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# GENERAL METHOD FOR PREPARING ALTROSIDES FROM 2,3-MANNO-EPOXIDES AND ITS APPLICATION TO SYNTHESIS OF ALTERNATIVE β-CYCLODEXTRIN WITH AN ALTROSIDE AS THE CONSTITUENT OF MACROCYCLIC STRUCTURE

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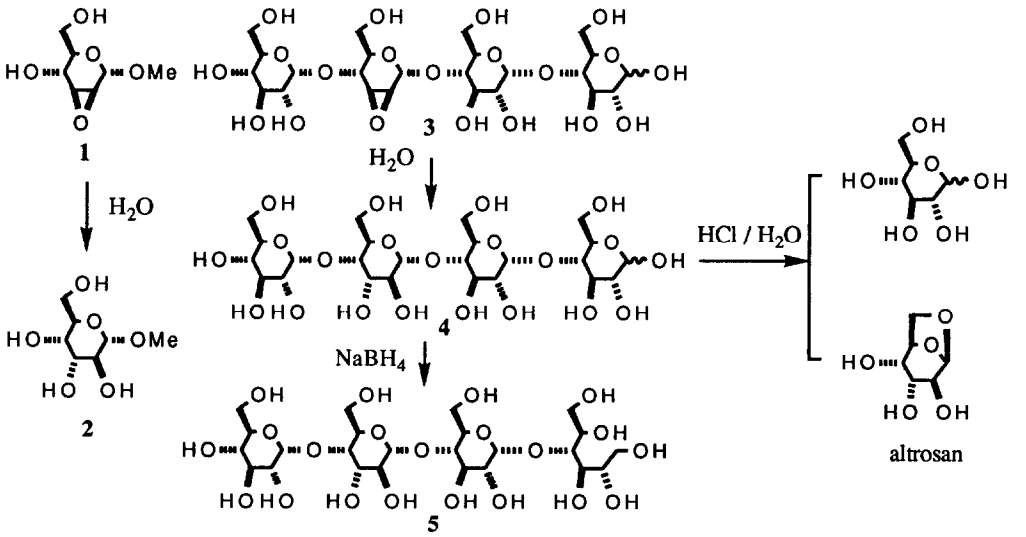
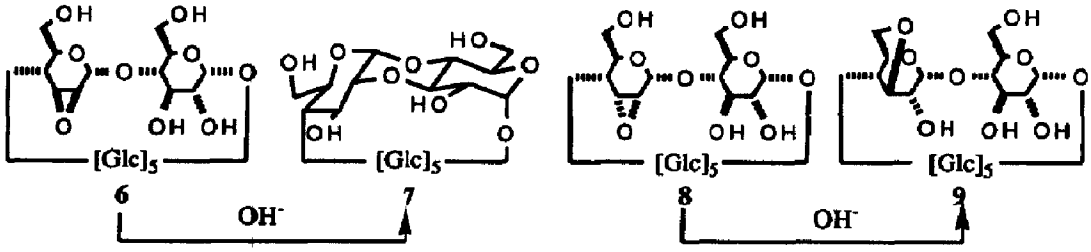
***Abstract:*** A general and convenient method for preparing altrosides from 2,3-manno-epoxides is described and as the application, $2^A(S),3^A(R)$-β-Cyclodextrin which has an altroside as the constituent was prepared and assigned;the altroside part has $^1C_4$ conformation predominantly.

In the previous paper,[2] we described that formation of altrosides is rather rare and limited to the monosaccharide systems in the reaction of 2,3-manno-epoxides with alkaline water and that, in the oligosaccharide systems, regardless of whether the system is cyclic or linear, the altroside formation is minor or negligible and the predominant reaction is the ether formation between the manno-epoxide part and the adjacent glucoside part.

In this report, we describe a general and convenient method for preparing the altrosides selectively. This simple method includes refluxing a solution of the epoxide in distilled water. Furthermore, we describe its application for converting a glucoside unit to an altroside unit in β-cyclodextrin system.






A solution of **1** (47.5 mg) or **3**[3] (114.0 mg) in water (25 or 40 mL) was refluxed for 4 d. The silica-gel TLC and reversed-phase HPLC of the solution demonstrated that the starting compound disappeared completely and only one product was produced. The product was separated by reversed-phase HPLC (Cosmosil 10C18, Nacalai) and lyophilized to give methyl α-altroside **2** (50 mg, 95.7%; $[\alpha]_D^{24}$ +117°[4] (c = 1.00, $H_2O$)) or the altroside derivative **4** (85.0 mg, 72.0%; $[\alpha]_D^{26}$ +152° (c = 0.99, $H_2O$)), respectively. The structure of **2** was determined by comparing its HPLC retention time and $^1H$ NMR spectrum with those of the authentic compound.[4] FAB mass spectra of the altrose derivative **4** and its reduction product **5** (63.3%; $[\alpha]_D^{26}$ +152° (c = 1.02, $H_2O$) contained the molecular ions respectively and acid-catalyzed hydrolysis of **4** gave glucose, altrose, and altrosan which was assigned by comparing its HPLC retention time with that of the authentic compound[5] prepared by the acid-catalyzed reaction of methyl altropyranoside and altropyranose in water, demonstrating that the epoxy part of **3** was converted to the altroside. Since sugars with reducing ends are unstable in alkaline water where the synthesis of altroside was carried out according to the reported method,[5] it is noteworthy that the present convenient method can be used without protecting the reducing end of sugar as shown in the case of **3**.

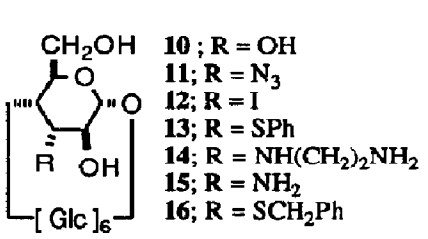
This selective and efficient method was applied to a cyclodextrin system. Cyclodextrins are cyclic oligosaccharides with rigid cavities composed of α-D-glucosides whose conformations are predominantly $^4C_1$. Alteration of the shape of cavity has been tried for the sake of obtaining a variety of molecular recognition; 2,3-anhydrocyclodextrins[3,6] (**6** and **8**), $3^A,2^B$-anhydrocyclodextrins **7**,[2] and 3,6-anhydrocyclodextrins **9**.[7,8] These alternative cyclodextrins have the deformed, but rigid cavities. α-D-Altrose is reported to be a conformationally flexible compound: the conformational energy of $^1C_4$ isomer (3.85 Kcal/mol) is similar to that of the $^4C_1$ isomer (3.65 Kcal/mol).[9] Therefore, replacement of one glucose unit by a α-D-altroside in cyclodextrin systems is expected to make the cavity flexible.

A solution of **6** (32.2 mg) in water (8 mL) was refluxed for 4 d. The silica-gel TLC and reversed-phase HPLC of the solution demonstrated that the starting compound disappeared completely and only one product was produced. The product was separated by reversed-phase HPLC (Cosmosil 10C18, Nacalai) and lyophilized to give $2^A$(S),$3^A$(R)-β-cyclodextrin **10** (hereafter abbreviated as altro-β-CD) (26.2 mg, 80%; $[\alpha]_D^{24}$ +132° (c = 1.01, $H_2O$)). The FAB mass spectrum of **10** contained the molecular ion at m/Z 1135 ($M + H^+$) which is the same to that of β-cyclodextrin. However, the HPLC retention time and $^1H$ (Fig. 1A) and $^{13}C$ NMR (Fig. 1B) spectra were different from those of β-cyclodextrin. To investigate the sugar composition, **10** was hydrolyzed with 5% HCl to give a mixture mainly consisted of glucose and a sugar. HPLC analysis (YMC-Pack PA, YMC) demonstrated that the sugar was altrosan. This result and the ratio of peak-area of the two sugars in HPLC demonstrated that **10** was constituted of six glucoses and one altrose.

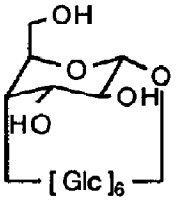
Treatment of **6** with strongly alkaline[2] or acidic water causes formation of $3^A,2^B$-anhydro-β-cyclodextrin **7** or cleavage of the cyclodextrin ring, respectively. Furthermore, employment of borate (pH 9.12) or acetate (pH 4.0) buffer solution as the solvent resulted rather in retarding the formation of **10** and increasing amount of

byproducts (7 and unidentified compounds). Therefore, the formation of **10** requires the presence of both proton and hydroxide anion in the aqueous solution.

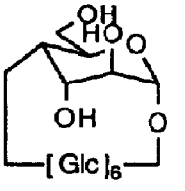
By $^{13}C$-, $^{1}H$, $^{1}H$-$^{1}H$ COSY, $^{13}C$-1H COSY and 1D- and 2D-HOHAHA NMR spectra, proton-signals of the altrose part of **10** were assigned (Fig. 1A). It is interesting to note that introduction of one altroside into the cyclodextrin caused unequivalency of the glucose units in the $^{1}H$ NMR spectrum. The coupling constant ($J_{1,2}$ = 6.6 Hz) of the altrose part is very different from that of α-D-altropyranose (3.3 Hz),[9] demonstrating that the predominant conformation of the altrose part in **10** is $^{1}C_4$ (**17a**) rather than $^{4}C_1$ (**17b**) which is somewhat preferred in the case of α-D-altropyranose. Since 3-modified altrose parts in other altro-β-CD



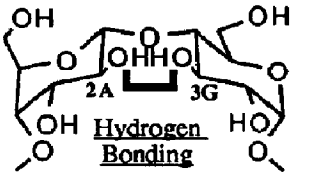

**10** ; R = OH
**11**; R = $N_3$
**12**; R = I
**13**; R = SPh
**14**; R = $NH(CH_2)_2NH_2$
**15**; R = $NH_2$
**16**; R = $SCH_2Ph$




**17a** ($^{1}C_4$)




**17b** ($^{4}C_1$)




**18**

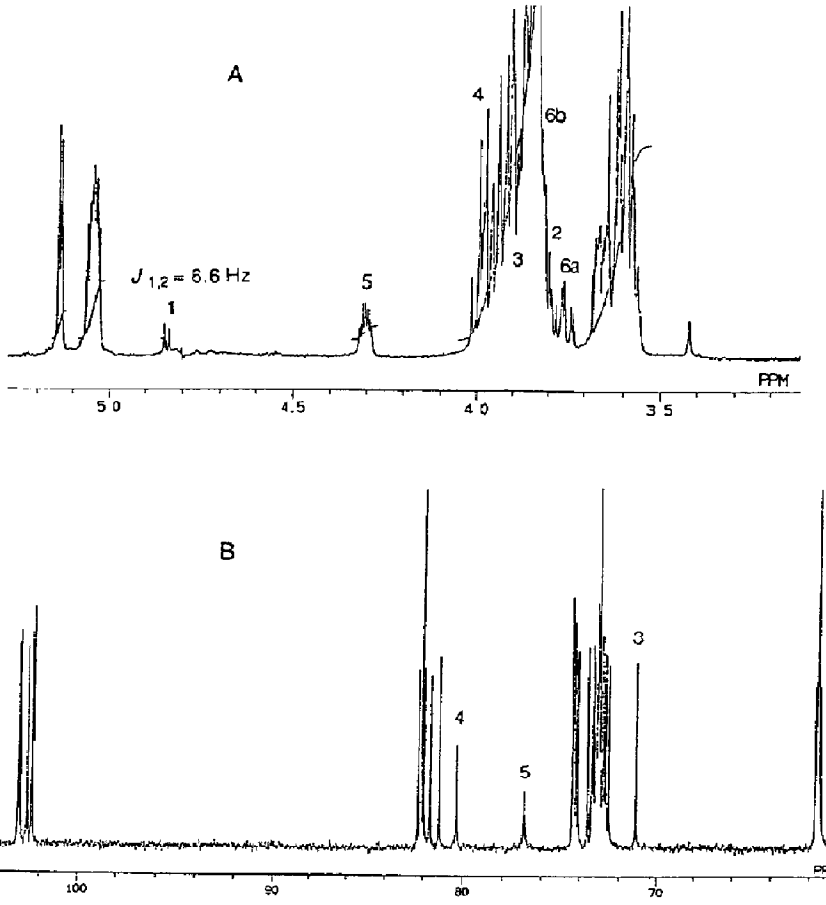



Fig. 1. $^{1}H$ (500 MHz, A) and $^{13}C$ (125 MHz, B) NMR Spectra of Altro-β-CD **10** in $D_2O$.

derivatives (**11** - **14**,[10] **15**,[11] and **16**[12]) have also predominantly the $^1C_4$ conformations, the main reason for $^1C_4$ must be attributed to a hydrogen bond of $2^A$-OH (the altrose part) with $3^G$-OH (the adjacent glucose part) as shown in **18**. Such a hydrogen bonding is not possible in the $^4C_1$ conformer where $2^A$-OH is axial. Thus, the small energy difference between the two conformations in α-D-altrose may produce conformational difference between in the monosaccharide state and in the cyclooligosaccharide state.

Change of the cavity shape arising from conformational change of the glucose part of cyclodextrins cannot be induced by the guest-binding because of the large energy difference between the two conformers of α-D-glucose (2.4 Kcal/mol for $^4C_1$ and 6.55 Kcal/mol for $^1C_4$ )[9] and the interglucosyl hydrogen bonding between 2-OHs and 3-OHs. On the other hand, the altro-β-CD **10** can change potentially its cavity shape when it binds an appropriate guest molecule.

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***References and Notes***

1. (a) Nagasaki University. (b) Daiichi College. (c) Suntory Institute.
2. K. Fujita, T. Tahara, H. Sasaki, Y. Egashira, T. Shingu, T. Imoto, and T. Koga, *Chem. Lett.* **1989**, 917.
3. K. Fujita, T. Tahara, S. Nagamura, T. Imoto, and T. Koga, *J. Org. Chem.* **52**, 636 (1987).
4. Reported $[\alpha]_D^{20}$; +126° (c = 3, $H_2O$); G. J. Robertson and W. Whitehead, *J. Chem. Soc.* 319 (1940); N. K. Richtmyer, "Advances in Carbohydrate Chemistry", ed. by W. W. Pigman and M. L. Wolfrom, Academic Press Inc., New York, Vol. **1**, pp. 54-57 (1945).
5. N. K. Richtmyer, "Advances in Carbohydrate. Chemistry," ed by W. W. Pigman and M. L. Wolfrom, Academic Press Inc., New York, Vol. **1**, pp. 50-53 (1945).
6. (a) K. Fujita, T. Tahara, Y. Egashira, H. Yamamura, T. Imoto, T. Koga, T. Fujioka, and K. Mihashi, *Chem. Lett.* **1988**, 705. (b) K. Fujita, T. Tahara, T. Imoto, and T. Koga, *J. Am. Chem. Soc.* **108**, 2030 (1986). (c) K. Fujita, S. Nagamura, T. Imoto, T. Tahara, and T. Koga, *ibid.* **107**, 3233 (1985). (d) K. Fujita, S. Nagamura, and T. Imoto, *Tetrahedron Lett.* **25**, 5673 (1984).
7. (a) K. Fujita, T. Kubo, and T. Ishizu, *Tetrahedron Lett.* **33**, 4199 (1992). (b) H. Yamamura and K. Fujita, *Chem. Pharm. Bull.* **39**, 2505 (1991) and references cited therein. (c) A. Gadelle and J. Defaye, *Angew. Chem. Int. Ed. Engl.* **30**, 78 (1991). (d) P. R. Ashton, P. Ellwood, I. Staton, and J. F. Stoddart, *ibid.* **30**, 80 (1991). (e) *Idem, J. Org. Chem.* **56**, 7274 (1991).
8. Recently, preparation of some interesting cyclooligosaccharides were reported: M. Nishizawa, H. Imagawa, Y. Kan, and H. H. Yamada, *Tetrahedron Lett.* **32**, 5551 (1991); N. Sakairi, L-X. Wang, and H. Kuzuhara, *J. Chem. Soc., Chem. Commum.*, 289 (1991); N. Sakairi and H. Kuzuhara, *Ibid.* 5551 (1991).
9. S. J. Angyal, *Angew. Chem.* **81**, 172 (1969); S. J. Angyal and V. A. Pickles, *Austral. J. Chem.* **25**, 1695 (1972)
10. K. Fujita, T. Tahara, H. Yamamura, K. Obe, and K. Koga, to be published; each compound was prepared by the reaction of **1** with the corresponding nucleophile.
11. K. Fujita, Y. Egashira, T. Imoto, T. Fujioka, K. Mihashi, T. Tahara, and T. Koga, *Chem. Lett.* **1989**, 432.
12. R. Breslow, N. Greenspoon, T. Guo, and R. Zarzycki, *J. Am. Chem. Soc.* **111**, 8296 (1989).

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