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Hetero-bifunctionalization of the secondary face of β-cyclodextrin: selective 3^G-sulfonylation and subsequent $2^G,3^G$-epoxidation of 3^A-azido-3^A-deoxy-*altro*-β-cyclodextrin

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Abstract—3^A-Azido-3^A-deoxy-*altro*-β-cyclodextrin, which has 20 different hydroxyl groups, was selectively sulfonylated by 1-naphthalenesulfonyl chloride at the 3^G-OH of the glucoside residue as well as the 2^A-OH of the altroside one. Alkali treatment of the 3^G-sulfonate gave successfully the $2^G,3^G$-epoxyalloside with the 3^A-azido group being left unaffected. Both the 3^G-sulfonate and $2^G,3^G$ -alloepoxide species of 3^A-azido-3^A-deoxy-*altro*-β-cyclodextrin not only have two sugar units being modified differently, but also can serve as versatile starting materials for the syntheses of bifunctional cyclodextrins with diverse combination of different functionalities.
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Cyclodextrins (CDs) have been attracting worldwide interests in various fields relating to host–guest recognition.[1] However, fine functionalization of CDs is no doubt the bottleneck for molecular designs based on them. Although some methodologies have become available for mono- or mono-facial functionalization,[2] methods for selective introduction of two different functionalities to the CD rims are extremely scarce. The routine method includes *random* stepwise sulfonylation of CDs[3] or *random* stepwise substitution of $6^A,6^B$-diiodo-β-CD with different reactants.[4] The only method available for *selective* introduction of two different functional groups to two specific positions was reported by us four years ago, in which $6^A,6^B$-*O*,*O*-mesitylenedisulfonyl-capped-β-CD was subjected to highly regioselective S_N2 reaction with imidazole on C-6^B (42% yield) compared with C-6^A (4%).[5] There have been no reports addressing the subject of hetero-bifunctionalization (even *random* ones) at the secondary hydroxyl side. Recently, we reported the first efficient method for selective hetero-bifunctionalization at the secondary hydroxyl side of β-CD: treatment of $2^A,2^B$-*O*,*O*-di(mesitylenesulfonyl)-β-CD with alkaline buffer gave $2^A,3^A$-mannoepoxy-2^B-*O*-mesitylenesulfonyl-β-CD in a yield up to 72%.[6] We describe here a novel strategy for the hetero-bifunctionalization at the secondary hydroxyl side: regioselective sulfonylation of functional *altro*-β-cyclodextrin.

altro-β-CD,[7] which can be made from β-CD by converting one glucoside unit to an altroside, has a flexible cavity and displays very unique molecular recognition properties in water.[8] Upon binding a flat guest such as 2-naphthalenesulfonate, it becomes more elliptical to better fit the geometry of guest and to restrict the guest orientation.[9] This property enabled *pre-inclusion-controlled* 2^A-*O*-sulfonylation of *altro*-β-CD and 3^A-azido-3^A-deoxy-*altro*-β-CD (**1**)[10] with guest-type sulfonylating reactants, 2-naphthalensulfonyl chloride[11] and mesitylenesulfonyl chloride,[12] respectively. The positional selectivity of sulfonylation on *altro*-β-CD is dependent on the structure of the sulfonylating reactant: 1-naphthalenesulfonyl chloride not only reacted with 2^A-OH but also gave the 3^G-sulfonate as the second major product.[13] This finding prompted us to investigate mono-*O*-sulfonylation of **1** with various arenesulfonyl chlorides with the aim to find the appropriate reactant giving the 3^G-sulfonate as a major product. We preliminarily tested 2-naphthalenesulfonyl, *p*- and *m*-nitrobenzenesulfonyl, and 1-naphthalenesulfonyl chlorides as the sulfonylating reactants and found that the

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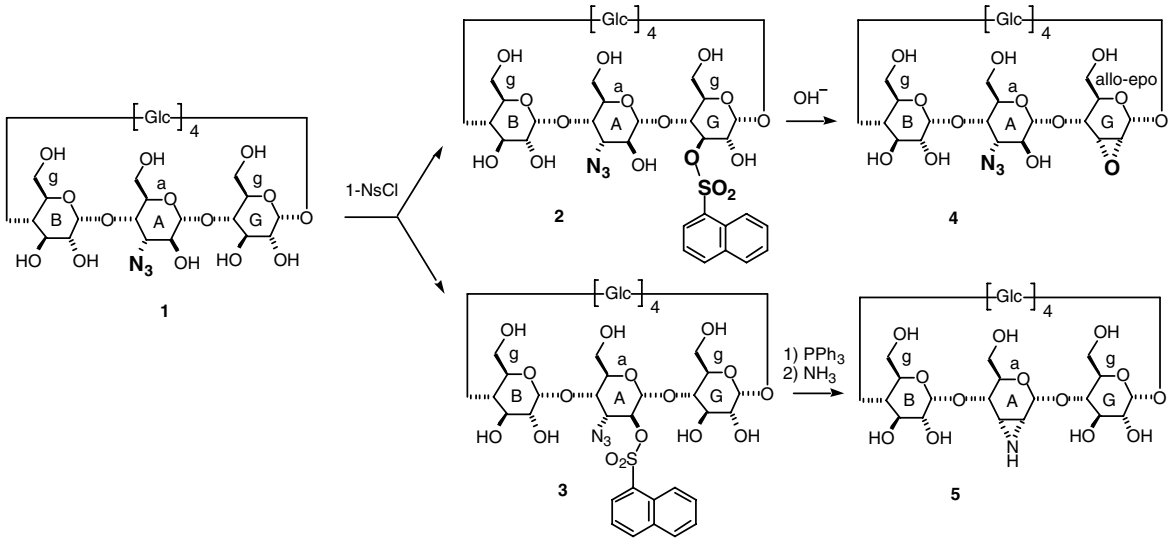
product ratio 3^G-sulfonate/2^A-sulfonate[14] increased in this order. The ratio became nearly 1 with *m*-nitrobenzenesulfonyl chloride and 1.3 with 1-naphthalenesulfonyl chloride. In this letter, we describe 3^A,3^G-hetero-bifunctionalization of *altro*-β-CD via selective reaction of 3^A-azido-3^A-deoxy-*altro*-β-CD (**1**) with 1-naphthalenesulfonyl chloride in an aqueous solvent. The major product, 3^A-azido-3^A-deoxy-3^G-*O*-sulfonyl-*altro*-β-CD (**2**) as well as its derivative 2^G,3^G-allo-epoxy-3^A-azido-3^A-deoxy-*altro*-β-CD (**4**) can serve as very important intermediates for the syntheses of novel bifunctional CD derivatives that are otherwise inaccessible (Scheme 1).

A solution of Na_2HPO_4 (575 mg) in a mixed solvent composed of CH_3CN (6 mL) and water (14 mL) was adjusted to pH 12 with concd aq NaOH. To this phosphate solution, 3^A-azido-3^A-deoxy-*altro*-β-CD (**1**) (2 g)[10] was added and then powdered 1-naphthalenesulfonyl chloride (1.2 g) was poured in at one portion. The mixture was stirred vigorously and the pH of the mixture was allowed to decrease during the reaction in order to reduce the decomposition of sulfonate products in alkaline condition. Ten minutes later, the mixture became neutral and was filtered. The filtrate was diluted with water (800 mL) and chromatographed on a reversed-phase Lobar column (Rp-18, size C). Sequential elution of the column with water (1 L), then a gradient from water to 30% aq ethanol (1 L for each) and finally a gradient from 30% to 40% aq ethanol (500 mL for each) afforded two major products, **2** (0.42 g, 18%) and **3** (0.33 g, 14%) together with the unreacted **1** (0.79 g, 40% recovery). The yield of **2** is considerably good and the reaction is undoubtedly a selective one since a random reaction would generate 20 regio-isomeric sulfonates and the average yield of each isomer is expected to be no more than 3% even if any possible disulfonylation and mass loss during the overall process are not taken into consideration.

Compounds **2** and **3** shared the same pseudo parent peak [M+Na^+] at *m*/*z* 1372 in the TOF-MS spectrum, indicating that they were the mono-sulfonates of **1**. Compound **3** is quite resistant to alkali, suggesting that the sulfonylation position should be O-2^A or O-6^A of the 3^A-azido-3^A-deoxy-altroside residue, otherwise some kind of anhydro species (2,3-mannoepoxy, 2,3-alloepoxy, or 3,6-anhydro) will be generated. To confirm this structure, compound **3** was transformed to **5** by reduction of the azido group followed by intramolecular S_N2 reaction. The ^1H and ^{13}C NMR and TOF-MS spectra of **5** were same as those of the known 2^A,3^A-alloepimino-2^A,3^A-dideoxy-β-CD,[12] demonstrating that **3** was the 2^A-*O*-sulfonate of **1**.

In contrast to **3**, compound **2** is unstable toward alkali and readily reacts in alkaline solution, generating the epoxide **4**. The structure of **2** was difficult to be determined directly from the NMR spectra. In order to determine the structure and to develop novel hetero-bifunctional cyclooligosaccharides, conversion of **2** to **4** was undertaken. A solution of **2** (100 mg) in 10 mL of 0.1 M aq $Ba(OH)_2$ was stirred at room temperature overnight and then neutralized with 1 M H_2SO_4. After the precipitates were filtered off, the solution was chromatographed on an anion exchange column (BIO-RAD AG® 1-X2 Resin) to remove the sulfonate salt. The fractions containing sugar species were combined and subjected to chromatography on a reversed-phase Lobar column (Rp-18, size B). Elution of the column with water (500 mL) and then with a gradient from water to 15% aq ethanol (500 mL for each) afforded **4** (64.8 mg, 76.6%).

Compound **4** gave the pseudo parent peak [M+Na^+] at *m*/*z* 1164 in the TOF-MS spectrum, suggesting that the sulfonate was converted to an epoxide. Since the ^1H and ^{13}C NMR spectral signals of 3^A-azido-3^A-deoxy-*altro*-β-CD[10] and 2^A,3^A-epoxy-β-CDs[16] have been already assigned independently, thus knowledge incorporated along with the 2D COSY NMR spectral examinations of **4** allowed the identification of the signals of the individual modified sugar units of **4**, and the results are shown in Figure 1. The ^{13}C NMR spectrum of **4** showed



Scheme 1. Selective preparation of hetero-bifunctional CDs (**2** and **3**) and their conversion to other functional CDs (**4** and **5**), respectively.

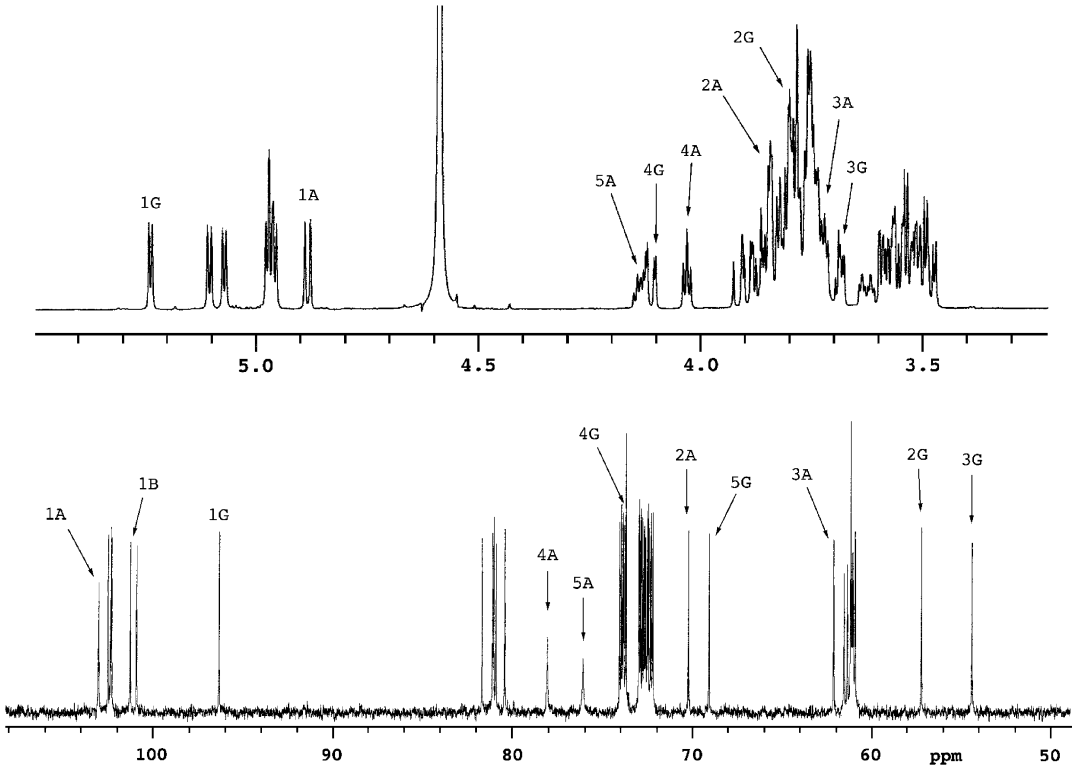


Figure 1. ^{13}C and ^{1}H NMR spectra of $2^{G},3^{G}$-alloepoxy-3^{A}-azido-3^{A}-deoxy-*altro*-β-CD (**4**) in D_2O (CH_3CN as internal standard: $\delta_{CH_3CN} = 1.98$ ppm, $\delta_{CH_3CN} = 1.70$ ppm).

two signals at very high field (δ_C 54.4 and 57.2, respectively), which have similar chemical shifts to those of the corresponding oxirane carbons of the 2,3-epoxy-cyclodextrins. In addition, the ^{1}H NMR spectrum displayed a notable coupling constant for the anomeric proton (δ 5.23, $J_{1,2} = 3.4$ Hz) of the 2,3-epoxy-pyranose, suggesting that the epoxide to be of an *allo*-type rather than a manno one.[15] HMBC experiments were carried out to clarify the sequential relationship between the modified sugar units. The HMBC spectra of **4** demonstrated clear correlation between the C-1^{A} (or H-1^{A}) of 3-azido-altroside and H-4 (or C-4) of the 2,3-alloepoxide, indicating the connection of O-4 of the 2,3-alloepoxide to C-1^{A}.

Based on the above analyses, compound **4** is reasonably assigned to $2^{G},3^{G}$-alloepoxy-3^{A}-azido-3^{A}-deoxy-*altro*-β-CD and compound **2** should be the 3^{G}-*O*-sulfonate of 3^{A}-azido-3^{A}-deoxy-*altro*-β-CD. Thus, we demonstrated a selective method to activate the 3^{G}-OH (together with 2^{A}-OH) among the 20 different competing groups of 3^{A}-azido-3^{A}-deoxy-*altro*-β-CD. 3^{G}-*O*-sulfonate **2** and $2^{G},3^{G}$-alloepoxy-3^{A}-azido-3^{A}-deoxy-*altro*-β-CD (**4**) can serve as very important intermediates for the syntheses of novel hetero-bifunctional CD derivatives, since the azido group is an amino-synthon which is stable under reaction conditions where the $2^{G},3^{G}$-epoxy ring is attacked by many kinds of appropriate nucleophiles to afford a variety of 3-functionalized glucoside residues and 2-functionalized altroside ones.[12] This method and our previous one[6] complement each other, making it possible to convert the G-ring of 3^{A}-functional monoaltro-β-cyclodextrins into any form of the four structural patterns: 2- or 3-functional altroside and 2- or 3-functional glucoside.

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