Epoxides of the Secondary Side of Cyclodextrins[1]

Abdul Rauf Khan, Lawrence Barton, and Valerian T. D'Souza*

Department of Chemistry, University of Missouri−St. Louis, St. Louis, Missouri 63121

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Per-epoxidation of cyclodextrin can provide valuable intermediates in the syntheses of custom-designed cyclodextrins because a nucleophilic ring opening of these epoxides can provide a variety of functional groups on its secondary side which can extend the chemistry and the utility of these molecules to new areas. The secondary side of cyclodextrin is important in binding and enzyme mimic studies,[2] and thus, the synthesis of cyclodextrins modified on this side is a significant development.

Syntheses of mono-epoxides on the secondary side of cyclodextrins *via* the sulfonation on this side have been successful. Sulfonation of the secondary side takes place at either the 2-[3] or 3-positions.[4] The mono 2-tosylated cyclodextrin produces the mono *manno*-epoxide[5] whereas the mono 3-sulfonated compound gives the mono *allo*-epoxide on treatment with a mild base.[3] The mono *manno*-epoxides of cyclodextrins have been extensively investigated as precursors for the preparation of 2-substituted cyclodextrin derivatives,[6] especially in enzyme mimic studies.[5,7] The mono *allo*-epoxide has also been used to synthesize a penicillinase model.[8] The cyclodextrin mono *manno*-epoxide reacts with a nucleophile to afford a 3-substituted derivative in which the conformation of the corresponding pyranose unit is inverted[5] from $^4C_1$ to $^1C_4$, whereas the mono *allo*-epoxide, on ring opening, does not undergo the ring inversion.[8]

It is commonly recognized that selective synthesis of cyclodextrins monosubstituted on the secondary side is a difficult process,[9,10] and complete modification of this side is believed to be even more demanding. Selective per-modification of one side of cyclodextrins is a complicated process[11] due to the presence of a large number of hydroxyl groups. Twelve hydroxyl groups with relatively rigid structures on the secondary side of α-cyclodextrin cause more crowding during its per-modification. Thus, it is a challenge to prepare both *manno*- and *allo*-heptakis(2,3-epoxy)-*β*-cyclodextrins, and these products have significant potentials in the field of cyclodextrin chemistry.

After our preliminary report of the synthesis of the *manno*-epoxide,[1] an alternative synthesis of this compound was published by Coleman et al.[12] The present paper describes strategies that were explored by us in attempts to synthesize both these epoxides[13] and includes experimental details for the synthesis of the *manno*-epoxide which has the advantage of having one step less than Coleman's procedure.

Results and Discussion

A. Synthesis of *manno*-Heptakis(2,3-epoxy)-*β*-cyclodextrin. The general strategy for the synthesis of *manno*-heptakis(2,3-epoxy)-*β*-cyclodextrin, as shown in Scheme 1, involves the deprotonation of all the hydroxyl groups at the 2-positions of cyclodextrin with sodium hydride to form the corresponding oxyanionic species. Subsequent addition of tosyl chloride to the oxyanion should yield heptakis(2-tosyl)-*β*-cyclodextrin which may further react with base to produce the corresponding epoxide. It has been shown that the mono oxyanion of *β*-cyclodextrin, generated by treatment with 1 equiv of sodium hydride, is trapped with *p*-toluenesulfonyl chloride to produce the mono 2-tosylated cyclodextrin.[14] It is conceivable that the per-epoxide formation can be carried out in a single step using a large excess of sodium hydride without isolating the tosylated derivative.

Unprotected *β*-cyclodextrin (**1**) reacts with sodium hydride to form an oxyanion which further reacts with 7 equiv of *p*-toluenesulfonyl chloride to produce a complex, inseparable mixture. NMR spectra of this mixture indicate that *p*-toluenesulfonyl chloride decomposes under these conditions and a possible mechanism for this decomposition is shown in Scheme 2. Since a similar decomposition scheme is unavailable for benzenesulfonyl chloride, this reagent was used instead in reactions with the oxyanion of *β*-cyclodextrin. However, the use of this reagent also affords an inseparable complex mixture containing derivatives of cyclodextrins with varying degrees of sulfonation on both the sides of the molecule. It is rationalized that these complications are due to the availability of primary and secondary hydroxyl groups for reaction with benzenesulfonyl chloride. The use of heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-cyclodextrin[15] (**2**) could ameliorate this situation.

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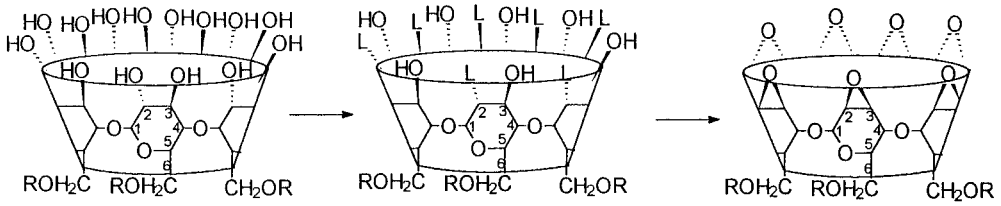
Scheme 1

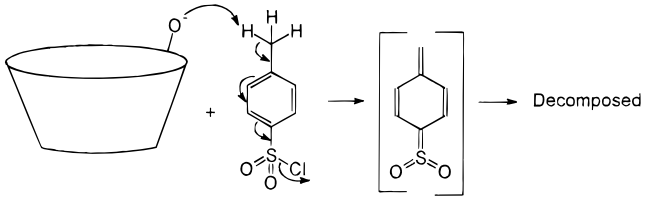


R = H; **1**
R = SiMe2*t*-Bu; **2**

R = H; **3**
R = SiMe2*t*-Bu; **4**
L = Leaving group, -OSO_2Ar

R = H; **5**
R = SiMe2*t*-Bu; **6**

Scheme 2



The secondary hydroxyl groups of **2** are deprotonated by 30 equiv of sodium hydride, under a dry atmosphere, to form the corresponding oxyanion. Subsequent addition of 8.4 equiv of benzenesulfonyl chloride to this form of cyclodextrin gives heptakis(2,3-epoxy-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**6**) in 62% yield (Scheme 1).

The epoxide is believed to be formed *via* an intermediate heptakis(2-*O*-benzenesulfonyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin. *p*-Toluenesulfonyl chloride is known[16] to react with **2** in pyridine to produce heptakis-(2-*O*-*p*-toluenesulfonyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**4**). A large excess of sodium hydride in the reaction mixture is expected to deprotonate the hydroxyl groups at 3-positions, which then displace the sulfonate groups at 2-positions to form epoxides. This is a reasonable assumption because mono 2-tosylated β-cyclodextrin is known to react with mild base to give mono *manno*-epoxide.[5] In an elegant investigation, Coleman et al. have isolated various intermediates and have formed the epoxide **6** from **4**.[12]

The proton and ^{13}C NMR spectra of crude **6** suggest a single compound with some impurities. The ^1H NMR spectrum (DMSO-d_6) shows a singlet at 5.27 ppm for the anomeric proton with the coupling constant ($J_{1,2}$) of 0 Hz. It is known that the coupling constants $J_{1,2}$ for *manno*- and *allo*-epoxide are 0 and 2.5−4.5 Hz, respectively,[17] and thus in our system the coupling constant of 0 is indicative of a *manno*-epoxide.[18,5]

The ^{13}C NMR spectrum (acetone-d_6) of crude compound **6** suggests seven-fold symmetry. Six carbon signals are observed at 96.04(C-1), 68.96(C-5), 68.03(C-4), 61.5(C-6), 53.12(C-3), 48.78(C-2) in addition to the peaks for the *tert*-butyldimethylsilyl groups at 25.6[$(CH_3)_3C$], 18.1 [$(CH_3)_3C$], and −5.37[$(CH_3)_2Si$]. The assignments of these peaks are made according to the mono *manno* epoxide, as reported by Pregel and Buncel.[18] A large upfield shift (25 and 20 ppm, respectively) is observed for the C-2 and C-3 carbons but this trend is less significant in the case of C-5 (3 ppm) carbons. Due to the silylation of the hydroxyl groups at the 6-positions, the C-6 carbons move 1 ppm downfield. Carbons (C-1 and C-4) adjacent to the epoxide carbons (C-2 and C-3) also exhibit a considerable upfield shift (6 and 14 ppm, respectively).

Compound **6** is unstable and decomposes at room temperature as well as under acidic conditions, for example in the presence of silica gel. Thus, the TLC of **6**, whose initial NMR clearly indicates an epoxide of **2**, shows the same R_f value (0.44) as that for **2** in a solvent system A (ethyl acetate:ethanol:water, 50:7:4, V/V). When compound **6** is passed through a flash column, using solvent B (ethyl acetate:ethanol:water, 25:2:2, V/V) as eluent, the NMR spectrum of the product reveals that it has reverted to **2**. The NMR spectra of **6**, recorded after standing for a few days, indicated the presence of **2**, providing additional proof of the instability of **6** at room temperature. The instability of **6** may be attributed to the presence of bulky *tert*-butyldimethylsilyl groups on the primary face of cyclodextrin. Molecular modeling[19] of **6** shows that the *tert*-butyldimethylsilyl groups at the 6-positions are tilted slightly toward the cavity, causing one group to come close to the identical group on the adjacent glucose unit resulting in steric interactions. These steric interactions may force the epoxide to open up under neutral or acidic conditions.

The hydroxyl groups at the 6-position of compound **6** are deprotected with tetrabutylammonium fluoride in refluxing THF to afford crude heptakis(2,3-epoxy)-β-cyclodextrin (**5**) in 52% yield (Scheme 1). Compound **5** may be stored for several days without decomposition and is purified by flash column chromatography[20] to afford 40% of pure product. Attempts to improve the yield of **5** were unsuccessful because of the decomposition of **6**.

The ^1H NMR (DMSO-d_6) spectrum of **5** gives a sharp singlet at 5.22 with a coupling constant, $J_{1,2} = 0$ Hz for the anomeric proton. This loss of coupling with H-2 and the absence of any other resonance in this region is consistent with *manno*-epoxide structure. Two doublets at 3.44 ppm (H-3) and 3.21 ppm (H-2), with coupling constants of 3.4 Hz, are in agreement with literature values.[18,5] The ^{13}C NMR spectrum (DMSO-d_6) of pure **5** has only six peaks, indicating the seven-fold symmetry of the molecule. The assigned peaks in the carbohydrate region are: δ 48.73(C-2), 53.13(C-3), 60.58(C-6), 67.74-(C-4), 69.34(C-5), 94.63(C-1). Desilylation of the hydroxyl groups at the 6-positions in **5** results in a ca. 1 ppm upward shift in the signals of the C-6 and C-1 carbons, whereas the rest of the carbons have almost the same chemical shift values as in **6**. According to Pregel and Buncel,[18] desilylation of the hydroxyl groups at the C-6 positions should cause a 1 ppm upfield shift, but the

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upfield shift in the signals of C-1 carbons may be due to the removal of bulky *tert*-butyldimethylsilyl groups. The epoxy carbons (C-2 and C-3) have large chemical shift changes (25 and 20 ppm, respectively), and carbons (C-1 and C-4), adjacent to the epoxide, have considerably smaller changes in chemical shift values (8 and 14 ppm respectively). These assignments are consistent with the proposed structure of the epoxide. The elemental analysis of compound **5** attests to the purity of the compound.

The discussion of the attempts to synthesize *allo*-heptakis(2,3-epoxy)-β-cyclodextrin is given in the Supporting Information.

Conclusions

Manno-heptakis(2,3-epoxy)-β-cyclodextrin is successfully synthesized using benzenesulfonyl chloride and sodium hydride after appropriate protection−deprotection of the primary side. However, the 3-position of cyclodextrins are unusually resistant to per-sulfonation and methods that have been successfully reported for mono-sulfonation fail to sulfonate all the hydroxyl groups at this position.[13] The *manno*-epoxide reported here opens up new avenues for synthesis of custom-designed cyclodextrins with a variety of functional groups.

Experimental Section

General Procedure. Thin layer chromatography was performed on plates (0.2 mm thickness, supported on alumina, Merck) in the solvent system: ethyl acetate:ethanol:water (50:7:4, V/V) A and charring with 50% methanolic sulfuric acid. Flash column chromatography was carried out on silica gel (240−600, Merck) according to the procedure of Still[20] *et al.* using ethyl acetate:ethanol:water (25:2:2, V/V) B, as eluent. Other solvent systems used were: hexane:ethyl acetate (95:5, V/V) C for TLC and hexane:ethyl acetate (95:4, V/V) D, as eluents for column chromatography.

Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**2**) was prepared according to the literature[15,18] and dried at 100 °C for 3 h prior to use. DMF was dried over CaH_2 for several days and decanted before use. THF was refluxed with CaH_2 and freshly distilled. Benzenesulfonyl chloride (Eastman) was distilled and stored in a sealed bottle. NaH (60% in oil) was purchased from Aldrich and used without processing.

Heptakis(2,6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**7**) was prepared according to the literature,[15] purified by column chromatography using solvent system C as eluent and then dried at 100 °C for 3 h before use. The R_f value for **7** in solvent system C is 0.47. Heptakis(2,6-*O*-trimethylsilyl)-β-cyclodextrin (**8**) was synthesized as described in the literature.[21] Pyridine was refluxed with CaH_2 and distilled before use. β-Naphthalenesulfonyl chloride, trimethylsilyl chloride, imidazole, and tetrabutylammonium fluoride (Aldrich) were all used without purification.

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Reaction of 1 with *p*-Toluenesulfonyl Chloride. β-Cyclodextrin (1 g, 0.88 mmol) was stirred overnight with NaH (0.247 g, 6.16 mmol) in DMF (40 mL) under dry nitrogen. Solid *p*-toluenesulfonyl chloride (1.176 g, 6.16 mmol) was added and the mixture further stirred for 2.5 h. Acetone was added in large excess to the reaction mixture causing precipitation of cyclodextrin and its derivatives. TLC analysis of the precipitate indicated a mixture. The ^{1}H NMR (DMSO-d_6) spectrum of the precipitate showed broad signals in the carbohydrate region and no signals in the aromatic region (δ 7.1−7.8). The ^{13}C NMR spectrum gave, in addition to the normal cyclodextrin peaks, signals at δ 125.5 to 129.8.

Heptakis(*manno*-2,3-epoxy-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (6). NaH (2.48 g, 62 mmol.) was stirred with **2** (4 g, 2.07 mmol) in DMF (120 mL) for 5 h under dry argon. Benzenesulfonyl chloride (2.72 g, 15.41 mmol) was syringed into this mixture, and it was further stirred for 30 min. On filtration, a clear filtrate was obtained which, on addition of a large excess of water, afforded an off-white precipitate. Upon filtration and drying the material in air, 2.3 g (62% yield) of crude compound **6** was obtained. The R_f value of **6** in solvent system A is the same as the starting material, suggesting that it decomposes on silica gel.

^{1}H NMR (acetone-d_6) δ 5.27 (1H, s, $J_{1,2} = 0$ Hz), 4.14 (1H, d, $J_{4,5} = 8.8$ Hz), 3.44 (1H, d, $J_{3,2} = 3.6$), 3.26 (1H, d, $J_{2,3} = 3.5$); ^{13}C NMR (DMSO-d_6) δ 96.04, 68.96, 68.03, 61.5, 53.12, 48.78, 25.6, 18.1 and −5.37.

Heptakis(*manno*-2,3-epoxy)-β-cyclodextrin (5). **6** (2 g, 1.107 mmol) was refluxed with tetrabutylammonium fluoride (5 mL, 1 M in THF) in THF (10 mL), for 4 h. Solvent was removed under reduced pressure at 60 °C, and a brown colored gumlike material was obtained. Addition of 20 mL of methanol produced a white precipitate which was filtered and washed with methanol. On drying, 560 mg of crude material (50% yield) was collected. The R_f value of this compound in solvent A is 0.44. A 250 mg amount of this material, dissolved in a minimum quantity of acetone, was eluted through a flash column using solvent B, and 100 mg of pure compound **5** in 40% yield was obtained.

^{1}H NMR (DMSO-d_6) δ 5.22 (1H, $J_{1,2} = 0$ Hz), 3.88 (1H, d, $J_{4,5} = 8.9$ Hz), 3.56 (3H, br), 3.44 (1H, d, $J_{3,2} = 3.4$ Hz), 3.21 (1H, d, $J_{2,3} = 3.4$ Hz); ^{13}C NMR (DMSO-d_6) δ 94.32, 69.35, 67.74, 60.58, 53.13, 48.73. Anal. Calcd for $C_{42}H_{56}O_{28}\cdot 3H_2O$: C, 47.46; H, 5.88. Found: C, 47.92; H, 6.24.

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Supporting Information Available: Discussion and experimental details of the attempts to synthesize *allo*-heptakis-(2,3-epoxy)-β-cyclodextrin (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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