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Note

Synthesis of some new deoxy sugar lactone derivatives

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Abstract

The preparation of 3-deoxy- and 2,3-dideoxy-aldonolactone derivatives from the corresponding esters of α,β-unsaturated aldono-1,5-lactones in good to excellent yields by hydrogenation is described. It is shown that, depending on the reaction conditions and the type of catalyst used, the 3-deoxy-aldonolactone or a mixture of 3-deoxy- and 2,3-dideoxy-aldonolactones is obtained. © 1997 Elsevier Science Ltd.

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Deoxy sugar lactones represent convenient key intermediates in the synthesis of deoxy sugars which are important because of their biological activities [1].

The synthesis of a number of 3-deoxy- and 2,3-dideoxy-aldonolactones has already been described [2–6]. We now report a rational method for the preparation of 4-*O*-acetyl-3-deoxy-2,6-di-*O*-tosyl-D-*arabino*-hexono-1,5-lactone [7] (**5**), or a mixture of **5** and the 2,3-dideoxy-D-*erythro*-hexono-1,5-lactone derivative **6** [7] from D-glucono-1,5-lactone (**1**) (Scheme 1). These compounds can be used for the preparation of 3-deoxy sugars, which do not occur naturally [8].

The conversion of D-glucono-1,5-lactone (**1**) into the corresponding α,β-unsaturated lactones by benzoylation [2] or by acetylation [9] in pyridine has already been investigated. To our knowledge the application of the tosylation reaction of **1** for the same purpose has not been fully described [10]. Selective mono-*O*-tosylation of D-ribono-1,4-lactone gave a mixture of 5-*O*-tosyl-, 2-*O*-tosyl-, and 2,5-di-*O*-tosyl-D-ribono-1,4-lactone [11]. The ditosylation of D-aldono-1,4-lactones afforded 2,5-ditosylates (pentonolactones) or 2,6-ditosylates (hexonolactones) [10] as main products. In a previous communication [7] we reported on the tosylation of **1**, in which a mixture of the saturated 2,6-di-*O*-tosyl and unsaturated 2,6-di-*O*-tosyl lactones was obtained. However, we found that tosylation of **1** [12] followed by acetylation in a 'one-pot' procedure led to the formation of a mixture of α,β-unsaturated and saturated lactones (**2** and **3**, respectively), in which the product **2** was dominant. Thus, treatment of **1** with 3 mol equiv of

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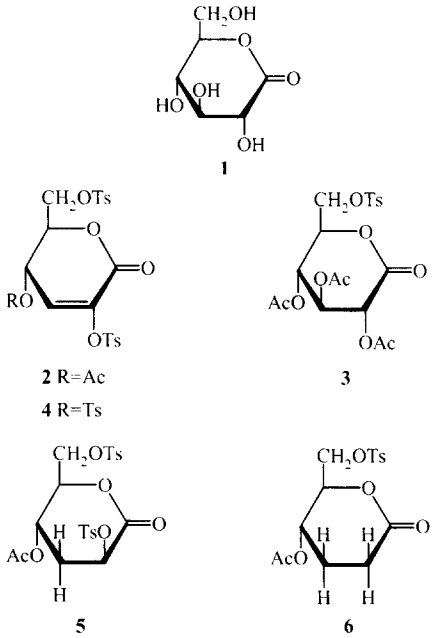
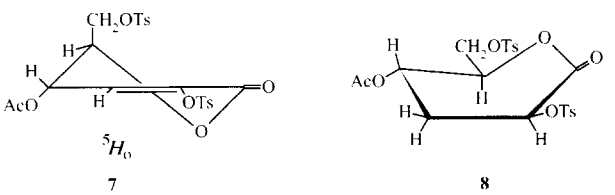


Scheme 1.

p-toluenesulfonyl chloride in dry pyridine at −10 °C for 24 h, and then at room temperature for 1 h, followed by acetylation afforded a mixture of 4-*O*-acetyl-3-deoxy-2,6-di-*O*-*p*-toluenesulfonyl-D-*erythro*-hex-2-enono-1,5-lactone (**2**) and 2,3,4-tri-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-D-glucono-1,5-lactone (**3**) in the ratio 1.7:1. However, when the reaction time of tosylation at −10 °C was prolonged to 168 h (and then at room temperature for 1 h) followed by acetylation, a mixture of compound **2** and 3-deoxy-2,4,6-tri-*O*-*p*-toluenesulfonyl-D-*erythro*-hex-2-enono-1,5-lactone (**4**) was obtained in the ratio of 3:1. Separation of the mixture of **2** and **3** as well as that of **2** and **4** was achieved by crystallization from methanol, yielding chromatographically pure **2** in yields of 40 and 70%, respectively. A further amount of **2** (8%) was obtained by chromatography on silica gel of the mother liquor from the first experiment. The minor products **3** and **4** were isolated by column chromatography on silica gel in the yields 28 and 19%, respectively.

The main product **2** was used for the synthesis of 3-deoxy- and 2,3-dideoxy-aldonolactone derivatives by catalytic hydrogenation [2]. Depending on the reaction conditions and the type of catalyst used, compound **5** or a mixture of **5** and **6** was obtained. Thus, stereoselective catalytic hydrogenation of **2** in the presence of 5% Pd–C in EtOAc at 0 °C for 4 h gave crystalline 4-*O*-acetyl-3-deoxy-2,6-di-*O*-*p*-toluenesulfonyl-D-*arabino*-hexono-1,5-lactone (**5**) in a yield of 93%. The stereoselectivity may be explained by considering that the enono-1,5-lactone exists in the $^5H_0$ conformation (**7**), in which the bulky exocyclic group has a quasi-axial orientation preventing attack from above the ring. The same consideration has been reported for 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone [9,13], 2,4-di-*O*-acetyl-3-deoxy-D-*glycero*-pent-2-enono-1,5-lactone [13], and 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone [2]. On the other hand, the ^{1}H NMR spectrum of **5** showed $J_{2,3}$ and $J_{2,3'}$ values of 8.25 and 10.70 Hz, which suggested a distorted-boat conformation (**8**) for this compound. Boat and half-chair conformations are compatible with the planar lactone group and have been proposed for other 1,5-lactones [14,15] (Scheme 2). When hydrogenation was carried out with 10% Pd–C at room temperature for 15 h, a mixture of **5** and the 2,3-dideoxy-D-*erythro*-hexono-1,5-lactone **6** and a mixture of polar products were obtained. The mixture of **5** and **6** was separated by chromatography on silica gel in 13 and 8% yields, respectively. The mixture of polar products could not be separated by chromatography. It was reacetylated using acetic anhydride in pyridine at room temperature for 24 h, whereupon further amounts of **5** and **6** were obtained. The formation of polar products indicated that the hydrogenation of **2** was accompanied by loss of the acetyl group at O-4. Formation of **6** indicated that hydrogenation of **2** was accompanied by hydrogenolysis of the C-2–O bond. It was assumed that *p*-toluenesulfonic acid thus liberated effected hydrolysis of the acetyl group at O-4. However, the tritosylate **4** was unaffected under the same reaction conditions. A possible reason that the hydrogenation did not take place is due to a steric effect of the bulky tosyloxy group at C-4. The products **2–6** were characterized by NMR data (Table 1) and mass spectra, as well as $[\alpha]_D$ values.

The δ-lactone structures of compounds **2–6** are confirmed by the corresponding mass spectra. Thus, compound **6** shows the characteristic signals at *m/z* 157 and 97, corresponding to δ-lactone structures [6].



Scheme 2.

Table 1
NMR data for **2–6**

Compound	^{1}H (δ in ppm, J in Hz)									
	H-2	H-2′	H-3	H-3′	H-4	H-5	H-6	H-6′	Ac	Ar*Me*
2	–	–	6.60d $J_{3,4}$ 3.94	–	5.60dd $J_{4,3}$ 3.94 $J_{4,5}$ 6.40	4.65m	4.24dd $J_{6,6'}$ 11.80 $J_{6,5}$ 6.40	4.15dd $J_{6,6'}$ 11.80 $J_{6',5}$ 4.43	2.10s	2.50s
3	5.15d $J_{2,3}$ 8.6	–	5.7t $J_{3,4}$ 9.0	–	5.25t $J_{4,5}$ 8.7	4.10m	3.95dd $J_{6,6'}$ 12.60 $J_{6,5}$ 3.60	3.90dd $J_{6,6'}$ 12.60 $J_{6',5}$ 2.90	2.10s	2.10s
4	–	–	6.45d $J_{3,4}$ 3.95	–	5.29q $J_{4,5}$ 6.3	4.55m $J_{5,4}$ 6.3	4.03dd $J_{6,6'}$ 12.30 $J_{6,5}$ 4.13	3.80dd $J_{6,6'}$ 12.30 $J_{6',5}$ 4.57	–	2.45s 2.46s 2.50s
5	5.25dd $J_{2,3}$ 8.25 $J_{2,3'}$ 10.70	–	2.45m	2.50m	5.10m	4.55m	4.30dd $J_{6,6'}$ 12.00 $J_{6,5}$ 4.00	4.18dd $J_{6,6'}$ 12.00 $J_{6',5}$ 3.00	2.10s	2.55s 2.60s
6	2.10m	2.15m	2.45m	2.55m	5.05m	4.60dd	4.25dd $J_{6,6'}$ 12.00 $J_{6,5}$ 3.20	4.10dd $J_{6,6'}$ 12.00 $J_{6',5}$ 4.30	2.00s	2.44s

Compound	^{13}C (δ in ppm)								
	C-1	C-2	C-3	C-4	C-5	C-6	Ar*Me*	CO*Me*	*C*OMe
2	156.17	137.02	129.35	76.68	63.64	66.13	21.73 21.63	20.46	169.24
3	167.34	71.22	70.37	69.15	70.14	67.81	21.52	20.26 20.35 20.51	169.66 169.67 170.23
4	155.57	137.4	130.05	76.78	68.65	66.56	21.70 21.73 21.80	–	–
5	164.90	74.40	31.70	76.50	69.10	67.40	21.65 21.60	20.70	169.40
6	175.70	23.60	27.60	76.93	70.80	66.98	21.50	20.50	169.60

1. Experimental

General methods.—Melting points (uncorrected) were determined on a Büchi SMP-20 apparatus. Optical rotations were measured on an automatic polarimeter Polamet A (Karl Zeiss, Jena). NMR spectra were recorded on a Bruker AC 250 E instrument for solns in $CDCl_3$ and chemical shifts are expressed in ppm, downfield to Me_4Si. TLC was performed on DC Alufolien Kieselgel 60 F (Merck), while column chromatography was carried out using Kieselgel 60 (0.063–0.2 mm; Merck). Mass spectra were obtained with an A.E.I. MS9 mass spectrometer (the first number denotes the *m/z* value, while ion abundances are given in parentheses).

*4-O-Acetyl-3-deoxy-2,6-di-*O-p-*toluenesulfonyl-*D-erythro-*hex-2-enono-1,5-lactone* (**2**) *and 2,3,4-tri-*O-*acetyl-6-*O-p-*toluenesulfonyl-*D-*glucono-1,5-lactone* (**3**).—D-Glucono-1,5-lactone (**1**) (3 g, 16.85 mmol) was dissolved in anhyd pyridine (60 mL) at room temperature. *p*-Toluenesulfonyl chloride (9.63 g, 50.55 mmol) was added while stirring during 5 min. The mixture was left at −10 °C for 24 h, then at room temperature for 1 h. Acetic anhydride (20 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then poured onto crushed ice (75 g), acidified with 6 M HCl to pH 2, and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concd. The syrupy residue was crystallized from MeOH to give chromatographically pure **2** (3.42 g, 40%): mp 135 °C; $[\alpha]_D$ +60.5° (*c* 0.99, $CHCl_3$); IR (KBr): *ν* 1770–1760 (α,β-unsaturated 1,5-lactone and acetate C=O), 1650 cm^{-1} (C=C–C=O). Mass spectrum: *m/z* 355 (55), 269 (10), 173 (15), 155 (100), 127 (15), 91 (95). Anal. Calcd for $C_{22}H_{22}O_{10}S_2$: C, 51.76; H, 4.34; S, 12.56. Found: C, 51.59; H, 4.48; S, 12.22.

The mother liquor was concd and purified by chromatography on silica gel (15 g) with 19:1 benzene–EtOAc to give an additional amount of **2** (0.68 g, 8%); total yield, 4.1 g (47.8%). Further elution with 3:1 benzene–EtOAc afforded **3** as a yellow syrup. An analytical sample of **3** was obtained by crystallization from 10:7 EtOAc–*n*-hexane: 2.16 g (28%); mp 89 °C; $[\alpha]_D$ +161.9° (*c* 0.36, $CHCl_3$). Mass spectrum: *m/z* 459 (M^+ + 1, 25), 287 (58), 245 (45), 215 (70), 172 (58), 155 (65), 91 (72), 69 (22), 43 (100). Anal. Calcd for $C_{19}H_{22}O_{11}S$: C, 49.78; H, 4.84; S, 6.99. Found: C, 49.54; H, 4.85; S, 7.12.

*4-O-Acetyl-3-deoxy-2,6-di-*O-p-*toluenesulfonyl-*D-erythro-*hex-2-enono-1,5-lactone* (**2**) *and 3-deoxy-2,4,6-tri-*O-p-*toluenesulfonyl-*D-erythro-*hex-2-enono-1,5-lactone* (**4**).—To a soln of D-glucono-1,5-lactone (**1**) (3 g, 16.85 mmol) in anhyd pyridine (60 mL) was added *p*-toluenesulfonyl chloride (9.63 g, 50.55 mmol) while stirring during 5 min. The mixture was left at −10 °C for 168 h, then at room temperature for 1 h. Acetic anhydride (20 mL) was added, and the mixture was stirred at room temperature for 1 h. Workup, as described above, gave pure **2** (6.05 g, 70.3%). Compound **4**, obtained from the syrupy mother liquor (2.01 g, 19%) by chromatography on silica gel with 9:1 benzene–EtOAc, had mp 121 °C; $[\alpha]_D$ −5.9° (*c* 0.34, $CHCl_3$). Mass spectrum of **4**: *m/z* 450 (M^+ − TsOH), 326 (55), 262 (80), 155 (90), 107 (40), 65 (55), 91 (100). Anal. (for **4**) Calcd for $C_{27}H_{26}O_{11}S_3$: C, 52.08; H, 4.21; S, 15.45. Found: C, 52.39; H, 4.04; S, 15.31.

*4-O-Acetyl-3-deoxy-2,6-di-*O-p-*toluenesulfonyl-*D-arabino-*hexono-1,5-lactone* (**5**).—A soln of **2** (1 g, 1.96 mmol) in EtOAc (60 mL) was hydrogenated over 5% Pd–C (0.125 g) at atmospheric pressure, at 0 °C during 4 h. The filtered soln was evaporated in vacuo and the residue crystallized from 2:1 CH_2Cl_2–*n*-hexane to give pure **5** (0.93 g, 93%): mp 172 °C; $[\alpha]_D$ +33.4° (*c* 0.066, CH_2Cl_2). Mass spectrum: *m/z* 355 (55), 172 (12), 155 (87), 127 (17), 91 (100), 43 (58). Anal. Calcd for $C_{22}H_{24}O_{10}S_2$: C, 51.55; H, 4.72; S, 12.51. Found: C, 51.79; H, 4.53; S, 12.37.

*4-O-Acetyl-3-deoxy-2,6-di-*O-p-*toluenesulfonyl-*D-arabino-*hexono-1,5-lactone* (**5**) *and 4-O-acetyl-2,3-dideoxy-6-*O-p-*toluenesulfonyl-*D-erythro-*hexono-1,5-lactone* (**6**).—A stirred soln of **2** (1 g, 1.96 mmol) in EtOAc (10 mL) was hydrogenated over 10% Pd–C (0.6 g) at atmospheric pressure, at room temperature for 15 h. The mixture was then filtered and evaporated. Column chromatography (9:1 benzene–EtOAc) of the syrupy residue gave pure **5** (0.13 g, 13%) and **6** (0.053 g, 8%), as an oil. To a mixture of polar products (0.7 g) in anhyd pyridine (10 mL) was added Ac_2O (5 mL). The mixture was stirred at room temperature for 24 h, then poured onto ice (30 g), acidified with 6 M HCl to pH 1, and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concd. Column chromatography of the syrupy residue gave pure **5** (0.45 g, 45%) and **6** (0.08 g, 12%). Total yields of **5** and **6** were 0.58 g (58%) and 0.13 g (20%), respectively. Mass spectrum of **6**: *m/z* 342 (M^+, 10), 298 (10), 220 (15), 171 (37), 157 (19), 155 (100), 97 (37), 43 (11). Anal. (for **6**) Calcd for $C_{15}H_{18}O_7S$: C, 52.62; H, 5.30; S, 9.36. Found: C, 52.59; H, 5.31; S, 9.41.

Acknowledgements

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