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$5^A,5^D$-DICARBOXY-β-CYCLODEXTRIN DERIVATIVES — A ROUTE FOR REGIOSELECTIVELY DIFUNCTIONALIZED PERMETHYL-β-CYCLODEXTRIN

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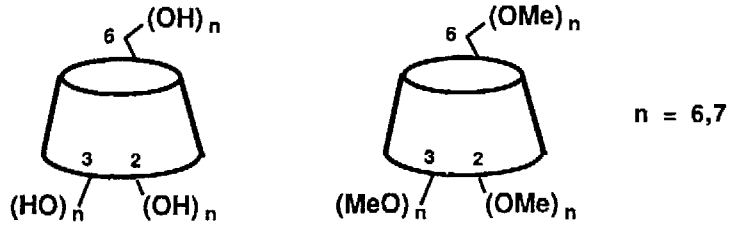
Diazide derivatives of β-cyclodextrin were converted to the corresponding dicarboxylic acid derivatives by the photo-decomposition of azide groups, which was found to proceed normally for both of $6^A,6^D$-diazido-$6^A,6^D$-dideoxy- and the corresponding per-O-methylated β-cyclodextrins. The $LiAlH_4$ reduction of the product obtained from the latter compound gave per-O-methylated-β-cyclodextrin which was demethylated at 6^A and 6^D positions.

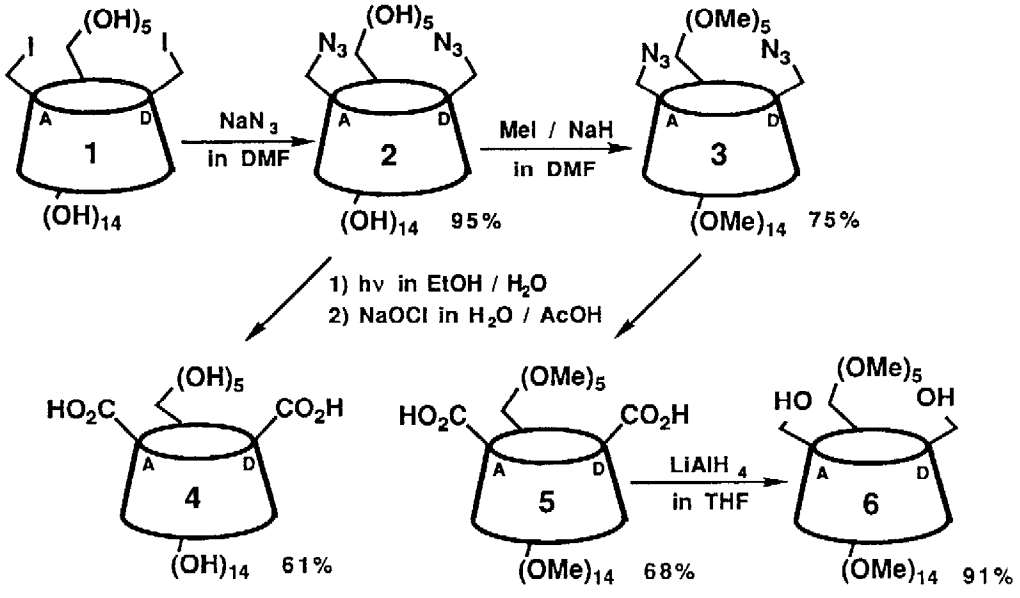
Cyclodextrin is one of the most important parent molecules for enzyme and receptor models which show various types of molecular recognition in an aqueous solution and significant amount of investigation on this subject has been reported during these three decades.[1] One of reasons why cyclodextrin occupies such important position in this field is its diverse possibilities for the introduction of various types of functional groups, i.e., general methods for selective modification at C2, C3 and C6 positions and regioselective difunctionalization at C6 positions of cyclodextrin are now established.[2] Among these modified cyclodextrins, per-O-methylated cyclodextrins have been attracting significant attentions due to their unique properties such as their high solubilities in organic solvents.[3]



Cyclodextrin Per-O-methylcyclodextrin

These O-methylated cyclodextrins are also interesting as enzyme and/or receptor models because of their different hydrophobicity at rim edges and hydrogen bond effects from original cyclodextrins. There, however, is no general method for modification of per-O-methylcyclodextrin.[4] We here report the synthetic method of per-O-methyl-β-cyclodextrin which is regioselectevely demethylated at 6^A and 6^D positions. The method also gives new cyclodextrin derivatives, $5^A,5^D$-dicarboxy-β-cyclodextrin derivatives, as intermediates which are expected to be useful for functionalization of cyclodextrin via amide formation.

The synthetic route is shown in scheme 1. The key step in the present method is the photo-decomposition of azide derivatives of cyclodextrin[5] which are



Scheme 1

easily obtained from the corresponding iodo derivatives by the reaction with NaN_3 in DMF. Thus, $6^A,6^D$-diazido-$6^A,6^D$-dideoxy-β-cyclodextrin (**2**)[6] (800 mg, 0.68 mmol) was photo-decomposed in EtOH/H_2O (1/1, 100mL) by using a medium pressure Hg lump at room temperature. The reaction could be monitored not only by TLC analysis of the reaction mixture but also by volumetric measurement of N_2 gas generated during the reaction. After 8 h irradiation, the solution was evaporated to dryness and the residual product was treated with NaOCl (1 g,0.013 mol) in H_2O/AcOH (3/1, 50 mL) for 5 h at room temperature.[7] The solvent was evaporated and the residue was reprecipitated from water by addition of tetrachloroethylene to afford $5^A,5^D$-dicarboxy-β-cyclodextrin (**4**). Permethylation of **4** by usual NaH/MeI[8] or BaO/$(Me)_2SO_4$[9] method ,however, gave none of cyclodextrin derivatives. The reaction seems to give decomposition products through carbanion formation at C5 position of glucuronic acid units in **4**. In contrast with **4**, the diazido derivative,**2**, was found to be normally methylated by NaH/MeI system to afford the corresponding per-O-methylated cyclodextrin (**3**) in good yield. The existence of CH_2N_3 groups in **3** is easily confirmed by ^{13}C-NMR signal at 52 ppm which is characteristic signal for this C6 carbon.[8] The photo-decomposition of **3** under the same conditions with those for **2** proceeds smoothly to afford the corresponding dicarboxy derivative (**5**). After treatment with NaOCl, the solution was acidified to pH 2 with aq. HCl and practically pure **5** was extracted with chloroform. Further purification of **5** could be achieved with usual silica gel chromatograph ($CHCl_3$/MeOH, 5/1), if necessary. The reduction of the carboxy moieties in **5** was carried out by the treatment with 2 equivalent $LiAlH_4$ in THF. Thus, the solution of **5** (200 mg, 0.14 mmol) in THF (10 mL) was added to the suspension of $LiAlH_4$ (11 mg, 0.29 mmol) in THF (2 mL) at room temperature. After 2 h, the solution was poured into 0.05N-HCl and

extracted with chloroform. The product was purified with silica gel chromatograph ($CHCl_3$/MeOH, 10/1) to give pure **6** as a white powder. The structures of **4** and **5** were confirmed by the following observations in NMR spectra (Fig.1 and Note 10), i.e. existence of carbonyl carbons at 174.24(**4**) and 173.0 ppm(**5**) in ^{13}C-NMR and characteristic H5 protons of glucuronic acid unit at 4.62(**4**) and 4.06 ppm(**5**) in ^{1}H-NMR. Although the structure of **6** is difficult to determine only

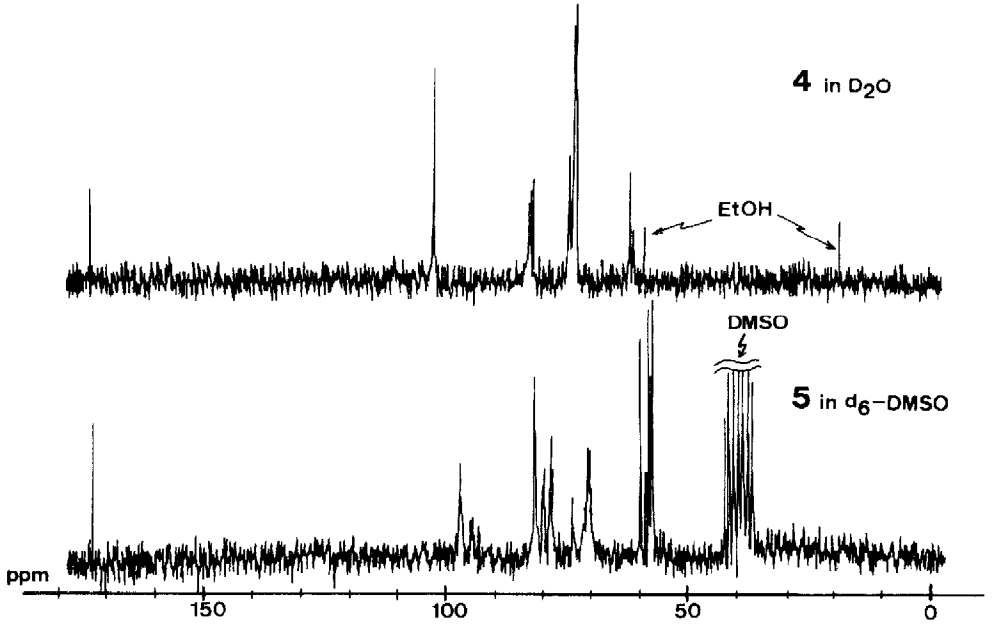
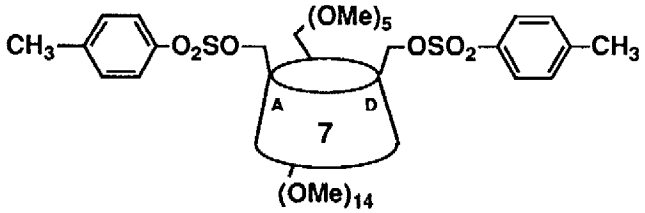


Fig. 1 ^{13}C-NMR spectra of **4** and **5**

by the NMR spectra because of lack of well isolated characteristic ^{13}C and/or ^{1}H signals, it was possible to confirm the structure by tosylation of **6**, i.e., the treatment of **6** with 2.5 equivalent of p-toluensulfonyl chloride in pyridine gives corresponding $6^A,6^D$-ditosylated permethyl-β-cyclodextrin (**7**).[11]

Although, only the example for $6^A,6^D$-isomer is shown in the present paper, it is evident that the present reaction is applicable to any type of azidocyclodextrins which have azide group(s) at C6 position(s). Furthermore, dicarboxy derivatives (**4** and **5**) obtained in the present procedure provide a new functionalization route for cyclodextrin by formation of amide or ester linkages with these carboxyl groups.[12] The applicability of **6** to functionalization of per-O-methylcyclodextrin is clearly shown by the easy tosylation of **6**. Since the various types of nucleophilic reaction is available for **7**, it is now possible



to regioselectively functionalize per-O-methylcyclodextrin by using **7** as the precursor.

Further applications of **4**, **5** and **6** to cyclodextrin modifications are now under way in our laboratory.

References and Notes.

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3) For example, see J. Szejtli, *Cyclodextrin and Their Inclusion Complex* ; Akademiai Kiado, Budapest, (1982).

4) The regiospecifically trisubstituted per-O-methylcyclodextrin was reported by following authors, though the synthetic methods was based on the random functionalization of cyclodextrin, a) J. Boger, R.G. Brenner, R. J. Knowles, *J. Amer. Chem. Soc.*, **101**, 7630, (1979).

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6) I. Tabushi, K. Kuroda, T. Mizutani, *J. Amer. Chem. Soc.*, **108**, 4514, (1986).

7) The treatment with NaOCl is necessary for complete oxidation of the corresponding aldehyde derivative which is the initial product in the present photo-decomposition reaction. See, D. Horton, A. E. Luetzow, O. Theander, *Carohydr. Res.*, **26**, 1, (1973).

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10) **4**:^{1}H-NMR(D_2O) δ5.16-5.03(m,H1,7H),4.62(d,J=9.0Hz,H5 of A,D-glucose units,2H), 4.0-3.53(m,other H,36H); Anal. Found(Calcd. for $C_{42}H_{66}O_{37}+5H_2O$),C,40.14(40.26), H,6.11(6.22). **5**:^{1}H-NMR(d_6-DMSO) δ5.36-5.05(m,H1,7H),4.06(d,J=8.2Hz,H5 of A,D-glucose units,2H),4.0-3.0(m,other H,93H); Anal. Found(Calcd. for $C_{61}H_{104}O_{37}$ $+H_2O$) C,50.93(50.62),H,7.52(7.38). **6**:^{1}H-NMR($CDCl_3$) δ5.28-5.0(m,H1,7H),3.95-3.15(m,other H,99H); ^{13}C-NMR($CDCl_3$) (heavily overlapped signals) 98.73(C1), 82.34,81.76(C2,C3,C4),71.35(C5,C6 of B,C,E,F,G-glucose units),61.65,61.48, 61.18,60.98,58.95,58.38(CH_3,C_6 of A,D-glucose units).

11) The ditosylate, **7**, is purified by silica gel chromatograph ($CHCl_3$/MeOH =15/1) (yield 72%). ^{1}H-NMR($CDCl_3$) δ7.77(d,J=8.1Hz,aromatic H,4H),7.20(d,J=8.1Hz, aromatic H,4H),4.9-5.2(m,H1,7H),2.41(s,CH_3,6H),2.9-4.1(m,other H,99H).

12) For example, the preliminary experiment shows that 5 gives corresponding dianilide derivative by the reaction with aniline using carbodiimidazole.

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