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Chemical Modification of Maltose. VI.[1] Selective *p*-Toluenesulfonylation of 1,6-Anhydro-4′,6′-*O*-benzylidene-*β*-maltose using Phase Transfer Catalysis[2]

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Treatment of 1,6-anhydro-4′,6′-*O*-benzylidene-*β*-maltose (**1**) in dichloromethane with 1.2 eq of tosyl chloride in the presence of tetrabutylammonium hydrogen sulfate and 4% sodium hydroxide gave the corresponding 2′-*O*-tosylate (**5**) as the main product (64.2%). Compound **5** is a versatile intermediate for the chemical modification of maltose.

Keywords——maltose; maltosan; benzylidene maltosan; selective tosylation; phase transfer catalysis; 2′-monotosyl maltosan; ^{1}H-NMR

Partially sulfonylated disaccharides are versatile intermediates for chemical modification of maltose[1,3] and for syntheses of higher oligosaccharides.[4] In order to carry out the synthesis of4-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-D-glucopyranose from maltose,[5] the 2′-*O*-sulfonylated maltose derivative was required as a key intermediate.

Selective *p*-toluenesulfonylation (tosylation) of 1,6-anhydro-4′,6′-*O*-benzylidene-*β*-maltose (**1**) with 4.1 molar equivalents of tosyl chloride (TsCl) in pyridine gave four partially tosylated products together with the fully tosylated products, but the yield of the 2′-*O*-tosylate (**5**) was only 1.7%.[3c] Tosylation of **1** with smaller amounts of TsCl, however, resulted in recovery of almost all of the starting material together with a small amount of **5**. Though it has been reported[6] that mesitylenesulfonyl chloride, a bulky sulfonylating reagent, reacts more selectively with one hydroxyl group in a vicinal diol than TsCl, we noticed that this reagent reacted with **1** too slowly to be useful for preparative purposes. While satisfactory results have been obtained using *N*-tosylimidazole for monotosylation of the vicinal diol,[7] an application of these conditions for selective tosylation of **1** gave unsatisfactory results.

Recently, phase transfer catalysis has been proven to be a useful technique in organic synthesis.[8] In the carbohydrate field, this procedure has been applied to the alkylation,[9] benzylation,[10] and methylenation[11] of monosaccharides. Therefore, by reference to a reported monotosylation of diol using a phase transfer catalyst,[12] tosylation of **1** was undertaken to provide **5** selectively.

Compound **1** in dichloromethane was treated with 1.2 equivalents of TsCl in the presence of tetrabutylammonium hydrogen sulfate and 4% sodium hydroxide solution. On stirring at room temperature, the reaction was completed within 1.5 h. From the organic layer, four products were isolated by column chromatography. They were designated **2** to **5** in order of decreasing *Rf* value; **5** was predominant.

Compounds **3**, **4**, and **5** were isolated in 11, 2, and 64.2% yields, and their structures were assigned as 1,6: 2,3-dianhydro-4-*O*-(4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranosyl)-*β*-D-mannopyranose (**3**),[13] 1,6-anhydro-4′,6′-*O*-benzylidene-2,2′-di-*O*-tosyl-*β*-maltose (**4**),[3c] and 1,6-anhydro-4′,6′-*O*-benzylidene-2′-*O*-tosyl-*β*-maltose (**5**),[13] respectively, by comparison with authentic samples.

Compound **2** was isolated as white needles in 6% yield. The proton nuclear magnetic resonance (^{1}H-NMR) data (Table I) suggested the structure to be 1,6: 2,3-dianhydro-4-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranosyl)-*β*-D-mannopyranose. Further structural confirmation was carried out by comparison of **2** with an authentic sample synthesized separately

by tosylation of **3** or by mild alkaline treatment of 1,6-anhydro-4′,6′-*O*-benzylidene-2,2′,3′-tri-*O*-tosyl-β-maltose[3c] to effect epoxide formation.

In selective benzoylation[14] or tosylation[3c] of **1**, the hydroxyl group at the C-2′ position of maltose showed the highest reactivity among the four secondary hydroxyl groups of **1**. Thus, in this selective tosylation, preferential formation of the 2′-tosylate (**5**) is in accord with expectation. In addition, in partially tosylated 1,6-anhydro-β-maltose derivatives, monoepoxide formation occurs under mild alkaline conditions at the D-glucose moiety bearing the 1,6-anhydro-β-linkage, in which the vicinal diol is located in a *trans*-diaxial orientation.[13] Because this selective tosylation proceeds under alkaline conditions, monoepoxide formation may occur simultaneously to yield **2** and **3**. It is remarkable that under the conditions mentioned above, tosylation of **1** scarcely proceeds in the absence of phase transfer catalysts.

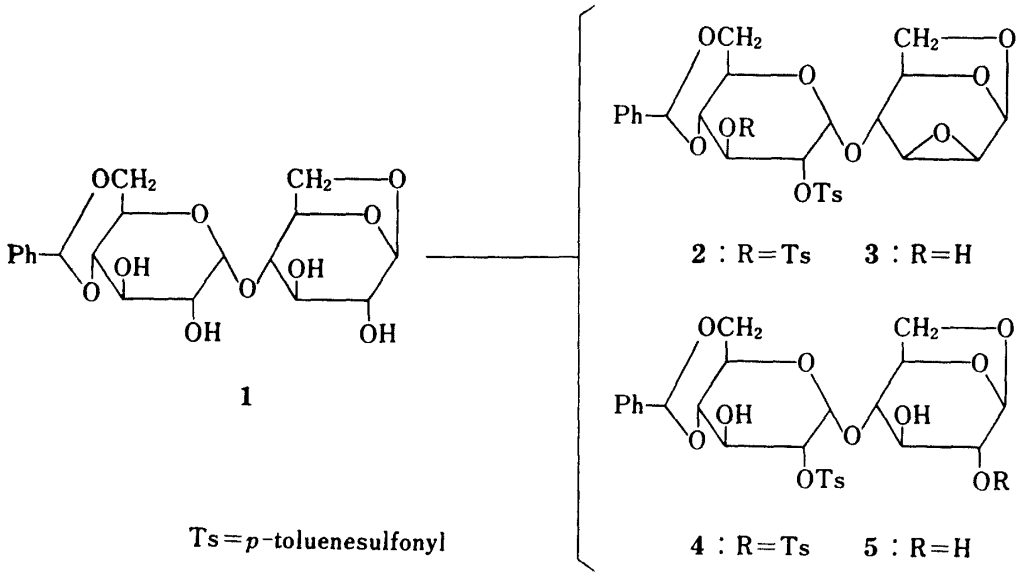

Chart 1

TABLE I. ^{1}H-NMR Spectral Data and *Rf* Values of the Products

Compd. No.	^{1}H-NMR (in $CDCl_3$, δ ppm) H-1	H-1′	$SO_2C_6H_4\underline{H}_3$	$C_6H_5C\underline{H}$	TLC *Rf* value[a] solvents	A[b]	B[c]
2	5.73 (d, *J*=3Hz)	5.57 (d, *J*=4Hz)	2.27, 2.48 (each 3H, s)	5.31		0.51	0.38
3	5.58 (d, *J*=3Hz)	5.26 (d, *J*=4Hz)	2.40	5.43		0.41	0.43
4	5.37 (br s)	5.33 (d, *J*=4Hz)	2.39, 2.46 (each 3H, s)	5.48		0.31	0.37
4[d]	5.28 (br s)	5.18 (d, *J*=4Hz)	2.36, 2.43 (each 3H, s)	5.52			
5	5.39 (br s)	5.25 (d, *J*=4Hz)	2.38	5.45		0.09	0.11
5[d]	5.24 (br s)	5.22 (d, *J*=4Hz)	2.43	5.51			

a) Performed on pre-coated silica gel plates 0.25 mm thick (Kiesel Gel 60 F_{254}, Merck).
b) Solvent A : CH_2Cl_2-acetone (9:1 v/v).
c) Solvent B : benzene-ether (1:3 v/v).
d) Measured in acetone-d_6.

Experimental[15]

Selective Tosylation of 1 with Phase Transfer Catalyst——A 4% (w/v) NaOH aq. solution (1 ml) was added to a suspension of **1**[3b] (207 mg, 0.5 mmol), tetrabutylammonium hydrogen sulfate (34 mg, 0.1 mmol),

and TsCl (112 mg, 0.6 mmol) in CH_2Cl_2 (35 ml). The mixture was stirred at room temperature for 1.5 h. The organic layer was separated, washed with H_2O (30 ml × 2), dried (Na_2SO_4), and concentrated to dryness. The residue (305 mg) was chromatographed on a column of silica gel with CH_2Cl_2–acetone (60: 1, 30: 1, and 10: 1, v/v). Compounds **2** (21 mg, 6%), **3** (30 mg, 10.9%), **4** (7 mg, 1.9%), and **5** (182 mg, 64.2%) were successively eluted in this order. The ^{1}H-NMR spectral data and *Rf* values on thin-layer chromatography (TLC) are presented in Table I.

Authentic 1,6: 2,3-Dianhydro-4-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (2)——1) A 0.5 N methanolic solution of MeONa (1.2 ml, 0.6 mmol) was added to a solution of 1,6-anhydro-4′,6′-*O*-benzylidene-2,2′,3′-tri-*O*-tosyl-β-maltose[3c] (280 mg, 0.32 mmol) in MeOH (15 ml). After being stirred overnight at room temperature, the mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (20 ml) and H_2O (15 ml). The organic layer was separated, washed with H_2O (10 ml × 3), and dried ($MgSO_4$). Removal of the solvent afforded a syrup which was crystallized from $CHCl_3$–MeOH as white needles (185 mg, 82.6%), mp 249—251°C, $[\alpha]_D^{25}$ +17.3° (c=0.95, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1606 (C=C of tosyl), 1178 (SO_2 of tosyl). *Anal.* Calcd for $C_{33}H_{34}O_{13}S_2$: C, 56.40; H, 4.88. Found: C, 56.38; H, 4.77.

The product was indistinguishable from **2** prepared by selective tosylation of **1**.

2) A mixture of **3**[13] (100 mg, 0.18 mmol) and TsCl (600 mg, 3.15 mmol) in dry pyridine (5 ml) was left to stand at room temperature for 4 d. The mixture was then poured into ice-H_2O (20 ml), and the resultant precipitate was collected by filtration. The air-dried crude tosylate was purified by column chromatography on silica gel with CH_2Cl_2–acetone (60: 1, v/v). From the earlier fractions, **2** (70 mg, 54.7%) was isolated. From the subsequent fractions, the starting material (**3**, 25 mg, 25%) was recovered.

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References and Notes

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15) Instruments used and conditions for chromatography were the same as in Part V unless otherwise indicated.