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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 Catalysis²⁾

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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; ¹H-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 of 4-*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 reported⁶⁾ 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 methylenation¹¹⁾ 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 *R_f* 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 (¹H-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 benzylation¹⁴⁾ 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. ¹H-NMR Spectral Data and *R_f* Values of the Products

Compd. No.	¹ H-NMR (in CDCl ₃ , δ ppm)			TLC <i>R_f</i> value ^{a)}		
	H-1	H-1'	SO ₂ C ₆ H ₄ H ₃	C ₆ H ₅ CH	solvents	A ^{b)} B ^{c)}
2	5.73 (d, <i>J</i> =3Hz)	5.57 (d, <i>J</i> =4Hz)	2.27, 2.48 (each 3H, s)	5.31		0.51 0.38
3	5.58 (d, <i>J</i> =3Hz)	5.26 (d, <i>J</i> =4Hz)	2.40	5.43		0.41 0.43
4	5.37 (br s)	5.33 (d, <i>J</i> =4Hz)	2.39, 2.46 (each 3H, s)	5.48		0.31 0.37
4^{d)}	5.28 (br s)	5.18 (d, <i>J</i> =4Hz)	2.36, 2.43 (each 3H, s)	5.52		
5	5.39 (br s)	5.25 (d, <i>J</i> =4Hz)	2.38	5.45		0.09 0.11
5^{d)}	5.24 (br s)	5.22 (d, <i>J</i> =4Hz)	2.43	5.51		

a) Performed on pre-coated silica gel plates 0.25 mm thick (Kiesel Gel 60 F₂₅₄, Merck).

b) Solvent A : CH₂Cl₂-acetone (9:1 v/v).

c) Solvent B : benzene-ether (1:3 v/v).

d) Measured in acetone-*d*₆.

Experimental¹⁵⁾

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 $\times$ 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 ^1H -NMR spectral data and R_f 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 $\times$ 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, $[\alpha]_D^{25} + 17.3^\circ$ ($c = 0.95$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1606 (C=C of tosyl), 1178 (SO_2 of tosyl). *Anal.* Calcd for $\text{C}_{33}\text{H}_{34}\text{O}_{13}\text{S}_2$: 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.