Heptakis-2,3-epoxy-β-cyclodextrin, a Key Intermediate in the Synthesis of Custom Designed Cyclodextrins

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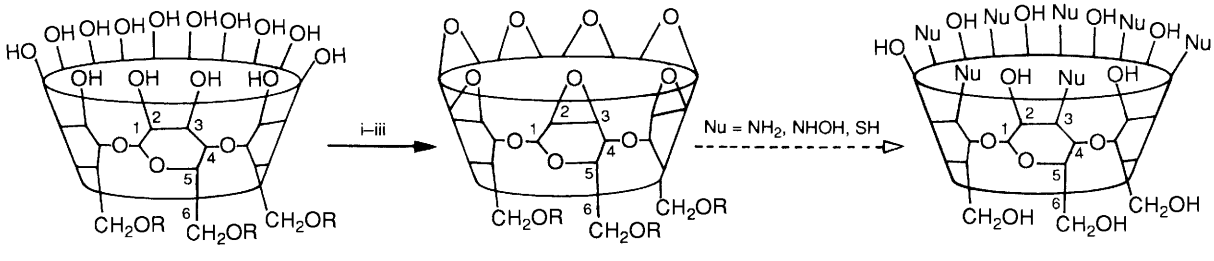
Heptakis-2,3-epoxy-β-cyclodextrin, a potentially key intermediate in the synthesis of custom designed cyclodextrins is synthesized and characterized.

Cyclodextrins, the torus-shaped cyclic oligomers of α-D-glucopyranose,[1] have been widely investigated in the last decade,[2–4] as complexing agents, catalysts, enzyme mimics *etc.* However, the main shortcoming of this, otherwise remarkable, molecule is that the functionalities available to it for useful chemical processes are limited simply to hydroxy groups. Attempts to remedy this situation have been fairly successful with regard to the side of the molecule containing the primary hydroxy groups[5] but limited with regard to the side containing the secondary hydroxy groups.[6] The 'secondary' side of cyclodextrins has been shown to be more important in applications of these important molecules than the 'primary' side.[7] Monofunctionalization of the 'secondary' side has been achieved with low yields.[6] We recently reported a convenient method for the derivatization of the 'secondary' side of cyclodextrins in higher yields.[8] We now report a key intermediate which will allow synthesis of cyclodextrins with a variety of functional groups on the 'secondary' side of the molecule. Heptakis-2,3-epoxy-β-cyclodextrin **4**, the key intermediate, can be synthesized from the known[9] heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **2** in two steps in 50% overall crude yield following Scheme 1. Cyclodextrins with any desired functional group can be synthesized from the epoxide by treating the latter with an appropriate nucleophile.

Compound **2**, which can be obtained in 90% yield[9] from β-cyclodextrin **1**, is treated with 30 equiv. of NaH in dry dimethylformamide (DMF) under an atmosphere of dry argon with stirring for 5 h. Benzenesulfonyl chloride (8.4 equiv.) is



1; R = H
2; R = *tert*-butyldimethylsilyl
3; R = *tert*-butyldimethylsilyl
4; R = H

Scheme 1. *Reagents and conditions*: i, NaH, DMF, room temp., dry atm., 5 h; ii, $C_6H_5SO_2Cl$ added to i, 30 min; iii, tetrabutylammonium fluoride, THF reflux, 4 h. Broken arrow represents reactions currently under investigation and will be the subject of a future communication.

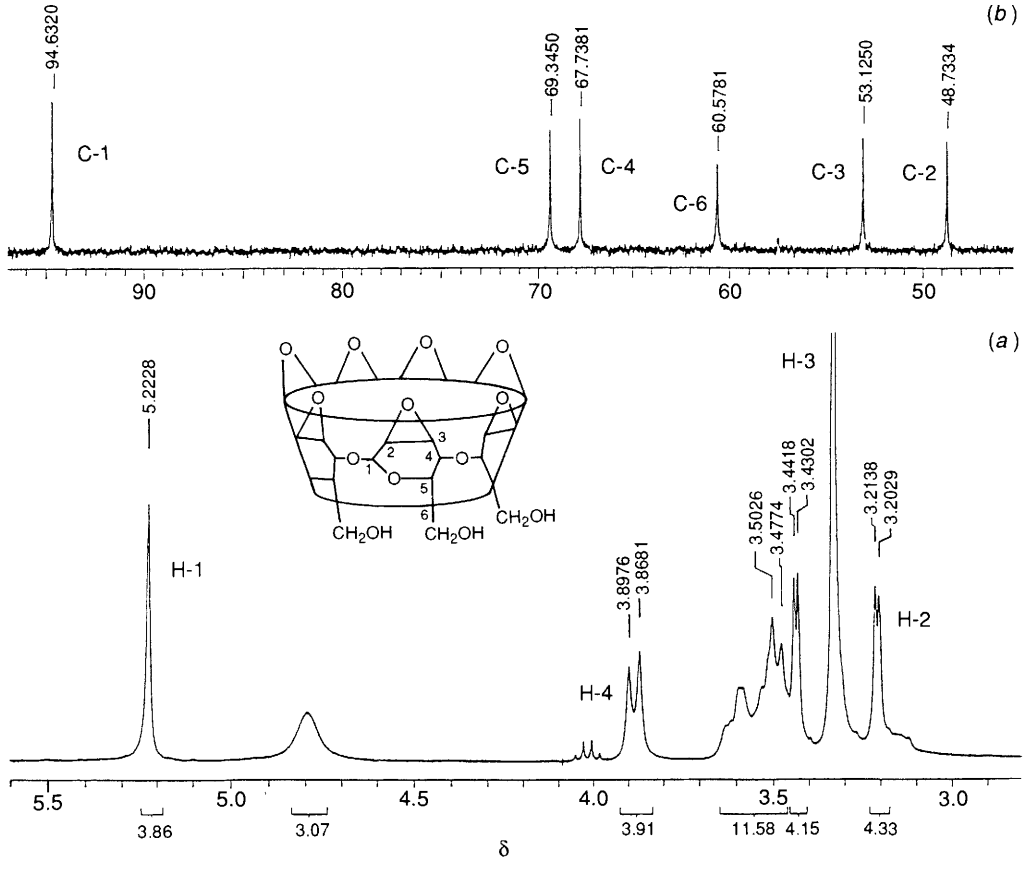


Fig. 1 (*a*) ^1H and (*b*) ^{13}C NMR spectra of hepatkis-2,3-epoxy-β-cyclodextrin **4** in [$^2H_1$]DMSO

allowed to react with the resulting oxyanions for 30 min at room temperature to form heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-epoxy)-β-cyclodextrin **3**. According to literature precedence,[8] the benzenesulfonyl chloride presumably reacts with the oxyanions at the 2-position to form heptakis(2-*O*-benzenesulfonyl-6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin.[10] The deprotonated hydroxy groups at the 3-position of this intermediate displace the sulfonate at the adjacent 2-position to form the epoxide.[11] The intermediate sulfonated derivative is isolated from the reaction mixture using a molar equiv. of NaH and characterized by ^1H and ^{13}C NMR spectroscopy. However, isolation of the intermediate is not necessary and **3** can be obtained from **2** in a single step. The work-up of the reaction mixture containing the epoxide **3** is fairly simple and involves filtration to remove the insoluble component and addition of water to precipitate the epoxide **3**. This epoxide has been characterized by ^1H and ^{13}C NMR spectroscopy.† The epoxide **3** is very unstable and subsequent reactions should be carried out on the crude mixture immediately. The epoxide **3** is desilylated by refluxing it with tetrabutylammonium fluoride for 4 h. Solvent is removed from the reaction mixture under reduced pressure and methanol added to the residue to afford a precipitate of crude epoxide **4** in unoptimized overall 50% yield from **2**. Crude **4** contains small amounts of impurities and can be purified by flash chromatography[12] on silica gel with a mixture of ethyl acetate, ethanol and water (25 : 2 : 1, v/v).

The elemental analysis and ^1H and ^{13}C NMR spectra (in [$^2H_1$]DMSO), shown in Fig. 2, attest to the purity and the structure of the epoxide **4**. The strongest evidence for the structure of the epoxide comes from the resonance due to H-1, which has moved from δ 4.8 (doublet with a coupling constant $J_{1,2}$ 3 Hz) in cyclodextrin to δ 5.2 with a coupling constant $J_{1,2}$ 0 in **4** indicating that it is a *manno*-epoxide.[9,11] The assignment of the other peaks in the ^1H NMR spectrum of **4**, based on the literature reports[9,11] of similar molecules, are made as follows: δ 3.21 (1 H, d, $J_{2,3}$ 3.4 Hz, H-2), 3.44 (1 H, d, $J_{3,2}$ 3.4 Hz, H-3), 3.45–3.65 (3 H, m, H-5 and H-6), 3.88 (1 H, d, $J_{4,5}$ 8.9 Hz, H-4), 4.8 (1 H, br, OH), 5.22 (1 H, s, H-1). The ^{13}C NMR spectrum in [$^2H_1$]DMSO shows only six peaks in the carbohydrate region assigned as follows: 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). It can be seen that whereas the peaks for C-5 and C-6 show little change in their chemical shifts from those of cyclodextrin, the other peaks are shifted considerably upfield. The carbons involved in the epoxide (C-2 and C-3) exhibit the largest shifts (25 and 20 ppm, respectively), and the carbons adjacent to the epoxide (C-1 and C-4) move considerably less (8 and 14 ppm, respectively). These assignments are consistent with the structure of the epoxide.

This is the second report of a peranhydro cyclodextrin and this one has greater promise to 'release cyclodextrin from the structural straightjacket'[13] than the previous[14] per-3,6-anhydrocyclodextrin. The epoxide **4** is very stable and can be stored for long periods without any precautions. It is reactive towards nucleophiles such as hydroxy amine and ammonia.‡ This epoxide is believed to have a wide range of applications. Reaction with nuclephiles in a manner analogous to such reactions[11] of mono-2,3-epoxy-α-cyclodextrin can yield custom designed cyclodextrins with any desired functionalities.

† ^1H NMR (acetone) δ 3.26 (1 H, d, $J_{2,3}$ 3.5, H-2), 3.44 (1 H, d, $J_{3,2}$ 3.6, H-3), 4.14 (1 H, d, $J_{4,5}$ 8.8, H-4), 5.27 (1 H, s, $J_{1,2}$ 0, H-1); ^{13}C NMR [$^2H_1$]DMSO δ −5.37 (Me-Si), 18.1 (C-Me), 25.6 (Me-C), 48.78 (C-2), 53.12 (C-3), 61.5 (C-6) 68.03 (C-4) 68.96 (C-5) and 96.04 (C-1).

‡ These reactions are currently under investigation and will be the subject of a future communication.

The availability of a variety of cyclodextrins will widen their use as complexing agents and catalysts. If the stereochemical outcomes of these reactions follow those of analogous reactions of mono-2,3-epoxy-α-cyclodextrin,[15] the new cyclodextrin will have interesting binding and other physical properties. It is also predicted that the epoxide may provide a new route to bind, covalently, biologically important molecules such as drugs and solve some of the problems associated with drug delivery.

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