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REGIOSELECTIVE SULFONATION OF A SECONDARY HYDROXYL GROUP OF CYCLODEXTRINS

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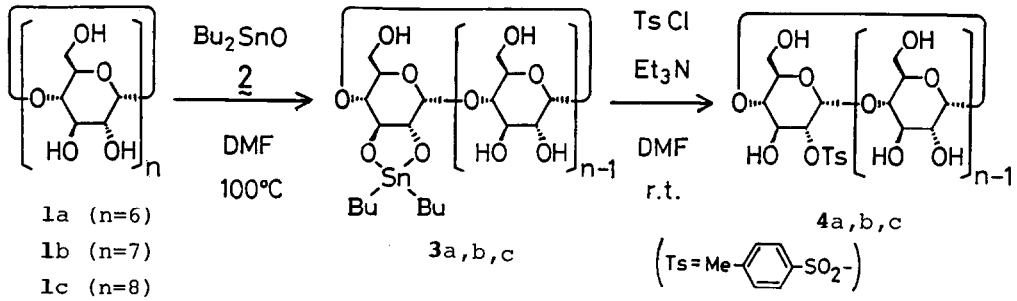
Abstract: A new and convenient procedure has been developed for the regioselective tosylation of a C-2 hydroxyl group of cyclodextrins *via* cyclic tin intermediate.

Cyclodextrin(CD)s (**1**) have attracted current interests as enzyme mimics[1] and chemical modification of CDs with various functional groups has been extensively investigated in order to produce more effective models.[2] Generally, the first important step to attach functional group to CD is sulfonation of hydroxyl groups. Since β-CD having a functional group on the secondary hydroxyl side (C-2, C-3) has demonstrated different enzyme-like activities from that on the primary hydroxyl side (C-6),[3] it is valuable to modify secondary side selectively. Recently, several studies on the regioselective sulfonation of less reactive secondary hydroxyls have been reported.[4-8] However, these methods are usually applicable to either α-CD or β-CD and lack generality. Secondary mono-sulfonate of γ-CD has not been prepared.

On the other hand, regioselective acylation or sulfonation of carbohydrates has been developed by use of organotin compounds. Di-*n*-butyltin oxide (**2**) is known to react with 1,2-diols and to form five-membered dibutylstannylidene derivatives.[9] Since alkyltin alkoxide is more nucleophilic than the original OH group, **2** has been used for selective activation of vicinal diol system in polyhydroxy compounds.[10] We describe here the results obtained from the application of this synthetic methodology to the sulfonation of CDs.

A mixture of β-cyclodextrin(**1b**) (227 mg, 0.20 mmol) and dibutyltin oxide (**2**) (125 mg, 0.50 mmol) in anhydrous DMF (5.0 ml) was stirred at 95-100°C for 2 hr under nitrogen. Then the mixture was cooled to 0°C and to this was added triethylamine (61 mg, 0.60 mmol), followed by a dropwise addition of *p*-toluenesulfonyl(tosyl) chloride (96 mg, 0.50 mmol) in DMF (3.0 ml). The resultant solution was stirred for 10 hr at room temperature and then concentrated *in vacuo* to *ca.* 1 ml. Acetone (50 ml) was added to the residual yellow syrup and the mixture was vigorously stirred for 20 min. The precipitate formed was collected by filtration, washed with acetone, and dried *in vacuo*. Then it was dissolved in water (*ca.* 10 ml), filtered if necessary, and subjected to a reversed-phase column chromatography.[11] After eluting with 50 ml of water, 140 mg



(62%) of unreacted β-CD was eluted with 10% aqueous CH_3CN and then, 82 mg of main product was eluted with 20% aqueous CH_3CN. This product was assigned to C-2 mono-tosylate (**4**b) on the basis of its physical data,[12] which were idetical with the authentic C-2 tosylate prepared by the method of Breslow *et al.*[7] Thus, **4**b was obtained in 32% yield from **1**b (83% yield based on the consumed **1**b). C-6 primary mono-tosylate (5b)[13] and C-3 mono-tosylate was not detected. However, a mixture of C-2 di-tosylates, whose structure was deduced from its ^{1}H- and ^{13}C-NMR spectra, was obtained in *ca.* 5% yield.

On TLC, **4**b is less polar than the C-6 tosylate (**5**b). The ^{1}H-NMR spectrum of **4**b in D_2O/DMSO-d_6 shows aromatic protons at δ 7.59 and 8.01, whereas that of 5b shows δ 7.61 and 7.86. The ^{13}C-NMR spectrum of **4**b (Fig.1) shows an upfield shift of C-1′,demonstrating that the tosyl group must be located at C-2. Fig.1 also shows a large downfield shift of C-2′ and an upfield shift of C-3′, which are consistent with the known shift effects of C-2 tosylation.

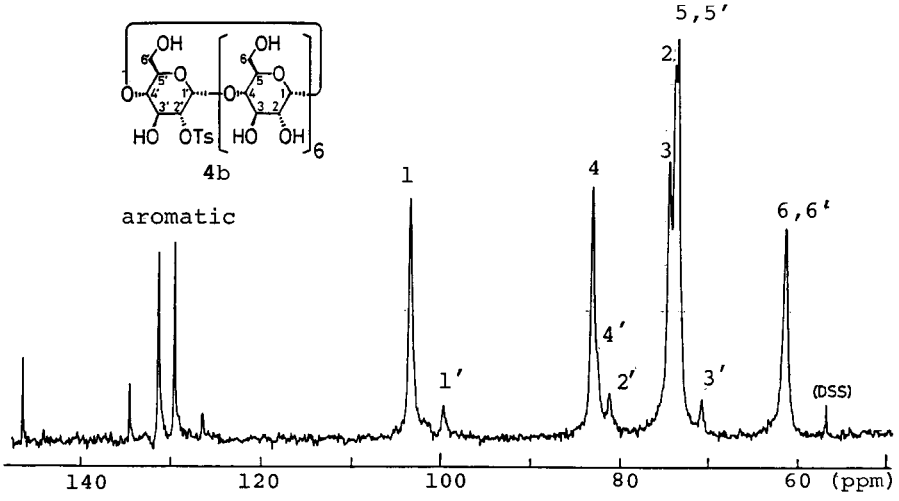
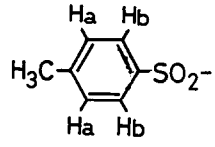


Fig. 1. ^{13}C-NMR spectrum of **4**b (20 MHz, DMSO-d_6, DSS)

According to the procedure mentioned above, C-2 mono-tosylate of α-CD (**4**a) and C-2 tosylate of γ-CD (**4**c) were obtained in 30% and 28% yield, respectively. These structures were assigned on the basis of their spectral data,[12] which were simular to those of **4**b. As shown in Table 1, the differences between δHa

Table 1. Differences of chemical shifts in ^{1}H-NMR spectra (360 MHz, D_2O, TMS)

	4a	**4**b	**4**c	**5**b	TsOH
$\delta_{Hb}-\delta_{Ha}$ (ppm)	0.41	0.42	0.44	0.25	0.35



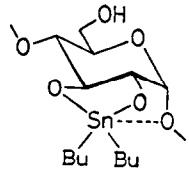
and δHb of **4**a-c are much larger than that of **5**b.

Table 2 shows downfield shifts of C-2′ and upfield shifts of C-1′ and C-3′ in the ^{13}C-NMR spectra of **4**a-c. In the cases of both α-CD and γ-CD, unreacted CDs were recovered (60-65%) and C-2 di-tosylates were obtained (*ca.* 5%).

Table 2. The shift effects in ^{13}C-NMR spectra

	4a	**4**b	**4**c	(ppm)
$\delta_1,-\delta_1$	-3.1	-3.8	-5.1	
$\delta_2,-\delta_2$	+7.0	+7.3	+6.2	
$\delta_3,-\delta_3$	-3.6	-3.7	-3.3	

Owing to the hydrolytic instability of tin alkoxides, no satisfactory way of monitoring the progress of stannylation was found and cyclic tin intermediates (**3**a-c) were not isolated. However, the products obtained suggest the selective formation of **3**, which is a consequence of the greater thermodynamic stability of the cyclic 2-stanna-1,3-dioxolane structure relative to acyclic alkoxytin derivatives. Szmant *et al.*[10b] also have reported the selective preparation of C-2 tosylates of methyl α-D-glucopyranoside derivatives *via* cyclic tin intermediates. They have suggested the formation of the coordination bond between tin and C-1 anomeric oxygen as shown in **6**. This coordination bond, which seems to be important for the selective tosylation at C-2 oxygen,[14] can be formed in the case of CDs. It seems to be another reason for the selectivity that C-2 hydroxyl groups of CDs are intrinsically more reactive than C-3 hydroxyls towards electrophiles.[15]



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Several reaction conditions were investigated to raise the yield of **4**b, (*e.g.*; molar ratio of Bu_2SnO / TsCl / Et_3N, addition of molecular sieves 4A, reaction temperature), but they have shown little effect (25-38% yield). Water remaining in the reaction mixture may repress the stannylation.

Thus, an efficient and general method for the selective tosylation of a C-2 hydroxyl of CDs has been developed with better yields than the reported.[4,7] So far, secondary sulfonations of CDs have been carried out under alkaline aqueous conditions (initial pH 10-13),[4-8] where the secondary sulfonates might decompose to epoxides. By contrast, this tosylation is carried out under non-aqueous, essentially neutral conditions, where most of functional groups are stable. Therefore, this procedure may be applicable not only to secondary mono-tosylation of modified CDs but also to secondary modification by electrophiles other than tosyl chloride.

References and Notes

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11. Lobar column LiChroprep RP-8 size A (Merck Ltd.) was used.
12. Satisfactory ^{1}H- and ^{13}C-NMR, IR, UV spectral and analytical data were obtained for **4**a,b,c using chromatographically homogeneous samples.
13. **5**b was prepared by the reaction of β-CD with tosyl chloride in pyridine.; *Cf.* L.D.Melton and K.N.Slessor, Carbohydr. Res., 18, 29 (1971).
14. Methyl β-D-glucopyranoside was not selectively esterified at C-2 position by the same method.; See ref. 10b.
15. For instance, heptakis(2,6-di-O-methyl)-β-CD has been prepared by the reaction with Me_2SO_4/BaO in DMF/DMSO.; B.Casu, M.Reggiani, G.G.Gallo, and A.Vigevani, Tetrahedron, 24,803 (1968).

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