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Synthesis of *manno*-2,3-epoxy-β-cyclodextrin on a soluble solid support

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Abstract—*Manno*-2,3-epoxy-β-cyclodextrin, an important synthon in the synthesis of β-cyclodextrin derivatives, is conveniently and efficiently synthesized on a polyethylene glycol based soluble solid support in good yields and excellent purity. © 2002 Published by Elsevier Science Ltd.

Cyclodextrins (CDs) are torus shaped cyclic oligosaccharides composed of 6, 7 or 8 α-(1,4) linked D-(+)-glucopyranose units, in α-, β- and γ-cyclodextrins, respectively (Fig. 1). These torus like molecules can form inclusion complexes with a wide variety of organic compounds.[1] Hence, CDs and their derivatives have been extensively studied as enzyme models.[2–4] Therefore, methods for the derivatization of CDs has become an important field of study.[5–7] However, for certain CD related studies, gram amounts of CD derivatives are required and to date all existing methods do not easily supply these amounts.

CD derivatization is challenging for the following reasons. Firstly, CDs contain three different hydroxyl groups; two distinct secondary (on the 2′ and 3′ carbons) and one primary hydroxyl (on the 6′ carbon) per glucose unit, which makes selective modification difficult. And secondly, the presence of many hydroxyl groups (21 in the case of β-CD) makes mono-substitution difficult and the production of di- and tri-substituted product becomes unavoidable. This leads to poor yields and/or difficult purification, moreover, the purification techniques used are often tedious and scale limiting, especially the modifications involving the secondary hydroxyls.[8–11]

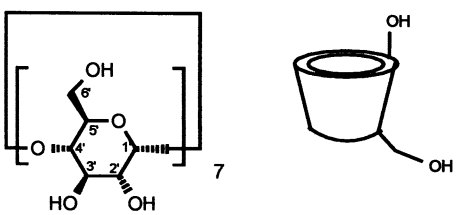

Figure 1. β-Cyclodextrin.

The two main methods for modification of the secondary hydroxyl groups of CDs involves the selective alkylation of the 2′ hydroxyl (the most acidic, $pK_a = 12.2$) or by nucleophilic opening at the 3′ position of the *manno*-2,3-epoxycyclodextrin (Fig. 2). Therefore, an efficient synthesis of *manno*-2,3-epoxy-β-cyclodextrin **1** would be extremely valuable and would lead to an efficient route to β-CD 3′ derivatives. The present paper describes a convenient and efficient synthesis of **1** that requires no difficult purification steps.

The traditional synthesis of **1**[11,12] involves the selective tosylation of the 2′ hydroxyl with tosyl chloride, followed by an intramolecular substitution by the 3′ hydroxyl to form the epoxide. This can be achieved directly from β-CD[10] or from (6-*O*-*tert*-butyldimethylsilyl)-β-CD **2**.[11,12] The use of **2** has several advantages. It makes the CD much more soluble in

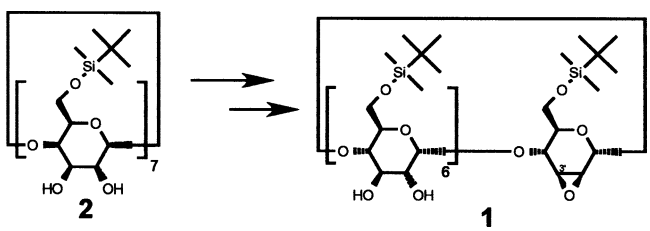

Figure 2. (6-*O*-*tert*-Butyldimethylsilyl)-β-CD **2** and *manno*-2,3-epoxy-β-cyclodextrin **1**.

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organic solvents, thus allowing chromatography on silica gel and avoids the interference of the 6′ groups during the synthesis. Compound **2** can be conveniently prepared with 7 equiv. of *tert*-butyldimethylsilyl chloride in pyridine.[13] The major drawback of the traditional route is that the subsequent tosylation step leads to a mixture of **2**, the desired mono-tosylated product and multi-tosylated products, giving poor yields (22–32%),[11,12] and in our hands requiring several purifications on silica gel.

To avoid the formation of multi-tosylated products, we attempted a solid-phase strategy. The idea was to use tosyl chloride on crosslinked polystyrene solid support, which is easily prepared from 1% crosslinked polystyrene **3** (Fig. 3). This way, the CD would become immobilized after the tosylation and further reaction on the CD would be unlikely. Moreover, an excess of **2**, could be used in the reaction and would be recovered in good purity after the reaction. Afterwards, the CD could be released from the solid support by formation of the epoxide **1** under basic conditions (KOEt/EtOH)[11] (Fig. 4).

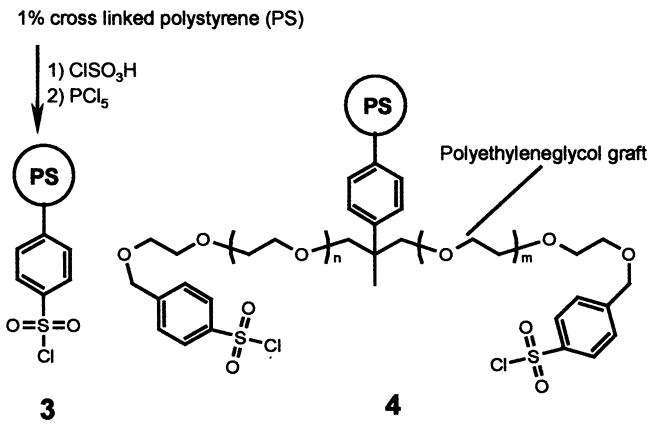

Figure 3. Tosyl chloride on solid supports.

Unfortunately, all our attempts to attach **2** to the 1% crosslinked polystyrene tosyl chloride resin **3** failed under a variety of conditions. We then decided to use Argo-Gel™ **4** resin, synthesized from the alkylation of Argo-Gel™ OH resin with 4-chloromethylbenzenesulfonic acid, followed by chlorination with PCl_5. This resin was more attractive since the reactive groups in Argo-Gels™ are grafted to the polystyrene core with polyethylene glycol. Hence, they are further from the core and in a more polar environment and therefore, should be more accessible to **2**. However, as with **3**, all attempts to attach **2** failed.

The failure of the reaction of **2** with the insoluble polystyrene resins is probably due to the fact that reactions on solid support are significantly slower than in solution, mainly because of restricted permeability of the reactants.[14] To overcome this problem we decided to use a liquid phase strategy,[15] where the polymer is soluble in the reaction medium, but can be precipitated out by the addition of another solvent at the end of the reaction to remove excess starting materials and reagents. The effect is a solid support, which has solution like reactivity. Moreover, the solubility of the support enables us to monitor the progress of the reactions and characterize the intermediates by NMR, which is difficult and inconvenient with the insoluble resins. Polyethylene glycol (PEG) is commonly used in liquid phase chemistry.[15] It is soluble in many organic solvents and can be precipitated from a reaction medium by the addition of ether. Also, the terminal hydroxyl group can be easily modified to produce a wide variety of functionalized soluble supports. With these properties in mind, tosyl chloride **5** (Fig. 4) was synthesized by alkylation of polyethylene glycol monomethyl ether (MW = 5000) with 4-chloromethylbenzenesulfonic acid sodium salt (obtained from the hydrolysis of 4-bromomethylbenzenesulfonyl chloride). The resulting sulfonic acid was recrystallized in EtOH, and chlorinated with oxalyl chloride.

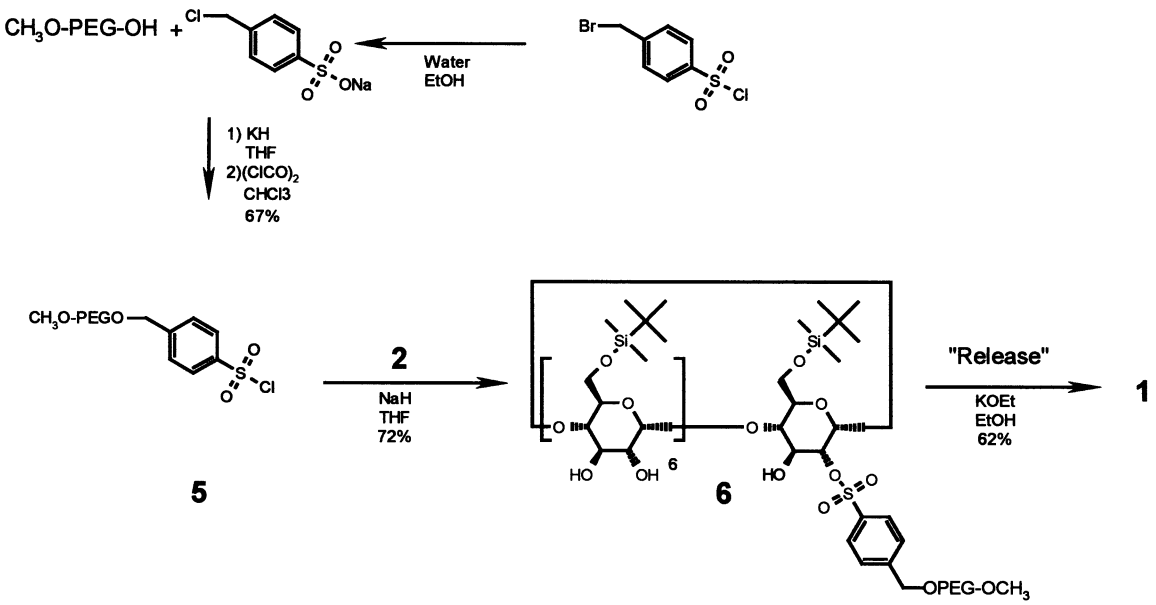

Figure 4. Synthesis of **1** on soluble solid support **5**.

Compound **2** (Fig. 4) was successfully attached to the support **5** using 3 equiv. of **2** in the presence of NaH in THF. Compound **6** was then precipitated from the medium by the addition of ether and the excess of **2** was recovered pure. The CD was then released from the support with KOEt in refluxing EtOH, and **1** (62% after purification) was obtained with ^{1}H and ^{13}C NMRs that conformed to published data.[11] Small amounts (<10%) of uncharacterized CD products were obtained, but were easily removed by silica gel chromatography. The formation of these impurities was minimized by using 5 equiv. of **2**, consequently no further purification was required. In any case, it seems that the difference in reactivity of PEG bound **2** and free **2** is enough to significantly reduce di-tosylation, presumably due to the steric effects of the PEG chain. The overall yield of **1** was >90% from **2** (taking into account recovered starting material).

In conclusion, the usefulness of liquid phase chemistry has been demonstrated with the development of a convenient and efficient method for the synthesis of gram amounts of **1**, using a novel PEG based tosyl chloride soluble solid support. This method is superior to the traditional solution phase method[11,12] (direct tosylation with NaH/TsCl, followed by epoxidation with KOEt) because it avoids any scale limiting purification steps. Moreover, the overall yield is >90% from **2** (45% from **5**) compared to yields of 20–30% (from **2**) with the traditional method. Therefore, this method will significantly facilitate the synthesis of larger amounts of CD derivatives. The synthesis of other CD derivatives using novel solid supports is being investigated.

Synthesis of PEG supported tosyl chloride (5)

4-(Bromomethyl)benzenesulfonyl chloride (10 g, 37.1 mmol, 1 equiv.) was dissolved in ethanol (22 ml) and water (0.7 g, 0.388 mmol, 1.05 equiv.) was added. The mixture was refluxed for 3 h. The solvent was removed and the residue dissolved in 50 ml of water before adding 1 equiv. NaOH. After freeze-drying, a 3:1 mixture of 4-(chloromethyl)benzenesulfonic acid sodium salt and 4-(bromomethyl)benzenesulfonic acid sodium salt (quantitative) was obtained as determined by NMR. A solution of polyethylene glycol methyl ether (MW = 5000) (30 g, 6 mmol, 1 equiv.) in dry THF (250 ml) was canulated, under nitrogen, on KH (2.06 g, 18 mmol, 3 equiv.) suspended in THF (50 ml). The mixture was stirred for 0.5 h before the addition of 4-(chloromethyl)benzenesulfonic acid sodium salt (2.9g, 12 mmol, 2 equiv.). The mixture was stirred under nitrogen for 1.5 h before the addition of a few drops of $NH_4Cl_{(satd)}$. The solvent was removed, the residue dissolved in a minimum of DCM and filtered on Celite. The product was then precipitated in ether, then slowly cooled to −10°C for 1 h before filtration. The residue was washed with ether and recrytallized from ethanol at 35°C. The sulfonic acid (21.98 g, 70%) was obtained. To a solution of the sulfonic acid (21.41 g, 4.12 mmol, 1 equiv.) in chloroform (210 ml) was added oxalyl chloride (1.57 g, 12.37 mmol, 3 equiv.) and a drop of DMF. The mixture was stirred for 1.5 h under nitrogen. The solvent was removed, the residue dissolved in a minimum of DCM and filtered on Celite. The product was then precipitated in ether and the mixture slowly cooled to −10°C for 1 h before filtration. The residue was then washed with ether. Compound **5** (20.28 g, 94%) was obtained. ^{1}H NMR, 500 MHz, ($CDCl_3$) δ: 8.03 (d, J = 8.5 Hz), 7.34 (d, J = 8.4 Hz), 4.71 (s), 3.5–3.85 (overlapped), 3.40 (s). 0.60% sulfur by elemental analysis (theoretical = 0.61%).

Synthesis of of *manno*-2,3-epoxy-β-cyclodextrin (1)

A solution of **2** (3.88 g, 2.01 mmol, 3 equiv.) in anhydrous THF (35 ml) was cannulated on NaH (80 mg, 2.01 mmol, 3 equiv.) under nitrogen. The mixture was agitated for 0.5 h before the addition of a solution of **5** (3.48 g, 0.67 mmol, 1 equiv.) in THF (35 ml). The solution was stirred for 1 h before the addition of 76 μL AcOH. The mixture was filtered through Celite and the solvent stripped to a minimum. The product was then precipitated in ether and slowly cooled to −10°C for 1 h before filtration. The residue was then washed with ether and 4.02 g (85%) of **6** was obtained. 15% of hydrolyzed **5** was detected by NMR (72% yield). Crude compound **6** (4.01 g, 0.566 mmol, 1 equiv.) was dissolved in anhydrous ethanol (40 ml) and a solution of potassium ethoxide 24% w/w in ethanol (199 mg, 0.566 mmol, 1 equiv.) was added under nitrogen. The mixture was refluxed 2.5 h and then cooled to rt. The polyethylene glycol was precipitated by the addition of ether at −10°C, filtered and washed with ether. The solvent was removed and pure **1** (569 mg, 62%) was obtained after chromatography on silica gel (20:30:1:1, chloroform:acetone:methanol:water). ^{1}H NMR (as in the literature),[11] 500 MHz, ($CDCl_3$) δ: 5.22 (s, H1), 4.92 (H1s, overlapped), 4.30 (d, H6), 4.12–3.55 (heavily overlapped), 3.43 (d, J = 3.4 Hz, H3), 3.20 (d, J = 3.5 Hz, H2), 0.90 (m, t-Bu), 0.05 (m, SiMe).

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