A Mild Procedure for the Preparation of 1,6-Anhydro-β-D-hexopyranoses and Derivatives

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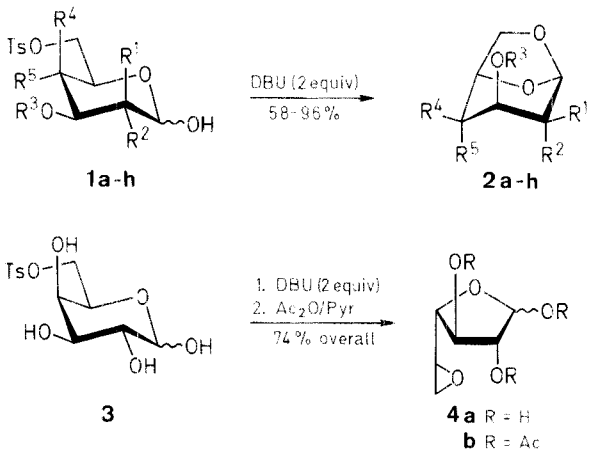
Treatment of reducing 6-*O*-tosyl-D-glycopyranoses **1** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the corresponding 1,6-anhydro-β-D-hexopyranoses **2** in high yields. Reaction was also performed on partly acetylated tosylates of carbohydrates.

1,6-Anhydro-β-D-hexopyranoses, which are useful synthons for the synthesis of complex oligosaccharides,[1,2] have been mostly prepared by a base-assisted intramolecular displacement of a good leaving group at either the primary[3-5] or the anomeric[6,7] position. Various Lewis acids were also described to promote cyclization of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose.[9] However, most of these methods require a definite configuration at the anomeric center[3,4] and/or the presence of a participating group at the C-2 position[6-8] of the precursor.

We now report a mild and general method for the preparation of 1,6-anhydrosugars, which involves 6-*O*-tosyl derivatives of reducing hexopyranoses as precursors and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a basic reagent. Reaction was performed on 6-*O*-tosyl-D-hexopyranoses of the D-*gluco* (**1a–d**), D-*manno* (**1e–g**) and the D-*galacto* (**1h, 3**) series.



1, 2	R^1	R^2	R^3	R^4	R^5
a	H	OAc	Ac	H	OAc
b	H	OH	H	H	OH
c	H	NHAc	H	H	OH
d	H	$NHCO_2CH_2CH{=}CH_2$	H	H	OH
e	OAc	H	Ac	H	OAc
f	OH	H	H	H	OH
g	OH	H	Bn	H	OBn
h	H	OAc	Ac	OAc	H

Tosylates **1a, 1e** and **1h** were prepared by regioselective cleavage of the anomeric acetate of the corresponding peracetylated 6-*O*-tosyl-D-glycopyranoses with hydrazine acetate in dimethylformamide.[9] Tosylates **1b, 1c, 1d, 1f, 1g** and **3** were obtained after selective tosylation of D-glucose, *N*-acetyl-D-glucosamine, *N*-allyloxycarbonyl-D-glucosamine,[10] D-mannose, 3,4-di-*O*-benzyl-D-mannose[11] and D-galactose, respectively. Tosylates **1a–c, 1f** and **3** have already been described in the literature and the physical constants of these derivatives were in complete agreement with those reported.

6-*O*-Tosyl-D-glycopyranoses **1a–h** and **3** were anomeric mixtures of reducing carbohydrates containing mainly the α-isomer as attested by ^{1}H-NMR spectroscopy (Table 1).

Cyclization reactions were performed in ethanol, except for acetylated tosylates **1a, 1e** and **1h** (dichloromethane). Products **2b** and **2f** were not isolated but directly acetylated to **2a** and **2c**, respectively. Yields were generally good to excellent (58% to 96%) in most of the reactions performed to date (Table 2). The 6-*O*-tosyl-D-galactose **(3)** did not lead to the expected 1,6-anhydro-β-D-galactopyranose but to the 5,6-anhydro isomer **4a** isolated after acetylation, as an α, β mixture of the furanosic derivatives **4b**. This result could be due to an intramolecular hydrogen bonding[12] in compound **3**, which avoiding the inversion from $^4C_1$ to $^1C_4$ conformations, prevent the nucleophilic substitution of the tosylate by the anomeric hydroxyl group. This assumption is supported by the behavior of the partially acetylated tosylate **1h** to give the peracetylated 1,6-anhydro-β-D-galactopyranose **2h** during the same treatment (Table 2).

The main advantage of using DBU as a basic promotor is probably due to the possibility of interconversion from the α- to the β-anomeric form (the only one reacting) during the nucleophilic substitution. This opportunity is of particular interest in the *manno* series, where the anomeric equilibrium is largely in favor of the unreactive α form.

This simple and efficient method of preparation of 1,6-anhydro-β-D-hexopyranoses affords the expected derivatives in a few steps from raw materials, and in contrast to most of the methods

Table 1. ^{1}H-NMR Data of Partly Protected Tosylates[a]

Product[b]	H-1	H-2	H-3	H-4	H-5	H-6	H-6′
1a (α)[c] (α/β) : 9/2)	5.39 (d, $J_{1,2}$ = 3.5)	4.79 (dd, $J_{2,3}$ = 10.2)	5.49 (dd, $J_{3,4}$ = 9.6)	4.93 (dd, $J_{4,5}$ = 9.9)	4.28 (ddd, $J_{5,6}$ = 2.3)	4.13 (dd, $J_{6,6'}$ = 11.0)	4.06 (dd, $J_{5,6'}$ = 5.2)
1a (β)[c]	4.72 (d, $J_{1,2}$ = 8.1)	4.82 (dd, $J_{2,3}$ = 9.5)	5.21 (dd, $J_{3,4}$ = 9.3)	4.97 (dd, $J_{4,5}$ = 9.0)	3.80 (m)	4.04–4.17 (m)	
1c (α)[d,e] (α/β : 3/1)	5.07 (d, $J_{1,2}$ = 3.4)	3.51 (dd, $J_{2,3}$ = 10.4)	3.69 (dd, $J_{3,4}$ = 8.5)	3.33 (dd, $J_{4,5}$ = 10.0)	3.99 (dd, $J_{5,6}$ = 1.8)	4.31 (dd, $J_{6,6'}$ = 10.5)	4.18 (dd, $J_{5,6'}$ = 6.1)
1c (β)[e]	4.59 (d, $J_{1,2}$ = 7.9)						
1d (α)[d,f] (α/β : 4/1)	5.09 (d, $J_{1,2}$ = 3.5)	3.56 (dd, $J_{2,3}$ = 10.6)	3.71 (dd, $J_{3,4}$ = 8.9)	3.35 (dd, $J_{4,5}$ = 10.0)	3.99 (ddd, $J_{5,6}$ = 1.8)	4.30 (dd, $J_{6,6'}$ = 10.5)	4.18 (dd, $J_{5,6'}$ = 5.9)
1d (β)[d]	4.62 (d, $J_{1,2}$ = 8.1)						
1e (α)[e] (α/β : 9/1)	5.16 (d, $J_{1,2}$ = 1.8)	5.23 (dd, $J_{2,3}$ = 3.4)	5.38 (dd, $J_{3,4}$ = 10.0)	5.15 (dd, $J_{4,5}$ = 10.1)	4.25 (ddd, $J_{5,6}$ = 4.4)	4.10 (m, $J_{5,6}$ = 4.4)	
1e (β)	4.93 (d, $J_{1,2}$ = 1.3)						
1g (α)[d,g] (α/β : 9/1)	5.13 (br s)	4.12 (m, $J_{2,3}$ = 2.5)	3.87 (dd, $J_{3,4}$ = 9.1)	3.77 (dd, $J_{4,5}$ = 9.7)	3.98 (ddd, $J_{5,6}$ = 3.1)	4.20 (dd, $J_{6,6'}$ = 10.5)	4.16 (dd, $J_{5,6'}$ = 4.1)
1h (α)[e] (α/β : 20/1)	5.49 (d, $J_{1,2}$ = 3.5)	5.12 (dd, $J_{2,3}$ = 10.6)	5.39 (dd, $J_{3,4}$ = 3.3)	5.42 (m, $J_{4,5} \approx 0$)	4.49 (m, $J_{5,6}$ = 6.9)	4.09 (dd, $J_{6,6'}$ = 10.1)	3.99 (dd, $J_{5,6'}$ = 5.5)

[a] 300 MHz; $CDCl_3$/TMS unless otherwise stated; δ, *J* (Hz).
[b] Anomeric configuration in parenthesis. All of the spectra contain additional signals corresponding with the tosylate substituent (2.45 ± 0.01, s, CH_3Ph; 7.40 ± 0.10 and 7.75 ± 0.10, 2m, $4H_{arom}$).
[c] Additional signals corresponding with the acetyl protective groups (1.98 ± 0.01, 2.03 ± 0.02, 2.09 ± 0.03, 3s).
[d] Spectra recorded in acetone-d_6.
[e] Additional signals corresponding with the *N*-acetyl protective group (1.93, s) and NH (7.07, br d).
[f] Additional signals corresponding with the *N*-allyloxycarbonyl protective group (4.50, m, CH_2–CH=CH_2; 5.29–5.13, 2m, CH_2–CH=CH_2; 5.91, m, CH_2–CH=CH_2) and NH (5.82, m).
[g] Additional signals corresponding with the benzyl protective groups (4.65, 4.68, m, 4H, CH_2Ph).

described in the literature, it is compatible with base-labile protective groups and should find synthetic applications in the field of oligosaccharides.

Pyridine and DMF were dried by refluxing over $CaCl_2$, CH_2Cl_2 over P_2O_5, then distilled and stored over 4 Å molecular sieves. DBU and *p*-toluenesulfonyl chloride were purchased from Fluka A.G., and purified by the Pelletier's method[13] prior to use. Silica gel (35–60 μm) was purchased from Amicon Co. Melting points were determined on a Büchi apparatus and were uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter in a 1 dm cell. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AM 300 spectrometer working respectively at 300 MHz and 75.5 MHz.

Preparation of Tosylates 1; General Procedure:

Method A: Hydrazine acetate (0.395 g, 4.3 mmol) is added in one portion to a solution of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-D-glycopyranose (1.50 g, 3.0 mmol) in DMF (3 mL) at 50 °C. After stirring for 5 min, the solution is left to attain room temperature. EtOAc (20 mL) is then added and the solution washed once with water (5 mL). The organic layer is dried (Na_2SO_4) and evaporated. The crude product obtained is chromatographed on silica gel using CH_2Cl_2/CH_3OH (20:1) as eluent (Table 1).

Method B: A solution of *p*-toluenesulfonyl chloride (1.6 g, 8.4 mmol) in pyridine (10 mL) is added dropwise over 30 min to a solution of the carbohydrate (7 mmol) in dry pyridine (20 mL), cooled near 0 °C and magnetically stirred. After 4 h at 0 °C, the reaction is quenched with CH_3OH (1 mL). After addition of $CHCl_3$ (50 mL), the solution is washed with water (2 × 10 mL), dried (Na_2SO_4), and evaporated. The product is then chromatographed on silica gel (Table 1).

2,3,4-Tri-O-acetyl-6-O-p-toluenesulfonyl-D-glucopyranose (**1a**): Prepared following Method A. Product obtained as an α/β mixture (9:2), yield: 85%.

$C_{19}H_{24}O_{11}S$	calc.	C 49.56	H 5.25
(460.4)	found	49.34	5.32

2-N-Allyloxycarbonyl-2-amino-2-deoxy-6-O-p-toluenesulfonyl-D-glucopyranose (**1d**): Prepared from 2-*N*-allyloxycarbonyl-2-amino-2-deoxy-D-glucopyranose[10] following Method B. Product recovered as an α/β mixture (4:1), yield 61%.

$C_{17}H_{23}NO_9S$	calc.	C 48.91	H 5.55	N 3.36
(417.4)	found	49.18	5.56	3.13

2,3,4-Tri-O-acetyl-6-O-p-toluenesulfonyl-D-mannopyranose (**1e**): Prepared following Method A. Product obtained as an α/β mixture (9:1), yield 80%.

$C_{19}H_{24}O_{11}S$	calc.	C 49.56	H 5.25
(460.4)	found	49.51	5.24

2,3,4-Tri-O-acetyl-6-O-p-toluenesulfonyl-D-galactopyranose (**1h**): Prepared following Method A. Product obtained as an α/β mixture (9:2), yield: 84%.

$C_{19}H_{24}O_{11}S$	calc.	C 49.56	H 5.25
(460.4)	found	49.67	5.15

3,4-Di-O-benzyl-6-O-p-toluenesulfonyl-D-mannopyranose (**1g**): Prepared from 3,4-di-*O*-benzyl-D-mannopyranose[11] following Method B. Product recovered as an α/β mixture (20:1), yield 60%.

$C_{27}H_{30}O_8S$	calc.	C 63.02	H 5.88
(514.6)	found	63.24	5.85

Preparation of 1,6-Anhydro-β-D-hexopyranoses 2; General Procedure:

DBU (0.61 g, 4 mmol) is added in one portion at room temperature to a magnetically stirred solution of 6-*O*-tosyl derivative **1** (2 mmol) in C_2H_5OH (20 mL); for fully acetylated compounds **1a, e, h**, CH_2Cl_2 is used as the solvent, and the order of addition of reagents is inverted. The mixture is stirred at room temperature until disappearance of the starting material (3–24 h). After evaporation of the solvent, the mixture is either chromatographed directly or acetylated first (for compounds **2b, f**) with a mixture acetic anhydride (2 mL) and pyridine (4 mL) (Table 2).

2-N-Allyloxycarbonyl-2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose (**2d**): Product recovered as a crystalline material (Table 2) after chromatography on silica gel (eluent: EtOAc); mp 76–77 °C.

Table 2. Compounds **2** Prepared

Starting Tosylate	Product	Yield[a] (%)	mp (°C)[b] (solvent)	$[\alpha]_D^{20}$[c]	Molecular Formula[d] or Lit. Data	^{1}H-NMR (solvent/TMS)[e]
1a	**2a**	58	108–109	−62.3°	mp 108–109[7]	$CDCl_3$: 2.12, 2.16, 2.18 (3s, 9H, $3CH_3$); 3.84 (dd, 1H, J = 6.1, 7.8, H-6′); 4.03 (dd, 1H, J = 1.0, 7.8, H-6); 4.60–4.65 (m, 3H, H-2, 4, 5); 4.86 (m, 1H, H-3); 5.43 (br s, 1H, H-1)
1b		87	(EtOH)	(c = 1.0, $CHCl_3$)	$[\alpha]_D$ −59°[7]	
1c	**2c**	96	189–191 (EtOAc)	−42.5° (c = 2.2, H_2O)	mp 190–191[4] $[\alpha]_D$ −45.2°[4]	
1d	**2d**	93	76–77	−22.6° (c = 2.8, acetone)	$C_{10}H_{15}NO_6$ (245.2)	acetone-d_6: 3.60–3.70 (m, 3H, H-2, 3, 4); 3.66 (dd, 1H, J = 5.8, 7.0, H-6); 4.23 (dd, 1H, J = 0.7, 7.0, H-6′); 4.54 (m, 2H, $CH_2CH{=}CH_2$); 4.66 (br m, 1H, H-5); 5.18, 5.30 (2m, 2H, $CH_2CH{=}CH_2$); 5.32 (br s, 1H, H-1); 5.94 (m, 1H, $CH_2CH{=}CH_2$); 6.07 (br d, NH)
1e	**2e**	58	89–90	−123.5°	mp 90–91[13]	$CDCl_3$: 2.06, 2.14, 2.16 (3s, 9H, $3CH_3$); 3.85 (dd, 1H, J = 5.9, 7.7, H-6′); 4.25 (dd, 1H, J = 1.0, 7.7, H-6); 4.63 (m, 1H, H-5); 4.81 (m, 1H, H-4); 5.00 (m, 1H, H-2); 5.27 (ddd, 1H, J = 1.6, 1.7, 1.7, H-3); 5.43 (dd, 1H, J = 1.6, 1.9, H-1)
1f		75	(EtOH)	(c = 1.0, $CHCl_3$)	$[\alpha]_D$ −123.6°[13]	
1g	**2g**	95	syrup	−58.8° (c = 1.0, $CHCl_3$)	$C_{20}H_{22}O_5$ (342.4)	acetone-d_6: 3.48 (d, 1H, J = 11.5, OH); 3.59 (ddd, 1H, J = 1.8, 5.5, 11.5, H-2); 3.60 (dd, 1H, J = 6.0, 7.0, H-6′); 3.71 (dd, 1H, J = 1.5, 1.6, H-4); 3.81 (m, J = 1.5, 1.5, 1.5, 5.5, H-3); 4.07 (dd, 1H, J = 1.1, 7.0, H-6); 4.62 (m, 1H, H-5); 4.52–4.64 (m, 4H, $2CH_2Ph$); 5.19 (m, 1H, H-1); 7.25–7.38 (m, $10H_{arom}$)
1h	**2h**	62	77–78 (Et_2O/EtOH)	−4.3° (c = 1.0, $CHCl_3$)	mp 77–79[7] $[\alpha]_D$ −5.0°[7]	$CDCl_3$: 2.04, 2.14, 2.14 (3s, 9H, $3CH_3$); 3.70 (dd, 1H, J = 5.2, 7.6, H-6′); 4.33 (d, 1H, J = 7.6, H-6); 4.50 (dd, 1H, J = 2.4, 5.2, H-5); 4.78 (dd, 1H, J = 1.2, 1.3, H-2); 5.25–5.33 (m, 2H, H-3, 4); 5.47 (dd, 1H, J = 1.2, 1.2, H-1)

[a] Yields of isolated and purified products.
[b] Uncorrected, measured with a Büchi apparatus.
[c] Optical rotations measured with a Perkin Elmer 241 polarimeter in a 1 dm cell.
[d] Satisfactory microanalyses obtained: C ± 0.16, H ± 0.12, N ± 0.24; except for **2g**, C −0.59 (see also experimental).
[e] Spectra recorded on a Bruker AM 300 (300 MHz).

$C_{10}H_{15}NO_6$	calc.	C 48.98	H 6.17	N 5.71
(245.2)	found	48.88	6.05	5.47

^{13}C-NMR (acetone-d_6/TMS): δ = 54.52 (C-2); 65.88, 65.91 ($\underline{C}H_2$–CH=CH_2, C-6); 71.93 (C-4); 73.32 (C-3); 77.14 (C-5); 101.92 (C-1); 117.49 (CH_2–CH=$\underline{C}H_2$); 134.18 (CH_2–$\underline{C}H$=CH_2); 156.37 (CO)

*3,4-Di-O-benzyl-1,6-anhydro-β-*D*-mannopyranose* **(2g):** Product recovered as a syrup after chromatography on silica gel (eluent: EtOAc/*n*-hexane, 2:3).

$C_{20}H_{22}O_5$	calc.	C 70.16	H 6.48	
(342.4)	found	69.57	6.54	

^{13}C-NMR (acetone-d_6/TMS): δ = 65.38 (C-6); 67.75 (C-2); 71.58, 74.34 ($\underline{C}H_2$Ph); 74.34 (C-4); 77.04, 77.49 (C-3, 5); 102.80 (C-1); 128.43–139.48 (C_{arom}).

1,2,3-Tri-*O*-acetyl-5,6-anhydro-D-galactofuranose (4b):
DBU (0.61 g, 4 mmol) and the tosyl derivative **3** (0.67 g, 2 mmol) are reacted in EtOH (20 mL) as given under the preparation of **2**. The product **4a** is acetylated with a mixture of acetic anhydride (2 mL) and pyridine (4 mL). Chromatographic purification on silica gel (eluent: EtOAc/*n*-hexane, 3:1) gives an anomeric mixture (α/β = 2:3); yield: 0.43 g (74%); syrup.

$C_{12}H_{16}O_8$	calc.	C 50.00	H 5.60	
(288.2)	found	49.89	5.67	

^{1}H-NMR ($CDCl_3$/TMS): δ =
for α-anomer: 2.09, 2.11, 2.12 (3s, 9H, $3CH_3$); 2.62 (dd, 1H, J = 2.6, 4.9, H-6'); 2.82 (dd, 1H, J = 4.1, 4.9, H-6); 3.23 (ddd, 1H, J = 2.6, 4.1, 5.7, H-5); 3.82 (dd, 1H, J = 5.7, 5.9, H-4); 5.31 (dd, 1H, J = 4.5, 7.3, H-2); 5.49 (dd, 1H, J = 5.9, 7.3, H-3); 6.32 (d, 1H, J = 4.5, H-1)
for β-anomer: 2.11, 2.14, 2.14 (3s, 9H, $3CH_3$); 2.76 (dd, 1H, J = 2.6, 5.0, H-6'); 2.83 (dd, 1H, J = 4.1, 5.0, H-6); 3.23 (ddd, 1H, J = 2.6, 4.1, 4.5, H-5); 4.02 (dd, 1H, J = 4.5, 4.9, H-4); 5.13 (dd, 1H, J = 1.5, 4.9, H-3); 5.20 (d, 1H, J = 1.5, H-2); 6.18 (s, 1H, H-1)

^{13}C-NMR ($CDCl_3$/TMS): δ =
for α-anomer: 20.38, 20.50, 20.97 ($3\underline{C}H_3CO$): 44.23 (C-6); 52.19 (C-5); 75.03, 75.13 (C-2,3); 82.11 (C-4); 93.37 (C-1); 169.34, 169.75, 170.23 ($3CH_3\underline{C}O$)
for β-anomer: 20.38, 20.50, 20.97 ($3\underline{C}H_3CO$): 43.99 (C-6); 51.17 (C-5); 77.54 (C-3); 80.53 (C-2); 84.47 (C-4); 99.37 (C-1); 169.08, 169.53, 169.95 ($3CH_3\underline{C}O$).

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