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REACTIONS OF THE BIS(*p*-TOLYLSULFONYLHYDRAZONE) OF PERIODATE-OXIDIZED METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDE WITH BOROHYDRIDE AND CYANOBOROHYDRIDE: NOVEL SYNTHESES OF UNSATURATED AND DEOXY SUGARS

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ABSTRACT

Periodate-oxidized methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) reacted with *p*-toluenesulfonylhydrazine to give the substituted bis(hydrazone) **2**, which was converted into an *N*-substituted epimino derivative (**3**) by treatment with sodium borohydride in ethanol. Compound **3** was further converted into the glyc-2-enoside **4** by heating it with sodium borohydride in 1,4-dioxane. Sodium cyanoborohydride in ethanol reduced **2** to an epimeric mixture of 2-deoxy-D-*arabino* (**5**) and D-*ribo* (**6**)-hexoside derivatives. In the presence of an acidic resin in the same solvent, however, compound **2** underwent hydrogenation to the bis(hydrazino) derivative (**7**). The mechanisms of these reactions are discussed.

INTRODUCTION

The hemialdal **1** obtained by periodate oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside is known to react with arylhydrazines to yield methyl 3-arylazo-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranosides, presumably via unstable monohydrazones[1] of **1**.

During studies on chemical utilization of the products of periodate oxidation of carbohydrates, we found that the substituted bis(hydrazone) (the title compound, **2**) of **1** was exclusively obtained on reaction of the hemialdal **1** and *p*-toluenesulfonylhydrazine, even when equimolar amounts of the reactants were used. The resultant bis(hydrazone) derivative undergoes novel reactions with borohydride and cyanoborohydride. This paper describes new synthetic routes to 2,3-unsaturated and 2-deoxy glycosides, starting from this hemialdal.

RESULTS AND DISCUSSION

The substituted bis(hydrazone) **2** was prepared, in good yield, by condensation

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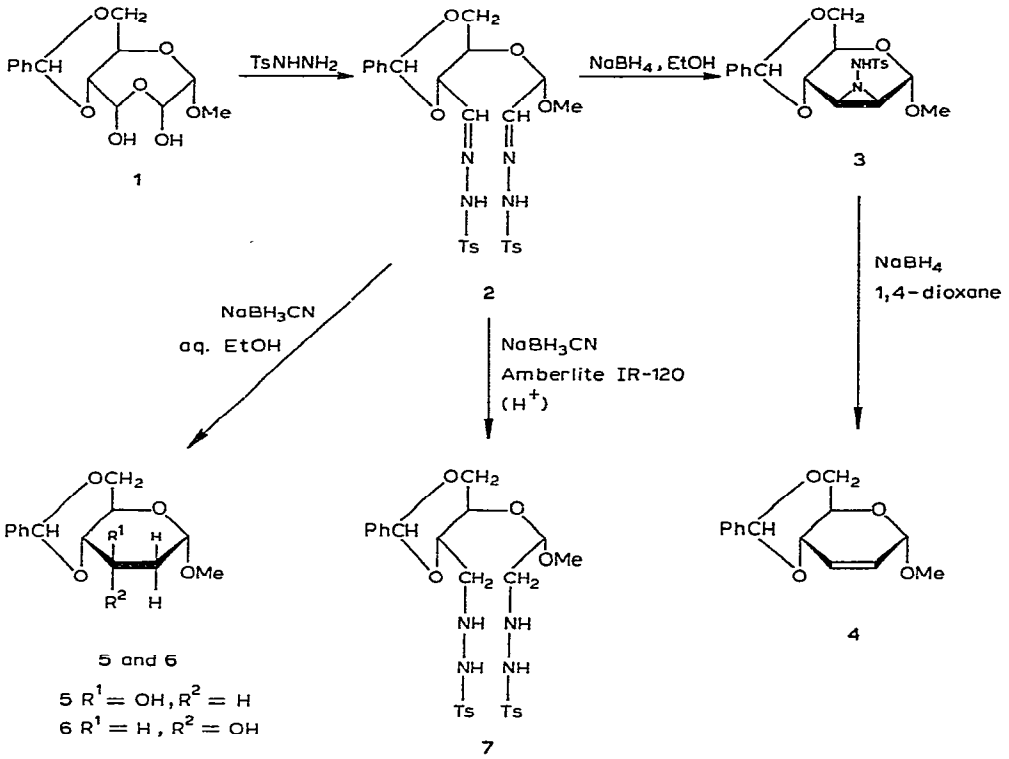
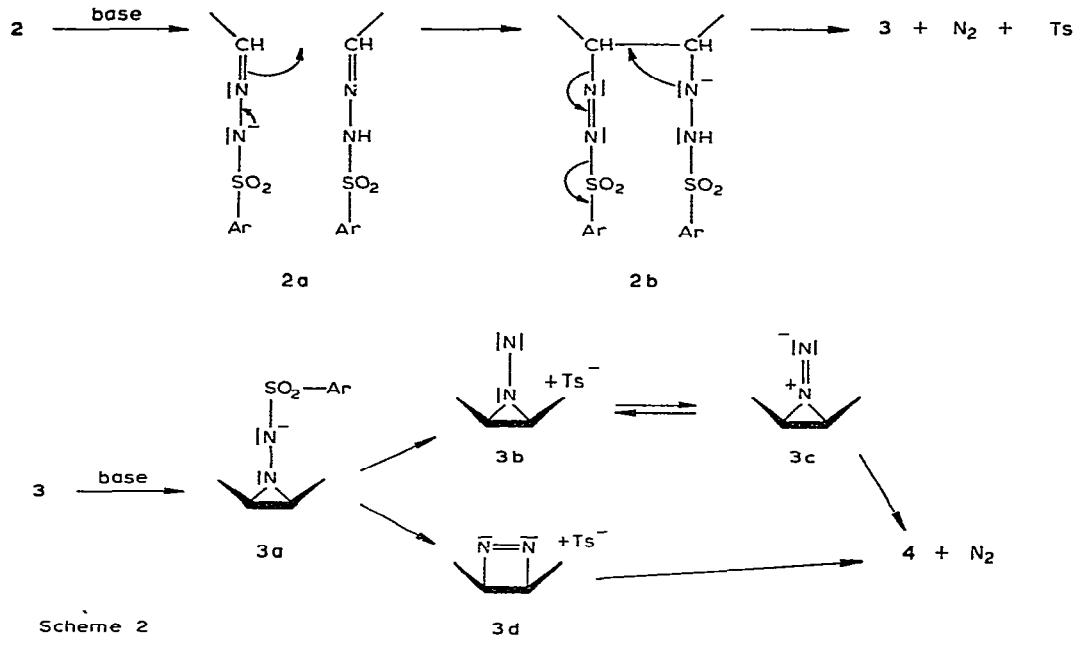


Scheme 1

of the hemiaidal **1** with a slight excess of *p*-toluenesulfonylhydrazine in ethanol (Scheme 1).

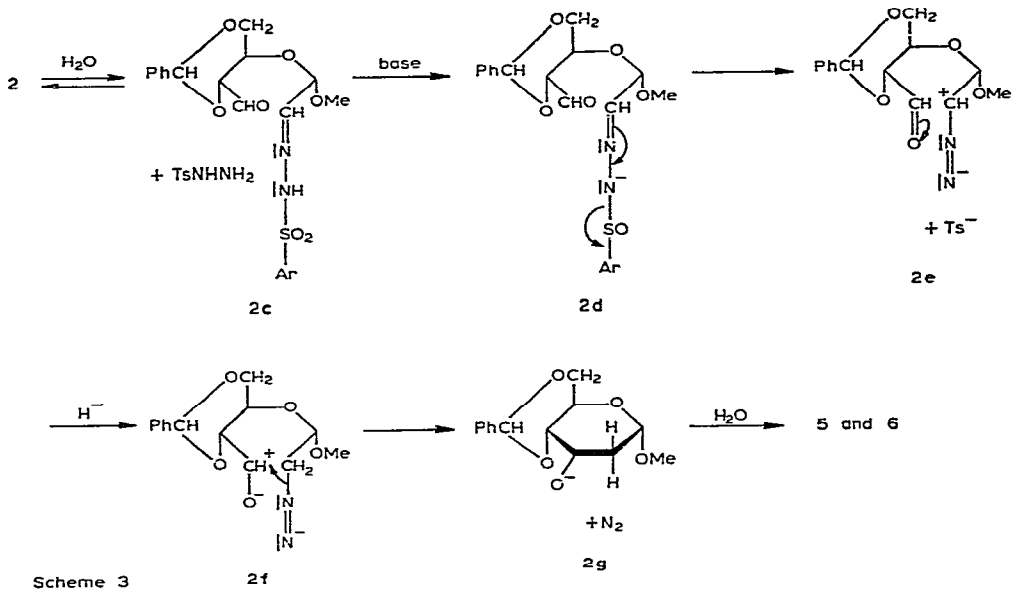
Treatment of the bis(hydrazone) **2** with sodium borohydride in ethanol gave a crystalline compound **3** in fairly good yield, together with a trace of a by-product **4**. Compound **3** is considered to be methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-(*N*-*p*-tolylsulfonyl)epimino-α-D-mannopyranoside from the following evidence. The ^{1}H n.m.r. spectrum indicated that the methoxyl and benzylidene groups were retained, whereas one of the *p*-tolylsulfonyl groups had been eliminated. The one-proton singlet resonating at low field (δ 5.01) apparently arose from the anomeric proton, by analogy with the high deshielding observed for hemiacetal protons in simple glycosides. The one-proton doublet at δ 2.85 and the one-proton quartet at δ 3.02 were assignable respectively to H-2 and H-3 on the pyranose ring. The low $J_{1,2}$ (0.0 Hz) and $J_{3,4}$ (0.1 Hz) couplings were indicative of the *manno* configuration, distorted strongly by the aziridine ring. Inspection of a molecular model indicated that both of the corresponding tetrahedral angles were ~90°. The broadened signal at δ 6.30 was ascribed to the imino proton, as it disappeared when deuterium oxide was added. These ^{1}H-n.m.r. parameters are in good agreement with those for methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-mannopyranoside as reported by Guthrie and Murphy[2]. Elementary analysis supported the structure assigned, but would also be in accord with other possible structures, namely, the hydrazones of the



Scheme 2

2-deoxyglyc-3-ulose and 3-deoxyglyc-2-ulose derivatives. However, the latter structures may be excluded, because the ^{1}H-n.m.r. parameters of compound **3** were quite different from those reported for the phenylhydrazones of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose and methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosidulose[3]. Concurrent formation of the *allo* isomer should be possible, but for a reason not yet known, such a compound was not isolated from the mixture. Cyclization to the aziridine derivative with sodium borohydride is a base-catalyzed, nonreductive reaction, as it also occurred with sodium methoxide; examination by t.l.c. of the mixture obtained by boiling the bis(hydrazone) **2** in 0.1M methanolic sodium methoxide indicated the presence of a spot identical with that of compound **3**, together with other spots. Furthermore, the product isolated by preparative t.l.c. gave an i.r. spectrum identical with that of compound **3**. A possible reaction-process is shown in Scheme 2. The reaction is initiated by abstraction of one of the imino protons with base, followed by exchange of electrons between two azomethine groups to form the aziridine derivative **3**. One of the hydrazine molecules is decomposed to gaseous nitrogen and the sulfinate anion in these sequential reactions, but it is uncertain which of the hydrazine molecules is eliminated.

The by-product **4** was obtained from **3** in higher yield under drastic conditions by changing the reaction solvent to 1,4-dioxane, and it was identified as methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside by comparing its physical constants, and i.r. and ^{1}H-n.m.r. spectra with those in the literature[4]. The overall yield was 26%, starting from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside. Compound **4** was also formed when compound **3** was boiled under reflux in dilute

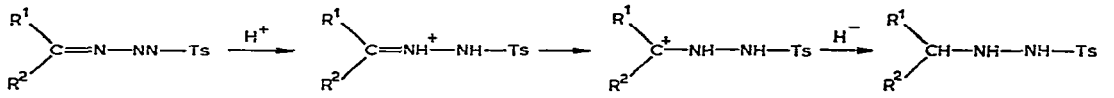


Scheme 3

sodium hydroxide in aqueous 1,4-dioxane. Therefore, conversion of compound **3** into the alkene **4** is also a base-catalyzed, non-reductive reaction, but it takes place at higher temperature than that for aziridine formation. This reaction is presumed to proceed through the mechanism shown in Scheme 2, where either an azamine **3c** or an azo derivative **3d** is formed from the deprotonated aziridine **3a** as an intermediate. Elimination of a molecule of nitrogen from either species gives the alkene **4**. The bis(hydrazone) **2** was reduced by cyanoborohydride, yielding a crystalline compound **5**, which was identified as methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside from its physical constants, t.l.c. mobility, and its i.r. and ^{1}H-n.m.r. spectra. A small proportion of an isomer **6** was obtained, whose m.p. and specific rotation were in good agreement with those of the *ribo* isomer. The mechanism of this unusual reaction may be explained as shown in Scheme 3. Partial hydrolysis of the bis(hydrazone) would give a monohydrazone **2c**, from which the *p*-toluenesulfinate anion is eliminated through the reaction pathway **2c**→**2g**. The C-2–C-3 bond may be formed by a subsequent shift of an electron from the CH_2–N bond to the carbonium carbon atom in **2f**. The resultant anion **2g** would take a proton from a molecule of water to form the 2-deoxy sugars **5** and **6**. Obviously, a hydrolytic step, using water in the reaction solvent, is involved in these sequential reactions, as no such reaction occurred under completely anhydrous conditions, but the exact point of this hydrolytic step is not established.

Cyanoborohydride behaved quite differently in the presence of a cation-exchange resin. The product (**7**) obtained from **2** was rather unstable in polar solvents, and gave a complex mixture of unknown degradation products on long keeping. The ^{1}H-n.m.r. spectrum of compound **7** revealed that a methoxyl, a benzylidene, and

two *p*-tolylsulfonyl groups remained, and two pairs of methylene protons having signals at higher fields (δ 2.81 and 3.10) were also indicated. Treatment with deuterium oxide resulted in disappearance of the four proton signals assigned to imino groups. From these ^{1}H-n.m.r. data, a bis(hydrazinomethylene) structure is proposed for compound **7**. The disappearance of u.v. absorption and the appearance of an imino band at 3275 cm^{-1} in the i.r. spectrum are consistent with this structure. It has been reported that 1-cyclohexyl-2-(*p*-tolylsulfonyl)hydrazine was isolated on reduction of the corresponding hydrazone with borohydride, as an intermediate compound leading to cyclohexane[5], and a possible mechanism for this type of reduction in acidic media may be as follows,



Thus, the mode of reaction of the bis(hydrazone) **2** with metal hydrides is highly dependent on the reagents and reaction media used. The presence or absence of a cation-exchange resin also had an influence on the mode of reaction.

EXPERIMENTAL

General methods. — Melting points were determined on a hot stage by using a Reichert melting point apparatus and are uncorrected. Specific rotations were measured in a 1-cm cell with a Union automatic digital polarimeter PM-101 (589 nm). Proton magnetic resonance (^{1}H-n.m.r.) spectra were obtained at 60 MHz in a Hitachi R-20A spectrometer with tetramethylsilane as the internal reference. Infrared spectra were recorded in Nujol mulls with a Hitachi EPI-G3 spectrophotometer. Ultraviolet spectra were obtained in a 1-cm cell with a Shimadzu UV-210 spectrophotometer. T.l.c. was carried out on precoated plates (Merck TLC Plate Silica Gel 60 F_{254}), developed with 4:1 (v/v) benzene–ethyl acetate, unless otherwise stated. For preparative thin-layer chromatography, thick plates coated with Wakogel B-5 were used. Spots were detected under a u.v. lamp or by spraying the plates with sulfuric acid. Evaporations were performed below 40° under diminished pressure.

*The bis-*p*-toluenesulfonyl(hydrazone) (2) of the hemialdal* **1**. — Periodate-oxidized methyl 4,6-*O*-benzylidene-α-D-glucopyranoxide[6] **1** (316 mg, 1.0 mmol) was added to a solution of *p*-toluenesulfonylhydrazine (447 mg, 2.4 mmol) in ethanol (12 ml), and the mixture was boiled for 15 min under reflux. The mixture was refrigerated overnight and the crystalline product **2** was recrystallized from ethanol, yield, 561 mg (91%), m.p. 146–148° (decomp), $[\alpha]_D^{25}$ −29.8° (*c* 1.0, pyridine); λ_{max}^{EtOH} 231 nm (ε 27,600); ν_{max} 3170 (NH), 1600 (aromatic C=C), 1145 cm^{-1} (SO_2); ^{1}H-n.m.r. (acetone-d_6): δ 2.25 (3-proton singlet, -CH_3 of Ts), 2.37 (3-proton singlet, -CH_3 of Ts), 3.08 (3-proton singlet, -OCH_3), 3.37–4.33 (4-proton multiplet, H-2,3,4, and 4′ of the D-erythrose moiety), 4.76 (1-proton doublet, *J* 6.0 Hz, -O-C*H*-OMe), 5.50 (1-proton singlet, Ph-C*H*=), 7.01 (1-proton doublet, -C*H*=N- of the glyoxal moiety), and

7.5–7.9 (16-proton multiplet, aromatic protons, -C*H*=N- of the D-erythrose moiety and 2 × =N-N*H*-).

Anal. Calc. for $C_{28}H_{32}N_4O_8S_2$: C, 54.35; H, 5.54; N, 9.06; S, 10.36. Found: C, 54.47; H, 5.23; N, 8.94; S, 10.31.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-(N-p-*tolylsulfonyl)epimino-α-*D-*manno-pyranoside* (**3**). — (*a*) *Reaction of* **2** *with sodium borohydride.* The bis(hydrazone) **2** (308 mg, 0.50 mmol) and sodium borohydride (38 mg, 1.0 mmol) were dissolved in ethanol (20 ml), and the solution was boiled under reflux for 1 h; more sodium borohydride (38 mg, 1.0 mmol) was added and the mixture was boiled for a further 2 h. The mixture was extracted three times with ethyl acetate (10 ml), and the combined extract was washed with water and evaporated to dryness to give a crystalline mass. T.l.c. indicated the presence of the epimine **3** (R_F 0.65) and a trace of the alkene **4** (R_F 0.85) as sulfuric acid-sensitive spots. Compound **3** was obtained pure by recrystallization of the crystalline mass from ethanol; yield, 97 mg (45%), m.p. 186–188°, $[\alpha]_D^{25}$ −1.4° (*c* 0.7, pyridine); λ_{max}^{EtOH} 231 nm (ε 15,760); ν_{max} 3190 (NH), 1600 (aromatic C=C), 1160 cm^{-1} (SO_2); ^{1}H-n.m.r. data (pyridine-d_5): δ 2.16 (3-proton singlet, -CH_3 of Ts), 2.85 (1-proton doublet, $J_{2,3}$ 8.0 Hz, H-2), 3.02 (1-proton quartet, $J_{3,4}$ 0.1 Hz, H-3), 3.31 (3-proton singlet, -OCH_3), 3.5–3.9 (3-proton multiplet, H-5,6, and 6'), 4.27 (1-proton quartet, $J_{4,5}$ 5.5 Hz, H-4), 5.01 (1-proton singlet, H-1), 5.61 (1-proton singlet, Ph-C*H*=), 6.30 (1-proton singlet, =N-N*H*-SO_2-), and 7.3–8.3 (9-proton multiplet, aromatic protons).

Anal. Calc. for $C_{21}H_{24}N_2O_6S$: C, 58.32; H, 5.59; N, 6.48; S, 7.41. Found: C, 58.40; H, 5.60; N, 6.52; S, 7.30.

(*b*) *Reaction of* **2** *with sodium methoxide.* A small amount of **2** was dissolved in 0.1M sodium methoxide in methanol, and the solution was boiled for 2 h under reflux. T.l.c. of the mixture indicated the presence of 3 spots (R_F 0.45, 0.65, and 0.85), together with unreacted **2** (R_F 0.35). The R_F value of **3** was 0.65. The mixture was chromatographed on a thick plate and the second fastest-moving zone was extracted with 10:1 (v/v) chloroform–methanol. The extract was evaporated to dryness to give an amorphous product. The i.r. spectrum of this product was identical with that of the aziridine **3** obtained in (*a*).

*Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranoside* (**4**). — (*a*) *Reaction of* **3** *with sodium borohydride.* Compound **3** (108 mg, 0.25 mmol) and sodium borohydride (95 mg, 2.5 mmol) were dissolved in 1,4-dioxane (20 ml), and the solution was heated for 4 h at 90°, until compound **3** could no longer be detected by t.l.c. The mixture was evaporated to dryness, and the residue was extracted five times with chloroform (5 ml). The combined extract was washed three times with water (5 ml) and evaporated to dryness, and the residue was fractionated on a column (0.9 cm i.d., 40 cm) of silica gel (Wakogel C-200) with 10:1 (v/v) benzene-ethyl acetate. Fractions containing **4** were pooled and crystallized from hexane; yield 35.5 mg (57%); m.p. 121–122° (lit.[4] 119–120°), $[\alpha]_D^{25}$ +126.0° (*c* 0.85, chloroform) (lit.[4] $[\alpha]_D^{25}$ +130 ±2° in chloroform); no appreciable u.v. absorption was observed above 210 nm; ν_{max} 735, 680 cm^{-1} (Ph); ^{1}H-n.m.r. data (chloroform-*d*):

δ 3.45 (3-proton singlet, -OCH_3), 3.7–4.4 (4-proton multiplet, H-4,5,6, and 6'), 4.88 (1-proton doublet, $J_{1,2}$ 2.0 Hz, H-1), 5.56 (1-proton singlet, Ph-C*H*=), 5.70 (1-proton sextet, $J_{2,3}$ 10.9, $J_{2,4}$ 2.2 Hz, H-2), 6.15 (1-proton doublet, $J_{3,4}$ 1.0 Hz, H-3), and 7.37 (5-proton multiplet, phenyl protons).

(*b*) *Reaction of* **3** *with sodium hydroxide.* A small amount of **3** was dissolved in 0.5M sodium hydroxide in 10:1 (v/v) 1,4-dioxane–water, and the solution was boiled for 3 h under reflux. T.l.c. of the mixture showed a single spot having R_F 0.85, the same as that of **4**. The mixture was chromatographed on a thick plate and the sulfuric acid-sensitive zone extracted with 10:1 (v/v) chloroform–methanol. The extract was evaporated to dryness to give an amorphous product, which had an i.r. spectrum identical with that of **4** obtained by route (*a*).

*Methyl 4,6-*O*-benzylidene-2-deoxy-*α*-*D*-*arabino (**5**) *and* D-ribo(**6**)-hexopyranoside.* — A solution of **2** (1.23 g, 2.0 mmol) and sodium cyanoborohydride (256 mg, 4.0 mmol) in 20:1 (v/v) ethanol–water (60 ml) was boiled for 1 h under reflux. More sodium cyanoborohydride (256 mg, 4.0 mmol) was then added and the mixture was heated for a further 2 h. The mixture was evaporated to dryness and the residue was extracted five times with chloroform (20 ml). The combined extract was washed three times with water (20 ml) and evaporated to dryness, and the residual syrup was fractionated on a column (1.6 cm i.d., 40 cm) of silica gel (Wakogel C-200) with 5:1 (v/v) benzene–ethyl acetate. Small amounts of the faster-moving **3** and **4** were eluted first, and then a mixture of the 2-deoxyglycosides, **5** and **6** (R_F 0.30) was obtained as a syrup. The glycoside **5** crystallized as fibrous needles from ether–hexane; yield 148 mg (28%), m.p. 151° (lit.[7] 151–152°), $[\alpha]_D^{25}$ +84.0° (*c* 0.63, chloroform) (lit.[7] $[\alpha]_D^{25}$ +90°, in acetone); no appreciable u.v. absorption above 210 nm; ν_{max} 3300 (OH), 730, 680 cm^{-1} (Ph); ^{1}H-n.m.r. data (chloroform-*d*): δ 2.00 (2-proton multiplet, H-2*a* and H-2*e*), 3.34 (3-proton singlet, -OCH_3), 3.3–4.4 (6-proton multiplet, H-3,4,5,6,6', and O*H*), 4.78 (1-proton quartet, $J_{1,2a}$ 3.9, $J_{1,2e}$ 1.1 Hz, H-1), 5.56 (1-proton singlet, Ph-C*H*=), and 7.2–7.6 (5-proton multiplet, Ph).

The mother liquor was evaporated to dryness, and the residue was fractionated on a column (0.9 cm i.d., 40 cm) of silica gel (Wakogel C-200) with 4:1 (v/v) ether–hexane. An additional crop of **5** was obtained from the fraction eluted in 65–80 ml of eluate (R_F 0.33, 4:1 ether–hexane). The *ribo* isomer **6** (R_F 0.24, 4:1 ether–hexane) was eluted with 85–105 ml of eluant. This fraction was evaporated and the residue crystallized from ether–hexane to give needles of **6**; yield 118 mg (22%); m.p. 120–123° (lit.[8] 118–120°), $[\alpha]_D^{25}$ +174.0° (*c* 0.6, chloroform) (lit.[8] $[\alpha]_D^{25}$ +155.6° in chloroform).

A solution of **2** and sodium cyanoborohydride in abs. ethanol was boiled under reflux, and the mixture was examined by t.l.c. Two spots (R_F 0.33 and 0.88) of unknown products were observed, but no spots corresponding to **5** and **6** were detected.

*2,4-*O*-Benzylidene-1-deoxy-3-*O*-[1-methoxy-2-(2-p-tolylsulfonyl)hydrazino]ethyl-1-(2-*p*-tolylsulfonyl)hydrazino-*D*-erythritol* (**7**). — Sodium cyanoborohydride (630 mg, 10 mmol) was added with constant stirring to a suspension of the bis(hydrazone) **2** (616 mg, 1.0 mmol) and Amberlite IR-120 (H^+, 10 ml, washed with 5 ml of methanol

several times before use) in methanol (15 ml). By the time effervescence had ceased, compound **2** had dissolved completely. The mixture was kept for another 1.5 h, and then filtered and the filtrate was evaporated to dryness. The crystalline product **7** was recrystallized from chloroform–ether; yield 540 mg (88%), m.p. 126–128°, $[\alpha]_D^{25}$ −39.2° (*c* 1.1, pyridine); λ_{max}^{EtOH} 227 nm (ε 20,600); ν_{max} 3275 (NH), 1600 (aromatic C=C), 1155 cm^{-1} (SO_2); ^{1}H-n.m.r. data (acetone-d_6): δ 2.41 (6-proton singlet, 2 × -C*H*$_3$ of Ts), 2.81 (2-proton doublet, -C*H*$_2$-NH- of the substituted hydrazinoethyl group, *J* 5.5 Hz), 3.10 (2-proton multiplet, H-1 and 1'), 3.33 (3-proton singlet, -OC*H*$_3$), 3.5–4.3 (4-proton multiplet, H-2,3,4, and 4'), 3.76 (2-proton broad singlet, 2 × -CH$_2$-N*H*-NH-), 4.31 (1-proton triplet, -O-C*H*-OMe), 5.47 (1-proton singlet, PH-C*H*=), 7.2–7.8 (13-proton multiplet, aromatic protons), and 7.56 (2-proton singlet, 2 × -N*H*-SO$_2$-).

Anal. Calc. for $C_{28}H_{36}N_4O_8S_2$: C, 54.17; H, 5.85; N, 9.03; S, 10.33. Found: C, 53.91; H, 5.86; N, 9.03; S, 10.33.

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