New method for the synthesis of 6-amino-6-deoxy-α-D-glucopyranosides

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A general method for the synthesis of 6-amino-6-deoxy-α-D-glucopyranosides from 3,4-di-*O*-acetyl-1,2-dideoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hex-1-enopyranose (3,4-di-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-D-glucal) is described. The key steps in the synthesis are addition of nitrosyl chloride to the above glycal, condensation of the resulting nitroso–chloro adduct with alcohols or phenols to provide α-glycosides of 3,4-di-*O*-acetyl-2-oximino-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hexopyranose, and conversion of the α-oximinoglycosides to α-glucoside derivatives. Propyl, isopropyl, phenyl, and L-menthyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosides are thus prepared and the last compound is converted to L-menthyl 6-amino-6-deoxy-α-D-glucopyranoside.

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Introduction

The natural occurrence of 6-amino-6-deoxy-D-glucose as an α-glycoside in the antibiotic Kanamycin-A (1) has created new interest in synthetic methods for establishing the α-glycosidic linkage between 6-amino-6-deoxy-D-glucose and the hydroxyl group of a desired aglycon. Although little has been reported in the literature along these lines, publications by two Japanese groups (2, 3) have provided evidence that Koenigs–Knorr type condensations can be employed for this purpose and indeed, Kanamycin-A has been synthesized by an application of these procedures (4, 5).

It is now established that the nitrosyl chloride adduct of 3,4,6-tri-*O*-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (3,4,6-tri-*O*-acetyl-D-glucal) reacts with alcohols to give α-glycosides of acetylated 2-oximino-D-*arabino*-hexopyranose (6). The oximinoglycosides are readily converted to α-glucosides by way of the corresponding ketoglycosides (7). The high degree of stereospecificity observed both in the glycosidation of the nitrosyl chloride adduct and in the borohydride reduction of the ketoglycoside prompted us to examine the possibility of applying the above method for a direct synthesis of acetylated 6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosides, since such compounds would be excellent precursors of 6-amino-6-deoxy-α-D-glucopyranosides.

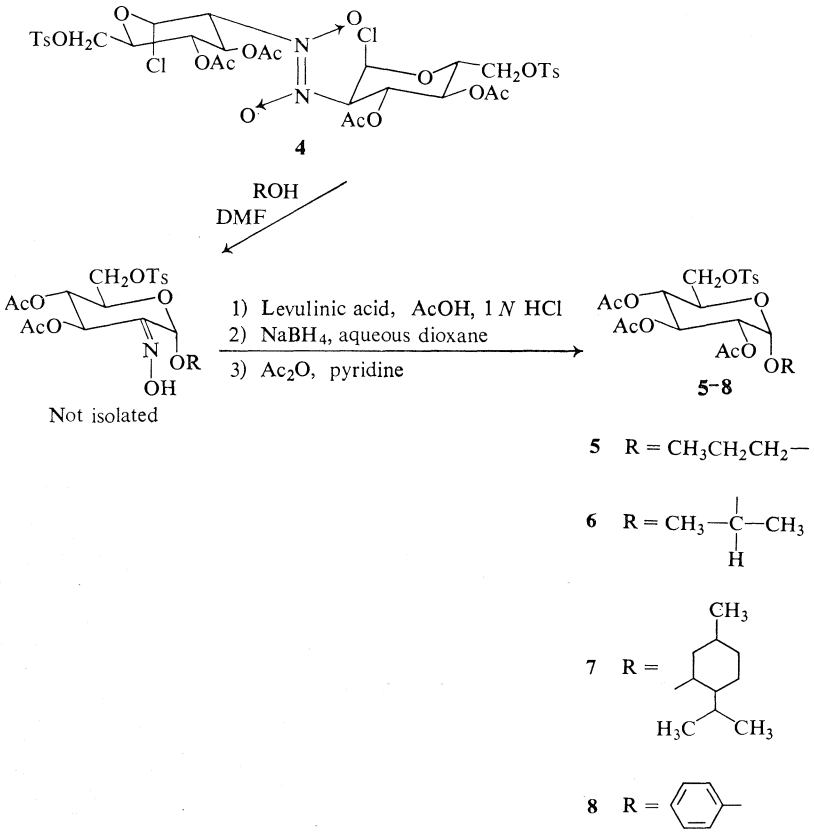
This paper is, therefore, concerned with the preparation of 3,4-di-*O*-acetyl-1,2-dideoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hex-1-enopyranose (**3**) and its conversion to 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosides (**5** to **8**) by way of dimeric 3,4-di-*O*-acetyl-2-deoxy-2-nitroso-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl chloride (**4**).

Results and Discussion

The readily available 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**1**) (8) was converted to 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl bromide (**2**) by a slight modification of the published method (9). Reduction of **2** with zinc dust in aqueous acetic acid provided, as expected, 3,4-di-*O*-acetyl-1,2-dideoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hex-1-enopyranose (**3**).[1]

Reaction of **3** with nitrosyl chloride as in the preparation of dimeric 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride (10, 11) afforded a mixture of two crystalline compounds from which the desired 3,4-di-*O*-acetyl-2-deoxy-2-nitroso-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosyl chloride (**4**) could be obtained only in low yields by repeated recrystallizations. The structure of the by-product which contains no nitrogen and analyses for $C_{17}H_{20}Cl_2O_8S$ is being investigated and will be discussed in a subsequent paper. However, when **3** was reacted with two equivalents of nitrosyl chloride at 0° for 3 h the nitrosyl chloride adduct **4** was formed in high yield. Structural evidence for **4** was obtained from its infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra and a first order analysis of the n.m.r. signals shown by H-1, H-2, and H-3 also permitted the assignment of α-*gluco* configuration to **4** (11). Physical and chemical properties of **4** such as the colorless nature of the crystals, the ability to produce light blue colored solutions and to react spontaneously with triethylamine to give triethylamine hydrochloride

[1]During the course of this work the preparation of 3,4-di-*O*-acetyl-1,2-dideoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hex-1-enopyranose (**3**) by a different route was published (13).



SCHEME 1

with simultaneous formation of a deep blue coloration characteristic of acetylated 2-nitrosoglycals suggested that the compound existed as a dimer in the crystalline state (11). The observed α-*gluco* configuration in **4** seems to offer further evidence for a four-center type addition mechanism as proposed by Lemieux and co-workers (10, 11).

Conversion of **4** into 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosides was accomplished by general procedures (6, 7) and is illustrated in Scheme 1.[2] Structures of compounds **5–8** thus prepared are shown in Table 1 with overall yields from **4**, physical constants, and n.m.r. parameters. The assignment of the α-*gluco* configuration is apparent from these n.m.r. parameters.

Conversion of L-menthyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**7**) to L-menthyl 6-amino-6-deoxy-α-D-glucopyranoside hydrochloride (**11**) by replacement of the tosyl group by azide followed by *O*-deacetylation and catalytic reduction of the azido group was performed by standard procedures well established in the literature (12). The structure of **11** was proved by i.r. and n.m.r. spectroscopy and by conversion to the crystalline *N*-acetate **12**.

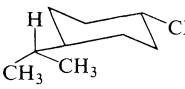
Experimental

Melting points are uncorrected. Infrared spectra were measured with a Perkin–Elmer Model 137 "Infracord" spectrophotometer. Nuclear magnetic resonance spectra were measured at 60 Mc.p.s. with a Varian A-60 spectrometer. Chemical shifts are given in τ values and refer,

[2]Although the oximino glycosides were not purified, in at least one case n.m.r. spectral analysis of the crude reaction product indicated the purity of the compound to be greater than 90%. Thus, the spectrum of crude isopropyl 3,4-di-*O*-acetyl-2-oximino-6-*O*-*p*-tolylsulfonyl-α-D-*arabino*-hexopyranoside showed the following signal pattern, characteristic of acetylated 2-oximino-α-D-*arabino*-hexopyranosides (6); τ 4.03 (singlet, H-1), τ 4.16 (doublet, H-2, $J_{2,3}$ = 9.0 c.p.s.) and τ 4.98 (triplet, H-3, $J_{3,4}$ = 9.0 c.p.s.).

TABLE 1

2,3,4-Tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranosides

Aglycon	Structure	Melting point °C	$[\alpha]_D^{24}$ ° in chloroform (concentration)	Overall yield based on **4** %	Chemical shifts (τ values) and spacings (c.p.s.)					
					H_1	H_2	H_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
$CH_3CH_2CH_2$—	**5**	123–125	+113.5 (1.93)	55	5.09	5.33	4.61	3.75	9.5	10.0
CH_3–CH(–CH_3)—	**6**	103–105	+128.3 (2.51)	56	4.96	5.36	4.63	3.75	9.75	10.05
	**7**	120–122	+76.3 (3.75)	60	4.93	5.28	4.53	3.75	9.0	10.05
	**8**	101–108	+109.9 (2.85)	55	4.45	5.13	4.40	4.0	9.0	10.0

unless otherwise stated, to spectra measured in deuteriochloroform with tetramethylsilane as the internal standard. Optical rotations were determined using a Carl–Zeiss Circular Polarimeter Model 0.01°. Thin-layer chromatography (t.l.c.) was performed on silica gel using ethyl acetate – *n*-hexane (1:1, 2:1) as the solvent system and 25% sulfuric acid as the detector. Anhydrous sodium sulfate was used for drying solutions and solvents were removed *in vacuo* at 40–45 °C.

Physical constants and n.m.r. parameters for compounds **5**–**8** are given in Table 1 along with the overall yields from **4**.

*3,4-Di-O-acetyl-1,2-dideoxy-6-O-p-tolylsulfonyl-*D-*arabino-hex-1-enopyranose (3)*

1,2,3,4-Tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**1**, 50 g) (8) was added in one portion to a solution of hydrogen bromide in glacial acetic acid (30–33%, 650 ml) at 4 °C and the mixture was shaken for 1.5 h without external cooling. The clear solution was poured on to crushed ice (2.5 kg) with stirring. The semicrystalline precipitate was collected by filtration and dissolved in ether (400 ml). Any insoluble material was separated by filtration and the filtrate freed from acids by appropriate washings, dried, and concentrated. (Should it become necessary to leave the solution over sodium sulfate overnight, a little methylene chloride is added to inhibit crystallization. Methylene chloride or chloroform is not recommended for the extraction). The residue (46.5 g) was used as such for the zinc reduction.

A mixture of acetic acid (257 ml), water (172 ml), and zinc dust (86 g) was stirred vigorously at 2–5 °C. A solution of the above compound (**2**, 92.9 g from two runs) in acetic acid (534 ml) and water (172 ml) was added dropwise during 1.5 h at such a rate that the temperature did not exceed 5 °C. The stirring was continued for additional 2.5 h. The reaction mixture was saturated with sodium chloride and work-up in the usual manner using ether as the extractant gave a residue which was crystallized from ethanol to give 57.4 g (86.7%) of pure **3** with m.p. 103 °C and $[\alpha]_D^{24}$ + 30° (*c*, 1.064 in chloroform). $\nu_{max}^{(Nujol)}$ 1730–1740 (carbonyl), 1640 (glycal double bond), 1585 (phenyl), 1165, and 1180 cm^{-1} (tosyl). The n.m.r. data, τ 7.93 (2 *O*-acetyl groups), 7.50 (CH_3), 3.52 (H-1, $J_{1,2}$ = 6.5 c.p.s., $J_{1,3}$ = 1.0 c.p.s.), 5.1 (H-2, $J_{2,3}$ = 3.5 c.p.s.), A_2B_2 type quartet at low field for 4 aromatic protons.

Anal. Calcd. for $C_{17}H_{20}O_8S$: C, 53.12; H, 5.20; S, 8.33. Found: C, 52.99; H, 5.22; S, 8.29.

*3,4-Di-O-acetyl-2-deoxy-2-nitroso-6-O-p-tolylsulfonyl-α-*D-*glucopyranosyl Chloride Dimer (4)*

A stock solution of nitrosyl chloride (10.4 g) (Matheson of Canada Ltd., Whitby, Ontario) in reagent grade methylene chloride (520 ml) was prepared at 0 °C under anhydrous conditions. To this solution (260 ml) maintained at 0 °C was added, with stirring, **3** (30 g) and the solution stirred for 2 h. The remaining portion of the stock solution was now added and the mixture stirred for an additional 1 h at 0 °C. After removal of the solvent the residual product was crystallized from chloroform (150 ml) and *n*-hexane (600 ml). Recrystallization in a similar manner afforded 24.9 g (71%) of pure **4**, m.p. 131–133 °C, $[\alpha]_D^{24}$ + 146.73° (*c*, 2.14 in chloroform). $\nu_{max}^{(Nujol)}$ 1740 (carbonyl), 1585 (phenyl), 1165 and 1180 cm^{-1} (tosyl). The n.m.r. data, τ 8.02 (2 *O*-acetyl groups), 7.57 (CH_3), 3.52 (H-1, $J_{1,2}$ = 3.75 c.p.s.), 4.71 (H-2, $J_{2,3}$ = 10 c.p.s.), 4.07 (H-3, $J_{3,4}$ = 9.5 c.p.s.), 4.88 (H-4) and an A_2B_2 type quartet at low field for the 4 aromatic protons.

Anal. Calcd. for $(C_{17}H_{20}ClNO_9S)_2$: C, 45.40; H, 4.44; Cl, 7.88; N, 3.11. Found: C, 45.23; H, 4.85; Cl, 8.10; N, 3.05.

*General Method for the Synthesis of Alkyl or Aryl 2,3,4-Tri-O-acetyl-6-O-p-tolylsulfonyl-α-*D-*glucopyranosides. Preparation of Isopropyl 2,3,4-Tri-O-acetyl-6-O-p-tolylsulfonyl-α-*D-*glucopyranoside (6)*

The procedure illustrated here is applicable in general for the synthesis of compounds **5**–**8**. Any modification in the work-up of individual compounds is described under separate headings.

A solution of **4** (5 mmole monomer) and isopropanol (7.5 mmole) in dry *N*,*N*′-dimethylformamide (8 ml) was

set aside at room temperature, under anhydrous conditions, for 60 h. The solvent was removed and a solution of the residue in methylene chloride (75 ml) was washed with water (5 × 50 ml), dried, and concentrated. The crude sirupy product (2.4 g) was dissolved in glacial acetic acid (17 ml) together with levulinic acid (2.95 g) and 1.12 *N* hydrochloric acid (5.1 ml). After stirring the mixture for 18 h at room temperature, it was diluted with methylene chloride (100 ml) and the resulting solution washed free of acids. After drying, the solvent was removed and the crude sirupy residue (2.1 g) dissolved in dioxane (23 ml). Water (2 ml) was added to the solution and the mixture was cooled with stirring to 5 °C. A solution of sodium borohydride (0.133 g) in dioxane (2 ml) and water (4 ml) was added dropwise maintaining the temperature at 5 °C. After the addition was complete, the mixture was stirred for 0.5 h at that temperature and for 1 h at room temperature. Excess borohydride was destroyed by the addition of acetic acid (2 ml) and the solvents were removed. The residual sirup was dried and acetylated at room temperature for 18 h with pyridine (10 ml) and acetic anhydride (6.6 ml). The sirupy residue obtained after usual work-up was crystallized from hot isopropanol (8 ml). $\nu_{max}^{(Nujol)}$ 1725 (carbonyl), 1580 (phenyl), 1165 cm^{-1} (tosyl). Additional n.m.r. data (Table 1), τ 7.59 (CH_3).

Anal. Calcd. for $C_{22}H_{30}O_{11}S$: C, 52.60; H, 5.97; S, 6.38. Found: C, 52.87; H, 6.17; S, 6.30.

n-Propyl 2,3,4-Tri-O-acetyl-6-O-p-tolylsulfonyl-α-D-glucopyranoside (5)

This compound was prepared by the general method described above with the difference that 22 ml acetic acid was used for the hydrolysis of the oxime. $\nu_{max}^{(Nujol)}$ 1725 (carbonyl), 1580 (phenyl), 1160 cm^{-1} (tosyl). Additional n.m.r. data (Table 1), τ 8.05, 8.0 (3 *O*-acetyl groups), 7.59 (CH_3), 9.1 (CH_3 of the *n*-propyl group), 8.1 – 8.9, and 6.2 – 6.9 (CH_2—CH_2 of the *n*-propyl group).

Anal. Calcd. for $C_{22}H_{30}O_{11}S$: C, 52.60; H, 5.97; S, 6.38. Found: C, 52.57; H, 6.21; S, 6.20.

L-*Menthyl 2,3,4-Tri-O-acetyl-6-O-p-tolylsulfonyl-α-D-glucopyranoside (7)*

The crude sirupy product obtained after the condensation of **4** with L-menthol as mentioned in the general method, was washed with *n*-hexane (2 × 3 ml) to remove excess L-menthol before subjecting it to hydrolysis. $\nu_{max}^{(Nujol)}$ 1725 (carbonyl), 1580 (phenyl), 1170 cm^{-1} (tosyl). Additional n.m.r. data, (Table 1), τ 9.06 – 9.39 (superimposed signals of the CH_3 groups), 7.55 (CH_3).

Anal. Calcd. for $C_{29}H_{42}O_{11}S$: C, 58.20; H, 7.01; S, 5.35. Found: C, 57.95; H, 6.71; S, 5.65.

Phenyl 2,3,4-Tri-O-acetyl-6-O-p-tolylsulfonyl-α-D-glucopyranoside (8)

The procedure was essentially the same as for **6**, except, after removal of *N,N'*-dimethylformamide the methylene chloride solution was washed with 0.05 *N* sodium hydroxide solution to remove excess phenol. For the hydrolysis, acetic acid (9 ml), levulinic acid (3.2 g), and 1.12 *N* hydrochloric acid (5.1 ml) were used. $\nu_{max}^{(Nujol)}$ 1725 (carbonyl), 1580 (phenyl), 1165 cm^{-1} (tosyl). Additional n.m.r. data (Table 1), τ 8.03, 7.99 (3 *O*-acetyl groups), 7.95 (CH_3), 2.2 – 3.2 (9 aromatic hydrogens).

Anal. Calcd. for $C_{25}H_{28}O_{11}S$: C, 55.98; H, 5.22; S, 5.97. Found: C, 55.78; H, 5.13; S, 6.65.

L-*Menthyl 6-Azido-6-deoxy-α-D-glucopyranoside (10)*

A solution of **7** (2.99 g, 5 mmole) and sodium azide (1.63 g, 25 mmole) in a mixture of *N,N'*-dimethylformamide (15 ml) and water (2 ml) was refluxed. The reaction was followed by t.l.c. and was complete after 2.15 h. The residue obtained after usual work-up was *O*-deacetylated in solution in methanol (18 ml), water (5 ml), and triethylamine (2 ml) at room temperature for 20 h. The solvents were removed and the product dried over P_2O_5 and crystallized from hot *n*-hexane (6 ml). The yield of pure **10**, m.p. 88–90 °C, $[\alpha]_D^{24}$ + 16.94° (*c*, 1.18 in methanol), was 82%. $\nu_{max}^{(Nujol)}$ 2100 (azide), 3350 cm^{-1} (OH).

Anal. Calcd. for $C_{16}H_{29}N_3O_5$: C, 55.97; H, 15.1; N, 12.24. Found: C, 55.71; H, 15.32; N, 12.14.

L-*Menthyl 6-Amino-6-deoxy-α-D-glucopyranoside Hydrochloride (11)*

Hydrogen was bubbled through a well stirred solution of **10** (0.686 g, 2 mmole) in methanol (10 ml) and 0.5 *N* hydrochloric acid (4 ml) in the presence of 10% palladium-on-carbon (0.1 g). The reduction was followed by i.r. spectroscopy (disappearance of the azide band at 2100 cm^{-1}) and was complete in 2.5 h. Work-up in the usual manner afforded a residue (600 mg) which was recrystallized from methanol (5 ml) and ether (50 ml) to give 0.597 g (84.4%) of pure **11**, m.p. 230° (d), $[\alpha]_D^{24}$ + 56.49° (*c*, 1.54 in water). $\nu_{max}^{(Nujol)}$ 1600 cm^{-1} ($NH_3^{\oplus}$). The n.m.r. data, τ 4.95 (doublet for H-1, $J_{1,2}$ = 3.0 c.p.s.), 9.16 (superimposed signals of the CH_3 groups of the aglycon moiety).

Anal. Calcd. for $C_{16}H_{32}ClNO_5$: C, 54.31; H, 9.05; N, 3.96. Found: C, 54.19; H, 9.15; N, 3.99.

L-*Menthyl 6-Acetamido-6-deoxy-α-D-glucopyranoside (12)*

To a stirred solution of **11** (0.265 g) in a mixture of methanol (10 ml) and water (3 ml) was added aqueous sodium hydroxide solution (30 mg in 2 ml water) followed by acetic anhydride (0.15 ml). After 0.5 h at room temperature work-up in the usual manner yielded 0.25 g (90.9%) of pure **12**, m.p. 216 °C. $[\alpha]_D^{24}$ + 54.71° (*c*, 1.59 in methanol). $\nu_{max}^{(Nujol)}$ 1640 (amide I), 1540 (amide II), 3350–3500 cm^{-1} (OH and NH).

Anal. Calcd. for $C_{18}H_{33}NO_6$: C, 60.16; H, 8.91; N, 3.89. Found: C, 60.24; H, 8.62; N, 3.70.

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