Synthesis of Monofacially Functionalized Cyclodextrins Bearing Amino Pendent Groups

Dragos Vizitiu, Caroline S. Walkinshaw, Borio I. Gorin, and Gregory R. J. Thatcher*

Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

Received June 25, 1997[⊗]

Derivatives of the cyclodextrins, αCD, *β*CD, and *γ*CD, in which all primary hydroxyls are substituted by amine pendant groups, may be synthesized efficiently from the per-6-bromo-6-deoxy-CD derivatives by direct reaction with amines. These ACD derivatives, which bear six, seven, or eight amine pendent groups, represent interesting biomimetic receptors and catalysts. The synthetic strategy relies on quantitative transformation and efficient purification as is demonstrated by preparation of 11 homogeneous ACD derivatives. The limitations of the synthesis and potential adaptations are illustrated by the synthesis of several more ACD derivatives to >95% purity. A synthetic route to a CD persubstituted with primary amine functionalities at the primary face, per-6-(aminomethyl)-6-deoxy-CD, yields an alternative reagent to the simple per-6-amino-6-deoxy-CD, which is more suitable for further synthetic transformations. The synthetic strategy is further adapted to preparation of a prototypical (6 + 1)-ACD derivative in which one primary position is substituted with a sulfide group and the remaining six primary face positions are substituted with amine pendent groups.

Introduction

The cyclodextrins αCD, *β*CD, and *γ*CD are naturally occurring cyclomaltooligosaccharides containing six, seven, and eight α-(1→4)-D-glucopyranosyl rings, respectively.[1] The use of synthetic CD derivatives as molecular scaffolds is of interest since the primary (6′) and secondary (2′ and 3′) hydroxyl groups may be used as points of functionalization.[2] However, the hydrophobic interior of these torus-shaped molecules has provided the focus of much of the chemistry and applications of cyclodextrins. The cavity binds hydrophobic, organic molecules of appropriate size, yielding inclusion complexes.[3] The potential utility of this inclusion phenomenon includes solubilization, encapsulation, and transport of small hydrophobic molecules including toxins and drugs.[4] The facile ionization of the hydroxyl groups on the secondary face annulus provides a nucleophilic site that has been seen as analogous to that of the serine proteases.[5] Thus, early studies proposed that substrate binding within the cavity, combined with the reactivity of the secondary annulus, made cyclodextrins ideal candidates for enzyme models.[6] In numerous cases, cyclodextrins provide acceleration of reaction, in contrast to true catalysis; however, both natural cyclodextrins and synthetic CD derivatives have been enduring features of the field of enzyme mimicry.[7] CDs remain attractive for study as enzyme mimics because of the incorporation of substrate binding and product release in aqueous solution within the catalytic mechanism.[8]

Derivatization at one or two of the 6′ carbons yields a mono- or difunctionalized primary face, respectively. This procedure is facile, although overall yields are often unsatisfactory.[9] Monofunctionalization of the secondary face is less facile and has been limited to a much smaller selection of pendent groups.[10] Many of these synthetic CD derivatives have been reported as enzyme models, utilizing in some cases the secondary face hydroxyls, and in other examples, the pendent, prosthetic group as the catalytic or reactive functionality.[6] Procedures for monofacial derivatization have been developed for both the primary face (all 6′ positions) and the secondary face (all 2′ and 3′ positions) of CD. Procedures for CD "perderivatization" yield both homogeneous and heterogeneous, modified cyclodextrins.[11] In the heterogeneous examples, the CD derivative is described by the degree of substitution. In these polysubstituted CD derivatives, the pendent groups have been utilized primarily to modify the bulk properties of the CD: to extend the hydrophobic cavity in order to influence binding and encapsulation and, most importantly, to increase the poor aqueous solubility of natural CD itself.

Monofacially functionalized CD derivatives persubstituted on the primary face with six, seven, or eight

* To whom correspondence should be addressed. Fax: (613) 545-6669. E-mail: thatcher@chem.queensu.ca.

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) Szetli, J. *Cyclodextrins and their inclusion complexes*; Akademiai Kiado: Budapest, 1982. Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.

(2) (a) Hanessian, S.; Benalil, A.; Laferriere, C. *J. Org. Chem.* **1995**, *60*, 4786. (b) Ashton, P. R.; Koniger, R.; Stoddardt, J. F.; Alker, D.; Harding, V. D. *J. Org. Chem.* **1996**, *61*, 903. (c) Yoon, J.; Hong, S.; Martin, K. A.; Czarnik, A. W. *J. Org. Chem.* **1995**, *60*, 2792.

(3) For example: Rudiger, V.; Eliseev, A.; Simova, S.; Schneider, H. J.; Blandamer, M. J.; Cullis, P. M.; Meyer, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2119.

(4) Komiyama, M. In *Comprehensive Supramolecular Chemistry*; Lehn, J. M., Ed.; Pergamon: New York, 1996; Vol. 3 and references therein. Eastburn, S. D.; Tao, B. Y. *Biotech. Adv.* **1994**, *12*, 325. Sjetli, J. *Pharm Technol. Int.* **1991**, *3*, 15. Schipper, N. G. M.; Hermens, W. A. J. J.; Romeijn, S. G.; Verhoef, J.; Merkus, F. W. H. M. *Int. J. Pharm.* **1990**, *64*, 61.

(5) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146. Palmer, D. R. J.; Buncel, E.; Thatcher, G. R. J. *J. Org. Chem.* **1994**, *59*, 5286.

(6) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. Tee, O. S.; Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739. Bozzi, M.; Hoeven, J. J.; Gadosy, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 8990. Tee, O. S. *Adv. Phys. Org. Chem.* **1994**, *29*, 1.

(7) Breslow, R.; Duggan, P. J.; Light, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 3982. Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 893. Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390.

(8) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(9) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirikata, H.; Fujita, *J. Am. Chem. Soc.* **1976**, *98*, 7855. Tabushi, I.; Shimokawa, K.; Fujita, K. *Tetrahedron Lett.* **1977**, *18*, 1527. Yoon, J.; Hong, S.; Martin, K. A.; Czarnik, A. W. *J. Org. Chem.* **1995**, *60*, 2792. Breslow, R.; Doherty, J. B.; Guillot, G.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227.

(10) Murakami, T.; Harata, K.; Morimoto, S. *Tetrahedron Lett.* **1986**. Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451. Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275.

S0022-3263(97)01154-7 CCC: $14.00

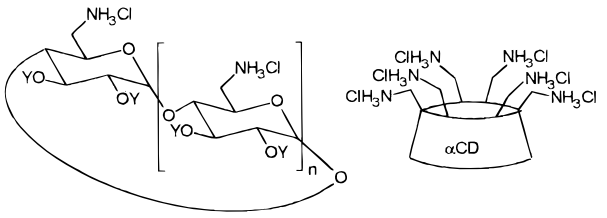


Figure 1. 6-Aminocyclodextrins.

pendent groups represent potentially interesting receptors and biomimetics (Figure 1). First, since the depth of the CD cavity is only one glucose residue (~7.9 Å), the corona formed from the pendent groups of a monofacially substituted CD may represent a significant alternate receptor to the cavity itself. Second, synergistic effects may be seen between the pendent groups, not seen in simple mono- or disubstituted CD derivatives.

Several attempts have been reported to couple CD to amino acids to form peptidomimetics, including monofacially substituted cyclodextrins.[12] An alternative strategy to the use of amino acids is to provide pendent groups that mimic the important peptide side chains. Amino-CD (ACD) derivatives with varied amine pendent groups provide a binding site rich in amino groups atop the hydrophobic binding site of the cavity (Figure 1). There are numerous examples of proteins with receptor sites rich in the basic residues Arg, Lys, and His, many atop hydrophobic pockets. Some of these are the functional receptor sites of proteins, such as the glycosaminoglycan sulfate binding site in, for example, antithrombin III.[13] Others are functional active sites of enzymes, for example, phosphatidylinositol-specific phospholipase C from *B. cereus*.[14] Further proteins, notably hemoglobin and serum albumin, possess hydrophobic, Lys-rich, binding sites that are capable of catalyzing unnatural reactions.[15] Water-soluble ACD derivatives combine these hydrophobic and electrostatic binding sites.

Despite recent advances, several obstacles remain to regioselective CD derivatization.[2,16] The most significant problems involve the peculiar difficulties in separation and purification, in particular using chromatography, which are amplified in charged CD derivatives. By using an efficient synthesis of the per-6-bromo-6-deoxy derivatives of αCD, *β*CD, and *γ*CD, the primary CD face may be per-substituted with a variety of pendent groups.[17] The syntheses of a number of ACD derivatives are reported herein, together with synthesis of a prototypical ACD in which one 6′ position is selectively modified with an alternative pendent group.

Results and Discussion

The most significant problems in regioselective CD synthesis are associated with difficulties in separation and purification, in particular using chromatography, which can be considerable in the case of charged CD derivatives. Low yields, often reported in the synthesis of CD derivatives exacerbate these problems. For example, in the synthesis of primary face functionalized, per-6-substituted 6-deoxy-*β*CD derivatives, incomplete or over-reaction leaves the problem of separating the fully heptasubstituted from hexa- and/or octasubstituted *β*CD derivatives, the physical properties of which are not distinctly different. A further peculiar complication is tight binding of some reaction byproducts within the CD cavity. Thus, quantitative conversions are required with suitable purification techniques that do not reduce the isolated yield excessively.

The predominant strategy for ACD synthesis has utilized halogenation at the 6′ position with in situ or subsequent substitution with azide, followed by efficient conversion to amine via the Staudinger reaction.,[18,19] Lehn's early strategies yielded isomeric products and required secondary face functionalization for purification.[19] Subsequently, several modifications have been reported leading to Defaye and co-workers' more recent perfacial bromination procedure using Br_2/PPh_3 in DMF.[16] However, Stoddart and co-workers have reported difficulties with the workup presented in this and a further paper. In its place, Stoddart's group employ selective precipitation and exhaustive Soxhlet extraction to remove impurities and byproducts, in particular, residual triphenylphosphine oxide.[2b] We have been using an alternative procedure in which the Vilsmeier−Haack reagent $[(CH_3)_2NCHBr]^+Br^-$ [20] is prepared and washed prior to reaction with unprotected CD.[17,21] In this way, a significant portion of the Ph_3PO can be removed before reaction with CD, hence reducing the subsequent effort required to remove this persistent byproduct. We have reported this procedure for synthesis of the per-6-deoxy-6-bromo derivatives of αCD, *β*CD, and *γ*CD and subsequent efficient conversion to a variety of monofacially substituted analogues including perazido, peramino, percyano, permercapto, and perthioureido CD derivatives.[17]

Preparation of per-6-amino-per-6-deoxy-CD derivatives has been reported.[22,23] Synthesis via the per-6-azido-per-6-deoxy-CD derivative permits efficient Staudinger con-

(11) Ashton, P. R.; Uwood, P. E.; Staton, I.; Stoddardt, J. F. *J. Org. Chem.* **1991**, *56*, 7274. Folkman, J.; Weisz, P. B.; Joullie, M. M.; Li, W. W.; Ewing, W. R. *Science* **1989**, *243*, 1490. Sakairi, N.; Kuzuhara, H.; Okamoto, T.; Yajima, M. *Bioorg. Med. Chem.* **1996**, *4*, 2187. Moriya, T.; Kurita, H.; Matsumoto, K.; Otake, T.; Mori, H.; Morimoto, M.; Ueba, N.; Kunita, N. *J. Med. Chem.* **1991**, *34*, 2301. Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203. Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130. Fujedi, P. *Carbohydr. Res.* **1989**, *192*, 366. Coleman, A. W.; Zhang, P.; Parrot-Lopez, H.; Ling, C. C.; Miocque, M.; Mascrier, L. *Tetrahedron Lett.* **1991**, *32*, 3997. Zhang, P.; Ling, C. C.; Coleman, A. W.; Parrot-Lopez, H.; Galons, H. *Tetrahedron Lett.* **1991**, *32*, 2769. Khan, A. R.; Barton, L.; D′Souza, V. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1112. Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203. Boger, J.; Brenner, D. G.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7630. Fugedi, P. *Carbohydr. Res.* **1989**, *192*, 366.

(12) Parrot-Lopez, H.; Djedaini, F.; Perly, B.; Coleman, A. W.; Galons, H.; Miocque, M. *Tetrahedron Lett.* **1990**, 1999. Cucinotta, V.; D'Allessandro, F.; Impellizzeri, G.; Pappalardo, G.; Rizzarelli, E.; Vecchio, G. *J. Chem. Soc. Chem. Commun.* **1991**, 293. Akerfeldt, K. S.; DeGrado, W. F. *Tetrahedron Lett.* **1994**, 4489.

(13) Jackson, R. L.; Busch, S. J.; Cardin, A. D. *Physiol. Rev.* **1991**, *71*, 481.

(14) Vizitiu, D.; Campbell, A. S.; Thatcher, G. R. J. *J. Mol. Recog.* **1996**, *9*, 197. Heinz, D. W.; Ryan, M.; Smith, M. P.; Weaver, L. H; Keana, J. F.; Griffith, O. H. *Biochemistry* **1996**, *35*, 9496.

(15) Thorn, S. N.; Daniels, R. G.; Auditor, M. M.; Hilvert, D. *Nature* **1995**, *373*, 228. Kikuchi, K.; Thorn, S. N.; Hilvert, D. *Nature* **1996**, *118*, 8184. Hollfelder, F.; Kirby, A. J.; Tawfik, D. S. *Nature* **1996**, *383*, 60. Elbaum, D.; Wiedenmann, B.; Nagel, R. *J. Biol. Chem.* **1982**, *257*, 8454.

(16) (a) Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78. (b) Baer, H. H.; Berenguel, A. V.; Shu Y. Y.; Defaye J.; Gadelle, A.; Gonzalez, F. S. *Carbohydr. Res.* **1992**, *228*, 307.

(17) Gorin, B. I.; Riopelle, R. J.; Thatcher, G. R. J. *Tetahedron. Lett.* **1996**, *37*, 4647.

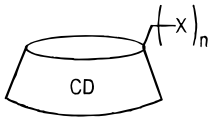
(18) Parrot-Lopez, H.; Ling, C−C.; Zhang, P.; Baszkin, A.; Albrecht, G.; de Rango, C.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5479.

(19) Boger, J.; Corcoran, R. J.; Lehn, J.-M., *Helv. Chim. Acta* **1978**, *61*, 2190.

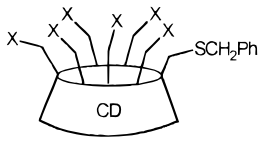
(20) Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 754.

(21) Borrajo, A. M. P.; Gorin, B. I.; Dostaler, S. M.; Riopelle, R. J.; Thatcher, G. R. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1185.

version to the per-6-amino-per-6-deoxy-CD and has the advantage that direct secondary face modification of the azide is possible without recourse to standard techniques of primary face protection. However, this route exacerbates the problem with residual Ph_3PO, and furthermore, the product per-6-amino-per-6-deoxy-CD has poor solubility in all common solvents in the free base form (e.g., DMSO, DMF, H_2O). Nevertheless, coupling of amino acids with per-6-amino-per-6-deoxy-CD has been reported.[2b] Reaction of per-6-aminoper-6-deoxy-CD with pyridyl carboxaldehydes and subsequent reduction is also a feasible route to extended pyridyl-ACD derivatives. However, the alternative route to ACD derivatives via direct amination of the per-6-bromo-per-6-deoxy-CD (**1**) is more facile, providing a pathway to a number of ACD derivatives.



1 X=Br
2 X=NH$(CH_2)_2$OH
3 X=NMe$(CH_2)_2$OH
4 X= NHCH$(CH_2OH)_2$
5 X=N$((CH_2)_2OH)_2$
6 X= NH$(CH_2)_2$OMe
7 X= NH$(CH_2)_2$NMe$_2$
8 X= NMe$(CH_2)_2$NMe$_2$
9 X= NCHNHCHCH
10 X= NH$(CH_2)_2C_6H_4$OH
11 X= NHCH$_2C_6H_5$
16 X= CN
17 X= CH_2NH_2
α n=6; β n=7; γ n=8



13 X=NMe$(CH_2)_2$OH

Per-6-[(2-hydroxyalkyl)amino]-6-deoxy-CD. Heating of **1** at 75−80 °C, in excess of amine, without solvent, resulted in quantitative conversion to the corresponding ACD. The reaction took 1−2 days for completion, depending on the amine used as starting material. With liquid amines, reaction was complete in 24 h, whereas with the molten amine, serinol, up to 48 h was required for completion. The amine excess was calculated as 10 equiv of amine/Br, serving both as reagent and solvent. The workup procedure requires removal of excess free amine by high-vacuum distillation, followed by precipitation in acetone and washing of the precipitate. Where distillation proved inefficient, direct acetone precipitation of the reaction mixture was performed. Our experience in handling cyclodextrins shows that temperatures higher than 80 °C lead to CD ring cleavage products, which cannot be removed cleanly at any stage of the workup. Accordingly, in both reactions and distillations, the temperature never exceeded 80 °C.

The crude solid resulting from acetone precipitation showed total conversion of **1** by ^{13}C NMR, but in every case, starting amine was present presumably as the HBr salt. Further purification could follow one of two routes. Route I: the amine excess was removed as the HBr salt. Acidification of the crude ACD product with HBr followed by exhaustive washings with hot abs. ethanol removed all the excess amine. Trace ethanol was removed by methanol washing, followed by thorough drying. Route II requires dissolution of the crude ACD product in a minimum amount of refluxing methanol followed by precipitation in acetone, washing and subsequent titration with aqueous HBr. The ACD products obtained by these methods were characterized as the per-HBr salts, as confirmed by elemental analysis. In some cases, the ACD derivatives were treated with anion-exchange resins in order to obtain the free amine forms. Per-6-[(2-methoxyhydroxyethylamino)]-6-deoxy-β-CD was synthesized in a similar fashion. Model reactions were also carried out with α- and γ-CD. The reactions between **1**α and **1**γ and either a primary amine, ethanolamine, or secondary amine, *N*-methylethanolamine, were successfully performed under conditions similar to those for reaction of **1**β. All ACD compounds were highly soluble in water, not only as HBr salts, but also as free bases, and consequently, all the NMR spectra were recorded in D_2O, displaying the high-symmetry expected from quantitative persubstitution of the primary face (Figure 1).

It is clear that the use of amine as reagent and solvent contributes to the quantitative conversion. Reaction with tris(hydroxymethyl)aminomethane (TRIS), which must be performed in a minimum amount of DMSO or DMF as solvent, does not proceed to completion. Further, when simple diethylamine was used, no reaction occurred because of the insolubility of **1** even at reflux (55 °C).

Per-6-[(2-aminoalkyl)amino]-6-deoxy-CD. Reaction of **1** with primary and secondary amine sites of 2-hydroxyethylamines is clearly facile. To examine competitive reaction of different amine sites and further extend the family of ACD derivatives, reactions with *N*,*N*-dimethylethylenediamine and *N*,*N*,*N*′-trimethylethylenediamine were examined. Reaction with *N*,*N*-dimethylethylenediamine, followed by acetone precipitation, yielded a solid product that by ^{13}C NMR showed complete substitution of the bromide with a pattern corresponding to displacement by primary amine alone. Purification to remove the excess amine was achieved after treatment with an anion-exchange resin, followed by exhaustive washing of the neutral ACD product with acetone. The reaction of **1** with *N*,*N*,*N*′-trimethylethylenediamine was carried out under the same conditions, but the result was different. In this case, a very small, but observable competitive substitution by the tertiary amine nucleophile was observed by ^{13}C NMR. Given the finding that a tertiary amine was nucleophilic toward **1**, the reaction with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was examined. Unfortunately, DMF was required as solvent, leading again to incomplete substitution. The ACD derivatives synthesized by these methods are highly soluble in water in salt and free base forms. Furthermore, there is no evidence from NMR, MS or combustion analysis of intramolecular or oligomerization reactions (Figure 2).

ACD Derivatives Bearing Amino Acid Side Chains. Direct imidazole substitution of **1** was attempted in order to obtain a per-6-imidazolyl-6-deoxy-CD. The reaction proceeded well in a minimum amount of DMF, at 75−80 °C, in 24 h. After removal of DMF, the remaining residue was precipitated in water. The poor aqueous solubility of the imidazolyl-substituted CD assisted in separation and purification, but raises concerns over the utility of

(22) Tagaki, W.; Yano, K.; Yamanaka, K.; Yamamoto, H.; Miyasaki, T. *Tetrahedron Lett.* **1990**, 3897. Matsui, Y.; Tanemura, E.; Nonomura, T. *J. Am. Chem. Soc.* **1993**, *66*, 2827.

(23) Synthesis of per-6-(methylamino)-6-deoxy-CD from direct condensation of amine with **1**β has been reported previously to proceed with high but incomplete substitution at the 6′ position (Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762. Eliseev, A. V.; Schneider, H. J. *J. Am. Chem. Soc.* **1994**, *116*, 6081).

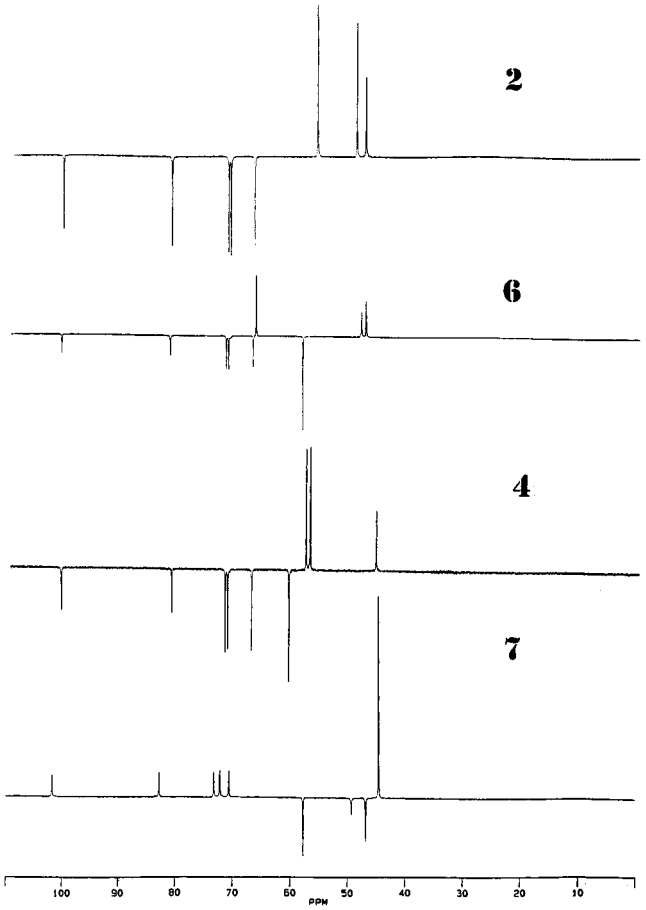


Figure 2. 100 MHz J-MOD ^{13}C NMR spectra for **2**, **6**β, **4**β, and **7**β.

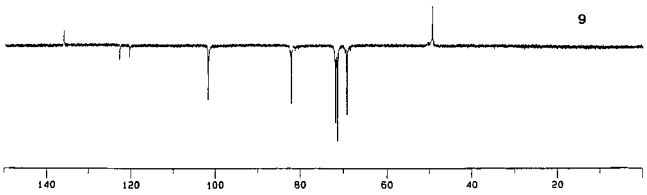


Figure 3. 100 MHz J-MOD ^{13}C NMR spectra for perimidazolide **9**β.

this ACD derivative. Excess imidazole was removed by purification route I (*vide supra*). Curiously, the product displayed an anomalous reversed phase for the imidazolyl-C_2' at $\delta \sim 136.24$ in the standard J-MOD ^{13}C NMR spectrum (Figure 3). The low intensity and the reversed phase of this C_2' signal is caused by the large J_{CH} coupling constant (220 Hz), and the assignment is confirmed by an heteronuclear shift correlation experiment. The imidazoyl-CD product was >95% pure by ^{13}C NMR but clearly showed evidence of small amounts of other products (Figure 3). Coupling of two CD units at the primary face by an imidazole linker has been reported. The ease of reaction of **1** with imidazole disallows synthesis of an histidyl-CD mimic by reaction of **1** with histamine.

To obtain a tyrosyl-CD mimic, reaction of tyramine with **1** was examined. We had shown that benzylamine reacted cleanly with **1** without cosolvent, although the product had limited aqueous solubility. For reaction with tyramine, DMF was required as solvent. After 24 h, the reaction mixture was worked up using route I, yielding an off-white solid product with limited water solubility. Elemental analysis confirmed quantitative substitution of the primary face, but the ^{13}C NMR of the product revealed competitive N and O substitution. Although *O*-protection would be required to obtain the homogeneous *N*-substituted ACD, this result clearly indicates the reactivity of **1** toward phenolate nucleophiles.

Per-6-(aminomethyl)-6-deoxy-CD. The per-6-cyano-6-deoxy-CD derivative (**16**) has clear potential as an ACD synthon, for example, in amino acid coupling, if effective reduction of the nitrile could be achieved. Nitrile reduction to the corresponding primary amine would provide an alternative ACD scaffold. However, it is well-known that catalytic hydrogenation of nitriles may give rise to a number of products, which include primary, secondary, and tertiary amines, imines, hydrocarbons, aldehydes, amides, and alcohols. The major product, derived as a result of these competing reactions, depends primarily on the catalyst, substrate, and reaction conditions. The potential for intramolecular reactions at the primary CD face suggests that the opportunity for side reactions may be enhanced in this case.

The nitrile **16** is obtained readily by reaction of **1** with KCN in dry DMF with heating at 75−80 °C for 24 h and subsequent purification. Nitrile hydrogenation was carried out in a Parr-pressure hydrogenator under a 50−55 psi H_2 pressure, at room temperature. Water was used as the reaction medium, although the nitrile was insoluble in water. PtO_2 was used as a catalyst, but no prehydrogenation of the catalyst was performed. A relatively large amount of catalyst (approximately 125 mg of PtO_2/1 mmol of CN) was selected in order to increase the rate of the main reaction. To minimize secondary amine formation an acidic medium was used. Various literature reports suggest that strong acids are required in order to prevent the addition reaction between primary amine and imine, but in our case the use of strong acid is severely limited by the stability of the cyclodextrin ring. A previous attempt at CD-nitrile hydrogenation reported a mixture of products.[16b] We employed an equimolar amount of HCl in a dilute aqueous solution to prevent the serious degradation observed when excess HCl was employed. Use of a milder acid, such as formic acid, did not yield the desired product, but ^{13}C NMR suggested formation of secondary and tertiary amines. In the absence of acid catalyst, no reaction occurred. The optimum reaction time was selected as 3 h to minimize undesired side reactions and since the nitrile was observed to be entirely consumed within this period. The subsequent workup procedure is extremely simple, involving only the filtration of the catalyst through a prewashed Celite bed followed by concentration of the clear filtrate. The ^{13}C NMR of the final product clearly indicates the seven major peaks of the desired product, in addition to a limited number of smaller side-product peaks (Figure 4). The product, obtained as the HCl salt, may be converted to free base form using anion-exchange resin. Surprisingly, in contrast to per-6-amino-6-deoxy-CD, per-6-(aminomethyl)-6-deoxy-CD is freely water soluble in base form. The purity of the per-6-(aminomethyl)-6-deoxy-CD obtained in this way was estimated at ≥98% on the basis of ^{13}C NMR. The synthetic utility of 6-amino-6-deoxy-CD itself is severely limited by the poor solubility of the free amino derivatives and Ph_3PO contamination. The route to per-6-(aminomethyl)-6-deoxy-CD described herein provides an alternative, improved, nucleophilic ACD synthon.

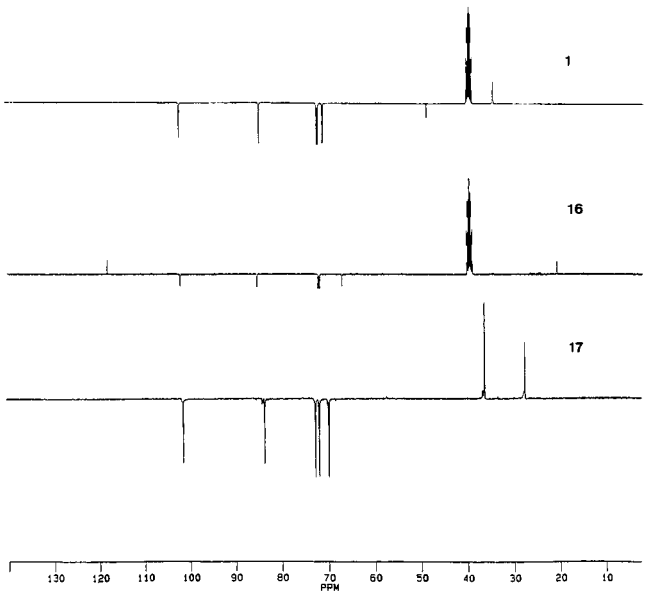


Figure 4. 100 MHz J-MOD ^{13}C NMR spectra for **1*β***, **16*β***, and **17*β***.

6 + 1 Substituted *β*CD. Monotosylation of *β*CD proceeds cleanly although in low yield after rigorous purification from water.[24] Displacement of the tosyl group by benzylthiolate proceeded to completion in 12 h, at 65−70 °C, in DMF. After evaporation of DMF, a crude solid remained, which was washed several times with water and then acetone. ^{13}C NMR of the resulting product indicated the presence of the benzyl disulfide, which could not be rigorously removed from the CD product, possibly because of tight-binding with the CD derivative, involving the hydrophobic cavity and p-stacking interactions. The crude mono-6-(benzylthio)-6-deoxy-*β*CD was brominated using the Vilsmeier−Haack reagent in an identical fashion to that used for simple *β*CD, yielding a product contaminated with dibenzyl disulfide. To obtain an example of (6 + 1)-*β*ACD, *N*-methylethanolamine was used to displace bromide. Reaction with the amine as reagent and solvent, at 75−80 °C, for 24 h afforded the (6 + 1)-*β*ACD, which was readily purified by evaporation of excess amine, precipitation in acetone, and acidification in water to pH 3 with 1 M HBr. The resulting emulsion was washed with chloroform, concentrated, and then washed with hot absolute ethanol. Precipitation from water allowed for the complete removal of the benzyl disulfide contaminant after filtration through Celite. The ^{13}C NMR spectrum of the product obtained from the filtrate showed the desired product 6 + 1 substitution pattern, confirmed by MS and elemental analysis.

Summary

An efficient synthetic route to ACD derivatives has been described and demonstrated by synthesis of 11 homogeneous ACD derivatives. The limitations of this route and potential adaptations are illustrated by the synthesis of several ACD derivatives to >95% purity. A new synthetic route to a CD persubstituted with primary amine functionalities at the primary face, per-6-(aminomethyl)-6-deoxy-CD, yields an alternative synthon to the simple per-6-amino-6-deoxy-CD, which is soluble in a range of polar solvents. Finally, the utility of the synthetic strategy to synthesis of (*n* + 1)-ACD derivatives is demonstrated by preparation of an homogeneous (6 + 1)-*β*ACD. ACD derivatives possess catalytic activity at physiological pH,[25] since reaction is not dependent upon ionization of a secondary hydroxyl: thus, (*n* + 1)-ACD derivatives in which one 6′ position is functionalized with an alternative receptor or catalytic group have significant scope as biomimetics.

Experimental Section

General Methods. Unless otherwise stated, chemicals were used as received. DMF was dried over CaH_2 prior to use and stored over the same. Cyclodextrins were recrystallized from water and dried under vacuum in a drying pistol over P_2O_5 at 100 °C prior to use. Reactions were performed under inert atmosphere (Ar or N_2) unless water was a component or byproduct of reaction. Routine ^1H and ^{13}C NMR spectra were recorded on a Bruker AC/F-200 or Bruker AM-400 spectrometer (at 50, 100, 200 or 400 MHz). High-field assigments are reported. Mass spectra were recorded on a VG mass spectrometer, using fast atom/ion bombardment (FAB, ion source) in a glycerol or thioglycerol matrix. Carbon, hydrogen, nitrogen, and oxygen analyses were carried out in a gas chromatography unit (Carlo Erba 1104) in which the sample is burned and the amount of the resulting gases are measured by thermal conductivity. CHN analyses involve combustion of the sample in oxygen; the resulting carbon dioxide, water, and nitrogen are measured by thermal conductivity and compared directly with known standards, most commonly acetanilide and nitroaniline. Oxygen is analyzed in a similar manner, but carbon monoxide is the gas formed and measured by thermal conductivity.

Per-6-bromo-6-deoxy-*β*-cyclodextrins (1). The bromination of cyclodextrin was carried out using the Vilsmeier−Haack reagent $[(CH_3)_2NCHBr]Br$, which was prepared by dropwise addition of Br_2 (2.75 mL, 53.3 mmole) to a solution of triphenylphosphine (14 g, 53.3 mmole) in 60 mL of dry DMF with vigorous stirring, under Ar. During the addition, the reaction mixture was not allowed to warm above 60 °C. The resulting precipitate was further stirred at rt for 30 min. After cooling to 0 °C, filtration of the reaction mixture under Ar afforded the iminium salt as a yellow crystalline solid. Successive washing on the filter with cold dry DMF, under Ar, resulted in the white crystalline Vilsmeier−Haack reagent, almost clean of the triphenylphosphine oxide side product. The yield was calculated as approximately 80% by isolation of the salt. However, in all subsequent usage, this reagent was used in situ without isolation and a value of 80% was assumed in calculations of molar equivalents. To the Vilsmeier−Haack reagent (12 equiv for αCD, 14 equiv for *β*CD, and 16 equiv for *γ*CD) were added 100 mL of dry DMF and recrystallized *β*-cyclodextrin (freshly dried, 3.4 g, 3 mmol), and the reaction mixture was heated at 75−80 °C, under Ar. It is extremely important not to exceed 80 °C, in which case the solution turns dark-brown and the yield is severely diminished. After 10−12 h, the DMF was removed under vacuum and the remaining oil was poured into 50 mL of 3 M sodium methoxide solution in methanol, previously cooled to 0 °C. After 1 h of stirring at rt, the mixture was precipitated in a large amount of cooled water and filtered followed by successive washings with methanol to afford **1** as a white solid, in 95% isolated yield: ^{13}C NMR (DMSO-d_6) δ 102.10 (C_1), 84.63 (C_4), 72.29 (C_3), 72.05 (C_2), 71.01 (C_5), 34.42 (C_6); MS (+FAB, Cs^+ source) M + H^+ 1576.

General Procedure: Per-6-(alkylamino)-6-deoxycyclodextrins (2−6). Per-6-(alkylamino)cyclodextrins were synthesized by treating **1** with an excess of alkylamine (10 molar equiv of amine per Br equivalent) at 80 °C for 24−48 h. The

(24) Zarzycki, R.; Hoehn, P.; Duong, B. *Minutes Int. Symp. Cyclodextrins, 6th* **1992**, 663.

(25) McCracken, P. G.; Vizitiu, D.; Walkinshaw, C. S.; Gorin, B. I.; Wang, Y.; Thatcher, G. R. J. Manuscript submitted.

reagent/solvent was removed under vacuum, and the residue was precipitated in acetone. After filtration, and washing with acetone, the solid was taken up in water and the pH was carefully brought down to 4 with 1 M HBr. The aqueous solution was evaporated under vacuum and further dried on the vacuum line. The resulting solid was washed three times with hot absolute ethanol in order to remove all of the unreacted starting amine. The last filtrate was perfectly clear. After drying on the vacuum line, persubstitution of the primary face was confirmed by ^{13}C NMR, MS, and elemental analysis.

Per-6-[(2-hydroxyethyl)amino]-6-deoxy-α-cyclodextrin (2a): ^{13}C NMR (D_2O) δ 101.11 (C_1), 82.29 (C_4), 72.30 (C_3), 71.20 (C_2), 67.59 (C_5), 56.47 (CH_2OH), 49.87 (NCH_2), 48.02 (C_6); MS (+FAB) M + H^+ 1231.3, M + H_2Br^+ 1313.2. Anal. Calcd for $C_{48}H_{90}N_6O_{30}\cdot 6HBr\cdot 4H_2O$: C, 32.23; H, 5.86; N, 4.70. Found: C, 32.04; H, 5.59; N, 4.55.

Per-6-[(2-hydroxyethyl)amino]-6-deoxy-β-cyclodextrin (2b): ^{13}C NMR (D_2O) δ 101.07 (C_1), 81.91 (C_4), 72.00 (C_3), 71.60 (C_2), 67.47 (C_5), 56.65 (CH_2OH), 49.83 (NCH_2), 48.24 (C_6); MS (+FAB) M + H^+ 1435.7. A sample for elemental analysis was passed through a column with basic exchange resin (Dowex 1-X8) to afford the free base form of the compound. Anal. Calcd for $C_{56}H_{105}N_7O_{35}\cdot H_2O$: C, 46.24; H, 7.41; N, 6.74; O, 39.6. Found: C, 46.53; H, 7.39; N, 6.63; O, 39.96.

Per-6-[(2-hydroxyethyl)amino]-6-deoxy-γ-cyclodextrin (2g): ^{13}C NMR (D_2O) δ 99.38 (C_1), 79.73 (C_4), 71.88 (C_3), 71.43 (C_2), 67.02 (C_5), 56.55 (CH_2OH), 49.79 (NCH_2), 48.29 (C_6); MS (+FAB) M + H^+ 1641.7. Anal. Calcd for $C_{64}H_{120}N_8O_{40}\cdot 8HBr\cdot 4H_2O$: C, 32.56; H, 5.81; N, 4.75. Found: C, 32.70; H, 5.56; N, 4.41.

Per-6-(*N*-methyl-*N*-(2-hydroxyethyl)amino)-6-deoxy-α-cyclodextrin (3a): ^{13}C NMR (D_2O) δ 99.21 (C_1), 79.67 (C_4), 71.89 (C_3), 71.55 (C_2), 66.37 (C_5), 56.83 (C6), 55.35 (CH_2OH, CH_2N), 41.55 (CH_3N); MS (+FAB) M + H^+ 1315.4. Anal. Calcd for $C_{54}H_{112}N_6O_{30}\cdot 6HBr\cdot 2H_2O$: C, 35.31; H, 6.15; N, 4.58. Found: C, 35.26; H, 6.12; N, 4.67.

Per-6-[*N*-methyl-*N*-(2-hydroxyethyl)amino]-6-deoxy-β-cyclodextrin (3b): ^{13}C NMR (D_2O) δ 99.80 (C_1), 80.65 (C_4), 71.70 (C_3, C_2), 66.57 (C_5), 56.85 (C6), 55.25 (CH_2OH, CH_2N), 41.74 (CH_3N); MS (+FAB) M + H^+ 1534.7, M + H_2Br^+ 1616.5, M + $H_3Br_2^+$ 1696.5. Anal. Calcd for $C_{63}H_{119}N_7O_{35}\cdot 7HBr\cdot 4H_2O$: C, 34.82; H, 6.21; N, 4.51; O, 28.71. Found: C, 34.42; H, 5.98; N, 4.42; O, 27.47.

Per-6-[*N*-methyl-*N*-(2-hydroxyethyl)amino]-6-deoxy-γ-cyclodextrin (3g): ^{13}C NMR (D_2O) δ 100.80 (C_1), 82.27 (C_4), 72.14 (C_3), 71.48 (C_2), 67.18 (C_5), 58.07 (C6), 56.86 (CH_2N), 55.39 (CH_2OH), 42.36 (CH_3N); MS (+FAB) M + H^+ 1753.5. Anal. Calcd for $C_{72}H_{136}N_8O_{40}\cdot 8HBr\cdot 5H_2O$: C, 34.71; H, 6.23; N, 4.50. Found: C, 34.51; H, 5.91; N, 4.51.

Per-6-[(1,3-dihydroxy-2-propyl)amino]-6-deoxy-β-cyclodextrin (4b): ^{13}C NMR (D_2O) δ 100.94 (C_1), 81.36 (C_4), 71.98 (C_3), 71.52 (C_2), 67.40 (C_5), 60.91 (C_2'), 57.96 (C_1'), 57.22 (C_3'), 45.84 (C_6); MS (+FAB) M + H^+ 1645.8 found. Anal. Calcd for $C_{63}H_{119}N_7O_{42}\cdot 7HBr\cdot 3H_2O$: C, 33.38; H, 5.87; N, 4.32. Found: C, 33.39; H, 5.67; N, 4.17.

Per-6-[bis(hydroxyethyl)amino]-6-deoxy-β-cyclodextrin (5b): ^{13}C NMR (D_2O) δ 99.35 (C_1), 79.81 (C_4), 72.59 (C_2), 71.77 (C_3), 69.89 (C_5), 58.19 (C_2'), 56.53 (C_1'), 55.77 (C_6); MS (+FAB) M + H^+ 1744.1. Anal. Calcd for $C_{70}H_{133}N_7O_{42}\cdot 4H_2O$: C, 46.27; H, 7.82; N, 5.40. Found: C, 46.20; H, 7.34; N, 4.96. Anal. Calcd for $C_{70}H_{133}N_7O_{42}\cdot 7HBr\cdot 4H_2O$: C, 35.58; H, 5.46; N, 4.15. Found: C, 35.74; H, 5.98; N, 3.84.

Per-6-[(2-methoxyethyl)amino]-6-deoxy-β-cyclodextrin (6b): ^{13}C NMR (D_2O) δ 100.98 (C_1), 81.84 (C_4), 72.00 (C_3), 71.58 (C_2), 67.35 (C_5), 66.83 (CH_2O), 58.67 (OCH3), 48.57 (NCH_2), 47.79 (C_6); MS (+FAB) M + H^+ 1534.6, M + H_2Br^+ 1616.5. Anal. Calcd for $C_{70}H_{133}N_7O_{42}\cdot 7HBr\cdot 4H_2O$: C, 34.82; H, 6.22; N, 4.51. Found: C, 34.92; H, 6.12; N, 4.51.

General Procedure. Per-6-[(*N*,*N*-dimethyl-2-aminoethyl)amino]-6-deoxy-cyclodextrins (7 and 8). Per-6-(*N*,*N*-dimethylethylenediamino)-β-cyclodextrins were synthesized by treating **1** with an excess of ethylenediamine (10 molar equiv amine per Br equivalent) at 80 °C for 12 h. The reagent/solvent was removed under vacuum, and the residue was precipitated in acetone. After filtration and washing with acetone, the solid was taken up in water and treated with Amberlite IRA-410 ion-exchange resin in the hydroxide form. The initial chloride commercial form of the resin was changed into the hydroxide form prior to use by washing with 20 volumes of 1 M NaOH followed by rinsing with 4 volumes of water. The resin load was calculated based on a ratio of 3.4 mequiv of anion/g wet resin, and the amount used was twice the calculated one. The exchange was performed by stirring the resin beads with the diluted aqueous solution of crude CD for 2 h at rt. Filtration and washing of the resin with water afforded a clear filtrate that was concentrated and dried. The solid residue was thoroughly washed with acetone to yield the pure CD-(ethylenediamino) derivatives in their free base form.

Per-6-[(*N*,*N*-dimethyl-2-aminoethyl)amino]-6-deoxy-α-cyclodextrin (7b): ^{13}C NMR (D_2O) δ 101.66 (C_1), 82.66 (C_4), 73.07 (C_3), 72.02 (C_2), 70.45 (C_5), 57.61 (C_2'), 49.19 (C_1'), 46.74 (C6), 44.53 (2·CH_3); MS (+FAB) M + H^+ 1625. Anal. Calcd for $C_{70}H_{140}N_{14}O_{28}\cdot 3H_2O$: C, 50.05; H, 8.76; N, 11.67. Found: C, 49.99; H, 8.11; N, 11.50.

Per-6-[(*N*,*N*,*N*′-trimethyl-2-aminoethyl)amino]-6-deoxy-β-cyclodextrin (8b): ^{13}C NMR (D_2O) δ 100.66 (C1), 81.97 (C4), 73.13 (C3), 71.98 (C2), 69.59 (C5), 57.59 (C_2'), 55.60 (C_2'), 55.41 (C_6), 44.60 (CH_3), 42.47 (2·CH_3); MS (+FAB) M + H^+ 1723.4. Anal. Calcd for $C_{77}H_{154}N_{14}O_{28}\cdot 7H_2O$: C, 49.98; H, 9.15; N, 10.60. Found: C, 50.50; H, 8.22; N, 9.81.

Per-6-imidazolyl-6-deoxy-β-cyclodextrin (9b). A mixture of **1b** (0.3152 g, 0.0002 mol) and imidazole (0.272 g, 0.004 mol) in a minimum amount of anhydrous DMF (0.3 mL) was stirred at 75−80 °C for 24 h. The reaction mixture was poured into 30 mL of H_2O with vigorous stirring. The resulting white precipitate was filtered and then taken in 20 mL of H_2O. HBr (1 M) was added slowly to the suspension until the pH of the resulting solution dropped down to 3. The aqueous solution was rotary evaporated and then further dried on the vacuum line. The resulting solid was washed three times with hot absolute ethanol in order to remove all of the unreacted imidazole. Removal of the ethanol traces from the final compound was achieved by succesive additions and evaporations of MeOH under vacuum, followed by vacuum drying to yield the **8b**·7HBr salt (0.3 g, 73%) as a white powder: ^{13}C NMR (D_2O) δ 136.24 (C_2'), 123.2 (C_4'), 120.65 (C_5'), 101.97 (C_1), 82.36 (C_4), 72.14 (C_3), 71.68 (C_2), 69.49 (C_5), 49.61 (C6); MS (+FAB) M + H^+ 1485.1.

Per-6-tyramino-6-deoxy-β-cyclodextrin (10b). Over a suspension of 3.84 g of tyramine (0.028 mol) in 12 mL of dry DMF at 70 °C was added in portions **1b** (3.152 g, 0.002 mol). One hour after the addition was completed, dossolution occurred and the reaction mixture darkened. The solution was stirred overnight at 75−80 °C to allow completion of the substitution. Evaporation of DMF, followed by precipitation in acetone, afforded a light-brown powder. The aqueous solution of the crude product was titrated with 1 M HBr to pH 3 and then rotavapped. The remaining residue was refluxed in absolute ethanol and filtered successively until the filtrate was clear. The resulting solid was concentrated from methanol in order to remove the ethanol traces to yield **10b**·7HBr as a white powder: ^{13}C NMR (D_2O) δ 154.54 (*ipso* COH), 129.88 (arom CH), 127.38 (*ipso*-C), 115.57 (arom CH), 101.26 (C_1), 82.40 (C_4), 72.12 (C_3), 71.59 (C_2), 67.67 (C_5), 49.78 (CH_2N), 48.73 (C_6), 31.00 (CH_2 phenol); MS (+FAB) M + H^+ 1967.5. Anal. Calcd for $C_{98}H_{133}N_7O_{35}\cdot 7HBr\cdot 10H_2O$: C, 43.34; H, 5.97; N, 3.61. Found: C, 43.01; H, 5.62; N, 3.80.

Per-6-(benzylamino)-6-deoxy-β-cyclodextrin (11b). See the general procedure for per-6-(alkylamino)-6-deoxy-cyclodextrin: ^{13}C NMR (D_2O) δ 130.49 (*ipso*-C), 130.34 (2 arom CH), 129.64 (1 arom CH), 129.01 (2 arom CH), 101.38 (C_1), 82.70 (C_4), 72.00 (C_3), 71.61 (C_2), 67.51 (C_5), 51.83 (benzyl CH_2), 48.77 (C_6); MS (+FAB) M + H^+ 1757.9. Anal. Calcd For $C_{91}H_{119}N_9O_{28}\cdot 7HBr\cdot 6H_2O$: C, 44.92 H, 5.72; N, 4.03. Found: C, 44.51; H, 5.20; N, 4.52.

Monotosyl-β-cyclodextrin (12). βCD (17.22 g, 0.015 mol) was dissolved at rt in 200 mL of 1% NaOH solution. To the stirring colorless solution was added 2.9 g of tosyl chloride (0.015 mol) dissolved in 11 mL of CH_3CN dropwise over 80 min. A white fine suspension was visible immediately after the start of the addition, and a bulk precipitation ended the

addition. The reaction mixture was stirred another 2 h at rt and then filtered. The filtrate was acidified to about pH 2−3 with 1 M HCl and the product allowed to precipitate at 2 °C overnight. Filtration afforded a white solid that combined with the previous precipitate yielded 2.4 g of crude product. Recrystallization from water (130 mL) afforded 1.22 g (0.000 95 mol, 6.3%) of material, homogeneous by NMR: ^{1}H NMR (DMSO-d_6) δ 7.75 (d, J = 7.5 Hz, 2H, *o*-Ar), 7.43 (d, J = 7.5 Hz, 2H, *m*-Ar), 5.72 (br, 14 H, s, OH), 4.84 (s, 6H, H_1), 4.77 (s, 1H, H_1'), 4.48 (br, 6H, pr OH), 4.34 (d, J = 8 Hz, 1H), 4.20 (m, 1H), 3.90−3.00 (m, 40H), 2.43 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 144.82 (*ipso*-Ar), 132.67 (*p*-Ar), 129.90 (*o*-Ar), 127.59 (*m*-Ar), 102.25, 101.94, 101.86 (C_1), 101.29 (C_1'), 81.67, 81.52, 81.44, 81.18 (C_4), 80.78 (C_4'), 73.08, 72.97, 72.74, 72.45, 72.38, 72.19, 72.05, 71.89 ($C_{2,3,5}$), 69.73 (C_6'), 68.93 (C_5'), 59.93, 59.54, 59.28 (C_6), 21.23 (CH_3).

Mono-6-(benzylthio)-6-deoxy-β-cyclodextrin (13). NaH (60% dispersion in oil, 0.4 g, 0.001 mol) was washed twice with dry toluene, under Ar. After removal of toluene, the remaining suspension was taken in 6 mL of dry DMF, and 0.117 mL of benzylmercaptan (0.001 mol) was added dropwise. The mixture was stirred at rt for 1 h to allow quantitative formation of the anion. Monotosyl-β-cyclodextrin (0.45 g, 0.000 35 mol) was added in one portion, and the reaction mixture was heated to 65−70 °C. Above 50 °C, the initial suspension became a clear solution. After 12 h, the DMF was rotavapped and the solid residue was taken in water to afford a white suspension. The precipitate was filtered and successively washed with water, acetone, and diethyl ether until no mercaptan smell could be detected: ^{1}H NMR (DMSO-d_6) δ 7.29 (br, 5H, Ar), 5.71 (br, 14H, sec OH), 4.83 (s, 6H, H_1), 4.53 (s, 1H, H_1'), 4.45 (br, 6H, pr OH), 3.9−3.2 (m, 42H), 2.96 (s, 2H, benzyl); ^{13}C NMR (DMSO-d_6) δ 138.92 (*ipso*-Ar), 129.40 (*o*-Ar), 128.98 (*m*-Ar), 127.36 (*p*-Ar), 102.35, 101.97, 101.64 (C_1), 85.04 (C_1'), 81.71, 81.56, 81.45 (C_4), 81.22 (C_4'), 73.07, 72.87, 72.45, 72.30, 72.20, 72.07 ($C_{2,3,5}$), 71.42 (C_5'), 59.88 (C_6), 41.62 (C_6'), 36.55 (C-benzyl).

Mono-6-(benzylthio)hexa-6-bromo-6-deoxy-β-cyclodextrin (14). The bromination of mono-6-(benzylthio)-β-cyclodextrin was carried out following the same procedure described above, using the Vilsmeier−Haack reagent [$(CH_3)_2$NCHBr]Br. Br_2 (0.193 mL, 3.75 mmol) was added dropwise to a solution of triphenylphosphine (0.9825 g, 3.75 mmol) in 4 mL of dry DMF with vigorous stirring, under Ar. The washed Vilsmeier−Haack reagent was combined with 6-(benzylthio)-β-cyclodextrin (0.2482 g, 0.2 mmol) in 3 mL of dry DMF and stirred overnight at 75−80 °C. After the known workup, 0.262 g of **14** was obtained as a white powder in 81% isolated yield: ^{1}H NMR (DMSO-d_6) δ 7.30 (br, 5H, Ar), 5.90 (Br, 14H, sec OH), 4.96 (s, 6H, H_1), 4.60 (s, 1H, H_1'), 4.2−3.1 (m, 42H), 3.05 (s, 2H, benzyl); ^{13}C NMR (DMSO-d_6) δ 138.78 (*ipso*-Ar), 129.35 (*o*-Ar), 128.82 (*m*-Ar), 127.29 (*p*-Ar), 101.96 (C_1), 85.12 (C_4'), 84.60, 84.23 (C_4), 72.31, 72.05, 71.08, 70.77, 70.37 ($C_{2,3,5}$), 41.61 (C_6'), 37.06 (C-benzyl), 34.35, 34.22 (C_6).

Mono-6-(benzylthio)hexa-6-[*N*-methyl-*N*-(2-hydroxyethyl)amino]-6-deoxy-β-cyclodextrin (15). 14 (0.162 g, 0.1 mmol) was stirred in 2 mL of *N*-methylethanolamine at 75−80 °C for 24 h. After evaporation of the excess amine, the residue was precipitated in acetone. Protonation with 1 M HBr to pH 3 afforded an emulsion that after extraction twice with chloroform resulted in a clear aqueous solution. The aqueous layer was further evaporated down and the remaining residue washed thoroughly with hot absolute ethanol. The last traces of benzyl disulfide were removed by filtration through a Celite bed of the suspension resulting from water precipitation. Evaporation of the clear solution afforded **15**·6HBr (110 mg, 53.1%) as a glassy solid: ^{13}C NMR (D_2O) δ 138.41 (*ipso*-Ar), 129.21 (*o*-Ar), 129.00 (*m*-Ar), 127.66 (*p*-Ar), 100.83, 100.32, 100.08, 99.64 (C_1), 82.71 (C_1'), 81.34, 80.97, 99.64 (C_4), 72.93, 72.02, 71.85, 71.76, 71.65, 71.44, 71.36 ($C_{2,3}$), 67.64, 67.12, 66.77, 66.54, 66.41, 66.27, 66.02 (C_5), 56.47 (C_6), 55.39, 55.23 (CH_2), 50.54 (C_6'), 42.26, 41.73 (CH_3), 37.00 (CH_2-benzyl); MS (+FAB) M + H^+ 1583.6. Anal. Calcd for $C_{67}H_{118}N_6O_{34}S$·6HBr·6H_2O: C, 36.96; H, 6.30; N, 3.86. Found: C, 36.96; H, 6.00; N, 4.12.

General Procedure for Per-6-cyano-6-deoxy-CD (16a,-h,g). The per-6-cyanoCD was formed from reaction of perbromoCD (1) with KCN (1.3n equiv; n = 6, 7, 8) in DMF with heating at 80 °C for 24 h. After evaporation of solvent, water was added, yielding an off-white precipitate that was filtered. Thorough washing with water and methanol was responsible for isolation of the nitrile product in 65−70% yield.

Per-6-cyano-6-deoxy-α-cyclodextrin (16a): ^{13}C NMR (DMSO-d_6) δ *118.35 (CN), 101.94 (C_1), 85.84 (C_4), 72.44 (C_3), 71.65 (C_2), 66.85 (C_5), 20.93 (C_6).*

Per-6-cyano-6-deoxy-β-cyclodextrin (16b): ^{13}C NMR (DMSO-d_6) δ 118.08 (CN), 102.11 (C_1), 85.32 (C_4), 72.16 (C_3), 71.84 (C_2), 67.01 (C_5), 20.64 (C_6).

Per-6-cyano-6-deoxy-γ-cyclodextrin (16g): ^{13}C NMR (DMSO-d_6) δ 118.11 (CN), 102.18 (C_1), 84.85 (C_4), 72.11 (C_3), 72.04 (C_2), 67.08 (C_5), 20.58 (C_6).

General Procedure for Per-6-(aminomethyl)-6-deoxy-CD (17). The per-6-cyano-6-deoxy-CD (0.2 mmol) was hydrogenated in a Parr-pressure hydrogenator under 50−55 psi H_2 pressure, at room temperature. The nitrile was taken in water (60 mL), and then the catalyst (n, 0.2, 125 mg PtO_2; n = 6, 7, 8) and the 1 M HCl (n, 0.2 mmols; n = 6, 7, 8) were added to the suspension. PtO_2 was used without prehydrogenation. After only 3 h of hydrogenation the reaction mixture was clear, and the reduction was stopped. Filtration of the catalyst suspension through a water prewashed Celite bed followed by evaporation of the aqueous solution afforded **17**·7HCl as a white solid.

Per-6-(aminomethyl)-6-deoxy-α-cyclodextrin (17a): ^{13}C NMR (D_2O) δ 101.30 (C_1), 84.00 (C_4), 73.11 (C_3), 71.63 (C_2), 69.77 (C_5), 36.05 (C_7), 27.67 (C_6); MS (+FAB) M + H^+ 1051.2.

Per-6-(aminomethyl)-6-deoxy-β-cyclodextrin (17b): ^{13}C NMR (D_2O) δ 101.33 (C_1), 83.51 (C_4), 72.70 (C_3), 71.90 (C_2), 69.83 (C_5), 36.20 (C_7), 27.72 (C_6); MS (+FAB) M + H^+ 1226.4.

Per-6-(aminomethyl)-6-deoxy-γ-cyclodextrin (17g): ^{13}C NMR (D_2O) δ 100.83 (C_1), 82.62 (C_4), 72.54 (C_3), 72.12 (C_2), 69.82 (C_5), 36.40 (C_7), 27.89 (C_6); MS (+FAB) M + H^+ 1401.7.

Acknowledgment. NSERC Canada is thanked for financial support.

JO9711549