}O_{31}N_2Na^+$ 2575.15; found 2576.9.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-*O*-benzyl-2$^{A–G}$,3$^{A–G}$,6^{B},6^{C},6^{E},6^{F},6^{G}-nonadecyl-6^{A},6^{D}-dideoxy-*N,N′*-(2-hydroxypropa-1,3-dienyl)-β-cyclodextrin (11):** $(Ac)_2O$ (254 mg, 2.5 mmol) was gradually added to a cooled solution of compound **9** (1.2 g; 0.414 mmol) in DMF/EtOH (1:1, 120 mL) and the mixture was stirred at room temp. under nitrogen overnight. Then the solvent was evaporated and the residue was dissolved in ethyl acetate and washed with water (50 mL × 4). The organic phases were dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (2:1 to 1:1 mixture of EtOAc/pentane) to give the product as a mixture of diastereoisomers and rotamers (1.09 g, 89%). R_f (EtOAc/pentane, 1:1) = 0.53. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.41–7.15 (m, 95 H, Ar-H), 5.85 (d, J = 4.5 Hz, 1 H, 1-H), 5.76 (d, J = 4.4 Hz, 1 H, 1-H), 5.59 (d, J = 8.3 Hz, 1 H, CH_2), 5.40 (d, J = 10.9 Hz, 1 H, CH_2), 5.27 (d, J = 11.9 Hz, 1 H, CH_2), 5.14 (d, J = 3.8 Hz, 1 H, 1-H), 5.01–4.96 (m, 4 H), 4.86–4.75 (m, 10 H), 4.67–4.30 (m, 21 H), 4.2–4.04 (m, 20 H), 3.89–3.69 (m, 14 H), 3.63–3.44 (m, 14 H), 2.95 (m, 1 H), 2.68 (m, 2 H), 2.15 (s, 1 H), 2.12 (s, 1 H), 2.10 (s, 2 H), 2.03 (m, 1 H), 1.87 (s, 1 H), 1.83 (s, 1 H) ppm. IR: $\tilde{\nu}$ = 3440 (OH), 3052 (Csp^2–H), 2921 (Csp^3–H), 1638 (N–C=O), 1450, 1267 (C–N), 1092 (C–OH), 1033, 734 (Ph), 696 (C–C) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{182}H_{194}O_{36}N_2Na^+$ 3007.33; found 3007.2.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-*O*-benzyl-2$^{A–F}$,3$^{A–F}$,6^{B},6^{C},6^{E},6^{F}-hexadecyl-6^{A},6^{D}-dideoxy-*N,N′*-(2-oxopropa-1,3-dienyl)-α-cyclodextrin (12):** Dess–Martin reagent (2.5 equiv., 0.625 mmol, 265.15 mg) was added to a solution of alcohol **10** (638.4 mg, 0.250 mmol), in anhydrous CH_2Cl_2 (56 mL). The reaction mixture was stirred at room temp. for 2 h, and then was quenched with Et_2O (8 mL) and a solution of satd. $NaHCO_3$ (8 mL) containing $Na_2S_2O_3$ (160 mg) and was then stirred for a further 1 h. Then it was extracted with Et_2O (6 × 40 mL) and washed with $NaHCO_3$ (6 × 20 mL) and water (6 × 20 mL). The organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (EtOAc/pentane, 1:2) to give the product as a white foam (560.2 mg, 86%). R_f (EtOAc/pentane, 1:1.5) = 0.5. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.49–7.16 (m, 80 H, Ar-H), 5.70–5.29 (m, 4 H), 5.01–3.52 (m, 74 H), 2.18–1.97 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 201.33 (C=O), 172.08, 171.71, 139.96, 139.77, 139.24, 139.13, 138.77, 138.55, 138.38, 138.22, 138.11, 137.80 (C_{ipso}), 129.99, 128.88, 128.75, 128.66, 128.52, 128.42, 128.32, 128.22, 128.05, 127.73, 127.56, 127.40, 127.27, 127.16, 127.07, 126.81, 126.55, 126.38, 126.29, 126.17 (CH_{Ph}), 105.26, 101.01, 100.10, 98.37, 97.86 (C-1), 85.36, 83.81, 82.94, 82.36, 81.70, 80.72, 80.43, 79.39, 78.93, 78.05, 76.73, 76.25, 75.79, 74.40, 73.97, 73.67, 73.58, 73.36, 73.15, 72.93, 72.59, 72.34, 72.19, 72.03, 71.54, 70.99, 70.28, 69.95, 69.63, 68.27 (CH, CH_2), 58.25, 53.98, 52.52, 51.07, 50.53 (C-6), 22.44, 22.29, 22.12, 21.55 (CH_3) ppm. MS (MALDI-TOF): calcd. for $C_{155}H_{164}O_{31}N_2Na^+$ 2573.12; found 2572.6.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-2$^{A–G}$,3$^{A–G}$,6^{B},6^{C},6^{E},6^{F},6^{G}-nonadecyl-6^{A},6^{D}-dideoxy-*N,N′*-(2-oxopropa-1,3-dienyl)-*O*-benzyl-β-cyclodextrin (13):** Dess–Martin reagent (2.5 equiv., 3.8 mmol, 1.612 g) was added to a solution of alcohol **11** (4.53 mg, 1.52 mmol) in anhydrous CH_2Cl_2 (45 mL). The reaction mixture was stirred at room temp. for 2 h and then was quenched with Et_2O (10 mL) and a solution of satd. $NaHCO_3$ (10 mL) containing $Na_2S_2O_3$ (160 mg) and was stirred for a further 1 h. Then it was extracted with Et_2O (6 × 40 mL) and washed with $NaHCO_3$ (6 × 20 mL) and water (6 × 20 mL). The organic phases were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (5:1 to 3:1 mixture of toluene/EtOAc) to give the product as a mixture of rotamers (3.66 g, 81%). R_f (toluene/EtOAc, 3:1) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38–7.22 (m, 95 H, Ar-H), 5.87 (d, J = 3.6 Hz, 1 H, 1-H), 5.58 (d, J = 3.8 Hz, 1 H, 1-H), 5.31 (m, 2 H), 5.08–4.71 (m, 13 H), 4.66 (d, J = 12.6 Hz, 1 H, CH_2), 4.59–4.32 (m, 25 H), 4.15–4.06 (m, 14 H), 3.97–3.84 (m, 12 H), 3.80–3.67 (m, 10 H), 3.58–3.44 (m, 10 H), 2.27 (d, 2 H), 2.07 (m, 6 H), 1.85 (s, 1 H), 1.73 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 200.9 (C=O), 172.05, 171.81, 139.26, 139.06, 138.57, 138.50, 138.39, 138.26, 138.22, 138.05, 137.95, 137.91, 137.61, 137.56 (C_{ipso}), 128.36, 128.26, 128.16, 128.12, 128.05, 127.95, 127.86, 127.80, 127.77, 127.66, 127.58, 127.51, 127.46, 127.39, 127.25, 126.93, 126.86, 126.63 (CH_{Ph}), 100.23, 99.95, 99.51, 99.28, 98.78, 97.91, 97.57 (C-1), 80.93, 80.66, 80.52, 80.44, 80.38, 80.23, 80.18, 80.07, 80.03, 79.86, 78.83, 73.35, 73.18, 73.11, 73.04, 72.94, 72.81, 72.45, 72.32, 72.16, 71.84, 71.79, 71.63, 69.70, 69.40, 69.24, 69.12, 69.05, 69.01, 68.81, 68.52, 68.48, 66.33, 65.78, 64.86 (CH, CH_2), 52.46, 51.92, 51,63, 50.42, 49.82 (C-6), 21.93, 21.55, 21.08 (CH_3) ppm. IR: $\tilde{\nu}$ = 3054 (Csp^2–H), 2985 (Csp^3–H), 1728 (C=O), 1649 (N–C=O), 1421, 1359, 1265 (C–N), 1040 (C–O), 744 (Ph) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{182}H_{194}O_{36}N_2Na^+$ 3005.32; found 3005.2.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-6^{A},6^{D}-dideoxy-*N,N′*-(2-oxopropa-1,3-dienyl)-α-cyclodextrin (14):** Compound **12** (560 mg, 0.219 mmol) was dissolved in a mixture of MeOH/EtOAc (1:1, 40 mL) and then Pd/C (10%, 58 mg) and TFA (cat.) were added. The reaction mixture was stirred overnight under H_2. Filtration through a Millipore membrane filter and evaporation of the solvent gave compound **14** (193 mg, 80%) as a white solid. ^{1}H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 5.05–4.93 (m, 2 H), 4.92–4.80 (m, 4 H), 4.30–3.70 (m, 18 H), 3.70–3.20 (m, 22 H), 2.12–1.91 (m, 6 H) ppm. ^{13}C NMR (75 MHz, D_2O, 25 °C, TMS): δ = 196.20 (C=O), 176.55, 175.46, 175.35 (C=O, Ac), 102.18, 101.86, 101.62, 101.37, 101.20, 100.95, 100.70, 100.30, 100.03, 99.79 (C-1), 84.10, 83.45, 83.28, 82.83, 82.61, 81.81, 81.54, 81.23, 80.70, 80.17, 79.97, 79.87, 73.86, 73.69, 73.62, 73.29, 73.20, 72.93, 72.83, 72.76, 72.62, 72.55, 72.47, 72.37, 72.08, 72.01, 71.92, 71.80, 71.67, 71.56, 71.43, 71.32, 71.22, 71.07, 70.23, 68.58 (CH, CH_2), 64.67, 60.75, 60.44, 60.06, 59.88, 52.14, 46.33 (C-6), 21.09, 20.79, 20.71, 20.40, 20.22 (CH_3) ppm. MS (MALDI-TOF): calcd. for $C_{43}H_{68}O_{31}N_2Na^+$ 1131.4; found 1132.5.

***N,N′*-Diacetyl-6^{A},6^{D}-diamino-6^{A},6^{D}-dideoxy-*N,N′*-(2-oxopropa-1,3-dienyl)-β-cyclodextrin (15):** Compound **13** (265 mg, 0.09 mmol) was

dissolved in MeOH/EtOAc (1:1, 20 mL), and then Pd/C (10%, 100 mg) and TFA (cat.) were added. The reaction mixture was stirred overnight under H_2. Filtration through a Millipore membrane filter and evaporation of the solvent gave the title compound **15** (114 mg, quantitative yield) as a white solid. ^{1}H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 5.09–5.06 (m, 7 H), 3.99–3.79 (m, 35 H), 3.73–3.54 (m, 30 H), 2.24 (br. s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, D_2O, 25 °C, TMS): δ = 200.09 (C=O), 171.3, 170.94 (C=O, Ac), 102.35, 102.22, 101.98, 101.13, 99.95, 99.53 (C-1), 82.34, 80.69, 79.47, 78.71, 74.73, 73.98, 72.81, 72.24, 71.93, 71.55, 70.99, 69.35, 66.55, 65.25, 62.77, 60.65, 59.49, 58.70, 58.12, 54.98 (CH, CH_2), 21.71, 21.52, 21.18 (CH_3) ppm. IR: $\tilde{\nu}$ = 3414 (OH), 2925 (Csp^3–H), 1734 (C=O), 1633 (N–C=O), 1363, 1156 (C–N), 1031 (C–O), 579 (C–C) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{49}H_{78}O_{36}N_2Na^+$ 1293,42; found 1293.42.

O-Benzyl-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-6^A,6^D-dideoxy-6^A,6^D-diiodo-α-cyclodextrin (16): α-CD-diol **8** (1.88 g, 0.78 mmol), PPh_3 (4.69 mmol) and imidazole (9.38 mmol) were dissolved in dry toluene (40 mL) under nitrogen at 75 °C. I_2 (4.69 mmol) was then added and the solution was stirred overnight at 75 °C. Satd. aq. $NaHCO_3$ (40 mL) was added and the reaction mixture was stirred for 5 min. Dilution with EtOAc (80 mL) followed. The organic layer was separated, washed with satd. aq. $Na_2S_2O_3$ and satd. aq. NaCl, dried with $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (EtOAc/pentane, 1:6 → 1:3) gave the pure compound (1.61 g, 0.61 mmol) as a white foam in 78% yield. R_f (EtOAc/pentane, 1:4) = 0.78. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.26–7.22 (m, 28 H, aromatic H), 7.15–7.11 (m, 52 H, aromatic H), 5.20 (d, J = 11.5 Hz, 2 H), 5.13 (d, J = 3.6 Hz, 2 H), 5.04 (d, J = 11.1 Hz, 2 H), 4.99 (d, J = 3.2 Hz, 2 H), 4.93 (d, J = 3.1 Hz, 2 H), 4.86 (d, J = 12.7 Hz, 2 H), 4.79 (d, J = 10.7 Hz, 2 H), 4.53 (d, J = 2.1 Hz, 2 H), 4.49 (m, 3 H), 4.42 (m, 14 H), 4.37 (m, 2 H), 4.11 (m, 8 H), 3.94 (m, 11 H), 3.75 (d, J = 9.6 Hz, 2 H), 3.65 (m, 4 H), 3.57 (d, J = 3.3 Hz, 2 H), 3.51 (m, 6 H), 3.46 (d, J = 3.3 Hz, 2 H), 3.43 (d, J = 3.3 Hz, 2 H), 3.37 (dd, J = 3.1, 9.8 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.65, 139.63, 139.56, 138.73, 138.53, 138.43, 138.39, 138.30 (C_{ipso}), 129.34, 128.68, 128.63, 128.54, 128.49, 128.45, 128.43, 128.27, 128.15, 128.09, 128.07, 128.00, 127.92, 127.79, 127.71, 127.48, 127.28, 127.22, 125.61 (CH_{Ph}), 99.66, 98.71 (C-1), 84.70, 81.16, 80.99, 80.86, 80.42, 79.62, 79.14, 78.88, 76.06, 75.83, 75.61, 73.88, 73.79, 73.20, 73.11, 72.92, 72.18, 71.61, 70.65, 69.78, 69.52 (CH, CH_2) ppm. MS (MALDI-TOF): calcd. for $C_{148}H_{154}I_2O_{28}Na^+$ 2656.86; found 2657.08.

6^A,6^D-Diazido-O-benzyl-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-6^A,6^D-dideoxy-α-cyclodextrin (17): α-CD-diiodide **16** (1.61 g, 0.61 mmol) and NaN_3 (3.48 mmol) were dissolved in DMF (36 mL) under N_2 and stirred overnight at 75 °C. Satd. aq. NaCl (150 mL) and EtOAc (300 mL) were added and the mixture was stirred for 10 min. The aqueous phase was then extracted with EtOAc and the combined organic layers were washed with satd. aq. NaCl, dried with $MgSO_4$ and concentrated under vacuum. Flash column chromatography followed (EtOAc/pentane, 1:4→1:2). The pure compound was obtained as a white foam (1.36 g, 0.55 mmol) in 90% yield. R_f (EtOAc/pentane, 1:4) = 0.78. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38–7.33 (m, 40 H, aromatic H), 7.27–7.22 (m, 40 H, aromatic H), 5.36 (d, J = 10.9 Hz, 2 H), 5.28 (d, J = 3.8 Hz, 2 H), 5.25 (d, J = 11.7 Hz, 2 H), 5.11 (d, J = 11.3 Hz, 2 H), 5.00 (m, 4 H), 4.95 (d, J = 5.2 Hz, 4 H), 4.91 (d, J = 5.0 Hz, 2 H), 4.70 (d, J = 12.4 Hz, 2 H), 4.61 (d, J = 11.9 Hz, 4 H), 4.55 (d, J = 5.1 Hz, 6 H), 4.50 (br. s, 6 H), 4.45 (br. s, 1 H), 4.26–3.96 (m, 20 H), 3.81 (d, J = 9.4 Hz, 2 H), 3.78 (d, J = 8.8 Hz, 2 H), 3.69 (m, 3 H), 3.60 (m, 6 H), 3.53 (dd, J = 3.1, 7.8 Hz, 2 H), 3.48 (d, J = 3.1 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.32, 139.28, 138.46, 138.27, 138.16, 138.06 (C_{ipso}), 128.42, 128.29, 128.20, 128.08, 128.03, 127.91, 127.78, 127.62, 127.53, 127.47, 127.42, 127.07, 127.00, 126.91 (CH_{Ph}), 98.99, 98.84, 98.28 (C-1), 80.89, 80.84, 80.70, 80.45, 80.03, 79.62, 79.31, 78.99, 78.43, 76.74, 75.92, 75.81, 75.10, 73.49, 73.15, 72.93, 72.63, 71.86, 71.64, 70.80, 69.47, 68.88 (CH, CH_2), 52.34 (C-N_3) ppm. MS (MALDI-TOF): calcd. for $C_{148}H_{154}N_6O_{28}Na^+$ 2487.07; found 2488.92.

6^A,6^D-Diamino-O-benzyl-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-6^A,6^D-dideoxy-α-cyclodextrin (18): The α-CD-diazide **17** (1.36 g, 0.55 mmol) was dissolved in THF (80 mL) under N_2. Ph_3P on styrene (loading capacity = 1.7 mmol/g, 1.58 g) was added and the suspension was stirred at room temperature for 3 h. A 1 M aq. NaOH solution (100 μL) was added and the reaction was heated at reflux at 66 °C overnight. Filtration through a fritted funnel followed, the resin beads were washed with water and EtOAc and finally the water phase was extracted with EtOAc. The combined organic layers were washed with satd. aq. NaCl, dried with $MgSO_4$ and concentrated under vacuum. The pure compound (1.08 g, 0.45 mmol) was obtained as a transparent syrup in 81% yield. R_f (EtOAc) = 0.33. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.22 (m, 80 H, aromatic H), 5.63 (d, J = 1.7 Hz, 1 H), 5.45 (d, J = 10.3 Hz, 1 H), 5.21 (d, J = 10.9 Hz, 2 H), 4.92 (d, J = 10.3 Hz, 2 H), 4.85 (d, J = 6.2 Hz, 4 H), 4.77 (m, 4 H), 4.59 (d, J = 5.1 Hz, 1 H), 4.54 (m, 4 H), 4.47 (dd, J = 5.9, 12.2 Hz, 6 H), 4.35 (m, 5 H), 4.23 (m, 3 H), 4.08 (m, 12 H), 3.86 (m, 10 H), 3.70 (dd, J = 10.5, 20.5 Hz, 6 H), 3.58 (d, J = 8.6 Hz, 3 H), 3.46 (d, J = 9.2 Hz, 3 H), 3.34 (d, J = 9.4 Hz, 3 H), 2.90 (d, J = 13.7 Hz, 2 H), 2.81 (d, J = 13.5 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.58, 139.55, 138.83, 138.60, 138.45, 138.34, 138.25 (C_{ipso}), 132.41, 132.28, 132.19, 129.72, 128.55, 128.49, 128.40, 128.24, 127.93, 127.83, 127.35, 126.63 (CH_{Ph}), 98.61, 98.52, 98.27 (C-1), 81.61, 81.23, 81.16, 81.03, 80.91, 80.10, 79.32, 78.19, 77.48, 76.51, 76.22, 75.76, 74.36, 73.73, 73.65, 73.59, 73.23, 72.48, 72.21, 72.13, 71.27, 69.92, 69.33 (CH, CH_2), 42.87 (C-NH_2) ppm. MS (MALDI-TOF): calcd. for $C_{148}H_{158}N_2O_{28}$ 2412.10; found 2412.42.

6^A,6^D-Diamino-O-benzyl-6^A,6^D-dideoxy-2$^{A–F}$,3$^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-N,N,N′,N′-tetramethyl-α-cyclodextrin (19): The α-CD-diamine **18** (0.84 g, 0.35 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and added dropwise to 96% HCOOH (1.60 mmol) under N_2. A 37% HCOH solution in MeOH, (1.39 mmol) was then added slowly to the solution and after 30 min $NaCNBH_3$ (2.79 mmol) was added. After 48 h, H_2O was added and the aqueous phase was extracted with CH_2Cl_2. The organic layers were washed with $NaHCO_3$ and satd. aq. NaCl, dried with $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography followed (EtOAc/pentane, 1:4, + 1% Et_3N → EtOAc + 1% Et_3N). The pure product was obtained as a colourless syrup in 76% yield (0.65 g, 0.26 mmol). R_f (EtOAc/pentane, 1:2) = 0.43. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.22 (m, 80 H, aromatic H), 5.36 (d, J = 3.6 Hz, 2 H), 5.31 (s, 1 H), 5.22 (d, J = 10.9 Hz, 2 H), 5.15 (d, J = 3.0 Hz, 2 H), 5.10 (d, J = 11.3 Hz, 2 H), 4.96 (s, 1 H), 4.93 (d, J = 2.6 Hz, 2 H), 4.87 (d, J = 11.8 Hz, 5 H), 4.58 (d, J = 11.9 Hz, 3 H), 4.48 (m, 15 H), 4.36 (d, J = 12.1 Hz, 2 H), 4.19 (dd, J = 6.7, 15.6 Hz, 4 H), 4.12 (d, J = 4.3 Hz, 2 H), 4.09 (d, J = 4.3 Hz, 2 H), 4.03 (d, J = 9.5 Hz, 7 H), 3.98 (d, J = 4.9 Hz, 2 H), 3.94 (d, J = 5.6 Hz, 2 H), 3.87 (m, 3 H), 3.62 (d, J = 10.4 Hz, 2 H), 3.53 (m, 6 H), 3.44 (s, 1 H), 3.39 (dd, J = 2.9, 9.7 Hz, 2 H), 3.03 (dd, J = 5.0, 13.4 Hz, 2 H), 2.27 (d, J = 13.7 Hz, 2 H), 2.12 (s, 12 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.84, 139.74, 139.72, 138.79, 138.71, 138.65, 138.51 (C_{ipso}), 128.53, 128.45, 128.38, 128.32, 128.20, 128.07, 127.84, 127.80, 127.70, 127.57, 127.15 (CH_{Ph}), 99.18, 98.98, 98.52 (C-1), 82.08,

81.49, 81.27, 80.96, 80.51, 79.67, 78.83, 78.30, 76.02, 75.88, 75.28, 73.61, 73.50, 73.12, 72.87, 72.76, 71.82, 71.65, 71.46, 69.27, 69.08 (CH, CH_2), 59.38 (C-6), 47.14 (CH_3) ppm. MS (MALDI-TOF): calcd. for $C_{152}H_{166}N_2O_{28}$ 2468.17; found 2468.47.

6^A,6^D-Diammonio-*O*-benzyl-$2^{A–F}$,$3^{A–F}$,6^B,6^C,6^E,6^F-hexadecyl-6^A,6^D-dideoxy-*N*,*N*,*N*′,*N*′-tetramethyl-*N*,*N*′-(2-oxopropa-1,3-dienyl)-α-cyclodextrin Dibromide (20): The α-CD-tetramethyldiamine **19** (0.34 g, 0.14 mmol) was dissolved in dry acetone (15 mL) under N_2. 1,3-Dibromoacetone (0.83 mmol) was added in one portion. After 24 h, the mixture was concentrated under vacuum and the residue was recrystallized with acetone/water to give the pure product (0.216 g, 0.09 mmol, 62%). R_f (CH_2Cl_2/MeOH, 9:1) = 0.27. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.28 (m, 80 H, aromatic H), 4.75 (m, 37 H), 4.14 (m, 7 H), 3.90 (m, 18 H), 3.51 (m, 18 H), 3.05 (m, 10 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 194.10 (C=O), 139.52, 139.44, 139.38, 139.25, 139.04, 138.80, 138.55, 138.41, 138.34, 138.24, 138.17, 138.01, 137.93, 137.83, 137.74, 137.61 (C_{ipso}), 129.66–126.91 (CH_{Ph}), 98.63, 98.28, 98.03, 96.99 (C-1), 83.27, 82.87, 80.72, 80.34, 80.13, 79.76, 79.45, 79.25, 78.51, 76.41, 75.60, 74.46, 74.20, 73.92, 73.64, 73.53, 73.34, 73.14, 72.75, 72.47, 71.59, 71.44, 69.72, 69.53, 69.44, 69.23, 68.23, 67.68, 66.86, 66.66, 66.52, 53.43, 53.28, 52.59, 52.38 (CH, CH_2, CH_3) ppm. IR: $\tilde{\nu}$ = 3062.35, 3030.11 (Csp^2–H), 2923.70 2928.07 (Csp^3–H), 1728.94 (C=O), 1496.10, 1454.33, 1359.47, 1263.36, 1208.28 (C–N), 1097.91, 1027.86 (C–O) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{155}H_{170}N_2O_{29}$ 2524.19; found 2524.30.

6^A,6^D-Diammonio-6^A,6^D-dideoxy-*N*,*N*,*N*′,*N*′-tetramethyl-*N*,*N*′-(2-oxopropa-1,3-dienyl)-α-cyclodextrin Dibromide (21): Compound **20** (108 mg, 0.04 mmol) was dissolved in $HOCH_2CH_2OCH_3$ (10 mL), Pd/C was added and the mixture was stirred under H_2 for 24 h. Filtration through a Millipore nylon membrane (0.45 μm, 47 mm) followed and the solvent was then evaporated. The pure compound was obtained in its hydrated form in 97% yield (42 mg). ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 4.96 (m, 6 H, 1-H), 3.84 (m, 22 H), 3.65 (m, 6 H), 3.44 (m, 32 H), 3.24 (m, 8 H), 2.64 (s, 6 H) ppm. ^{13}C NMR (250 MHz, D_2O, 25 °C): δ = 101.76–101.28 (C-1), 83.87, 83.34, 81.93, 81.20, 77.05, 76.74, 76.24, 76.15, 75.36, 74.29, 74.04, 73.77, 73.40, 73.29, 73.20, 72.76, 72.52, 72.44, 71.88, 71.68, 71.62, 71.38, 66.91, 66.60, 66.46, 66.36, 65.27, 64.92, 64.86, 61.52, 60.89, 60.36, 58.71, 58.30–58.15, 53.78, 53.53, 53.48 (CH, CH_2, CH_3) ppm. IR: $\tilde{\nu}$ = 3429.63 (OH), 2928.07 (Csp^3–H), 1724.46 (C=O), 1631.03, 1454.02, 1384.32, 1275.10, 1203.76 (C–N), 1151.28, 1091.60, 1039.88 (C–O) cm^{-1}. MS (ES+): calcd. for $C_{43}H_{75}N_2O_{29}^+$ 1083.45; found 1083.50.

Procedure for Determining the Rate of Oxidation: Each assay was performed on 14 samples (2 mL each) of the appropriate substrate at different concentrations in 100 mM phosphate buffer containing 64 mM H_2O_2 and either **14** or **15** (1 mg, 2 mL) or with nothing as a control. The reactions were followed at 25 °C by analysing the UV absorption at an appropriate wavelength (see below) typically for 30 min for aniline oxidation and for 5 h for benzyl alcohol oxidation. The velocities were determined as the slope of the progress curve of each reaction 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 by using non-linear least-squares regression fitting to the V_{max} versus S curve, k_{cat} was calculated as V_{max}/[cyclodextrin] and k_{uncat} was determined as the slope from a plot of V_{uncat} versus S. The following extinction coefficients (25 °C, pH 7) and wavelengths were determined and used: 2-aminophenoxazine-3-one: 0.42 mM^{-1} cm^{-1} (pH 7.0); 5-amino-2-hydroxy-*N*,*N*′-bis(*p*-hydroxyphenyl)-1,4-benzoquinonediimine: 1.59 mM^{-1} cm^{-1} (pH 7.0); 4-methyl-2-nitrophenol: 1.06 mM^{-1} cm^{-1} (pH 7.0); 5-methyl-2-nitrophenol: 2.26 mM^{-1} cm^{-1} (pH 7.0); benzaldehyde: 1.23 mM^{-1} cm^{-1} at 285 nm; acetophenone: 0.32 mM^{-1} cm^{-1} at 300 nm; 2-hydroxybenzaldehyde: 2.92 mM^{-1} cm^{-1} at 325 nm; 2-methoxybenzaldehyde: 2.75 mM^{-1} cm^{-1} at 323 nm.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **5**–**21**.

Acknowledgments

We thank the Lundbeck Foundation and the University of Copenhagen for financial support.

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Received: September 25, 2009
Published Online: November 24, 2009

