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SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-L-*lyxo*-HEXOSE (DAUNOSAMINE) HYDROCHLORIDE FROM D-GLUCOSE*

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ABSTRACT

Three different approaches starting from 1,2-*O*-isopropylidene-α-D-glucofuranose were tested for the synthesis of daunosamine hydrochloride (**24**), the sugar constituent of the antitumor antibiotics daunomycin and adriamycin. The third route, affording **24** in ~5% overall yield in 11 steps, constitutes a useful, preparative synthesis. 3,5,6-Tri-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose was converted *via* methyl 2,3-anhydro-β-D-mannofuranoside into methyl 2,3:5,6-dianhydro-α-L-gulofuranoside, the terminal oxirane ring of which was split selectively on reduction with borohydride, to afford methyl 2,3-anhydro-6-deoxy-α-L-gulofuranoside (**31**). Compound **31** was converted into methyl 2,3-anhydro-5-*O*-benzyl-6-deoxy-α-L-gulofuranoside, which was selectively reduced at C-2 on treatment with lithium aluminum hydride, affording methyl 5-*O*-benzyl-2,6-dideoxy-α-L-*xylo*-hexofuranoside. Subsequent mesylation, and replacement of the mesyloxy group by azide, with inversion, afforded methyl 3-azido-5-*O*-benzyl-2,6-dideoxy-α-L-*lyxo*-hexofuranoside, which could be converted into either **24** or methyl 3-acetamido-5-*O*-acetyl-2,3,6-trideoxy-α-L-*lyxo*-hexofuranoside, which can be used as a starting material for the synthesis of daunomycin analogs.

INTRODUCTION

Daunosamine (**24**), the sugar component of the cytostatically active, anthracycline antibiotics daunomycin (daunorubicin) and adriamycin (doxorubicin)[1], was first synthesized in 1967, by Marsh *et al.*[2], starting from L-rhamnose. In 1975, a more economical synthesis was published by Horton and Weckerle[3], using D-mannose as the starting material. Recently, two patents, that of Whistler[4] and a Japanese one[5], described two different approaches, both starting from D-glucose. They differ in the sequence of the four steps necessary for converting D-glucose into **24** (*a*, OH-2 → H; *b*, OH-3 → NH_2, *c*, OH-5 → OH; and *d*, OH-6 → H), but have two features in common: they first introduce the amino group (step *b*) and the last transformation involves step *a*, for which both routes use a similar 1,2-ene intermediate.

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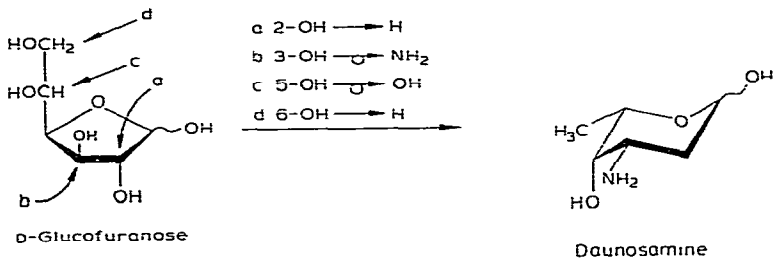


Scheme 1. Steps necessary in the conversion of D-glucose into daunosamine.

As the introduction of the amino group onto C-3 makes the succeeding steps more complicated, we have attempted to devise different approaches, also starting from D-glucose, but introducing the amino group later in the synthesis.

DISCUSSION

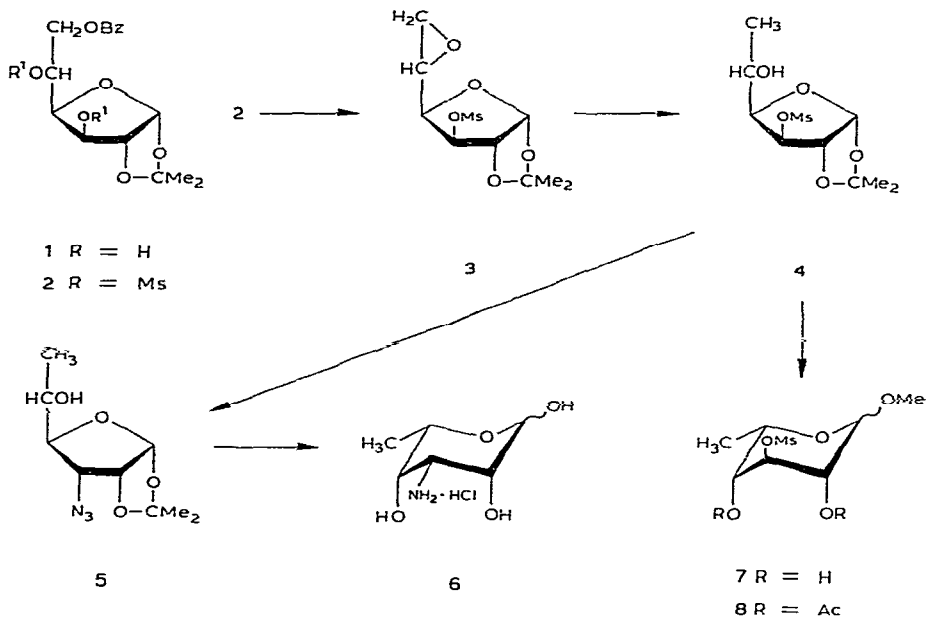
Route 1 (*c→d→b→a*)

6-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**1**) was converted into the 3,5-dimesylate **2**, which, on treatment with sodium methoxide, afforded the known[7] 5,6-anhydro-L-idose derivative **3**. Reduction of the oxirane ring in **3** was achieved with lithium aluminum hydride below 0°, leaving the mesyloxy group unaffected and giving the 6-deoxy derivative **4** in excellent yield (94%). Replacement of the mesyloxy group in **4** by azide, with inversion of configuration, proved to be very slow, as, even after 80 h in aqueous *N,N*-dimethylformamide at 125°, some unreacted **4** could be detected by t.l.c.

Neither the speed of the reaction, nor the yield of the desired product **5**, could be substantially influenced by changing the reaction conditions, and azide **5** could only be obtained, after column chromatography, in a yield of ~10%. These difficulties were to be expected, as the mesyloxy group in **4** is *exo* (equatorially) oriented in the *cis*-fused ring-system, which is an unfavorable arrangement for a rearside attack. The azide anion, being a strong, but relatively small, nucleophile, is able to replace *exo*-oriented mesyloxy groups in similar, fused five-membered ring-systems[8], but, in compound **4**, a methyl group of the isopropylidene substituent (pointing in the direction of the approaching reagent) causes further steric inhibition.

Despite the fact that, on reduction of the 3-azido derivative **5** in the presence of palladium, and subsequent hydrolysis with hydrochloric acid, it could be readily converted into the known[9] 3-amino sugar **6**, this approach had to be rejected, because of the low yield of **5**.

To overcome the steric inhibition of the azide exchange-reaction, the isopropylidene group of mesylate **4** was removed by treatment with hydrochloric acid in methanol, and the unseparated, anomeric mixture (**7**) of the resulting methyl pyranosides was acetylated to **8**. The anomeric ratio of this mixture was determined by the n.m.r. data ($\alpha:\beta \sim 1:1$), which also excluded the presence of the theoretically



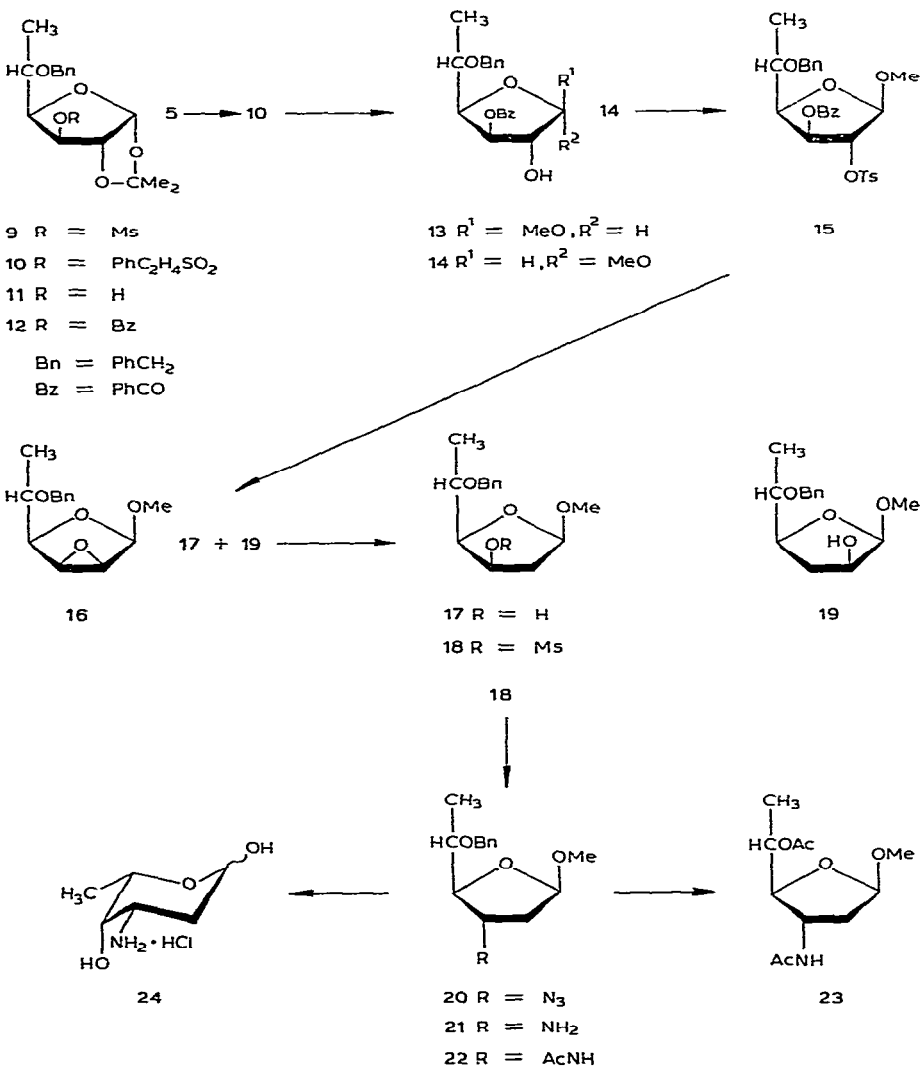
possible furanosides. The substitution reaction of the mesyloxy group in **8** was very fast, but an inseparable mixture of at least 6 compounds was obtained. This is not surprising, as the acetoxyl groups on C-2 and C-4 are *trans*-diaxially situated in respect of the mesyloxy group on C-3, and consequently, can readily form cyclic 2,3- or 3,4-acetoxonium ions that can be opened by the azide on C-2, 3, and 4, respectively. For avoiding these complications, an alternative, synthetic approach was taken into consideration.

Route 2 (*c*→*d*→*a*→*b*)

The 6-deoxy mesylate **4** was treated with benzyl chloride and sodium hydroxide, to give, besides some unchanged starting-material, the 5-*O*-benzyl derivative **9** as the main component, and a further crystalline compound (**10**) in which not only OH-5, but the methyl group of the 3-mesyloxy substituent was also benzylated[10]. The mesyloxy group of **9** was removed reductively by means of lithium aluminum hydride, and the free OH-3 group formed in compound **11** was benzoylated. On treatment with methanolic hydrogen chloride, the ester **12** so obtained gave a 3:1 mixture of the methyl α- (**13**) and β-furanoside (**14**), which could be separated only by column chromatography. The α anomer **13** was converted *via* its 2-tosylate **15** into the 2,3-anhydro-L-gulofuranoside **16**, containing all of the substituents on one side of the tetrahydrofuran ring. This is an essential steric requirement for the next step, as reduction with lithium aluminum hydride gives the desired 2-deoxy derivative **17** in almost quantitative yield, and only traces of the corresponding 3-deoxy isomer **19** could be detected by t.l.c.

Reduction of the corresponding methyl 2,3-anhydro-β-furanoside should give

the 2-deoxy derivative as only a minor component[11], due to the steric hindrance of the methoxyl group, preventing the attack of the hydride at C-2. The 2-deoxy furanoside **17** was converted into the mesylate **18**, the mesyloxy group of which was readily replaced by azide, with inversion of the configuration, giving **20** in high yield (93%). Reduction of the azide group in the presence of palladium as the catalyst is a much faster process than the reductive cleavage of the 5-*O*-benzyl group; consequently, the 3-amino-5-*O*-benzyl derivative **21** could be isolated after 1 h, and it was characterized as its crystalline *N*-acetyl derivative **22**. When the hydrogenation was continued for 4 days, complete reduction of both groups took place, and the syrup obtained gave, on acetylation, *N*,*O*-diacetyldaunosamine as its crystalline methyl α-furanoside **23**. When the syrup obtained by complete hydrogenation was hydrolyzed



with aqueous hydrochloric acid, daunosamine hydrochloride (**24**) was obtained in a yield of 75%.

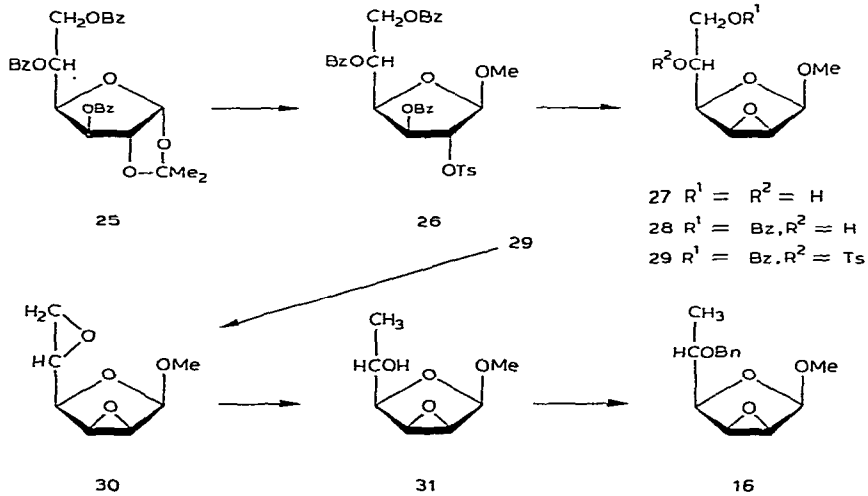
Route 3 (c→d→a→b; variation of route 2)

As mentioned in the previous approach, separation of the methyl 3-*O*-benzoyl-5-*O*-benzyl-α,β-furanosides (**13** and **14**) could only be achieved by tedious, column chromatography, and therefore a new strategy was decided on for synthesis of the key intermediate **16**.

The known 3,5,6-tri-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**25**) was converted by methanolysis and subsequent tosylation into the methyl 2-*O*-tosyl-β-furanoside **26** which, according to its physical data (m.p. 143–145°, $[\alpha]_D^{20}$ −105.4°) was different from the compound described by Bell *et al.*[12] (m.p. 125–127°, $[\alpha]_D^{20}$ −61.9°). The latter was probably a mixture of the anomers, as, in the synthesis of **26**, a material having similar properties was obtained as a crude product which, according to the n.m.r. data, was a mixture of the anomers. For increasing the yield of the β anomer, the mother liquors of the recrystallization, containing mainly the α anomer, were equilibrated with hydrochloric acid containing methanol, but, instead of equilibration, debenzoylation occurred, leading to inseparable mixtures.

Treatment of tosylate **26** with methanolic sodium methoxide led, *via* debenzoylation and subsequent elimination of *p*-toluenesulfonic acid, to epoxide **27**. This was partially benzoylated, and the crystalline 6-benzoate **28** was tosylated, to give **29**. Treatment of this mixed ester with sodium methoxide afforded the diepoxide **30**, the terminal oxirane group of which could be selectively reduced by borohydride, furnishing methyl 2,3-anhydro-6-deoxy-α-L-gulofuranoside (**31**). Benzylation of **31** at OH-5 gave **16**, the key intermediate in the synthesis already mentioned.

The last of these synthetic approaches afforded, not only daunosamine hydrochloride (**24**) from the readily available 1,2-*O*-isopropylidene-α-D-glucofuranose in an 11-step synthesis, without recourse to chromatographic purification at any of the



stages, but also, intermediates that can be used in the synthesis of anthracycline glycosides containing daunosamine and its analogs in the furanose form.

EXPERIMENTAL

General methods. — After organic solutions had been dried with sodium sulfate, all evaporations were conducted in a rotary evaporator under diminished pressure. Melting points are uncorrected. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1) if not stated otherwise. T.l.c. was effected on Kieselgel G with ethyl acetate (*A*), ethyl acetate–carbon tetrachloride 3:1 (*B*), 2:1 (*C*), 1:1 (*D*), 1:2 (*E*), 1:3 (*F*), and 1:5 (*G*), and with ethyl acetate–ethanol 9:1 (*H*) and 1:1 (*I*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (62–200 μm). ^{1}H-N.m.r. spectra (90 MHz) were recorded at room temperature with a Varian EM-390 spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. Coupling constants are given in Hz.

6-O-Benzoyl-1,2-O-isopropylidene-3,5-di-O-(methylsulfonyl)-α-D-glucofuranose (**2**). — A stirred solution of 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**1**; 146 g) in pyridine (900 mL) was treated with mesyl chloride (108 mL) below +10°. The mixture was kept for 4 h at room temperature, and then poured onto ice. The precipitated crystals were filtered off and washed with water, to give, after recrystallization from acetone (2 L) plus ethanol (2.5 L), pure **2** (205 g, 95%), m.p. 182–183°, $[\alpha]_D^{20}$ −17.7°; R_F 0.65 (*E*); ^{1}H-n.m.r. data: δ 6.0 (d, $J_{1,2}$ 5 Hz, H-1), 3.25 and 3.14 2 mesyl-Me), and 1.34 and 1.50 (CMe_2).

Anal. Calc. for $C_{18}H_{24}O_{11}S_2$: C, 44.99; H, 5.03; S, 13.35. Found: C, 44.82; H, 5.15; S, 13.12.

5,6-Anhydro-1,2-O-isopropylidene-3-O-(methylsulfonyl)-β-L-idofuranose (**3**). — To a stirred solution of compound **2** (192 g) in dry chloroform (1.4 L) was added 4M methanolic sodium methoxide (200 mL). The temperature rose to 44°, and was maintained there, by gentle heating, for 20 min. The mixture was then washed with water, dried, and evaporated. On crystallization from ethanol (800 mL) the residue gave pure epoxide **3** (86 g, 77%), m.p. 100–101°, $[\alpha]_D^{20}$ −8.5°; R_F 0.5 (*D*); lit.[7] m.p. 96.5–98.5°, $[\alpha]_D^{20}$ −7.4°.

6-Deoxy-1,2-O-isopropylidene-3-O-(methylsulfonyl)-β-L-idofuranose (**4**). — To a stirred solution of **3** (78 g) in dry oxolane (800 mL) was added lithium aluminum hydride (22 g) in small portions, below −20°. Thereafter, the slurry was stirred for 45 min at −5°. For decomposing the excess of hydride, ethyl acetate (80 mL), water (22 mL), 15% aqueous sodium hydroxide (22 mL), and water (66 mL) were successively added below +10°. The inorganic salts were filtered off, and washed with ethyl acetate, the filtrate and washings were combined and evaporated, and the solid residue was recrystallized from ethyl acetate–light petroleum, to give pure **4** (73.6 g, 94%), m.p. 132–133°, $[\alpha]_D^{20}$ −35.6°; R_F 0.3 (*D*); ^{1}H-n.m.r. data: δ 6.0 (d, $J_{1,2}$ 4 Hz,

H-1), 5.05 (d, $J_{3,4}$ 3 Hz, H-3), 4.82 (d, H-2), 4.08 (m, H-5), 3.1 (mesyl-Me), 1.5 and 1.32 (CMe_2), and 1.26 (d, $J_{5,6}$ 5 Hz, H-6).

Anal. Calc. for $C_{10}H_{18}O_7S$: C, 42.54; H, 6.43; S, 11.36. Found: C, 42.66; H, 6.52; S, 11.15.

3-Azido-3,6-dideoxy-1,2-O-isopropylidene-β-L-talofuranose (**5**). — To a stirred solution of mesylate **4** (42 g) in *N*,*N*-dimethylformamide (570 mL) and water (30 mL) was added sodium azide (20 g). The mixture was stirred for 80 h at 128–130°. (Higher temperatures must be avoided, as decomposition of the starting material then takes place.) The mixture was evaporated, the residue was partitioned between chloroform and water, and the chloroform solution was washed with water, dried, and evaporated. The residue was freed of decomposition products (R_F 0.1 and 0.6), as well as of unreacted starting-material (R_F 0.3), by column chromatography using solvent *D* for elution. The fractions having R_F 0.5 were evaporated, to give, after recrystallization from light petroleum, pure azide **5** (3.35 g, 9.8%), m.p. 66–68°, $[\alpha]_D^{20}$ +116°; ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 1.6 and 1.42 (CMe_2), and 1.35 (d, $J_{5,6}$ 4 Hz, H-6).

Anal. Calc. for $C_9H_{15}N_3O_4$: C, 47.15; H, 6.60; N, 18.33. Found: C, 47.40; H, 6.72; N, 18.10.

3-Amino-3,6-dideoxy-L-talose hydrochloride (**6**). — A solution of azide **5** (2.3 g) in ethanol (40 mL) was hydrogenated in the presence of 8% Pd–C catalyst (1 g) for 2 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was dissolved in water (40 mL) and acidified with 5M hydrochloric acid to pH 1. The solution was kept at room temperature for 5 days, and then evaporated. Ethanol was added to, and evaporated from, the residue, which became crystalline. The crude product was dissolved in the minimum volume of water, and ethanol was added to incipient turbidity. The solution was concentrated to half its volume, and the crystals were filtered off and washed with ethanol, to give pure **6** (1 g, 44.7%), m.p. 170–171° (dec.), $[\alpha]_D^{20}$ −22.4° (water); lit.[9] m.p. 168–170° (dec.), $[\alpha]_D^{20}$ −25° (*c* 1.07, water).

Methyl 6-deoxy-3-O-(methylsulfonyl)-L-idopyranosides (**7**). — A solution of **4** (7 g) in 2M methanolic hydrochloric acid (100 mL) was kept for 6 h at room temperature, and then made neutral with solid sodium hydrogencarbonate; the precipitated salts were filtered off, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, dried, and evaporated, to yield a mixture (**7**) of the anomers as a colorless syrup (5.6 g, 86.5%); R_F 0.50 (*A*).

Anal. Calc. for $C_8H_{16}O_7S$: C, 37.49; H, 6.29; S, 12.51. Found: C, 37.55; H, 6.03; S, 12.23.

Methyl 2,4-di-O-acetyl-6-deoxy-3-O-(methylsulfonyl)-L-idopyranosides (**8**). — A solution of the anomeric mixture **7** (5 g) in pyridine (50 mL) was treated with acetic anhydride (8 mL). After one day at room temperature, the mixture was processed in the usual way, to give, after evaporation of the chloroform, the acetylated anomers **8** as a colorless syrup (5.5 g, 83%), R_F 0.5 (*D*).

Anal. Calc. for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 42.12; H, 5.70; S, 9.14.

Treatment of compound **8** with sodium azide in *N,N*-dimethylformamide (as described for **4**) led after 1 h, according to t.l.c., to complete consumption of the starting material, but at least 6 different spots of almost equal intensity could be detected.

5-O-Benzyl-6-deoxy-1,2-O-isopropylidene-3-O-(methylsulfonyl)-β-L-idofuranose (**9**) and *5-O-benzyl-6-deoxy-1,2-O-isopropylidene-3-(2-phenethylsulfonyl)-β-L-idofuranose* (**10**). — To a stirred solution of compound **4** (56 g) in *N,N*-dimethylformamide (400 mL) were simultaneously added benzyl chloride (36 mL) and powdered potassium hydroxide (24 g) in small portions during 30 min, the temperature of the mixture being kept between 25 and 28° by gentle cooling. Thereafter, stirring was continued for 1 h at this temperature. The slurry that formed was filtered off, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution was washed with water, dried, and evaporated. The crude product so obtained was separated by column chromatography, using solvent *F* for elution. The fractions having R_F 0.85 were combined and evaporated, and recrystallization of the residue from ether–light petroleum gave pure compound **10** (3.22 g, 3.5%), m.p. 121–123°, $[\alpha]_D^{20}$ −27°; ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 4.62 (s, benzyl-CH_2), 1.5 and 1.32 (CMe_2), and 1.26 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{24}H_{30}O_7S$: C, 62.32; H, 6.54; S, 6.93. Found: C, 62.39; H, 6.66; S, 6.82.

On evaporation, the fractions having R_F 0.5 gave a residue which, on recrystallization from ether–light petroleum afforded pure compound **9** (39.2 g, 53%), m.p. 89–91°, $[\alpha]_D^{20}$ −39.7°; ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 4.65 (s, benzyl-CH_2), 2.97 (mesyl-Me), 1.5 and 1.3 (CMe_2), and 1.25 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{17}H_{24}O_7S$: C, 54.82; H, 6.50; S, 8.61. Found: C, 54.95; H, 6.63; S, 8.52.

After elution of compound **9** from the column, elution was continued with ethyl acetate, affording unreacted starting-material (12.8 g, 22.8%).

5-O-Benzyl-6-deoxy-1,2-O-isopropylidene-β-L-idofuranose (**11**). — *Method a.* To a solution of mesylate **9** (31 g) in dry ether (600 mL) was added lithium aluminum hydride (7 g) in small portions at 0°. When addition of the hydride was complete, the mixture was boiled for 6 h, and then kept overnight at room temperature. The excess of hydride was decomposed as described for compound **4**. The inorganic salts were filtered off, and washed with ethyl acetate. The washings and filtrate were combined, and evaporated, and the solid residue was recrystallized from ether–hexane, to give pure **11** (23 g, 94%), m.p. 108–110°, $[\alpha]_D^{20}$ +18.4°; R_F 0.7 (*D*); ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 4.62 (s, benzyl-CH_2), 1.48 and 1.3 (CMe_2), and 1.35 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.35; H, 7.70.

Method b. A solution of compound **10** (3 g) was treated with lithium aluminum

hydride (0.7 g) according to method *a*, to yield compound **11** (1.7 g, 89%), identical with that obtained by method *a*.

*3-O-Benzoyl-5-O-benzyl-6-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose* (**12**). — To a stirred solution of compound **11** (20 g) in pyridine (60 mL) was added benzoyl chloride (10 mL) dropwise, below +10°. The mixture was kept for 3 h at room temperature, and then poured into ice–water (600 mL). The product was extracted with chloroform, to give, after the usual processing, evaporation, and recrystallization of the residue from ethanol, pure **12** (24.9 g, 92%), m.p. 91–93°, $[\alpha]_D^{20}$ −23.6°: R_F 0.85 (*F*); ^{1}H-n.m.r. data: δ 6.0 (d, $J_{1,2}$ 4 Hz, H-1), 4.72 (s, benzyl-CH_2), 1.55 and 1.32 (CMe_2), and 1.16 (d, $J_{5,6}$ 6 Hz. H-6).

Anal. Calc. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.10; H, 6.72.

*Methyl 3-O-benzoyl-5-O-benzyl-6-deoxy-α-*L*-idofuranoside* (**13**) *and its β anomer* (**14**). — A solution of the isopropylidene derivative **12** (22 g) in 0.35M methanolic hydrochloric acid (440 mL) was kept for 16 h at room temperature. The solution was then made neutral with solid sodium hydrogencarbonate, the salts formed were filtered off, and the filtrate was evaporated. The residue was dissolved in chloroform, the solution washed with water, dried, and evaporated, and the residue obtained was separated by column chromatography, using solvent *F* for elution. The fraction having R_F 0.4 gave, on evaporation and recrystallization from ether–light petroleum, the pure *β* anomer **14** (3.5 g, 17%), m.p. 80–82°, $[\alpha]_D^{20}$ +144°; ^{1}H-n.m.r. data: δ 4.95 (d, $J_{1,2}$ 5 Hz, H-1), 4.45 (s, benzyl-CH_2), 3.4 (OMe), and 1.15 (d, $J_{5,6}$ 6 Hz. H-6).

Evaporation of the fractions having R_F 0.3 gave the *α* anomer **13** as a colorless syrup (10 g, 48.5%), $[\alpha]_D^{20}$ −17°; ^{1}H-n.m.r. data: δ 4.96 (s, H-1), 4.75 (s, benzyl-CH_2), 3.42 (OMe), and 1.22 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found for **13**: C, 67.51; H, 6.85. Found for **14**: C, 67.80; H, 6.58.

*Methyl 3-O-benzoyl-5-O-benzyl-6-deoxy-2-O-*p*-tolylsulfonyl-α-*L*-idofuranoside* (**15**). — To a solution of the *α* anomer **13** (7.3 g) in pyridine (40 mL) was added tosyl chloride (5 g), and the solution was kept for 24 h at room temperature. Thereafter, it was heated on a steam bath for 6 h. The solution was cooled, and poured onto ice, to give, after the usual processing, evaporation, and recrystallization of the solid residue from ethanol–water (or methanol), pure **15** (6.2 g, 56.5%), m.p. 95–97°, $[\alpha]_D^{20}$ +29.7°; R_F 0.80 (*F*); ^{1}H-n.m.r. data: δ 5.03 (s, H-1), 3.38 (OMe), 2.40 (tosyl-Me), and 1.14 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{28}H_{30}O_8S$: C, 63.86; H, 5.74; S, 6.09. Found: C, 63.55; H, 5.85; S, 5.92.

*Methyl 2,3-anhydro-5-O-benzyl-α-*L*-gulofuranoside* (**16**). — *Method a.* To a vigorously stirred solution of compound **15** (15.4 g) in chloroform (100 mL) was added 4.65M methanolic sodium methoxide (8 mL) below 5°. The mixture was stirred at this temperature for 30 min, and then washed with water, dried, and evaporated. The residue was freed of accompanying methyl benzoate by column chromatography, using solvent *F* for elution. On evaporation, the fraction having R_F 0.4 gave **16** as a

colorless syrup (6.65 g, 97%), $[\alpha]_D^{20}$ −54.3°; ^{1}H-n.m.r. data: δ 4.96 (s, H-1), 4.67 (s, benzyl-CH_2), 3.47 (OMe), and 1.27 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.03; H, 6.95.

Method b. To a stirred solution of epoxide **31** (4 g) in *N,N*-dimethylformamide (100 mL) were simultaneously added benzyl chloride (7 mL) and powdered potassium hydroxide (20 g) in small portions during 30 min at 25–30°. The mixture was stirred for 1 h at this temperature, and then filtered, and the filtrate evaporated. The residue was dissolved in chloroform, and the solution was washed with water, dried, and evaporated. After column chromatography (solvent *E*), the residue gave pure **16** (4 g, 64%), identical with that obtained by method *a*.

*Methyl 5-O-benzyl-2,6-dideoxy-α-*L-xylo-*hexofuranoside* (**17**). — To a stirred solution of epoxide **16** (6.5 g) in dry ether (250 mL) was added lithium aluminum hydride (3 g) at −20°, and stirring was continued for 30 min at −10°. Thereafter, the temperature was raised to 0°, and, after 30 min, the mixture was processed as described for compound **4**. Evaporation of the filtrate gave **17** as a colorless syrup (6.4 g, 98%), $[\alpha]_D^{20}$ −47°; R_F 0.5 (*E*): ^{1}H-n.m.r. data: δ 5.07 (dd, $J_{1,2}$ 5, $J_{1,2'}$ 2 Hz, H-1), 4.7 (s, benzyl-CH_2), 3.31 (OMe), and 1.25 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.52; H, 7.63.

*Methyl 5-O-benzyl-2,6-dideoxy-3-O-(methylsulfonyl)-α-*L-xylo-*hexofuranoside* (**18**). — A solution of compound **17** (12.4 g) in pyridine (40 mL) was treated with mesyl chloride (6 mL) below +10°. The mixture was kept for 4 h at room temperature, to give, after the usual processing, evaporation, and recrystallization of the residue from ether–light petroleum, pure **18** (12.6 g, 77.5%), m.p. 69–71°, $[\alpha]_D^{20}$ −87.2°; R_F 0.4 (*E*); ^{1}H-n.m.r. data: δ 5.1 (dd, $J_{1,2}$ 5, $J_{1,2'}$ 2 Hz, H-1), 4.70 (s, benzyl-CH_2), 3.38 (OMe), 2.97 (mesyl-Me), and 1.26 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; S, 9.71. Found: C, 54.59; H, 6.80; S, 9.65.

*Methyl 3-azido-5-O-benzyl-2,3,6-trideoxy-α-*L-lyxo-*hexofuranoside* (**20**). — To a stirred solution of mesylate **18** (12.6 g) in *N,N*-dimethylformamide (150 mL) was added sodium azide (4 g), and the mixture was heated for 30 min at 120°. Thereafter, it was evaporated, the residue obtained was dissolved in chloroform, and the solution was washed with water, dried, and evaporated, to give pure **20** as a pale-yellow syrup (9.8 g, 93%), $[\alpha]_D^{20}$ −45.4°; R_F 0.85 (*F*); ^{1}H-n.m.r. data: δ 4.98 (dd, $J_{1,2}$ 5, $J_{1,2'}$ 2 Hz, H-1), 4.61 (s, benzyl-CH_2), 3.29 (OMe), and 1.24 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.41; H, 6.75; N, 14.97.

*Methyl 3-acetamido-5-O-benzyl-2,3,6-trideoxy-α-*L-lyxo-*hexofuranoside* (**22**). — A solution of azide **20** (2.5 g) in ethanol (50 mL) was hydrogenated at room temperature in the presence of 10% Pd–C catalyst (1 g) for 1 h. According to t.l.c. (*I*), the starting material (R_F 0.95) was converted into the amine **21** (R_F 0.5). The suspension was filtered, the filtrate was evaporated, the residue was dissolved in pyridine (8 mL), and acetic anhydride (2 mL) was added. The mixture was stirred for 30 min at room temperature, to give, after the usual processing, and evaporation of the

chloroform solution, crude **22**, which was re-crystallized from ether (2 g, 76%), m.p. 115–117°, $[\alpha]_D^{20}$ −57°; R_F 0.5 (*A*) and 0.85 (*H*); ^{1}H-n.m.r. data: δ 4.95 (dd, $J_{1,2}$ 5, $J_{1,2'}$ 2 Hz, H-1), 4.62 (s, benzyl-CH_2), 3.27 (OMe), 1.88 (s, *N*-acetyl-Me), and 1.2 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.76. Found: C, 65.45; H, 7.93; N, 4.62.

*Methyl 3-acetamido-5-O-acetyl-2,3,6-trideoxy-α-*L-lyxo-*hexofuranoside* (**23**). — A solution of azide **20** (2.5 g) in ethanol (50 mL) was hydrogenated in the presence of 10% Pd–C catalyst (3 g) for 4 days at room temperature. Thereafter, the catalyst was filtered off, and the filtrate was evaporated. The residue was dissolved in pyridine (10 mL), and acetic anhydride (2.5 mL) was added. The mixture was kept overnight at room temperature, and evaporated. The solid residue was recrystallized from ether, to give pure **23** (1.17 g, 53%), m.p. 123–125°, $[\alpha]_D^{20}$ −106°; R_F 0.45 (*H*); ^{1}H-n.m.r. data: δ 4.95 (d, $J_{1,2}$ 5 Hz, H-1), 3.25 (OMe), 2.05 and 1.95 (*N*- and *O*-acetyl-Me), and 1.2 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found: C, 53.73; H, 7.95; N, 5.65.

*3-Amino-2,3,6-trideoxy-*L-lyxo-*hexose* (*daunosamine*) *hydrochloride* (**24**). — Azide **20** (2.4 g) was hydrogenated as described for **23**. The suspension was filtered, the filtrate evaporated, the residue dissolved in water (15 mL), and the solution acidified with M hydrochloric acid to pH 1. The solution was then heated on a steam bath for 1.5 h, cooled, and evaporated, and the solid residue was filtered with the aid of ethanol (giving 0.8 g). The filtrate was evaporated, and the residue again filtered with the aid of ethanol, to yield a second crop of **24** (0.4 g). Overall yield 1.2 g (75%), m.p. 168° (dec.), $[\alpha]_D^{20}$ −56° (*c* 1, water); lit.[4] m.p. 168–170° (dec.), $[\alpha]_D^{23}$ −65.4° (equil.; *c* 1.3, water).

*Methyl 3,5,6-tri-O-benzoyl-2-O-*p*-tolylsulfonyl-β-*D*-glucofuranoside* (**26**). — To a solution of tribenzoate[6] **25** (220 g) in chloroform (600 mL) was added 1.2M methanolic hydrochloric acid (3.2 L). The solution was kept for 1.5 h at 45° cooled to room temperature, and made neutral by addition of solid sodium hydrogencarbonate. The precipitated salts were filtered off, the filtrate was evaporated, and the residue was dissolved in chloroform, and the solution washed with water, dried, and evaporated. The residue was dissolved in pyridine (500 mL), and tosyl chloride (120 g) was added. The solution was kept for three days at room temperature, and was then poured onto ice–water (4 L). The precipitate was filtered off, washed with water, and dried. The crude material so obtained was (according to n.m.r. data) a 2:3 mixture of the α and β anomers (R_F 0.65 and 0.75). This material was recrystallized first from ethanol (2.5 L), and then from a 2-fold, thereafter from a 2.5-fold, and, finally, from a 3-fold volume of ethyl acetate, to give pure β anomer **26** (109 g, 41%), m.p. 143–145°, $[\alpha]_D^{20}$ −105.4°; R_F 0.75 (*G*); ^{1}H-n.m.r. data: δ 5.04 (s, H-1), 3.45 (OMe), and 2.4 (tosyl-Me); lit.[12] m.p. 125–127°, $[\alpha]_D^{20}$ −61.9° (*c* 4.5, chloroform).

Anal. Calc. for $C_{35}H_{32}O_{11}S$: C, 63.62; H, 4.88; S, 4.85. Found: C, 63.75; H, 4.95; S, 4.68.

Methyl 2,3-anhydro-β-D-mannofuranoside (**27**). — To a solution of tosylate **26** (64.5 g) in chloroform (250 mL) was added 4.4M methanolic sodium methoxide (30 mL). The slurry formed was stirred for 15 min at room temperature, and then it was made neutral with solid carbon dioxide, and the solid material was filtered off. The filtrate was extracted with water (3 × 50 mL), and the aqueous extracts were combined, and evaporated. The residue so obtained, containing traces of methyl benzoate and sodium tosylate, was pure enough for the next step, but could be purified by column chromatography, using solvent *H*. Evaporation of the fractions having R_F 0.35 gave pure **27** as a colorless syrup (16 g, 91%), $[\alpha]_D^{20}$ −90°; ^{1}H-n.m.r. data: δ 4.92 (s, H-1) and 3.4 (OMe).

Anal. Calc. for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.55; H, 6.98.

Methyl 2,3-anhydro-6-O-benzoyl-β-D-mannofuranoside (**28**). — To a stirred solution of epoxide **27** (63.5 g) in pyridine (250 mL) was added benzoyl chloride (58 mL) dropwise during 30 min at −10°. The mixture was stirred for 30 min at room temperature, and was then processed in the usual way, to give, after evaporation of the chloroform solution and recrystallization of the residue from ether, pure **28** (47 g). A second crop (13.5 g) was obtained from the mother liquor, giving an overall yield of 60.5 g (60%), m.p. 86–88°, $[\alpha]_D^{20}$ −50°; R_F 0.8 (*A*), 0.5 (*F*).

Anal. Calc. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.73; H, 5.82.

The mother liquor, containing, besides **28**, the corresponding 5,6-dibenzoate (R_F 0.8, *E*), was evaporated, and the residue was dissolved in methanol, and the solution treated with methanolic sodium methoxide, to give, after the usual processing, the (debenzoylated) starting-material **27** (17.7 g, 28%).

Methyl 2,3-anhydro-6-O-benzoyl-5-O-p-tolylsulfonyl-β-D-mannofuranoside (**29**). — To a solution of 6-benzoate **28** (51 g) in pyridine (150 mL) was added tosyl chloride (45 g), and the mixture was kept for two days at room temperature. Thereafter, it was poured into water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol, to give **29** (66.9 g, 85%), m.p. 98–100°, $[\alpha]_D^{20}$ −40°; R_F 0.3 (*F*); ^{1}H-n.m.r. data: δ 4.93 (s, H-1), 3.45 (OMe), and 2.28 (tosyl-Me).

Anal. Calc. for $C_{21}H_{22}O_8S$: C, 58.05; H, 5.10; S, 7.38. Found: C, 58.15; H, 5.17; S, 7.06.

Methyl 2,3:5,6-dianhydro-α-L-gulofuranoside (**30**). — To a vigorously stirred solution of tosylate **29** (66.5 g) in chloroform (500 mL) was added 5M methanolic sodium methoxide (50 mL) at 30°. The mixture was stirred for a further 30 min at 30–32°, and then washed with water. Evaporation of the dried solution gave crude diepoxide **30**, which was freed of methyl benzoate by column chromatography, using solvent *D* for elution. Evaporation of the fractions having R_F 0.4 gave pure **30** as a colorless syrup (17.5 g, 86%), $[\alpha]_D^{20}$ −123°; R_F 0.75 (*C*); ^{1}H-n.m.r. data: δ 5.0 (s, H-1) and 3.52 (OMe).

Anal. Calc. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.02; H, 6.52.

Methyl 2,3-anhydro-6-deoxy-α-L-gulofuranoside (**31**). — To a stirred solution of diepoxide **30** (3 g) in water (50 mL) was added sodium borohydride (2 g) at room

temperature, without cooling. Further borohydride (3 × 1 g) was added at 1-h intervals, the temperature of the mixture rising to 40°. The solution was then extracted with chloroform (3 × 50 mL), and the extracts were combined, dried, and evaporated, to give **31** as a colorless syrup (2 g, 65%), $[\alpha]_D^{20}$ −76°; R_F 0.35 (*C*); ^{1}H-n.m.r. data: δ 4.97 (s, H-1), 3.45 (OMe), and 1.26 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.12: H, 7.28.

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