FACILE SYNTHESIS OF 1,2-ANHYDRO-5-*O*-TOSYL-β-D-MANNOFURANURONO-6,3-LACTONE*

Nada VUKOJEVIC[a], Tatjana DRAMICANIN[a], Biljana PERIC[b], Mirjana POPSAVIN[b], Janos CSANADI[b] and Dusan MILJKOVIC[b]

[a] *Department of Organic Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Yugoslavia*

[b] *Institute of Chemistry, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovica 3, 21000 Novi Sad, Yugoslavia*

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A two-step synthesis of 1,2-anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone (**1**) has been achieved starting from D-glucofuranurono-6,3-lactone (**2**). Tosylation of **2** gave a mixture of 5-monotosylate **3** and 2,5-ditosylate **4** which were separated by crystallization followed by column chromatography. Acetylation of **3** gave 1,2-di-*O*-acetyl-5-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**5**) in the good yield. Treatment of ditosylate **4** with potassium carbonate in dry acetone afforded 1,2-anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone in 50% yield.

Key words: D-Glucofuranurono-6,3-lactone; 1,2-Anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone; 1,2-Anhydrosugars; Carbohydrates; Uronolactones.

1,2-Anhydro sugars[1] (Brigl anhydrides) are suitable intermediates for the syntheses of various carbohydrate derivatives including certain biologicaly active compounds[2,3]. In this paper we wish to report a novel and convenient route to 1,2-anhydro derivative of D-mannofuranurono-6,3-lactone (**1**) starting from D-glucofuranurono-6,3-lactone (**2**). To this end, we have reinvestigated tosylation of **2**, which was earlier described by Itoh and Tajima[4]. They have found that selective tosylation of **2** (with two moles of tosyl chloride, at room temperature) gave a mixture of 5-monotosylate and 2,5-ditosylate in 30 and 31% yield, respectively, whereupon the anomeric configurations of these compounds were not assigned. We have studied selective tosylation of **2** with three molar equivalent of tosyl chloride whereupon a mixture of 5-monotosylate **3** and 2,5-ditosylate **4** was obtained (Scheme 1). Direct crystallization of the mixture from acetone–petroleum ether (1 : 2) afforded pure ditosylate **4** in 50% yield. The remaining mother liquor was

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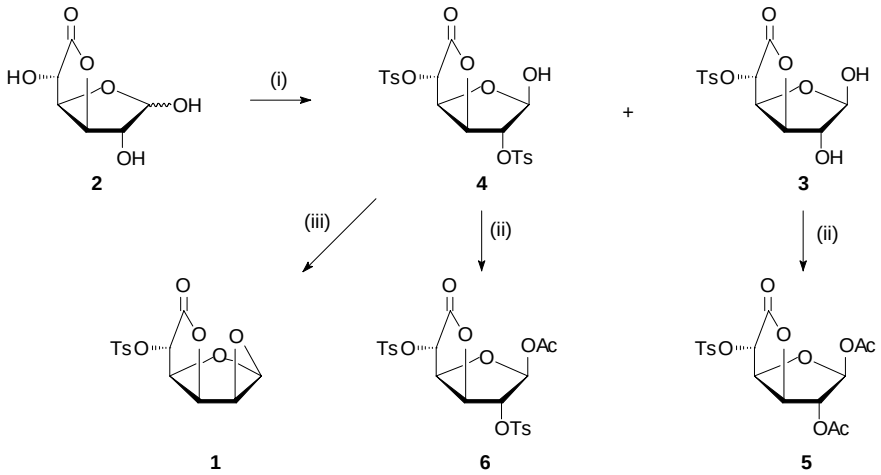
purified by column chromatography to give pure monotosylate **3**. The presence of free hydroxy groups in **3** was also confirmed by its conversion into the corresponding 1,2-diacetate. Thus treatment of **3** with acetic anhydride in pyridine gave 1,2-di-*O*-acetyl-5-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**5**) as the only reaction product in the yield of 46%. By using analogous experimental procedure compound **4** was also converted into the corresponding acetate **5**. The structures of both compounds **5** and **6** were confirmed by ^{1}H and ^{13}C NMR spectra (see Experimental).



SCHEME 1 (i) TsCl (3 eq.), Py, 0 °C; (ii) Ac_2O, Py; (iii) K_2CO_3, acetone

The subsequent important step leading towards the target epoxy derivative **1** included the C-2 inversion in 2,5-di-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**2**). This was achieved by treatment of **4** with potassium carbonate in dry acetone at room temperature for 48 h, whereupon l,2-anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone (**1**) was obtained in the yield of 50%. The structure of **1** was confirmed by ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectrum of **1** shows a signal at 4.69 ppm (ddd) due to H-2 (J(2,3) = 4.9; J(1,2) = 1.3 and J(2,4) = 0.6). The long-range J(2,4) coupling (W-coupling) definitely proved the *cis* arrangement of H-2 and H-4. This further means that potassium carbonate-mediated OH deprotonation of **4** was followed by an intramolecular displacement of C-2 tosyloxy function with inversion of configuration at the electrophylic center. Compound **1** is a convenient intermediate for the introduction of various functionalities at the anomeric center.

EXPERIMENTAL

Melting points were determined on a Buchi SMP 20 apparatus and were not corrected. Optical rotations were measured on an automatic polarimeter Polamat A (Zeiss, Jena). ^{1}H (250 MHz) and ^{13}C

(62.9 MHz) NMR spectra were recorded on a Bruker AC 250 E instrument; chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz, downfield to tetramethylsilane. Mass spectra were obtained with an A.E.I. MS9 mass spectrometer (ion abundances are given in parentheses after *m/z* value). Thin-layer chromatography (TLC) was performed on DC Alufolien Kieselgel 60 F (Merck). Column chromatography was carried out on Kieselgel 60 (0.063–0.2 mm; Merck).

5-*O*-Tosyl-β-D-glucofuranurono-6,3-lactone (**3**) and 2,5-Di-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**4**)

To a solution of compound **2** (l.5 g, 8.5 mmol) in dry pyridine (30 ml) tosyl chloride (4.8 g, 25 mmol) was added at 0 °C. The mixture was left at –10 °C for 24 h, then acidified with aqueous 6 M HCl (to pH 2) and extracted with dichloromethane. The combined extracts were washed with water, dried and evaporated. Direct crystallization of the residue from dichloromethane–petroleum ether (2 : 1) afforded pure compound **4** (2.05 g, 50%) in the form of colourless crystals, m.p. 170 °C; $[\alpha]_D$ +20.5° (*c* 0.2, $(CH_3)_2CO$). ^{1}H NMR spectrum (CD_3SOCD_3): 7.35–7.95 m, 8 H (2 × Ts); 5.50 d, 1 H, *J*(4,5) = 6.4 (H-5); 5.28 d, 1 H, *J*(1,OH) = 3.7 (H-1); 4.90 d, 1 H, *J*(4,3) = 4.9 (H-3); 4.74 dd, 1 H, *J*(3,4) = 4.9, *J*(4,5) = 6.4 (H-4); 4.62 s, 1 H (H-2); 2.43 s, 6 H (2 CH_3, 2 × Ts). ^{13}C NMR spectrum (CD_3SOCD_3): 168.8 (C=O); 128.0–146.2 (Ts); 100.8 (C-1); 83.3 (C-3); 81.7 (C-2); 75.2 (C-4); 73.3 (C-5); 21.3 (CH_3). Mass spectrum, *m/z*: 467 ($M + H^+ - H_2O$), 391 (30), 307 (65), 289 (30), 154 (100), 91 (45). For $C_{20}H_{20}O_{10}S_2$ (484.5) calculated: 49.58% C, 4.16% H, 13.24% S; found: 49.80% C, 4.03% H, 13.05% S.

The mother liquor was concentrated and purified chromatographically on column of silica gel with dichloromethane to give an additional amount of **4** (0.32 g, 8%); total yield 2.37 g (58%). Further elution afforded pure **3** as a yellow syrup. An analytical sample of **3** was obtained by crystallization from acetone–petroleum ether 2 : 1 (0.73 g, 26%) m.p. 115 °C; $[\alpha]_D$ +72.4° (*c* 0.38, $(CH_3)_2CO$). ^{1}H NMR spectrum (CD_3SOCD_3): 7.50–7.90 m, 4 H (Ts); 6.79 d, 1 H, *J*(1,OH) = 4.2 (OH-1, exchangable with D_2O); 5.61 d, 1 H *J*(OH,2) = 4.0 (OH-2 exchangable with D_2O); 5.50 d, 1 H, *J*(5,4) = 6.3 (H-5); 5.15 d, 1 H *J*(1,OH) = 4.2 (H-l); 4.72 d, 1 H, *J*(3,4) = 4.6 (H-3); 4.57 dd, 1 H, *J*(4,5) = 6.3, *J*(3,4) = 4.6 (H-4); 3.97 d, 1 H, *J*(2,OH) = 4.0 (H-2); 2.48 s, 3 H (CH_3, Ts). ^{13}C NMR spectrum (CD_3SOCD_3): 169.4 (C=O); 128.0, 130.3, 132.4, 145.7 (Ts); 104.0 (C-1); 84.6 (C-3); 77.2 (C-2); 75.5 (C-4); 74.4 (C-5); 21.3 (CH_3). ^{1}H and ^{13}C assignation is based on homo-decoupling and 2D carbon–proton correlation experiments. Mass spectrum, *m/z*: 331 ($M + H^+$), 313 (90, $M + H^+ - H_2O$), 172 (20), 155 (80), 101 (45), 91 (100). For $C_{13}H_{14}O_8S$ (330.3) calculated: 47.27% C, 4.27% H, 9.71% S; found: 47.45% C, 4.35% H, 9.80% S.

1,2-Di-*O*-acetyl-5-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**5**)

A solution of compound **3** (0.35 g, 1 mmol) and acetic anhydride (3 ml) in dry pyridine was stirred at room temperature for 1 h. The reaction mixture was acidified with 6 M HCl (to pH 2) and extracted with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The syrupy residue was crystallized from dichloromethane–hexane to give pure **5** (0.2 g, 46%), m.p. 170 °C. ^{1}H NMR spectrum ($CDCl_3$): 7.26–7.89 m, 4 H (Ts); 6.25 s, 1 H (H-1); 5.27 s, 1 H (H-5); 5.11 m, 2 H (H-2, H-3); 5.04 m, 1 H (H-4); 2.47 s, 3 H (CH_3, Ts); 2.13 and 1.90 s, 6 H (2 × CH_3, Ac). ^{13}C NMR spectrum ($CDCl_3$): 168.9 and 168.4 (C=O, Ac); 167.9 (C=O lactone); 128.3–145.9 (Ts); 98.5 (C-1); 81.5 (C-3); 77.9 (C-4); 76.3 (C-5); 71.2 (C-2); 21.8 (CH_3, Ts); 20.5 (2 overlapping CH_3, Ac). For $C_{17}H_{18}O_{10}S$ (414.4) calculated: 49.27% C, 4.38% H, 7.74% S; found: 49.11% C, 4.15 % H, 8.00% S.

1-*O*-Acetyl-2,5-di-*O*-tosyl-β-D-glucofuranurono-6,3-lactone (**6**)

To a solution of compound **4** (0.26 g; 0.5 mmol) in dry pyridine (6 ml) acetic anhydride (3 ml) was added. The mixture was stirred at room temperature for 1 h. After work up, as described above, the crude product **6** was obtained as an oil. Column chromatography on silica gel (dichloromethane) afforded pure **6** which was crystallized from dichloromethane–hexane to give the colourless crystals (0.13 g, 49%), m.p. 166 °C. ^{13}C NMR spectrum (CD_3SOCD_3): 168.8 (C=O, Ac); 167.9 (C=O, lactone); 127.9–146.2 (Ts); 98.1 (C-1); 81.7 (C-3); 81.1 (C-2); 76.4 (C-5); 71.9 (C-4); 21.1 (2 CH_3, 2 Ts); 20.3 (CH_3, Ac). For $C_{22}H_{22}O_{11}S_2$ (526.5) calculated: 50.19% C, 4.21% H, 12.18% S; found: 49.81% C, 4.30% H, 12.45% S.

1,2-Anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone (**1**)

To a solution of compound **4** (0.90 g, 1.8 mmol) in dry acetone (10 ml) potassium carbonate (0.2 g, 1.4 mmol) was added. The mixture was stirred at room temperature for 48 h, then filtered and evaporated. Column chromatography (dichloromethane–ethyl acetate) of the residue gave pure **1** (0.25 g, 50%), m.p. 131 °C; $[\alpha]_D$ +25.5° (*c* 0.5, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$): 7.39–7.84 m, (Ts); 5.82 d, (H-1); 5.54 dd, 1 H (H-3); 4.69 ddd, *J*(1,2) = 1.3, *J*(2,3) = 4.9, *J*(2,4) = 0.6 (H-2); 4.49 s, 1 H (H-5); 3.97 dd, 1 H, *J*(3,4) = 3.0, *J*(2,4) = 0.6 (H-4); 2.48 s, 3 H (CH_3, Ts). ^{13}C NMR spectrum ($CDCl_3$): 170.1 (C=O, lactone); 128.1–146.1 (Ts); 102.1 (C-1); 80.1 (C-5); 79.9(C-2); 79.2 (C-3); 69.9 (C-4); 21.7 (CH_3, Ts). For $C_{13}H_{12}O_7S$ (312.3) calculated: 50.00% C, 3.87% H, 10.27% S; found: 49.83% C, 3.71% H, 10.03% S.

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