A chiral approach to 2-deoxystreptamine[1]

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A new synthesis of 2-deoxystreptamine (**21**), a component of numerous antibiotics, was developed. Starting from D-mannose, it proceeds through chiral intermediates and is designed to furnish starting points for the preparation of stereospecifically modified derivatives of the *meso* compound **21**. 1,2-Dideoxy-1-nitro-D-*manno*-heptitol (**2**), obtainable from mannose by the nitromethane method, was protected as the 4,5:6,7-di-*O*-isopropylidene derivative **4**, which was mesylated or triflated in position 3. From the sulfonic esters (**5** and **6**) two different routes involving displacement by azide, partial deacetonation at O-6,7, periodate oxidation, and cyclization of the resulting nitroaldohexose derivatives converged to give 1L-(1,3/2,4,6)-6-azido-1,2-*O*-isopropylidene-4-nitro-1,2,3-cyclohexanetriol (**19**) as a key intermediate. Catalytic hydrogenation then afforded optically active 4,5-*O*-isopropylidene-2-deoxystreptamine (**23**), isolated as its *N,N'*-diacetyl derivative **24**. Deacetonation of **19** gave the azidonitrotriol **15**, which was reduced to **21**. The potential utility of the chiral intermediates for stereospecific syntheses of deoxystreptamine-containing aminoglycosides is discussed.

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On a mis au point une nouvelle synthèse de la désoxy-2 streptamine (**21**), un composant de plusieurs antibiotiques. Utilisant le D-mannose comme produit de départ, cette synthèse procède par le biais d'intermédiaires chiraux et il est prévu qu'elle pourra fournir des points de départ pour la préparation de dérivés modifiés d'une façon stéréospécifique du composé *méso* **21**. Le didésoxy-1,2 nitro-1 D-*manno*-heptitol (**2**), que l'on peut obtenir à partir du mannose en faisant appel à la méthode au nitrométhane, a été protégé sous la forme du dérivé di-*O*-isopropylidène-4,5:6,7 (**4**) et l'on a ensuite transformé en dérivé mésylé ou triflé en position 3. À partir des esters sulfoniques (**5** et **6**), deux voies différentes impliquant une substitution par un ion azoture, une déacétonation partielle en O-6,7, une oxydation periodique et une cyclisation des dérivés nitroaldohexoses qui en résultent convergent pour donner l'azido-6 *O*-isopropylidène-1,2 nitro-4 cyclohexanetriol-1,2,3 1L(1,3/2,4,6) (**19**), un intermédiaire clé. L'hydrogénation catalytique fournit ensuite la *O*-isopropylidène-4,5 désoxy-2 streptamine optiquement active (**23**) qui a été isolée sous la forme de son dérivé *N,N'*-diacétylé (**24**). La déacétonation du composé **19** fournit l'azidonitrotriol **15** qui est réduit en **21**. On discute de l'utilité potentielle d'intermédiaires chiraux dans les synthèses stéréospécifiques d'aminoglycosides contenant la désoxystreptamine.

[Traduit par la revue]

Introduction

2-Deoxystreptamine (**21**) is a pivotal component of numerous important aminoglycoside antibiotics, several of which are in clinical use (1). Early syntheses in the laboratories of Nakajima *et al.* (2) and Suami *et al.* (3) embodied elegant concepts in certain stages but, being predicated on the use of achiral starting materials such as "benzeneglycols" (cyclohexadienediols) and *myo*-inositol, they did not lend themselves to, nor were they intended for, the synthesis of stereospecifically substituted, chiral derivatives of **21**. The same was true for an approach departing from 4,6-dinitropyrogallol (4) and for the more recent and convenient, high-yielding synthesis from 4,5-epoxycyclohexene reported by Prinzbach *et al.* (5). By contast, any approach based on the conversion of a sugar into an aminocyclitol inherently offers the possibility of generating asymmetrically structured derivatives. This is a desirable feature, for although **21** itself is achiral, as a constituent of antibiotics it invariably bears a substituent (i.e., a glycosyl residue) at one or other of its chemically equivalent but enantiotopic positions 4 and 6, or unequal substituents at both. Similarly, either one of the amino groups may occur alkylated, rendering the compound chiral. For example, the *N*-methyl-2-deoxystreptamine (hyosamine) present in destomycin A is levorotatory, whereas hygromycin B contains the dextrorotatory enantiomer (1). With their classical streptamine synthesis, Wolfrom *et al.* (6) have paved the way from *N*-acetyl-D-glucosamine into the diaminocyclitol series, utilizing the nitroalkane cyclization methodology (7), and by further elaboration of this approach Suami and Rinehart and co-workers (8) did in fact avail themselves of the chirality present in this amino sugar to synthesize optically active inosadiamines including (−)-hyosamine, the 1*S*-amino-3*R*-methylamino analog of **21**. Géro and co-workers (9) used carbohydrate-related D-(−)-quinic acid as an alternative resource for chiral aminocyclitol syntheses.

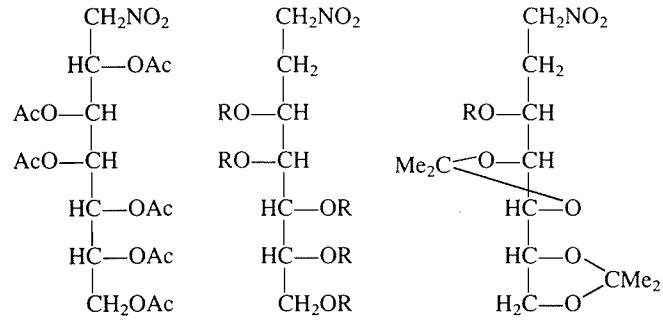
We report here a chiral synthesis of **21**, which departs from commercial D-mannose and proceeds through a number of intermediates that are potentially suitable for the stereospecific preparation of both *O*- and *N*-substituted derivatives.

Results and discussion

Known 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol hexaacetate (**1**) was prepared from D-mannose by the nitromethane method (10). Although **1** can be dehydroacetoxylated (with sodium bicarbonate), and the resulting 1-nitroalkene then hydrogenated to give 1,2-dideoxy-1-nitro-D-*manno*-heptitol pentaacetate (**2**) (10, 11), we chose to perform this transformation in one step by reductive elimination with sodium borohydride in acetonitrile solution. Subsequent *O*-deacetylation (Zemplén) gave the pentaol **3**, which was acetonated to furnish

[1]This project was initiated by I.A. during a postdoctoral sojourn (1978), and preliminary results were communicated at the 62nd Canadian Chemical Conference, Vancouver, June 1979 (Abstract OR-91). Completion of the work was reported by H.H.B. and B.R. at the 191st ACS National Meeting, New York City, April 1986 (Abstract CARB-45).

[2]Revision received February 9, 1987.



1 **2** R = Ac **4** R = H
3 R = H **5** R = SO_2Me
6 R = SO_2CF_3

the 4,5;6,7-di-*O*-isopropylidene derivative **4**.[3] Mesylation and triflation of **4** afforded, respectively, the sulfonates **5** and **6**. In the 300-MHz ^1H nmr spectrum of **5**, the proton signal that occurred at lowest field and was, therefore, attributable to the hydrogen atom at the sulfonylated position was determined to be coupled to the two methylene protons H-2 and -2′, which resonated at high field, both on account of the mutual splitting patterns and by homonuclear shift correlation. This established C-3 as the site of sulfonylation. Overall yields of **5** and **6** from D-mannose were in the range of 20–25%. Two alternative routes toward the synthetic goal were elaborated from here, differing in the order by which the carbocycle was generated and the second nitrogen function introduced.

For route A (see Scheme 1), the mesylate **5** was selectively deacetonated at the 6,7 position by trifluoroacetic acid in toluene, and the resulting 4,5-mono-*O*-isopropylidene derivative **7** was cleaved with sodium metaperiodate to afford 5,6-dideoxy-2,3-*O*-isopropylidene-4-*O*-methylsulfonyl-6-nitro-*al*-D-*arabino*-hexose (**8**). Nitroalkane cyclization of this sugar, effected by sodium methoxide in methanolic solution, led to a mixture of epimeric cyclitols that could be isolated crystalline upon chromatographic separation. The structures **9** (for the less-mobile, higher-melting, and slightly preponderant epimer) and **10** (for the other component) followed from clearly resolved and readily interpretable ^1H nmr spectra. At first glance, one might have expected the axial-OH epimer **10** to exceed the equatorial-OH epimer **9** by approximately 0.9 kcal/mol in conformational energy, and since the reaction conditions employed for the cyclization probably favored thermodynamic control,[4] one should have anticipated an equilibrium of 85:15 (at 25°C) in favor of **9**, the desired epimer. Such a selectivity was not obtained, and inspection of Dreiding models suggests a possible explanation. It can be seen that, because of the considerable distortion imposed, in both compounds, on the cyclohexane chair by the *trans*-fused dioxolane ring, the axial OH group in **10** recedes in an outward direction from the opposing, coaxial hydrogen atoms. This may diminish nonbonding interaction and, consequently, the energy difference to the equatorially substituted counterpart **9**. Fortunately, it proved possible to isolate **9** directly from the mixture by fractional crystallization, thanks to its lower solubility, and, by doing so under epimerizing conditions (in the presence of a catalytic amount of base), part of **10** could be converted into **9**, which was thus obtained in 70% yield without resort to chromatography.

The *trans*-fused cyclic ketal groups in **9** and **10** were very acid labile, as was to be expected. When, in an early experiment, the alkaline mixture from the cyclization was processed with a sulfonic acid-type resin for deionization, loss of acetone occurred. Similarly, partial deacetonation was observed after prolonged exposure of the crystalline compounds to the laboratory atmosphere. Although not required for the present synthesis, a sample of **10** was deliberately methanolyzed under acid catalysis, and the highly crystalline triol **11** so obtained was characterized further through its triacetate **12**. Similar deacetonation of **9** gave the (amorphous) triol **13**, characterized likewise as its crystalline triacetate **14**. Unambiguous ^1H nmr data obtained for **12** and **14** reaffirmed the structures of the epimers.

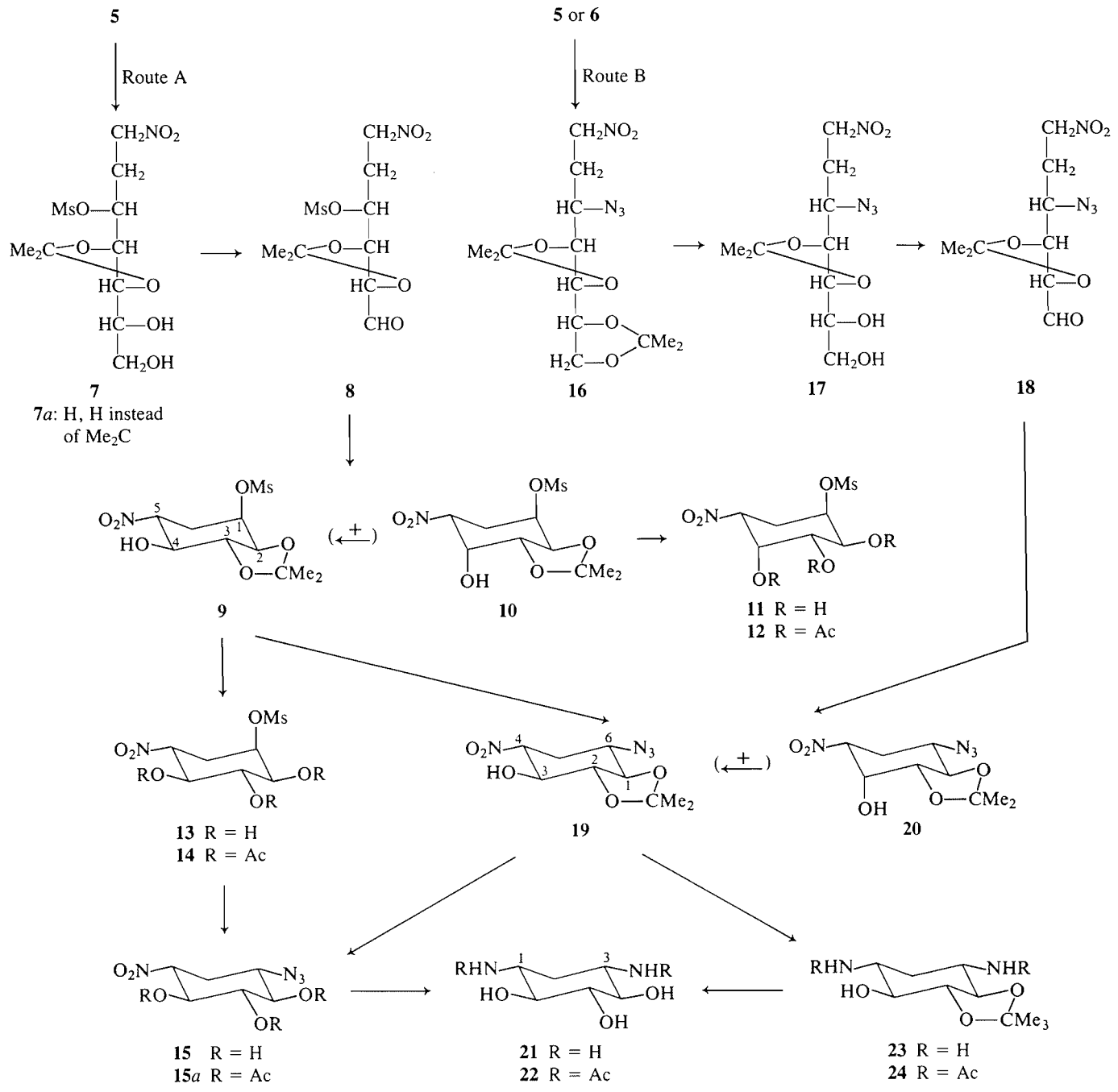
With the nitrocyclitol **9** and its progeny **13** in hand, we proceeded to introduce the second nitrogen function. Both mesylates underwent displacement by azide ion, **13** with lithium azide in *N*,*N*-dimethylformamide (3 h at 100°C), and **9** also in this fashion or, more cleanly, under phase transfer conditions in benzene–water (3 days at 80°C) that entailed less decomposition. Unfortunately, the vicinal hydroxy-nitro groupings in **9** and **13** lost their stereochemical integrity in these displacement reactions; partial epimerization occurred at the carbinol positions, which vitiated the epimer separation previously performed. Thus, **13** gave a mixture from which the desired azidonitrotriol **15** was isolated crystalline by chromatography. This product was identical with **15** prepared from **19** (see later on). A second product, although not isolated pure, was judged to be the 3-epimer since it showed a similar infrared spectrum and was partly converted into **15** by base-catalyzed epimerization. Similarly, **9** furnished a mixture of the corresponding 1,2-*O*-isopropylidene derivatives **19** and[5] **20**. The products **15**, **19**, and **20** constitute a junction with the synthetic route B that is now to be delineated, and it will be seen in that context that separation of **19** and **20**, although somewhat laborious, is not a serious problem.

For route B, the mesylate **5** was first converted into the 3-azido-3-deoxy-D-*gluco*-heptitol derivative **16**. As reported by us elsewhere (12), treatment of **5** with tetrabutylammonium azide in boiling toluene had provided **16**, but only in 46% yield owing to interference of a competing reaction. This side reaction, which led to nitrocyclopropane derivatives, was of much interest in its own right (12); however, for the present purpose it was desirable to suppress it as far as possible to improve the yield of **16**. After considerable experimentation, displacement under phase transfer conditions using sodium azide and tetrabutylammonium hydrogen sulfate in benzene–water at 56°C was found to give a 76% yield and to minimize the

[3]Care should be exercised in the deionization of the alkaline reaction mixture obtained from **2**, which contains the nitronate of **3**, to avoid Nef reaction (10). In one large-scale experiment, in which the precaution of cooling was not observed and the crude product acetonated directly, the yield of **4** was diminished and a by-product, isolated in 7% yield, arose, which on spectroscopic evidence was judged to be methyl 2-deoxy-3,4:6,7-di-*O*-isopropylidene-α,β-D-*manno*-heptopyranoside.

[4]Prolongation of the reaction time did not seem to change the product ratio significantly.

[5]In the hope of forestalling such epimerization, we examined a mesylate displacement by azide in the 3-(trimethylsilyl) ether that was readily prepared from **9**. The attempt failed completely, giving a mixture of unidentified, chromatographically slow-moving products and no trace of the expected, fast-moving trimethylsilyl ether of **19**. The latter had been prepared for comparison from pure **19** (see route B), and when subjected to the same reaction conditions it, too, suffered similar degradation. A mixture of **19** and **20** can probably be prepared more rationally from crude **9** + **10** without their prior separation.



SCHEME 1

proportions of by-products, but the conversion was very slow, requiring 6 days for completion. Its performance at 80 or 100°C led to larger proportions of the unwanted products. A great improvement resulted from use of the triflate **6**, which, under similar phase transfer conditions but applied at room temperature for a few hours only, gave **16** in yields of 84% or better, and no cyclopropano by-products were detected. Compound **16** was then selectively 6,7-deacetonated with trifluoroacetic acid in toluene; a certain amount of full deacetonation occurred in the process, but the resulting tetraol could be reacetonated for recycling, and the 4,5-mono-*O*-isopropylidene derivative **17** was thus obtained in 88% yield. Subsequent periodate oxidation produced the aldehydo sugar **18** as an unstable intermediate that was not characterized but immediately subjected to methoxide-catalyzed ring closure, which furnished a mixture of **19** and its epimer **20**, similar in composition to that obtained from **9** by route A. The more stable isomer **19** was isolated from the mixture in 69% yield by direct crystallization, performed under conditions that allowed part of **20** to epimerize. The well-resolved ^{1}H nmr spectrum of **19** unambiguously indicated the all-equatorial substituent orientation in the compound. The epimer **20** that remained in the mother liquor was not isolated pure on a preparative scale, but a small sample was procured by column chromatography for nmr analysis, which ascertained its structure and configuration. Deacetonation of **19** quantitatively afforded crystalline **15**.

Hydrogenation over Adams catalyst converted **15** into 2-deoxystreptamine (**21**), and **19** into the latter's optically active, 4,5-*O*-isopropylidene derivative **23** that was isolated as a crystalline *N*,*N*′-diacetyl compound (**24**), which had previously

been obtained (13) in racemic form.[6] *N*-Acetylation of **21** and deacetonation of **24** yielded identical *N,N'*-diacetyl-2-deoxystreptamine (**22**).

Conclusion

With the preparation of 2-deoxystreptamine the ultimate success of our synthetic design has been demonstrated. It is to be stressed, however, that chemical synthesis of such chiral intermediates as **15**, **19**, **23**, and **24** was the primary goal of the enterprise.[7] These intermediates or conventionally prepared analogs such as the *N,N'*-diethoxycarbonyl or -dibenzyloxycarbonyl derivatives of **23**, which are known in racemic form only (16), are expected to open new avenues to stereospecific, total syntheses of deoxystreptamine-containing aminoglycosides where glycosylations specifically at O-4 or O-6 are required. Syntheses in that area have previously been accomplished (1) by use of racemic synthons of type **24**, but the necessary separation of diastereomers was generally troublesome and yields were often modest, as may be gleaned from several examples (16–18). Furthermore, it is to be expected that the unequal nitrogen functions present in **15** or **19** can be reduced to the amine stage in a stepwise fashion, which should allow mono-*N*-alkylation or -acylation to be effected stereospecifically. Such a protocol should prove valuable for synthetic designs in the area of destomycin A, hygromycin B, and the butirosins. Studies to exploit this chemistry along the lines indicated are in progress in our laboratory.

Experimental

Melting points were determined in capillaries with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at ~25°C in a Perkin–Elmer 241 polarimeter. Infrared (ir) data were recorded with a Perkin–Elmer 783 instrument from Nujol mulls for solid samples, and from neat films for syrups. Proton magnetic resonance (^{1}H nmr) spectra were taken at 300 MHz with a Varian XL 300 spectrometer from solutions in deuteriochloroform ($CHCl_3$ lock signal at δ 7.23), unless noted otherwise. Signal patterns are given as s = singlet, d = doublet, q = quartet, t = triplet, quin = quintet, sx = sextet, or m = multiplet, occasionally modified by prefixes b = broad, c = complex, or n = narrow. The ^{13}C nmr data were recorded with the same instrument, at 75.43 MHz. Column chromatography was performed with silica gel Merck 9385 (particle size, 20–45 μm), and analytical thin-layer chromatography (tlc) with precoated plates Si250F of J. T. Baker Chemical Co. The following solvent combinations (v/v) were used for chromatography, unless otherwise specified: A, methanol–$CHCl_3$ 1:2; B, the same, but 1:3; C, ether–hexane 1:1; D, EtOAc–hexane 1:1; E, the same, but 1:1.5; F, the same, but 1:2; G, the same, but 1:3; H, the same, but 1:4; and I, the same, but 1:19.

*1,2-Dideoxy-1-nitro-*D*-*manno*-heptitol pentaacetate (**2**)*

Crystalline 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol hexaacetate (**1**) (10) (7.00 g) was dissolved in CH_3CN (70 mL, dried over molecular sieve), and to the chilled (0°C) solution was added $NaBH_4$ (0.56 g) followed by a few drops of ethanol. Gradual replacement of **1** by slightly less-mobile **2** was seen in tlc (Et_2O). The mixture was processed after 1 h by stirring it with Amberlite IR-120(H^+) resin until H_2 evolution ceased, decolorizing the filtrate with activated charcoal, and evaporating it with several sequential additions of methanol. The dry residue was dissolved in 5 mL of warm ethanol from which **2** crystallized on refrigeration. The mother liquor was evaporated, and the residue similarly crystallized from ethanol, to give a second crop of **2**, for a total of 5.241 g (85%), mp 91–93°C (lit. (11) mp 98–99°C); ν_{max}: 1740 (OAc) and 1555 (NO_2) cm^{-1}; no OH band. The product was sufficiently pure for further use, although a trace contaminant was present (tlc).

*1,2-Dideoxy-1-nitro-*D*-*manno*-heptitol (**3**)*

To a chilled (0°C) solution of **2** (14.2 g) in absolute methanol (650 mL) was added solid $NaOCH_3$ (10.34 g), and the mixture was stirred for 3 h at 0°C, after which tlc (solvent A) indicated complete replacement of **2** (R_f 0.95) by product ($R_f \sim 0.6$, with tailing due to the presence of base). The continuously chilled mixture was deionized with Dowex 50-X8(H^+) resin, and the clear, yellowish solution evaporated to dryness *in vacuo*, with portionwise addition of fresh methanol towards the end. The crude, dry product weighed 5.555 g (76%); in several runs performed on a 1–2 g scale, yields of 80–85% were obtained. Crude **3** was usable for the next step. An analytical sample, crystallized and recrystallized from ethanol, showed mp 116–118°C (lit. (11) mp 116–117°C); $[\alpha]_D$ +15° (*c* 3.2, water); ν_{max}: 3300 (bd, OH) and 1550 (NO_2) cm^{-1}; no ester CO band.

*1,2-Dideoxy-4,5;6,7-di-*O*-*isopropylidene-1-nitro-*D*-*manno*-heptitol (**4**)*

To a suspension of **3** (5.612 g) in reagent-grade acetone (280 mL) containing 2,2-dimethoxypropane (15 mL) was added freshly dried, anhydrous $CuSO_4$ (20 g). The mixture was stirred under ice cooling, and when it had reached +4°C, concentrated H_2SO_4 (2.0 mL) was added dropwise. Stirring was then continued at room temperature for 18–20 h. The formation of **4** ($R_f \sim 0.4$) was indicated by tlc (solvent G; R_f 0 for **3**). After neutralization of the mixture by stirring it with solid $NaHCO_3$, the supernatant was filtered through sintered glass with the aid of Celite, and evaporated to give a brownish oil. This was chromatographed on a column (4 × 10 cm) of silica gel, with solvent H as the eluant. The yield of chromatographically homogeneous, oily **4** (dried in high vacuum) was 6.16 g (81%); $[\alpha]_D$ +18° (*c* 1, $CHCl_3$); ν_{max}: 3450 (sharp, OH), 1545 (NO_2), 1430, 1370, 1250–1200, 1150, 1065, and 840 cm^{-1}; δ ($CDCl_3$): 4.56 (cm, 2H, AB part of ABMX system, H-1,1'), 4.19 (octet, H-6), 4.00 and 3.65 (m, 2 and 3H, H-3,4,5,7,7'), 3.75 (~s, exchangeable, OH), 2.48 (dtd, *W* 34 Hz, H-2), and 2.12 (dtd, *W* 36 Hz, H-2'); 1.42, 1.34, 1.335, 1.33 (s, 4 × 3H, $2Me_2C$). *Anal.* calcd. for $C_{13}H_{23}NO_7$ (305.3): C 51.14, H 7.59, N 4.59; found: C 51.21, H 7.65, N 4.40.

In several experiments using **3** of variable purity, the early chromatographic fractions of **4** contained a slightly more mobile by-product (see footnote 3), which was removed by rechromatography with solvent C.

*1,2-Dideoxy-4,5;6,7-di-*O*-*isopropylidene-3-*O*-*methylsulfonyl-1-nitro-*D*-*manno*-heptitol (**5**)*

Methanesulfonyl chloride (8 mL) in dry pyridine (26 mL) was added dropwise to a solution of **4** (6.16 g) in dry pyridine (50 mL), stirred at 0°C. After 1.5 h the reaction was complete (tlc, solvent D). The mixture was stirred for 10 min with some added water, poured onto crushed ice, and extracted with chloroform (2 × 120 mL). The extract was washed twice with $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated with several added portions of toluene. The crude, oily **5** so obtained was chromatographed on silica gel (200 g) with solvent H. The fractions containing the product gave an oil (6.60 g, vacuum dried; 85%) that crystallized partially on storage in a desiccator overnight. Recrystallization from a minimum aount of EtOAc – petroleum ether gave pure **5** (5.874 g, 76%) as large, colorless plates, mp 74–75°C; $[\alpha]_D$ +24.3° (*c* 1.3, $CHCl_3$); ν_{max}($CHCl_3$): 1554 (NO_2), ~1370 (several bands, including NO_2 and OMs), and 1178 (OMs) cm^{-1}; OH band absent; ^{1}H nmr data (assignments confirmed by HOMCOR method), δ: 5.00 (septet, $J_{3,4}$ = 2.7, $J_{2,3}$ = 4.35; $J_{2',3}$ = 8.0 Hz, H-3), 4.58 (cm, 2H, H-1,1'), 4.22 (dd, $J_{3,4}$ = 2.7, $J_{4,5}$ = 7.2 Hz, H-4), 4.15

[6]According to regular organic nomenclature, **24** is 1L-(1,3/2,4,6)-4,6-diacetamido-1,2-*O*-isopropylidene-1,2,3-cyclohexanetriol; its enantiomer would receive the prefix 1D. In terms of the nomenclature (14) usually employed in the field of aminoglycoside antibiotics, **24** is 1,3-di-*N*-acetyl-4,5-*O*-isopropylidene-2-deoxystreptamine, and its enantiomer would be the corresponding 5,6-*O*-isopropylidene derivative.

[7]An analogous chiral compound, the 5,6-*O*-cyclohexylidene derivative of **21**, has been prepared semisynthetically from natural neamine (15).

(dd, $J_{6,7}$ = 6.1, J_{gem} = 8.55 Hz, H-7), 4.03 (dt, $J_{5,6}$ = 8.6, $J_{6,7}$ = 6.1, $J_{6,7'}$ = 5.2 Hz, H-6), 3.93 (dd, J = 5.2 and 8.5 Hz, H-7′), 3.78 (dd, J = 7.2 and 8.55 Hz, H-5), 3.08 (s, 3H, OSO_2Me), 2.45 (cm, 2H, H-2,2′), and 1.40s, 1.36s, 1.31s (6, 3, and 3H, $2Me_2C$). *Anal.* calcd. for $C_{14}H_{25}NO_9S$ (383.4): C 43.85, H 6.57, S 8.36; found: C 43.67, H 6.51, S 8.19.

*1,2-Dideoxy-4,5;6,7-di-*O*-isopropylidene-1-nitro-3-*O*-(trifluoromethylsulfonyl)-*D*-*manno*-heptitol (**6**)*

A solution of trifluoromethanesulfonic anhydride (5.7 mL) in dry CH_2Cl_2 (20 mL) was added dropwise, over a period of 45 min, to a solution of **4** (8.70 g) in dry CH_2Cl_2 (60 mL) and pyridine (10 mL), stirred at 0°C. After an additional 15 min, tlc (solvent: CH_2Cl_2) indicated complete conversion of **4** (R_f 0.15) into **6** (R_f 0.40). The mixture was poured into, and shaken with, ice water; after phase separation, the aqueous phase was extracted once with CH_2Cl_2, and the combined organic phase was washed with 2% H_2SO_4 followed by ice-cold $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated at room temperature to give a syrup which, upon trituration with 5 mL of methanol, afforded a crystalline material. Isolated after short refrigeration, washed with methanol, and dried *in vacuo*, this first crop of **6** (7.385 g, 59%) melted at 77–79°C with decomposition (prior darkening from 68°C); $[\alpha]_D$ +23.9° (*c* 1, $CHCl_3$). Processing of the mother liquor furnished a second crop of crystalline **6** (1.05 g, 8.4%). The mother liquor therefrom, processed as before, left a syrup (~2 g) still rich in **6** (tlc); it could also be used in a subsequent operation (see preparation of **16**).

Compound **6** is rather unstable and tends to decompose rapidly at room temperature. It may be stored for some weeks at −20°C but is best utilized immediately. The ^{1}H nmr data, δ: 5.30 (m, $J_{3,4}$ = 2.3, $J_{2,3}$ ~ 4, $J_{2',3}$ ~ 8 Hz, H-3), 4.56 (cm, 2H, H-1,1′), 4.28 (dd, $J_{3,4}$ = 2.3, $J_{4,5}$ = 7.5 Hz, H-4), 4.17 (dd, $J_{6,7}$ = 6.1, J_{gem} = 8.6 Hz, H-7), 4.03 (~dt, $J_{5,6}$ =8.8 Hz, H-6), 3.92 (dd, $J_{6,7'}$ = 5.2, J_{gem} = 8.6 Hz, H-7′), 3.70 (dd, $J_{4,5}$ = 7.5, $J_{5,6}$ = 8.7 Hz, H-5), 2.57 (cm, 2H, H-2,2′), and 1.42s, 1.39s, 1.37s, 1.32s (4 × 3H, $2Me_2C$).

*1,2-Dideoxy-4,5-*O*-isopropylidene-3-*O*-methylsulfonyl-1-nitro-*D*-manno-heptitol (**7**)*

A solution of **5** (1.24 g) in toluene (9 mL) was cooled to −20°C, and 90% CF_3CO_2H (0.7 mL) was added. Oily **7** began to separate within a few minutes. The mixture was stirred magnetically for 30 min, then made homogeneous by the addition of a small amount of EtOAc, and immediately neutralized by agitation with solid sodium carbonate. The filtered solution was evaporated to give an oil that, according to tlc (solvent D), was a 3:1 mixture of **7** (R_f 0.25) and unreacted **5** (R_f 0.7). Chromatography of the material on a column (25 × 2 cm) of silica gel with solvent D as the eluant produced **5** (0.355 g), and subsequent elution with EtOAc furnished **7**. The recovered **5** was subjected to an identical hydrolysis (but on one-quarter scale), which gave an additional crop of **7** for a combined yield of 1.012 g (92%); $[\alpha]_D$ +9° (*c* 2.3, water), +25° (*c* 0.5, EtOAc); ir data, ν_{max}: 3400 (bd, OH), 1550 (NO_2), 1380–1330, 1250, 1175 (OMs), 1060, 925, 875, and 800 cm^{-1}; ^{1}H nmr ($CDCl_3$), δ: 5.02 (dt, $J_{2,3}$ = 3.4, $J_{3,4}$ = 3.5, $J_{2,3'}$ = 8.4 Hz, H-3), 4.58 (m, 2H, H-1,1′), 4.30 (dd, $J_{3,4}$ = 3.5, $J_{4,5}$ = 7.2 Hz, H-4), 3.9–3.6 (m, 4H, H-5,6,7,7′), 3.09 (s, 3H, CH_3SO_3), 3.02 (bs, 2H, OH), 2.47 (cm, 2H, H-2,2′), 1.40 and 1.37 (s, 3H each, Me_2C). *Anal.* calcd. for $C_{11}H_{21}NO_9S$ (343.4): C 38.47, H 6.16, N 4.08; found: C 38.70, H 5.91, N 3.86.

When a sample of **7** that had been stored at +4°C for 2 months was triturated with EtOAc it failed to dissolve fully, and part of the material crystallized, mp 97–98°C. Recrystallized from hot methanol, the fine needles showed mp 98°C; $[\alpha]_D$ +12° (*c* 1.2, water); ν_{max}: 3540 (sharp) and 3400–3250 (bd, OH), 1540 (NO_2), and multiple sharp bands in the 1200–800 cm^{-1} region. An ^{1}H nmr spectrum (D_2O) indicated retention of the mesyl function but absence of isopropylidene methyl groups. It was concluded that slow deacetonation, perhaps catalyzed by traces of acid left in the sample of **7**, had generated the tetraol **7***a*. *Anal.* calcd. for $C_8H_{17}NO_9S$ (303.3): C 31.68, H 5.65, S 10.58; found: C 31.95, H 5.79, S 10.44.

*5,6-Dideoxy-3,4-*O*-isopropylidene-4-*O*-methylsulfonyl-6-nitro-*al*-*D*-arabino-hexose (**8**)*

Sodium metaperiodate (0.60 g) was dissolved in an ice-cooled solution of **7** (1.012 g) in water (50 mL). The oxidation of **7** to give more mobile **8** (tlc, solvent D) was complete within 15 min. After addition of ethylene glycol (5 drops) the solution was concentrated by evaporation, with several sequential additions of ethanol, whereby solid $NaIO_3$ was deposited. The latter was removed by filtration and washed with ethanol, and the filtrate evaporated to give a colorless syrup. The syrup was taken up in $CHCl_3$ and the filtered solution was washed with a small amount of water, dried ($MgSO_4$), and evaporated. The resulting, chromatographically homogeneous syrup (0.95 g) showed broad ir absorption at 3400 cm^{-1} (presumably due to aldehyde hydrate); other prominent peaks were at 1555 (NO_2), ~1350, 1180, 1170, and 930 cm^{-1}. An ^{1}H nmr spectrum ($CDCl_3$) showed an aldehydic proton signal, δ 9.51, integrating to only 0.3 H. However, an analytical sample dried in high vacuum at 56°C for 18 h gave C,H values in agreement with the free-aldehyde structure **8**. *Anal.* calcd. for $C_{10}H_{17}NO_8S$ (311.3): C 38.58, H 5.50; found: C 38.60, H 5.53.

*1L-(1,2,4/3,5)-2,3-*O*-Isopropylidene-1-O-(methylsulfonyl)-5-nitro-1,2,3,4-cyclohexanetetrol (**9**) and 1L-(1,2/3,4,5)-2,3-*O*-isopropylidene-1-*O*-(methylsulfonyl)-5-nitro-1,2,3,4-cyclohexanetetrol (**10**)*

A solution of aldehyde **8** (2.33 g) in dry methanol (100 mL) containing $NaOCH_3$ (1 g) was allowed to stand at 25°C for 30 min, during which period **8** (R_f ~ 0.2, elongated spot) was consumed and two products having R_f 0.50 and 0.55 were formed, with the less mobile one (**9**) predominating slightly over the other (**10**) (tlc, solvent D). The solution was neutralized by stirring it with a *carboxylic acid*-type cation exchange resin (Amberlite IRC-50, H^+, or equivalent), which after filtration was washed exhaustively with methanol. The filtrate was evaporated and the resulting syrup dried in a high vacuum to give a mixture of **9** and **10** as a fluffy foam (2.193 g, 94%). Although for the preparation of **9** this mixture was processed as described in a subsequent paragraph, a mixture obtained in a similar experiment was partially separated by column chromatography on silica gel with solvents G and F, to characterize **9** and **10**. Pure and almost-pure fractions of either epimer were obtained.

The fractions of **9** (R_f 0.50) gave crystalline product, mp 147–148°C (dec.), after recrystallization from 99% ethanol; $[\alpha]_D$ −20.7° (*c* 1.4, $CHCl_3$); δ ($CDCl_3$): 5.25 (nm, H-1), 4.69 (ddd, $J_{5,6e}$ = 5, $J_{4,5}$ = 9.5, $J_{5,6a}$ = 12.5 Hz, H-5), 4.42 (td, $J_{4,OH}$ = 4, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.88 (t, $J_{2,3}$ = 10, $J_{3,4}$ = 9.5 Hz, H-3), 3.62 (dd, $J_{1,2}$ = 2, $J_{2,3}$ = 10 Hz, H-2), 3.09 (s, 3H, CH_3SO_3), 2.78 (d, J = 4 Hz, OH-4, superposed on ddd, which is clearly revealed after D_2O exchange, $J_{1,6e}$ = 3, $J_{5,6e}$ = 5, $J_{6a,6e}$ = 14.5 Hz, H-6e), 2.25 (quin, $J_{1,6a}$ = 3, $J_{5,6a}$ = 12.5, $J_{6a,6e}$ = 14.5 Hz, H-6a), 1.46 and 1.445 (s, 3H each, Me_2C). *Anal.* calcd. for $C_{10}H_{17}NO_8S$ (311.3): C 38.58, H 5.50, S 10.30; found: C 38.34, H 5.65, S 10.29.

Fractions of pure **10** (R_f 0.55) gave crystals from CH_2Cl_2–hexane, mp 130°C, and 130–131°C after recrystallization; $[\alpha]_D$ +6° (*c* 0.8, $CHCl_3$); δ ($CDCl_3$): 5.26 (nm, H-1), 5.09 (nm, H-4), 4.69 (ddd, $J_{4,5}$ = 2.5, $J_{5,6e}$ = 5.5, $J_{5,6a}$ = 12 Hz, H-5), 4.11 (dd, $J_{3,4}$ = 2.7, $J_{2,3}$ = 9.9 Hz, H-3), 3.86 (dd, $J_{1,2}$ = 2.2, $J_{2,3}$ = 9.8 Hz, H-2), 3.07 (s, 3H, CH_3SO_3), 2.65 (cm, 2H, H-6a,6e), 2.43 (d, $J_{4,OH}$ = 3 Hz, OH), 1.44 and 1.425 (s, 3H each, Me_2C). *Anal.* calcd. as for **9**; found: C 38.42, H 5.43, S 10.37.

Preparative isolation of **9** in good yield was achieved by fractional crystallization, coupled with base-catalyzed epimerization of the epimer **10**. Thus, the aforementioned amorphous mixture of **9** and **10** (2.19 g) was dissolved in 99% ethanol (2.5 mL), and seeded with **9**. Crystallization was allowed to proceed, undisturbed, at room temperature for 2 h. The mixture was diluted with ethanol (15 mL), the supernatant decanted, and the first crop of **9** (209 mg) washed with ethanol and collected. The combined supernatant and washings were evaporated with addition of CH_2Cl_2 to give a syrupy residue, which was dissolved in 2.5 mL of ethanol containing 10 mg of $NaOCH_3$. Seeding with **9** and storage of the mixture at room temperature

overnight produced a second crop of **9** (1.147 g), isolated after dilution with ethanol as described before. Three repetitions of the procedure, using progressively smaller volumes of solvent, gave additional crops (191, 125, and 43 mg), for a total of 1.715 g of **9** (78.3% of the original mixture). The crops melted in the range 136–143°C (dec.) and were contaminated by small amounts of **10**. For further purification, the material was dissolved in CH_2Cl_2 and the solution washed twice with water, dried (Na_2SO_4), and evaporated. One or two recrystallizations from ethanol of the recovered material gave chromatographically pure **9**, mp 147–148°C (dec.). All mother liquors were combined and reprocessed with $NaOCH_3$ as described, and a total of 1.54 g (70%) of pure **9** was eventually obtained.

It was observed that both **9** and **10** slowly underwent partial deacetonation when exposed to the laboratory air for prolonged periods. Such samples became incompletely soluble in $CHCl_3$ and showed a new, immobile spot in tlc (solvent D).

*1L-(1,2/3,4,5)-1-O-(Methylsulfonyl)-5-nitro-1,2,3,4-cyclohexanetetrol (**11**) and its 2,3,4-triacetate **12***

A solution of **10** (100 mg) in methanol (3 mL) was acidified with 3 drops of 1 *M* HCl and left overnight at room temperature, then heated briefly (2 min) to 60°C for a completion of the hydrolysis, which was monitored by tlc (solvent D). Evaporation with several added portions of methanol followed by 95% ethanol quantitatively gave crystalline **11**, which was recrystallized from hot methanol; mp 173°C (dec.), $[\alpha]_D$ −32.7° (*c* 1.4, 1:1 MeOH–DMF); ν_{max}: 3470 and 3410 (OH), 1335 (NO_2), 1170 (MsO), 1090–1070, 1030, 1000, 980, 900, and 870 cm^{-1}. *Anal.* calcd. for $C_7H_{13}NO_8S$ (271.2): C 30.99, H 4.83, N 5.16, S 11.82; found: C 31.19, H 4.85, N 4.92, S 11.89.

To a suspension of **11** (20 mg) in acetic anhydride (1 mL) was added BF_3–Et_2O (5 drops), with initial ice-cooling. All of **11** dissolved rapidly. The solution was kept at ambient temperature for 1 h and then brought to dryness. Trituration of the residue with a small amount of 95% ethanol gave **12** as fine needles, mp 191–192°C; $[\alpha]_D$ −71° (*c* 0.4, $CHCl_3$); ν_{max}: 1750 (ester CO) and 1553 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$; assignments confirmed by HOMCOR method), δ: 6.19 (nm, H-4), 5.31 (nm, H-1), 5.26 (dd, $J_{1,2}$ = 2.8, $J_{2,3}$ = 10.9 Hz, H-2), 5.15 (dd, $J_{3,4}$ = 3.0, $J_{2,3}$ = 10.9 Hz, H-3), 4.85 (ddd, $J_{4,5}$ = 2.7, $J_{5,6e}$ = 5, $J_{5,6a}$ = 12.5 Hz, H-5), 3.08 (s, 3H, CH_3SO_3), 2.77 (dtd, $J_{4,6e}$ = −1.2, $J_{5,6e}$ = 5, $J_{1,6e}$ = 4, $J_{6a,6e}$ = 15 Hz, H-6e), 2.64 (quin, $J_{1,6a}$ = 2.3, $J_{5,6a}$ = 12.5, $J_{6a,6e}$ = 15 Hz, H-6a), and 2.08, 2.07, 2.00 (s, 3H each, OAc). *Anal.* calcd. for $C_{13}H_{19}NO_{11}S$ (397.4): C 39.29, H 4.82, S 8.07; found: C 39.50, H 4.83, S 7.97.

*1L-(1,2,4/3,5)-1-O-(Methylsulfonyl)-5-nitro-1,2,3,4-cyclohexanetetrol (**13**) and its 2,3,4-triacetate **14***

A suspension of the acetonide **9** (300 mg) in ether (15 mL) containing 90% CF_3CO_2H (0.3 mL) was boiled under reflux. Deacetonation monitored by tlc (solvent D), to give nearly immobile **13**, was slow under these conditions but was accelerated upon addition of several drops of methanol to render the medium homogeneous, and it was complete after 3 h. Solvent removal and evaporation of several added portions of ether–methanol, followed by pure ether, from the material gave **13** (262 mg, quantitative) as a white, low-melting (50–60°C), amorphous powder after drying *in vacuo* over KOH; $[\alpha]_D$ −30° (*c* 1.2, methanol); ν_{max}: 3500–3200 (OH), 1550 (NO_2), 1170 (MsO), 1120–1070, 1000 (weak), 975, 900, 860–820, 780, and 720 cm^{-1}. *Anal.* calcd. for $C_7H_{13}NO_8S$ (271.2): C 30.99, H 4.83; found: C 30.91, H 4.82.

A sample of **13** (20 mg) was treated with acetic anhydride (1 mL) and BF_3–Et_2O (2 drops). The reaction mixture was allowed to dry in the air, leaving **14** as a crust of beautiful crystals that were washed with a small amount of cold methanol; mp 197–198°C, unchanged on recrystallization from methanol; $[\alpha]_D$ −61.9° (*c* 0.8, $CHCl_3$); ν_{max}: 1740 (ester CO) and 1563, 1543 cm^{-1} (a doublet for NO_2; compare the single band in **12**). The fingerprint region was clearly distinct from that of **12**. The ^1H nmr ($CDCl_3$; assignments confirmed by HOMCOR method), δ: 5.61 (~t, $J_{3,4}$ = 9.5, $J_{4,5}$ = 10 Hz, H-4), 5.40 (~t, $J_{2,3}$ = 10.5, $J_{3,4}$ = 9.5 Hz, H-3), 5.27 (nm, H-1), 5.00 (dd, $J_{1,2}$ = 3, $J_{2,3}$ = 10.5 Hz, H-2), 4.94 (ddd, $J_{5,6e}$ = 4.5, $J_{4,5}$ = 10, $J_{5,6a}$ = 13 Hz, H-5), 3.13 (s, 3H, CH_3SO_3), 2.76 (dt, $J_{1,6e}$ = $J_{5,6e}$ = 4.5, $J_{6a,6e}$ = 14.5 Hz, H-6e), 2.35 (quin, $J_{1,6a}$ = 2.2, $J_{5,6a}$ = 13, $J_{6a,6e}$ = 14.5 Hz, H-6a), and 2.06, 2.01, 2.00 (s, 3H each, OAc). *Anal.* calcd. for $C_{13}H_{19}NO_{11}S$ (397.4): C 39.29, H 4.82, S 8.07; found: C 39.37, H 4.65, S 8.21.

*6-Azido-4-nitro-1,2,3-cyclohexanetriol (**15**)*

*(a) From **13***

Compound **13** (200 mg) and LiN_3 (100 mg) were heated in dry *N,N*-dimethylformamide (2 mL) at 100°C for 3 h, under exclusion of atmospheric moisture. Thin-layer chromatography with solvent B indicated conversion of **13** (R_f 0.55) into products giving a strong spot (R_f 0.65) for **15** and a weaker spot (R_f ~ 0.57) attributed to the 3-epimer, differentiated from **13** by its color shade (5% H_2SO_4 spray, heat). The solvent was removed *in vacuo* at 50°C and by several coevaporations with added toluene. The brown syrup obtained was mixed with a few drops of water and triturated with $CHCl_3$ containing a small amount of methanol. The organic solution was washed with water, dried ($MgSO_4$), concentrated, and applied to a column of silica gel (6 g) for chromatography with solvent B. Colorless crystalline material was obtained from several fractions, totalling 115 mg (72%). Chromatographically homogeneous **15** (R_f 0.65) showed mp 163–166°C (dec.); $[\alpha]_D$ −21.0° (*c* 2.5, methanol); ν_{max}: 3400 (OH), 2110 (N_3), and 1550 (NO_2) cm^{-1}. Fractions in which the less abundant product (R_f 0.57) was enriched were dissolved in a small volume of methanol containing a catalytic amount of $NaOCH_3$, seeded with **15**, and allowed to dry slowly in an open vessel placed over KOH in an unevacuated desiccator. The dry residue then indicated (tlc) preponderance of **15**. *Anal.* calcd. for $C_6H_{10}N_4O_5$ (218.2): C 33.03, H 4.62, N 25.68; found: C 33.11, H 4.66, N 25.68.

*(b) From **19***

Slow evaporation (overnight) of a solution of **19** (100 mg) in methanol (2 mL) containing 5 drops of 1 *M* HCl, in a lightly covered Petri dish, gave a dry crust of stout crystals of **15** (84 mg after washing with small amounts of ether, EtOAc, and ether again); mp 169–170°C with decomposition from 165°C; $[\alpha]_D$ −20° (*c* 1.1, methanol). The ir spectrum was identical with that of **15** obtained from **13**.

*(c) Triacetate **15**a*

An analytical sample of **15** was treated on a watchglass with a few drops of acetic anhydride and a droplet of BF_3–Et_2O. Slow evaporation of the reagent in the air left **15***a* as a dry residue of long needles that were washed with ether–hexane; mp 140°C; ν_{max}: 2100 (N_3), 1750 (ester CO), and 1560 (NO_2) cm^{-1}; δ ($CDCl_3$): 5.59 (t, $J_{2,3}$ = $J_{3,4}$ = 10 Hz, H-3), 5.10 (septet, 2H, H-1,2), 4.66 (ddd, $J_{4,5e}$ = 4.5, $J_{3,4}$ = 10.7, $J_{4,5a}$ = 13.1 Hz, H-4), 3.63 (ddd, $J_{5e,6}$ = 4.5, $J_{1,6}$ = 9.5, $J_{5a,6}$ = 12.8 Hz, H-6), 2.63 (dt, $J_{4,5e}$ = $J_{5,6e}$ = 4.5, $J_{5a,5e}$ = 13.1 Hz, H-5e), 2.10 (q, line separation ~ 13 Hz, H-5a), 2.08, 2.00, and 1.99 (s, 3H each, OAc), and 1.55 (bs, H_2O). The presence of water of crystallization, not removed after drying the substance *in vacuo* at 80°C, was surprising, but was confirmed also by a broad ir band at 3200 cm^{-1} and by the combustion data. *Anal.* calcd. for $C_{12}H_{16}N_4O_8 \cdot 1.5\ H_2O$ (371.3): C 38.81, H 5.16, N 15.09; found: C 38.89, H 4.97, N 14.97.

*3-Azido-1,2,3-trideoxy-4,5;6,7-di-O-isopropylidene-1-nitro-D-glucoheptitol (**16**)*

*(a) From mesylate **5** by an improved procedure*

A mixture of mesylate **5** (9.59 g), NaN_3 (14 g), $Bu_4N^+HSO_4^-$ (8 g), water (50 mL), and benzene (250 mL) was efficiently stirred in a jacketed reaction vessel, the outer chamber of which contained boiling acetone. Monitored by tlc (solvent H), the reaction was estimated to be about 50% complete after 3 days. Additional NaN_3 (6 g) and $Bu_4N^+HSO_4^-$ (4 g) was introduced, and after a further 3 days only traces of **5** (R_f 0.12) were visible. The main product **16** (R_f 0.42) was accompanied by small proportions of by-products having R_f 0.49 and 0.29. The benzene layer was washed 4 times with water, dried (Na_2SO_4), and evaporated. The amber syrup so obtained (9.08 g) was chromatographed on a column of silica gel (83 × 2.5 cm) with solvent I. Mixture fractions were rechromatographed on a similar column. The combined fractions of **16**, homogeneous in tlc with solvent H, nevertheless contained a slow-moving impurity (R_f 0.03) as revealed

by tlc with CH_2Cl_2. This impurity was removed by passage of the product through a column (20 × 2.8 cm) by means of CH_2Cl_2. The evaporated eluate was decolorized with activated charcoal in ethanol, and final evaporation gave **16** as a syrup (6.281 g, vacuum dried; 76%), $[\alpha]_D$ +15° (*c* 0.7, $CHCl_3$), indistinguishable by ir and nmr spectra from the preparation previously described (12).

The by-products having R_f 0.49 and 0.29 were isolated in amounts of 501 and 47 mg, respectively. Both lacked N_3 absorption in the ir and were identical with the cyclopropano derivatives previously encountered (12), according to their ^1H nmr spectra.

(b) From triflate 6

To a solution of NaN_3 (15 g) and $Bu_4N^+HSO_4^-$ (8 g) in water (30 mL) was added crystalline **6** (8.374 g) followed by benzene (60 mL). The mixture was efficiently stirred at room temperature. Monitoring of the reaction by tlc was difficult because of similar mobilities of **6** and **16**; however, with CH_2Cl_2 as the solvent, **16** was seen to migrate marginally more slowly. (It also charred to a darker spot than **6**, after spraying the plate with dilute sulfuric acid and heating it on a hot-plate.) Although the reaction was close to completion after 1 h, stirring was continued overnight. The phases were then separated, the aqueous phase was extracted with benzene, and the combined benzene phases were washed 5 times with water, dried (Na_2SO_4), and evaporated, to give crude **16** (6.79 g), $[\alpha]_D$ +13.1° (*c* 0.8, $CHCl_3$). The colored syrup was purified by passage through silica gel (25 g) with CH_2Cl_2 as the solvent. The eluate gave on evaporation pure **16** (5.308 g, 84.1%) as a colorless syrup, $[\alpha]_D$ +14.6° (*c* 0.9, $CHCl_3$). The ^1H nmr data were the same as those for the product obtained under (*a*).

The mother liquor that had remained in the preparation of the crystalline batch of **6** (*vide supra*) here utilized was subjected to azide displacement in the same way, furnishing an additional 434 mg of **16**. Based on alcohol **4**, the yield was therefore 61%. In a similar operation (but on one-half scale), a two-step yield of 71% was achieved. Finally, a 93% yield from **4** was obtained when the alcohol was triflated as described but isolation of crystalline **6** was dispensed with and the entire, crude triflate syrup was used for azide displacement. The product was less pure (tlc; $[\alpha]_D$ +13.4°), but could be used for the preparation of **19**.

*3-Azido-1,2,3-trideoxy-4,5-*O*-isopropylidene-1-nitro-*D*-*gluco*-heptitol (17)*

Pure **16** (8.55 g) in toluene (80 mL) was treated at −30°C with 90% CF_3CO_2H (5 mL). After 15 min, tlc (solvent E) showed **17** (R_f 0.2) and a considerable amount of remnant **16** (R_f 0.75). Further acid (5 mL) was added, and after another 15 min the formation of immobile product was observed, even though some **16** was still present. The reaction was quenched by stirring the mixture for 0.5 h with solid $NaHCO_3$ (25 g), then shaking it with added water (40 mL) and ethyl acetate (10 mL). The phases were separated, and the organic phase was washed exhaustively with water. The organic phase contained unreacted **16**, which was isolated and subjected to an identical acid treatment (with appropriately adjusted volumes). All aqueous extracts were combined; they contained **17** as well as tetraol resulting from over-hydrolysis. Neutralization of excess $NaHCO_3$ with acetic acid followed by exhaustive extraction of the aqueous phase with ethyl acetate gave an extract that, after concentration to a volume of 100 mL, washing once with water at that stage, drying, and complete solvent removal, furnished the main crop of **17** as a syrup (6.38 g). The remaining aqueous phase was evaporated to dryness, to give a residue of salts containing tetraol. By acetonation of this material (compare the preparation of **4** from **3**), 580 mg of regenerated **16** was obtained, which yielded another 250 mg of **17** upon partial hydrolysis as just described. The total yield of **17** was therefore 6.63 g (88%); $[\alpha]_D$ +18.8° (*c* 0.9, EtOAc); ν_{max}: 3500–3200 (OH), 2110 (N_3), and 1550 (NO_2) cm^{-1}; δ ($CDCl_3$): 4.55 (dd, 2H, J = 6.4 and 7.1 Hz, H-1,1′), 4.08 (dd, $J_{3,4}$ = 3, $J_{4,5}$ = 7.2 Hz, H-4), 3.98 (~t, $J_{4,5}$ = 7.2, $J_{5,6}$ = 7.3 Hz, H-5), 3.85 (m, H-6), ~3.70 (two partially overlapping dd, $J_{6,7}$ and $J_{6,7'}$ = 5.1–5.2 Hz, H-7,7′), 3.49 (ddd, W = 17 Hz, H-3), ~2.40 (cm, 2H, H-2,2′), 1.9 (broad band, 2H, exchangeable with D_2O, 2OH), 1.44 and 1.36 (s, 3H each, Me_2C). *Anal.* calcd. for $C_{10}H_{18}N_4O_6$ (290.3): C 41.38, H 6.25, N 19.30; found: C 41.23, H 6.41, N 19.09.

*1L-(1,3/2,4,6)-6-Azido-1,2-*O*-isopropylidene-4-nitro-1,2,3-cyclohexanetriol (19)*

(a) From 17 via 18

A solution of diol **17** (6.63 g) in water (100 mL) was mixed with a solution of $NaIO_4$ (5.35 g) in water (50 mL), at 25°C. Oxidation was complete within a few minutes (tlc with EtOAc: R_f 0.7 → R_f 0.85). Ethylene glycol (0.3 g) was added after 10 min, and the solution was then extracted with EtOAc (4 × 100 mL), concentrated to a small volume, and extracted twice more with EtOAc. The dried extracts were evaporated to give syrupy aldehyde **18** (5.58 g, 95%, dried under oil-pump vacuum).

The entire syrup (**18**) was immediately dissolved in reagent-grade methanol (100 mL), and $NaOCH_3$ (0.5 g) in methanol (50 mL) was added with swirling. Thin-layer chromatography with solvent H indicated that the inhomogeneous starting material (R_f 0.0–0.25), which may have contained aldehyde hydrate or hemialdal, or already some cyclization product, was converted after 1 h into product(s) giving a single spot (R_f 0.25). The reaction mixture was concentrated to a small volume and then distributed between water and EtOAc. Repeated extractions of the water phase, and washing (H_2O), drying (Na_2SO_4), and evaporation of the EtOAc extracts gave syrupy product (5.0 g). Concentration of the combined water phases to a small volume, addition of 0.2 mL of glacial acetic acid, and several further extractions performed alternately with benzene and with EtOAc gave an additional crop of syrup (570 mg). Excess CH_2Cl_2 was added to, and evaporated from, the combined syrupy material, which was then taken up in 5 mL of 95% ethanol. After brief heating to dispel remnant CH_2Cl_2 the solution was stored overnight at ambient temperature for crystallization. A first crop of white crystals (1.181 g) of slightly impure **19**, mp 162–167°C, was collected and washed with 95% ethanol. The mother liquor was evaporated to a syrup, which was briefly heated (5 min; steam bath) with 2-propanol (3 mL) containing 10 mg of $NaOCH_3$. On subsequent seeding and standing (20 h) a second crop of crystals (0.834 g) was formed. The process was repeated several times, using 2-propanol or 95% ethanol as the solvent, until 4.11 g of crystalline product was eventually accumulated (73.6% from **18**, or 69.7% from **17**). The various fractions melted in the range of 147–167°C and contained small proportions of the epimer **20** as evidenced by nmr spectra. (In tlc with solvent E the epimers had similar R_f values of 0.55–0.60, but mixtures tended to give a double spot, with **19** migrating marginally faster.) For further purification, the material was dissolved in 4:1 benzene–CH_2Cl_2 and the solution was washed once with water, dried, and evaporated. The recovered crystalline product was then recrystallized once more from 95% ethanol, to give 3.60 g of pure **19**, mp 171°C; $[\alpha]_D$ −12.7° (*c* 0.8, $CHCl_3$). Processing of the mother liquor with $NaOCH_3$ as described above, and recrystallization of the crystals obtained, gave another 250 mg of pure **19**, for a total yield of 3.85 g (65% from **17**); ir, ν_{max}: 3500 (OH), 2100 (N_3), and 1550 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$), δ: 4.46 (ddd, $J_{4,5e}$ = 5, $J_{3,4}$ = 9, $J_{4,5a}$ = 12.5 Hz, H-4), 4.39 (dt; t after D_2O exchange; $J_{3,OH}$ = 3,3 $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 3.72 (ddd, $J_{5e,6}$ = 4.8, $J_{1,6}$ = 9.6, $J_{5a,6}$ = 11.5 Hz, H-6), 3.50 (~t, $J_{1,2}$ = 9.3, $J_{1,6}$ = 9.6 Hz, H-1), 3.41 (t, $J_{1,2} \approx J_{2,3}$ = 9.35, H-2), 2.92 (d, exchangeable, J = 3.3 Hz, OH), 2.65 (dt, $J_{4,5e} \approx J_{5e,6}$ = 4.85, $J_{5a,5e}$ = 13.4 Hz, H-5e), 1.95 (ddd, $J_{5a,6}$ = 11.5, $J_{4,5a}$ = 12.6, $J_{5a,5e}$ = 13.4 Hz, H-5a), 1.47 and 1.46 (s, 3H each Me_2C). *Anal.* calcd. for $C_9H_{14}N_4O_5$ (258.3): C 41.85, H 5.46, N 21.70; found: C 41.61, H 5.77, N 21.52.

For additional characterization, a 50-mg sample of **19** was converted quantitatively into its *3-(trimethylsilyl) ether* by treatment for 2 h with hexamethyldisilazane (0.3 mL) in refluxing EtOAc (3 mL), in the presence of 3 mg of powdered $(NH_4)_2SO_4$. The ether was isolated by evaporation of the solution with added, excess EtOAc followed by toluene, washing with water, and drying of the colorless syrup obtained, *in vacuo*, whereupon it readily and completely crystallized on scratching. The ether had mp 76°C; R_f 0.85 (tlc, solvent F); ν_{max}:

2100 (N_3), 1550 (NO_2), and 1250, 850 (Si-C) cm^{-1}; ^1H nmr ($CDCl_3$), δ: 4.44 (ddd, $J_{4,5e}$ = 5, $J_{3,4}$ = 8.9, $J_{4,5a}$ = 12.9 Hz, H-4), 4.26 (~t, width 18.7 Hz, H-3), 3.66 (ddd, $J_{5e,6}$ = 4.8, $J_{1,6}$ = 10.1, $J_{5a,6}$ = 11.4 Hz, H-6), 3.46 (dd, $J_{1,2}$ = 9, $J_{1,6}$ = 10.1 Hz, H-1), 3.31 (dd, $J_{1,2}$ = 9.1, $J_{2,3}$ = 9.7 Hz, H-2), 2.52 (dt, $J_{4,5e} \approx J_{5e,6}$ = 4.9 Hz, $J_{5a,5e}$ = 13.3 Hz, H-5e), 1.98 (~sx, J = 11.5, 12.8, and 13.3 Hz, H-5a), 1.44 and 1.42 (s, 3H each, Me_2C), and 0.08 (s, 9H, Me_3Si).

Mother liquors remaining after the aforedescribed procedures of isolation and recrystallization of **19** contained **19** together with comparable amounts of its 3-epimer **20**, as was clearly revealed by ^1H nmr spectra that showed good separation of signals for the two components, except for overlapping H-4 signals. Epimerism at C-3 was indicated for **20** by a downfield shift and small splittings for the signal of equatorial H-3, and by deshielding of the H-1 and H-5a signals caused by an axial OH-3 group. Although attempted preparative separation of the epimers by column chromatography was inefficient, a small fraction containing virtually pure **20** could so be secured for spectral analysis; δ: 4.99 (nm, H-3), 4.44 (ddd, $J_{3,4}$ = 2.85, $J_{4,5e}$ = 4.9, $J_{4,5a}$ = 12.7 Hz, H-4), 3.99 (~t, $J_{1,2} \approx J_{1,6} \approx$ 9.8 Hz, H-1), 3.60 (ddd, $J_{5e,6}$ = 4.7, $J_{1,6}$ = 10.1, $J_{5a,6}$ = 11.7 Hz, H-6), 3.38 (dd, $J_{2,3}$ = 1.9, $J_{1,2}$ = 9.4 Hz, H-2), 2.49 (dt, H-5e), 2.33 (~sx, J = 11.7 and 12.7, and $J_{5a,5e}$ = 13.5 Hz, H-5a), ~1.5 (broad, exchangeable; OH), 1.46 and 1.445 (s, 3H each, Me_2C).

It was found that crystalline samples of **19** sometimes gave a weak spot (R_f ~ 0.33) in addition to the main spot (R_f 0.6) in tlc with solvent E. The intensity of the former, though always low, seemed to vary with the solvent of application and with the time span of the sample's exposure to silica gel. The phenomenon was probably due to reversal of the cyclization occurring to a minor extent under certain conditions. A substance (presumably **18**) that had the same R_f value accumulated in mother liquors of **19** and was found to be reconvertible into the mixture of epimeric cyclitols by treatment with $NaOCH_3$ in methanol.

(b) From ***9***

To a solution of **9** (100 mg) in warm benzene (8 mL) was added NaN_3 (200 mg), $Bu_4N^+HSO_4^-$ (135 mg), and water (2 mL). The vigorously stirred mixture was boiled under reflux for 3 days. The mixture was then diluted with water and benzene, and the benzene phase was washed several times with water, dried ($MgSO_4$), treated with activated charcoal, and evaporated to give a colorless syrup; R_f 0.6 (strong) and 0.35–0.45 (traces; tlc with solvent E). The slow-moving contaminants were removed by passage of the material through a small column of silica gel (6 g) by means of solvent F. The purified syrup (60 mg, 72%) crystallized on trituration with a few drops of 95% ethanol and seeding with **19**. The ir spectrum matched that of pure **19** in all of its features, but additional peaks present in the fingerprint region were attributable to accompanying **20** (by comparison with the spectrum of isolated **20**). The ^1H nmr spectrum was a superposition of those of **19** and **20**, suggesting a ratio of roughly 4:1 for these components.

*2-Deoxystreptamine (**21**) and N,N'-diacetyl-2-deoxystreptamine (**22**)*

Azidonitrotriol **15** (125 mg) in water (20 mL) containing 1 *M* HCl (1.5 mL) was hydrogenated overnight, at ordinary temperature and pressure, with prehydrogenated Adams catalyst (from 90 mg of PtO_2). Evaporation of the optically inactive filtrate, followed by trituration of the residue with 95% ethanol, gave **21** as the crystalline dihydrochloride (136 mg, 100%); it partially sublimed above 300°C and decomposed at about 325°C (lit. (19) mp 325°C (dec.)). The ir spectrum was identical in every detail with that of an authentic sample kindly provided by Bristol Laboratories, Syracuse, N.Y.

A sample of the dihydrochloride was converted into the *N,N'*-diacetyl derivative **22** by treatment with acetic anhydride and triethylamine in methanol–water. Washed with methanol–ether, the crystalline **22** melted with decomposition at 297–300°C, with prior darkening from 290°C (lit. (20) mp 292°C (dec.)). The ir spectrum was identical with that of **22** prepared from an authentic sample of **21**, as well as with that of **22** obtained from the acetonide **24** in the following way. Compound **24** (144 mg) was dissolved in methanol (0.6 mL) with the aid of sonication, and 1:4 concentrated HCl – methanol (5 drops) was then added. After 5 min the reaction appeared to be largely finished (tlc with 1:4 methanol–EtOAc), and **22** began to crystallize. Collected after 2 days and washed with methanol, the crystals (109 mg, 88%) showed mp 299–301°C (dec., with darkening from ~292°C); ^{13}C nmr data (D_2O, dioxane reference signal at 67.4 ppm), δ: 174.8 (CO), 76.7 (C-5), 75.1 (C-4,6), 50.5 (C-1,3), 33.3 (C-2), and 22.9 (Me), in excellent agreement with reported (21) data; [α] 0.0° in the spectral region 365–589 nm (*c* 1.4, water).

*1L-(1,3/2,4,6)-4,6-Diacetamido-1,2-O-isopropylidene-1,2,3-cyclohexanetriol (N,N'-diacetyl-4,5-O-isopropylidene-2-deoxystreptamine, **24**)*

Platinum dioxide (775 mg) suspended in ethanol (12 mL) was prehydrogenated. Glacial acetic acid (1.08 g, 18 mmol) was then added to the suspension, followed by a solution of **19** (775 mg, 3 mmol) in warm ethanol (8 mL). The mixture was vigorously shaken under hydrogen at ordinary temperature and pressure for 5 h. Progress of the reaction was monitored by tlc (1:4 methanol–EtOAc), which indicated gradual disappearance of **19** (R_f 0.9) and formation of nearly immobile diamine **23**, with several intermediary products of intermediate mobilities being visible. The catalyst was filtered off and washed exhaustively with ethanol, and acetic anhydride (1.3 mL) was added to the filtrate. After 30 min the solution was evaporated *in vacuo* (bath temperature 30°C), and several portions of added ethanol were evaporated from the residue until the acidic smell had vanished. Crystallization of the syrup from about 2 mL of ethanol to which 4 drops of saturated, methanolic ammonia had been added gave a first crop (392 mg) of **24**. Processing of the mother liquor by use of ethanol, ethanol–acetone, and acetone as solvents gave several additional crops for a total of 608 mg (70.8%). The crops melted with decomposition in the range of 250–260°C, dependent on the rate of heating. Recrystallized from ethanol, **24** had mp 253–255°C (lit. (13) mp 193–195°C for racemic compound); ν_{max}: 3350 and 3280 (OH, NH), 1660, 1630 and 1560, 1530 (amide I and II) cm^{-1}; δ ($CDCl_3$): 5.57 and 5.49 (bd, 1H each, J = 7–8 Hz, exchangeable, NH), 3.98, 3.85, and 3.75 (bm, 1H each, H-1,3,6), 3.47 (cm, 2H, H-4,5), 2.52 (dt, $J_{1,2e}$ = $J_{2e,3}$ = 4.8, $J_{2a,2e}$ = 12.9 Hz, H-2e), 2.00 and 1.96 (s, 3H each, Ac), and 1.43 (s, 6H, Me_2C). The optical rotation in methanol (*c* = 6.8, and in parentheses, *c* = 1.36) was noticeably concentration dependent: $[\alpha]_{365}$ −12.7° (−10.3°), $[\alpha]_{436}$ −3.8° (−2.4°), $[\alpha]_{546}$ −0.25° (+0.40°), $[\alpha]_{578}$ +0.1° (+0.65°), $[\alpha]_D$ +0.15° (+0.80°). *Anal.* calcd. for $C_{13}H_{22}N_2O_5 \cdot 0.5\,H_2O$ (295.3): C 52.87, H 7.85, N 9.48; found: C 52.65, H 7.78, N 9.30.

A sample of **24** was *O*-acetylated (acetic anhydride – pyridine); the *acetate* (R_f 0.45, tlc with 1:4 methanol–EtOAc) showed $[\alpha]_{365}$ +53.9°, $[\alpha]_{436}$ +38.6°, $[\alpha]_{546}$ +24.4°, $[\alpha]_{578}$ +21.9°, $[\alpha]_D$ +21.3° (*c* 1.5, $CHCl_3$).

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