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Preparation of $2^A,3^A$-alloepimino-$2^A,3^A$-dideoxy-β-cyclodextrin as a versatile scaffold candidate for the hetero-$2^A,3^A$-bifunctionalization

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Abstract—3^A-Azido-3^A-deoxy-*altro*-β-cyclodextrin, although having as many as 20 different hydroxyl groups, was selectively sulfonylated at the 2^A-OH of the altrose residue by 2-mesitylenesulfonyl chloride to give 3^A-azido-3^A-deoxy-2^A-*O*-mesitylenesulfonyl-*altro*-β-cyclodextrin. A one-pot reduction–intramolecular substitution of the latter afforded the title compound as a promising intermediate for the introduction of two different functional groups to two different positions of one sugar unit, which has not been succeeded hitherto.

Construction of cyclodextrin-based functional molecules such as artificial enzymes and receptors relies upon the sophisticated functionalizations of cyclodextrins (CDs).[1] A wealth of methodologies have been reported for the functionalizations of the primary hydroxyl sides.[1,2] However, only a couple of methods, that is, direct alkylation of CD and nucleophilic ring opening of the CD 2,3-epoxides, are available for selective mono-, homo-bi-, and per-functionalization, and none for selective hetero-bifuctionalization of the secondary face of CDs.[1–3] The bottleneck seems to be the lack of versatile intermediates other than 2,3-epoxy-CDs[1–3] for incorporating functionalities, and it is expected to be broken by the development of the thia- and aza-analogs of 2,3-epoxy-CDs. Recently, we succeeded in the preparation of the thia-analog, $2^A,3^A$-alloepithio-$2^A,3^A$-dideoxy-β-CD and its application for the synthesis of 3^A, 6^A-anhydro-2^A-deoxy-2^A-thio-β-CD.[4]

Altro-β-CD, which was made from β-CD by converting one glucoside unit to altroside,[5] was demonstrated to form the elliptically distorted cavity with flexibility and undergo unique induced-fit conformational change upon the binding of a guest molecule.[6] That is, 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.[7] This flexibility of cavity stems from the conformational flexibility of the altroside unit which is in an equilibrium among $^1C_4$, $^OS_2$, and $^4C_1$ conformers.[8] Based on this finding, we carried out a *pre-inclusion-controlled modification* of *altro*-β-CD with a guest-type sulfonylating reactant, 2-naphthalensulfonyl chloride and succeeded in the selective 2^A-*O*-sulfonylation.[9] This high selectivity, suggesting that the chlorosulfonyl group is enforced to direct toward 2^A-OH by the restricted orientation of the naphthyl group in the cavity, prompted us to investigate a *pre-inclusion-controlled* sulfonylation of regiospecifically functionalyzed *altro*-β-CDs in order to prepare bifunctional CDs with flexible cavities.

We report here selective 2^A-*O*-sulfonylation of 3^A-azido-3^A-deoxy-*altro*-β-CD (**1**)[3] to give bifunctional *altro*-β-CD **2** and its transformation to the aza-analog of $2^A,3^A$-alloepoxy-β-CD **3** which is a potential versatile scaffold to prepare β-CDs and *altro*-β-CDs bearing *hetero-functionalities* on C-2^A and C-3^A of the same sugar unit A (Scheme 1).

A solution of **1** (500 mg) and Na_2HPO_4 (75 mg) in 30% aq CH_3CN (3.7 mL) was adjusted to pH 12 with concd

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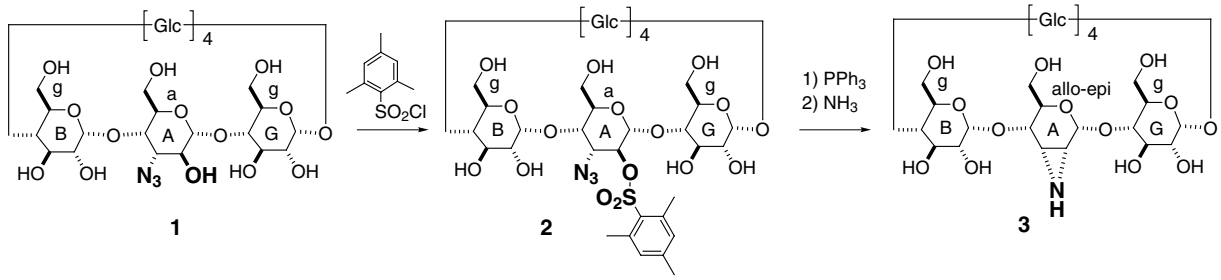

Scheme 1. Selective preparation of 3^A-azido-3^A-deoxy-2^A-*O*-sulfonyl-*altro*-β-CD (**2**) and its transformation to 2^A,3^A-alloepimino-2^A,3^A-dideoxy-β-CD (**3**). The marks, a, allo-epi, and g denote altroside, 2,3-dideoxy-2,3-epimino-alloside, and glucoside, respectively.

aq NaOH, and thermostated at 40 °C. To this phosphate solution, powdered 2-mesitylenesulfonyl chloride (435 mg) was poured in at one portion. The mixture was stirred vigorously and the pH was allowed to decrease to neutral (it took ca. 15 min). The mixture was diluted with water (500 mL) and filtered. The filtrate was chromatographed on a reversed-phase Lobar column (Rp-18, size C) with an elution of water (1 L) and then a gradient elution of water 45% aq ethanol (1.5 L for each) to afford **2** (86.4 mg, 15%) together with the recovery of unreacted **1** (234 mg, 47%).

Compound **2** gave the parent peak [M+Na^+] at *m*/*z* 1364 in the TOF MS spectrum, indicating that **2** was the mono-sulfonate of **1**. Since the azido-substituted carbon C-3^A should show the largest upfield shift among all the carbons, the 2D COSY NMR spectra of **2** allowed us to easily recognize the unit A and assign most of its carbon and proton signals (Fig. 1): δ_C 99.1 (C-1^A), 75.3 (C-2^A), 58.8 (C-3^A), 73.5 (C-4^A), and 69.3 (C-5^A); δ_H 4.75 (br s, H-1^A), 4.63 (br s, H-2^A), 4.10 (br t, $J_{2,3} = J_{3,4}$ = ca. 3.9 Hz, H-3^A), and 3.96 (dd, $J_{3,4} = 4.1$ Hz, $J_{4,5} = 8.9$ Hz, H-4^A). The very low chemical shift of C-3^A (ca. 12 ppm lower than those of the normal ones) is consistent with the attachment of azido group at this position. In comparison with the NMR spectra of **1**, obvious downfield shift of C-2^A ($\Delta\delta$ −4.7) and moderate upfield shifts of C-1^A and C-3^A ($\Delta\delta$ 4.7 and 3.5) on both sides were observed. This chemical shift pattern is well consistent with the sulfonylation of C-2.[10] Therefore, compound **2** was tentatively assigned to 3^A-azido-3^A-deoxy-2^A-*O*-mesitylenesulfonyl-*altro*-β-CD, and this assignment was supported by the large downfield shift of H-2^A ($\Delta\delta$ = ca. 0.8).

To confirm this structure where the azido and sulfonyl groups are attached to the same sugar unit as well as to develop another type of versatile scaffold to prepare β-CDs hetero-bifunctionalized at their secondary hydroxyl sides, compound **2** was successively converted to the aziridine **3**.

A solution of **2** (50 mg) and triphenylphosphine (100 mg) in DMF (0.5 mL) was stirred for 30 min at 50 °C. After addition of water (0.5 mL), the mixture was filtered, and the precipitate was washed with water (2 mL). Aq ammonia (28%, 0.15 mL) was added to the combined filtrate and the mixture was stirred for 90 min at room temperature. The mixture was then neutralized with 1 M HCl and chromatographed on a cation-exchange column (BIO-RAD, AG® 50W-X2 Resin, size Φ1 cm × 12 cm) with a gradient elution from water (200 mL) to 5% aq ammonia (200 mL) to afford **3** (28 mg, 67%).

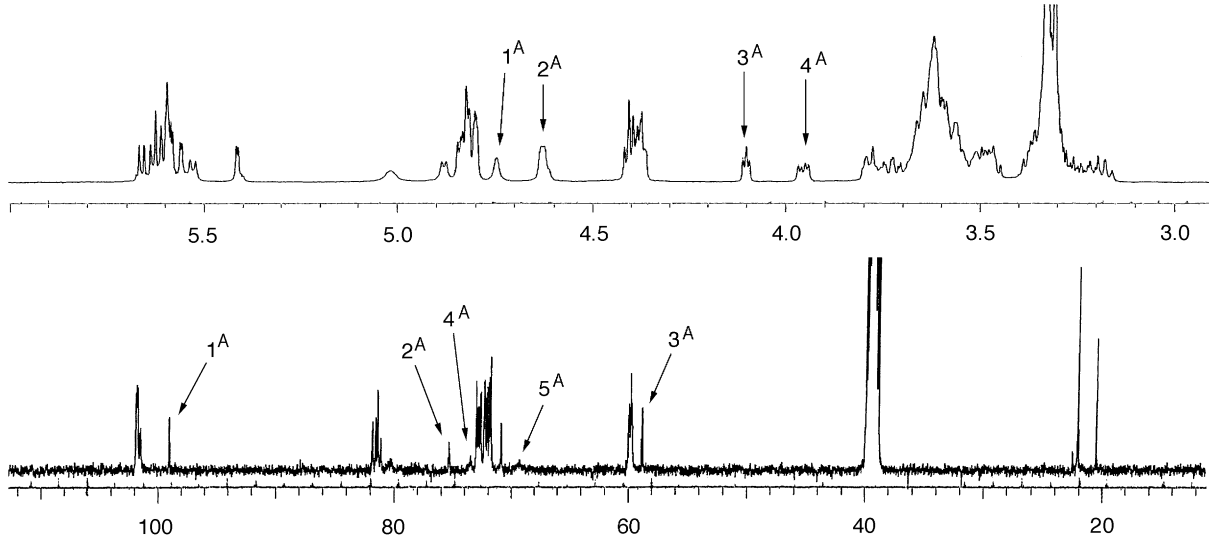

Figure 1. Partial ^1H and ^{13}C NMR spectra of compound **2** in DMSO-d_6.

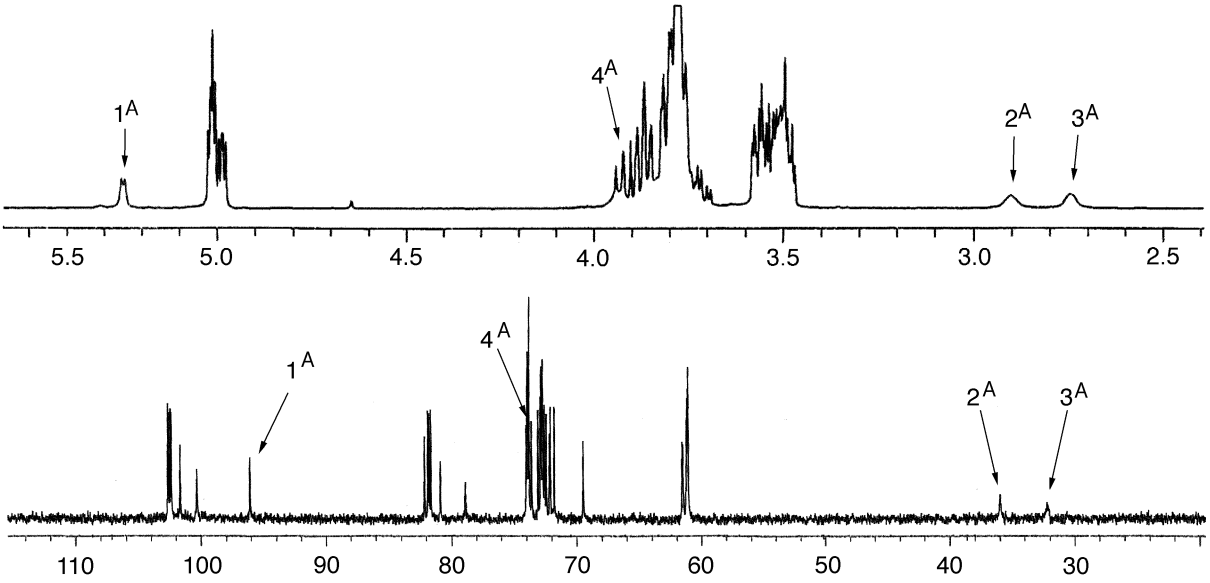

Figure 2. ^{1}H and ^{13}C NMR spectra of compound **3** in D_2O.

The 2D COSY NMR spectra (D_2O) of **3** enabled the assignment of some carbons and protons of sugar unit A: δ_C 96.1 (C-1^A), 36.0 (C-2^A), 32.2 (C-3^A), and ca. 73.6 (C-4^A); δ_H 5.25 (d, $J_{1,2}$ = 5.3 Hz, H-1^A), 2.90 (br s, H-2^A), and 2.75 (br s, H-3^A), and 3.93 (d, $J_{3,4}$ = 9.4 Hz, H-4^A) as shown in Figure 2. Successful reduction of azido group is evidenced by the very low chemical shift of C-3^A. However, the substituent at C-3^A is obviously not a NH_2 group because the chemical shift of C-3^A is over 20 ppm lower than the corresponding value of 3^A-amino-3^A-deoxy-β-CD.[3] This chemical shift difference matches well that between ethylenediamine (δ_C 41.5) and ethyleneimine (δ_C 18.2).[11] On the other hand, the C-2^A was extremely upfield shifted ($\Delta\delta$ = ca. −39!), almost to the same region of C-3^A, strongly implying that the substitution of 2^A-sulfonate group by an amino group occurred upon the reduction of the C-3^A-azide (**2**). These observations together with the MS spectrum which demonstrated a molecular ion peak [M+Na^+] at *m/z* 1138 suggests that **3** is a 2^A,3^A-epimine species. In fact, the chemical shift differences $\Delta\delta_{C\text{-}3^A}$ ca. 42 and $\Delta\delta_{C\text{-}2^A}$ 37 between **3** and β-CD[3] are basically the same of that between ethylene imine (δ_C 18.2) and ethylene glycol (δ_C 63.4).[11]

The allo-type structure of **3** is suggested by the rather large coupling constant ($^3J_{1,2}$ = 4.4 Hz) between H-1^A and H-2^A, which is similar to the corresponding $^3J_{1,2}$ of 2^A,3^A-alloepoxy-β-CD (3–4 Hz)[13] but obviously different form that of 2^A,3^A-mannoepoxy-β-CD (ca. 0 Hz).[14] Comparison of the chemical shift differences between **3** and the 2^A,3^A-epoxy-β-CDs also indicated that the epimine structure of **3** was of an allo-type rather than a manno-one.[12,13] This assignment is consistent with the geometrical chemistry of the reaction, that is, reduction of the azido group does not alter the absolute conformation of C-3^A while the subsequent intramolecular attack of the generated 3^A-amino group at the C-2^A (S_N2) results in an inversion of the absolute conformation of C-2^A.

The formation of **3** and the allo structure of the epimino group support the determination of the structure of **2**. Thus, **2** and **3** were assigned as 3^A-azido-3^A-deoxy-2^A-*O*-mesitylenesulfonyl-*altro*-β-CD and 2^A,3^A-alloepimino-2^A,3^A-dideoxy-β-CD, respectively. A variety of the nucleophilic reactions on the epimine derivatives[15] reported previously promise that **2** will afford a number of β-CDs and *altro*-β-CDs[16] bearing hetero-bifunctionalities on C-2^A and C-3^A at their secondary hydroxyl sides.

The present result that highly selective 2^A-*O*-activation occurred in the pre-functionalyzed *altro*-β-CD even in the presence of the functionality suggests that '*modification based on orientation-control by pre-inclusion*' is a powerful tool for preparing hetero-bifunctional CDs and the related compounds.

References and notes

1. Motherwell, W. B.; Bingham, M. J.; Six, Y. *Tetrahedron* **2001**, *57*, 4663; Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997; Atwood, J. L., Davis, J. E., MacNicol, D. D., Vogtle, F., Eds. Comprehensive Supramolecular Chemistry; Pergamon Elsevier: Oxford, UK, 1996; Vol. 3, Cyclodextrins.
2. Kahn, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.
3. Yuan, D.-Q.; Tahara, T.; Chen, W.-H.; Okabe, Y.; Yang, C.; Yagi, Y.; Nogami, Y.; Fukudome, M.; Fujita, K. *J. Org. Chem.* **2003**, *68*, 9456.
4. Fukudome, M.; Okabe, Y.; Sakaguchi, M.; Morikawa, H.; Fujioka, T.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2004**, *45*, 9052.
5. Fujita, K.; Ohta, K.; Ikegami, Y.; Shimada, H.; Tahara, T.; Nogami, Y.; Koga, T.; Saito, K.; Nakajima, T. *Tetrahedron Lett.* **1994**, *35*, 9577.
6. Fujita, K.; Chen, W.-H.; Yuan, D.-Q.; Nogami, Y.; Koga, T.; Fujioka, T.; Mihashi, K.; Immel, S.; Lichtenthaler, F. W. *Tetrahedron: Asymmetry* **1999**, *10*, 1689.

7. Chen, W.-H.; Fukudome, M.; Yuan, D.-Q.; Fujioka, T.; Mihashi, K.; Fujita, K. *Chem. Commun.* **2000**, 541; Lindner, H. J.; Yuan, D.-Q.; Fujita, K.; Kubo, K.; Lichtenthaler, F. W. *Chem. Commun.* **2003**, 1730.
8. Angyal, S. J. *Aust. J. Chem.* **1968**, *21*, 2737; Dowd, M. K.; French, A. D.; Reilly, P. J. *Carbohydr. Res.* **1994**, *264*, 1; Lichtenthaler, F. W.; Mondel, S. *Carbohydr. Res.* **1997**, *303*, 293.
9. Fukudome, M.; Fujioka, T.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2001**, *42*, 293.
10. Fujita, K.; Nagamura, S.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5673.
11. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tabellen zur Structuraufklaerung organischer verbindungen mit spektroskopischen methoden (Dritte Auflage)*; Springer-Verlag: Berlin, 1986, C173, C177, H65, and H85.
12. The chemical shift differences $\Delta\delta_{C\text{-}2^A}$ 21.2 and $\Delta\delta_{C\text{-}3^A}$ 22.8 between **3** and $2^A,3^A$-alloepoxy-β-CD are very similar to, but those between **3** and $2^A,3^A$-mannoepoxy-β-CD ($\Delta\delta_{C\text{-}2^A}$ 14.1 and $\Delta\delta_{C\text{-}3^A}$ 22.7) are different from $\Delta\delta_C$ 21.3 between ethylene imine (δ_C 18.2) and ethylene oxide (δ_C 39.5).[11] In addition, the chemical shift differences $\Delta\delta_{H\text{-}2^A}$ 0.88 and $\Delta\delta_{H\text{-}3^A}$ 0.91 between **3** and $2^A,3^A$-alloepoxy-β-CD are also very similar to $\Delta\delta_H$ 0.93 between ethylene imine (δ_H 1.61) and ethylene oxide (δ_H 2.54),[11] whereas the differences $\Delta\delta_{H\text{-}2^A}$ 0.50 and $\Delta\delta_{H\text{-}3^A}$ 0.81 between **3** and $2^A,3^A$-mannoepoxy-β-CD are not. These comparisons also suggest that **3** is an alloepimine rather than a mannoepimine.
13. Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030.
14. Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390.
15. Rai, K.; Lokanatha, L. M.; Hassner, A. *Adv. Strained Interesting Org. Mol.* **2000**, *8*, 187; Stamm, H. *fuer Praktische Chemie* **1999**, *341*, 319; Mitsunobu, O. In *Comprehensive Organic Synthesis*; Winterfeldt, E., Ed.; Pergamon: Oxford, 1991; Vol. 6, p 93; Stamm, H.; Onistschenko, A.; Buchholz, B.; Mall, T. *J. Org. Chem.* **1989**, *54*, 193; Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Pees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 47; Deyrup, J. A. *Chem. Heterocycl. Compd.* **1983**, *42*, 1; Laurent, A. *Bull. Soc. Chim. Belg.* **1983**, *92*, 797; Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic: New York, 1969; Raftley, M. A.; Cole, R. D. *J. Biol. Chem.* **1966**, *241*, 3457; Fanta, P. E. In *Heterocyclic Compounds with Three- and Four- Membered Rings, Part 1*; Weissberger, A., Ed.; Interscience: New York, 1964; p 524.
16. The S_N2 reactions on **3** are expected to give two type of products, glucoside-type and altroside-type, on the analogy of the reaction of $2^A,3^A$-alloepoxy-β-CD. See Ref. 3.