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Note

Preparation of hexopyranose 2-tosylates and their facile conversion into 1,2-anhydro hexopyranoses by internal displacement *

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1,2-Anhydro sugars continue to receive considerable attention as glycosyl donors having high stereoselectivity in coupling reactions yielding oligosaccharides and as monomers for the preparation of polysaccharides containing (1 → 2)-hexopyranosyl sequences. Thus, two methods have been reported for the synthesis of 1,2-anhydro sugars other than the long-known Brigl's anhydride[1]. In the first method, hexopyranose derivatives having the *manno* and *talo* configurations were prepared by the intramolecular displacement reaction of an oxyanion on C-2 and α-disposed chloride on C-1[2–4]. For derivatives having the *gluco* and *galacto* configurations, it was necessary to prepare β-fluorides from the α-chlorides as the latter are not able to undergo intramolecular back-side attack[5–7]. This made the synthesis more complicated. In the second method, 1,2-anhydro gluco- and galacto-pyranose derivatives were prepared by direct epoxidation of the corresponding glycals[8]. It seemed, however, that it would be difficult to prepare 1,2-anhydro compounds having a *cis* arrangement of the 3-hydroxy group and the epoxide ring by this method.

It is known that 1,4-anhydro sugars have been prepared both by the reaction of OH-4 with C-1 bearing a halogen and by reaction of OH-1 with C-4 bearing a tosylate group[9]. Up to now the synthesis of 1,2-anhydro sugars by intramolecular displacement reactions of an oxyanion at an anomeric center with C-2 bearing a tosylate group have not been reported. Initial experiments showed that the ditosylation of 3,4,6-tri-*O*-benzyl-D-mannopyranose (**4**) followed by hydrolysis gave complex products[2]. Furthermore, 2-sulfonates of pyranosides are generally resistant to S_N2 displacement; ring contraction or elimination often occurs during this reaction[10]. The preparation of hexopyranose 2-tosylates, their behavior towards

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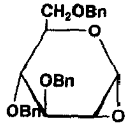

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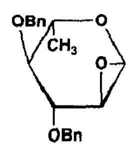

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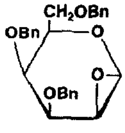

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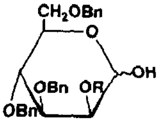

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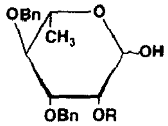

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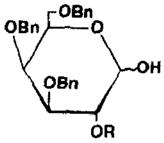

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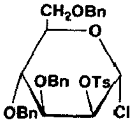

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Bn = Benzyl
Ts = Tosyl

bases, and their ability to undergo intramolecular displacement reactions to achieve ring closure thus became interesting topics for study.

We report a simple method for the preparation of 3,4,6-tri-*O*-benzyl-2-*O*-tosyl-D-manno- (**5**), 3,4-di-*O*-benzyl-6-deoxy-2-*O*-tosyl-L-manno- (**7**), and 3,4,6-tri-*O*-benzyl-2-*O*-tosyl-D-galacto-pyranose (**9**) and describe the conversion of these tosylates into the corresponding 1,2-anhydro hexopyranose derivatives having the D-*gluco* (**1**), L-*gluco* (**2**), and D-*talo* (**3**) configurations.

RESULTS AND DISCUSSION

The starting diols **4**, **6**, and **8** were prepared from the corresponding 1,2-*O*-ethylidene hexopyranose acetates[11] by benzylation and hydrolysis. The traditional reaction of **4** with tosyl chloride in pyridine produced only a small amount of **5** (18%). The main product gave a fast moving spot in TLC which was identified as 3,4,6-tri-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-α-D-mannopyranosyl chloride (**10**) by FABMS and ^{1}H NMR measurements. Compound **10** is quite stable; it is not readily hydrolyzed to **5** and was unchanged when boiled in THF with potassium *tert*-butoxide for 8 h.

It was found that in the presence of anhydrous potassium carbonate the treatment of **4**, **6**, and **8** with tosyl chloride in pyridine produced **5**, **7**, and **9** in reasonable yields (56–64%). No chlorides, such as compound **10**, or other byproducts were detected in TLC. The starting materials recovered after separation could

TABLE I

Tosylation of benzyl-protected hexopyranoses

Starting material	Method	Reagent	Solvent	Temperature (°C)	Time (h)	Product [a]	Yield (%)
4	A	TsCl, K_2CO_3	Pyridine	25	24	**5**	64
6	A	TsCl, K_2CO_3	Pyridine	25	24	**7**	61
8	A	TsCl, K_2CO_3	Pyridine	25	24	**9**	56
4	B	TsCl	Pyridine	25	8	**5** **10**	18 64
4		TsCl, Bu_4NBr 5% NaOH	Toluene	25	72	No reaction	
4		TSI [b]	CH_2Cl_2	Reflux	24	No reaction	
8	C	Bu_2SnO, TsCl, Bu_4NI	Toluene	80	36	**9**	36

[a] **5**, 3,4,6-Tri-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-D-mannopyranose; **7**, 3,4-di-*O*-benzyl-6-deoxy-2-*O*-*p*-tolylsulfonyl-L-mannopyranose; **9**, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-D-galactopyranose; **10**, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-α-D-mannopyranosyl chloride. [b] TSI, *p*-tolylsulfonylimidazole.

be reused, but various attempts to improve the direct yields of **5**, **7**, and **9** failed. Thus, selective tosylation of the *O*-stannylene derivative of diol **8**, in which OH-2 is equatorial, yielded 36% of the 2-tosylate (**9**) and a trace of an unknown compound moving faster than **9** in TLC. The reaction conditions and yields are listed in Table I.

We also tried to generate 2-tosylates from protected intermediates. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-tosyl-α-D-mannopyranoside and methyl 3,4-di-*O*-benzyl-6-deoxy-2-*O*-tosyl-α-L-mannopyranoside were prepared from methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside and methyl 3,4-di-*O*-benzyl-6-deoxy-α-L-mannopyranoside, respectively, by treatment with tosyl chloride in pyridine. However, these methyl 2-tosyl pyranosides were not hydrolyzed when heated in 3:1 80% HOAc–1 N HCl under reflux for 24 h or even longer.

The tosylates **5**, **7**, and **9** are all white crystalline compounds that are very stable on storage. Their physical constants are listed in Table II.

The conformational analysis of 2-tosylates **5**, **7**, and **9** was carried out by ^1H NMR analysis utilizing the modified Karplus equation[12]. For this purpose, detailed assignments of the ^1H NMR spectra were necessary; for this, single-frequency

TABLE II

Physical and analytical data for the 2-tosylates

Compound [a]	Mp (°C)	$[\alpha]_D^{20}$ (°) (*c* 0.5, $CHCl_3$)	Molecular formula	Analysis (%)					
				Calculated			Found		
				C	H	S	C	H	S
5	90– 91	−13.2	$C_{34}H_{36}O_8S$	67.53	6.00	5.30	67.86	6.09	5.10
7	155–156	30.4	$C_{27}H_{30}O_7S$	65.04	6.06	6.43	65.15	6.21	6.14
9	144–145	36.2	$C_{34}H_{36}O_8S$	67.53	6.00	5.30	67.27	5.98	5.21

[a] See Table I, footnote *a* for compound names.

TABLE III

^1H NMR chemical shifts and H–H coupling constants of the 2-tosylates

Compound [a]	Chemical shifts (δ)						
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′
5	5.32 (d)	4.83 (dd)	3.95 (dd)	3.67 (t)	3.99 (ddd)	3.59–3.67 (m, 2 H)	
7	5.29 (d)	4.83 (dd)	3.91 (dd)	3.45 (t)	3.91 (m)	1.28 (d, 3 H)	
9	5.47 (d)	4.84 (dd)	3.93 (dd)	3.89 (m)	4.15 (t)	3.51 (dd)	3.45 (dd)
	Aromatic H	CH_2Ph	CH_3Ar	OH			
5	7.82–7.07 (m, 19 H)	4.79–4.39 (m, 6 H)	2.357 (s, 3 H)	3.17 (br, 1 H)			
7	7.83–7.18 (m, 14 H)	4.85, 4.57, 4.39 (d, 1 H)(d, 1 H)(s, 2 H)	2.367 (s, 3 H)	2.50 (br, 1 H)			
9	7.70–7.14 (m, 19 H)	4.77–4.39 (m, 6 H)	2.377 (s, 3 H)	3.05 (br, 1 H)			
	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	
5	1.5	3.0	9.6	10.0	2.0	6.0	
7	1.7	3.1	9.7	10.0	6.5		
9	3.9	11.4	2.7	0	5.8		

[a] See Table I, footnote *a* for compound names.

decoupling was used. The presence of the tosylate function at C-2 caused a downfield shift of the signals for H-2, which appeared as doublets of doublets due to first-order couplings with H-1 and H-3. The ^1H NMR data for compounds **5** and **7** are consistent with favored $^4C_1$ and $^1C_4$ conformations, respectively. For compound **9**, the large $J_{2,3}$ value (11.4 Hz) indicates a *trans*-diaxial relationship between H-2 and H-3 whereas $J_{4,5}$ is so small that it could not be measured. So the favored conformation is judged to be a slightly distorted $^4C_1$ chair. The ^1H NMR data are listed in Table III, and the vicinal-proton torsional angles deduced by the modified Karplus equation are given in Table IV.

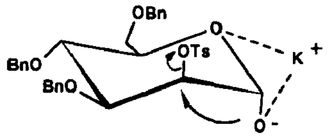
To synthesize the target 1,2-anhydro sugars, the tosylates were initially treated with potassium *tert*-butoxide. The desired results were obtained in the cases of

TABLE IV

H–H torsion angles (°) [a] for the 2-tosylates calculated by the modified Karplus equation

Compound [b]	$Ø_{1,2}$	$Ø_{2,3}$	$Ø_{3,4}$	$Ø_{4,5}$	Conformation
5	280	305	176	181	$^4C_1$
7	57	55	184	181	$^1C_4$
9	50	190	56	285	$^4C_1$

[a] Torsion angles are measured clockwise from the (projection of the) C–H bond nearest the observer.
[b] See Table I, footnote *a* for compound names.



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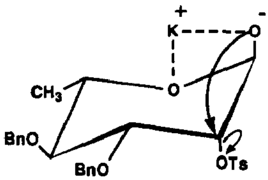

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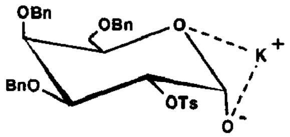

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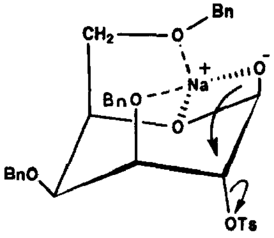

D

compounds **5** and **7**, in that ring closure was achieved almost quantitatively within 20 min at room temperature. The 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D- (**1**) and 1,2-anhydro-3,4-di-*O*-benzyl-6-deoxy-α-L-gluco-pyranose (**2**) thus obtained crystallized spontaneously after workup. But when **9** was treated with potassium *tert*-butoxide, at least four new spots were observed in TLC while the spot of **9** disappeared. We suggest that this finding could be explained in terms of intramolecular complexations of the 1-*O*-metalated reactants, with the high ring-closure rates of the potassium salts of **5** and **7** resulting from the preferential formation of the α-anions **A** and **B** in their $^4C_1$ and $^1C_4$ conformations, respectively. For the potassium salt of **9**, the similarly complexed α-anion **C** is not suitably disposed for a displacement involving back-side attack.

Addition of excess sodium hydride to **9** in THF produced 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose (**3**) as the major product, with a small amount of a byproduct. We propose the structure **D** for the sodium salt of **9**, which displays a pseudo crown ether geometry and the correct conformation for the ring closure reaction. The syrup obtained after workup was crystallized from 3:1 petroleum ether–ethyl acetate to give **3** in 46% yield. More **3** remained in the mother liquor, which was not further worked up. Even in this case the method is convenient by comparison with a previous synthesis[4] involving an oxidation–reduction inversion at C-4 of methyl α-D-mannopyranoside.

The ^{1}H NMR spectra of target compounds **1** and **3** are identical with those published[4,5], and the structure of compound **2** was confirmed by ^{1}H NMR and elemental analysis.

EXPERIMENTAL

General methods.—These were as described previously[6].

Tosylation of diols **4**, **6**, *and* **8**.—*Method A.* To a stirred solution of **4**, **6**, or **8** (1 mmol) in dry pyridine (5 mL) was added recrystallized tosyl chloride (2.5 mmol), followed by anhyd K_2CO_3 (1 mmol). The mixture was stirred for 8 h or more until TLC indicated that the ratio of starting material to product was no longer changing. Then CH_2Cl_2 (10 mL) was added and the mixture was washed with 0.5 N HCl, water, 5% $NaHCO_3$, and water, dried over anhyd Na_2SO_4, and concentrated. The syrup thus obtained was purified on a column of silica gel with 1:2 EtOAc–petroleum ether as eluent. The solid product obtained on concentration was recrystallized from 1:3 EtOAc–petroleum ether. Further details are given in Tables I–III.

Method B. To a stirred solution of **4** (1 mmol, 450 mg) in dry pyridine (5 mL) was added tosyl chloride (475 mg, 2.5 mmol), and the mixture was stirred overnight until TLC indicated that the starting material had disappeared. The mixture was worked up as in Method A. The resulting syrup was fractionated on a column of silica gel with 1:3 EtOAc–petroleum ether to give **5** (88 mg, 18%) and **10** (402 mg, 65%). Compound **10**: ^{1}H NMR: δ 7.11–7.8 (m, 19 H, aromatic), 6.19 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 4.93 (dd, 1 H, $J_{2,3}$ 3.4 Hz, H-2), 4.43–4.8 (m, 6 H, 3 CH_2Ph), 4.19 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 4.0 (ddd, 1 H, $J_{4,5}$ 9.7, $J_{5,6}$ 4.3, $J_{5,6'}$ 1.5 Hz, H-5), 3.91 (t, 1 H, H-4), 3.78 (dd, 1 H, $J_{6,6'}$ 11.2 Hz, H-6), 3.66 (dd, 1 H, H-6′), and 2.37 (s, 3 H, ArCH_3); FABMS (negative ion): m/z 621 and 623, intensity ratio 3:1 ($[M-H]^-$ having ^{35}Cl and ^{37}Cl, respectively), 585, 467, and 171 (base peak).

Method C. Compound **8** (450 mg, 1 mmol) and dibutyltin oxide (274 mg, 1.1 mmol) were suspended in dry MeOH (10 mL), and the mixture was boiled under reflux until it became clear. Evaporation of the solvent gave the *O*-stannylene derivative of **8**, which was dissolved in toluene (10 mL). Tosyl chloride (380 mg, 2 mmol) and tetrabutylammonium iodide (74 mg, 0.2 mmol) were added, and the mixture was stirred at 80°C until TLC indicated no further change in the ratio of product to starting material. The toluene was removed in a rotary evaporator and the residue was subjected to column chromatography.

1,2-Anhydro-3,4,6-tri-O-benzyl-α-D-glucopyranose (**1**).—To a solution of tosylate **5** (60 mg, 0.1 mmol) in dry THF (2 mL) was added potassium *tert*-butoxide (17 mg, 0.15 mmol). The solution became yellow immediately. After 5 min stirring TLC indicated that **5** had disappeared. The mixture was evaporated to dryness and the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc. The extracts were combined and concentrated to give **1** as white crystals (41 mg, 96%). Recrystallized from petroleum ether–EtOAc it had mp 80–81°C, lit.[5] 77–78°C; ^{1}H NMR ($CDCl_3$): δ 7.38–7.17 (m, 15 H, aromatic H), 4.99 (dd, 1 H, $J_{1,2}$ 2.6 Hz, H-1), 4.83–4.52 (m, 6 H, 3 CH_2Ph), 3.98 (dd, $J_{1,3}$ 1.0, $J_{3,4}$ 7.8 Hz, H-3), 3.79–3.61 (m, 4 H, H-4, 5, 6, 6′), and 3.07 (d, 1 H, $J_{1,2}$ 2.6 Hz, H-2).

1,2-Anhydro-3,4-di-O-benzyl-6-deoxy-α-L-glucopyranose (**2**).—To a solution of **7**

(50 mg, 0.1 mmol) in dry THF (2 mL) was added potassium *tert*-butoxide (17 mg, 0.15 mmol). The same procedure was used as for compound **1**. The white crystalline **2** (31 mg, 94%) thus obtained was recrystallized from 3:1 petroleum ether–EtOAc, mp 53–54°C; $[\alpha]_D^{20}$ $-9.4°$ (c 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.23 (m, 10 H, aromatic H), 4.87 (dd, 1 H, $J_{1,2}$ 2.4 Hz, H-1), 4.83–4.64 (m, 4 H, 2 CH_2Ph), 3.93 (dd, 1 H, $J_{3,4}$ 7.9 Hz, H-3), 3.72 (m, 1 H, H-5), 3.15 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 3.05 (d, 1 H, $J_{1,2}$ 2.4 Hz, H-2), and 1.25 (d, 3 H, $J_{5,6}$ 7.1 Hz, H_3-6). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.61; H, 6.79. Found: C, 73.65; H, 6.73.

1,2-Anhydro-3,4,6-tri-O-benzyl-β-D-talopyranose (**3**).—To a solution of **9** (60 mg, 0.1 mmol) in dry THF (3 mL) was added NaH (80% in oil, 50 mg, washed with petroleum ether before use). The mixture was stirred at room temperature for 2.5 h. TLC (2:1 petroleum ether–EtOAc) revealed two new spots, and the absence of **9**. The intensity ratio of the spot given by **3** (R_f 0.15) to that from the byproduct (R_f 0.8) was ca. 4:1. The mixture was evaporated to dryness and the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc. Evaporation of the extract gave a syrup, which was dissolved in ca. 1 mL of 3:1 petroleum ether–EtOAc. After cooling in an ice-bath 20 mg (46%) of white crystalline **3** was collected and recrystallized, mp 83–84°C, lit.[4] 77°C; ^1H NMR ($CDCl_3$): δ 7.37–7.23 (m, 15 H, aromatic H), 4.99 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.88–4.35 (6 d, 6 H, 3 CH_2Ph), 3.90 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 4.3 Hz, H-3), 3.86 (dt, 1 H, $J_{4,5}$ 1.2, $J_{2,4}$ 1.2 Hz, H-4), 3.73 (td, 1 H, $J_{5,6} = J_{5,6'} =$ 6.4 Hz, H-5), 3.58 (dd, 1 H, $J_{6,6'}$ 9.7 Hz, H-6), 3.38 (dd, 1 H, H-6′), and 3.29 (m, 1 H, H-2).

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