ethanol at 65°. An ethanol solution of 0.0175 mol of sodium ethoxide was added and the mixture was cooled to room temperature. To this was added 13.70 g (0.0875 mol) of ethyl iodide and after refluxing 1.5 hr an additional 5.26 g of ethyl iodide was added and reflux was continued another 1.5 hr. By this time the solution was neutral and it was allowed to cool and stand overnight. About two-thirds of the ethanol was removed by distillation, then 80 ml of water and 40 ml of ether were added. The separated ethereal solution was washed repeatedly until a negative test for iodide was observed. Evaporation of the ether left 4.7 g (91%) of crude product. Recrystallization from absolute methanol then 70% ethanol gave 1.1 g (21%) of very pure product, mp 116–117°. The infrared spectrum had nitrile absorption at 2210 cm^{-1} characteristic of conjugated CN as in **4**. The nmr spectrum in $CDCl_3$ had a triplet (3 H) at 0.93 ppm and a quartet (2 H) at 4.14 ppm showing an ethyl bonded to an oxygen.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.19; H, 7.05; N, 4.60.

2-Cyano-2-methyl-6,6-diphenylcyclohexanone (7). Repetition of the above reaction with methyl iodide gave 33% pure product after vacuum sublimation and recrystallization from ether, mp 134.5–135°. The infrared spectrum in dioxane showed unconjugated nitrile at 2240 cm^{-1} and a shoulder at 2250 cm^{-1}. The nmr spectrum in $CDCl_3$ had a singlet (3 H) at 1.42 ppm, an aromatic (10 H) at 7.23 ppm, and methylenes (6 H) at ~2.85 ppm.

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.06; H, 6.68; N, 4.64, 4.77.

2-Cyano-6-isopropyl-2-methyl-6-phenylcyclohexanone (8). Similarly **2l** and methyl iodide gave an oil which was vacuum distilled and crystallized with difficulty. Recrystallization from 30–60 petroleum ether gave a 40% yield, mp 77.5–78.5°. The nmr spectrum ($CDCl_3$) had a doublet (3 H) at 0.45 ppm, a doublet (3 H) at 0.94 ppm, a singlet (3 H) at 1.12 ppm, a singlet (1 H) at 1.99 ppm, a septet (6 H) at 2.56 ppm, and an aromatic (5 H) at 7.32 ppm.

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.92; H, 8.29; N, 5.49. Found: C, 80.14; H, 8.12; N, 5.65.

Acknowledgment. We thank Lehigh University, Dr. Ned Heindel, and Mr. Richard Conley for running and assistance in interpreting the nmr spectra.

Registry No.—**1d,** 53586-66-6; **1f, 53586-67-7; 1h,** 18072-65-6; **1i,** 18072-67-8; **1j,** 53586-68-8; **1k,** 53586-69-9; **1l,** 53586-70-2; **1m,** 18072-66-7; **1n,** 18072-68-9; **2a** enol form, 53586-71-3; **2a** keto form, 4513-77-3; **2b** enol form, 53586-72-4; **2b** keto form, 10219-83-7; **2c** enol form, 53586-73-5; **2c** keto form, 15719-03-6; **2d** enol form, 53586-74-6; **2d** keto form, 53586-75-7; **2e** enol form, 53586-76-8; **2e** keto form, 15595-78-5; **2f** enol form, 53586-77-9; **2f** keto form, 53586-78-0; **2g** enol form, 53586-79-1; **2g** keto form, 15595-79-6; **2h** enol form, 53586-80-4; **2h** keto form, 53586-81-5; **2i** enol form, 53586-82-6; **2i** keto form, 53586-83-7; **2j** enol form, 53586-84-8; **2j** keto form, 53586-85-9; **2k** enol form, 53586-86-0; **2k** keto form, 53586-87-1; **2l** enol form, 53586-88-2; **2l** keto form, 53586-89-3; **2m** enol form, 53586-90-6; **2m** keto form, 53586-91-7; **2n** enol form, 53586-92-8; **2n** keto form, 53586-93-9; **3,** 53586-94-0; **4,** 53586-95-1; **6,** 53586-96-2; **7,** 53586-97-3; **8,** 53586-93-4.

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Aminocyclitols. 31. Synthesis of Dideoxystreptamines[1]

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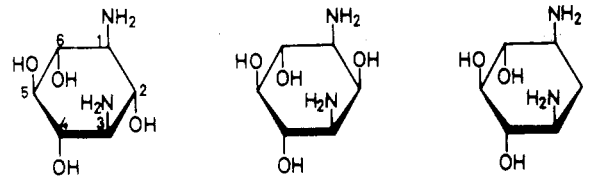
All four predicted positional isomers of dideoxystreptamine have been synthesized. From the two mesylates (**10a** and **10b**), 2,4-(**4a**) and 4,6-dideoxystreptamine (**7a**), together with the acetyl derivatives of two other diaminocyclohexanediols (**11** and **12**), were obtained. 2,5-Dideoxystreptamine (**5a**) was synthesized regioselectively in good yield *via* an intermediate 1,3-hydrazino compound (**15a**) obtained by hydrazinolysis of 1,4-*cis*-diepoxycyclohexane (**14**). 4,5-Dideoxystreptamine (**6a**) was prepared from the dimesylates **17** and **19**.

In 1969, Rinehart and his coworkers[2] described the first successful bioconversion of streptamine (**1**)[3] and 2-epistreptamine (**2**)[4] to semisynthetic neomycin A and B using mutants of *Streptomyces fradiae* in a fermentation media containing **1** and **2**. Very recently, two papers[5,6] on the bioconversion of aminocyclitols to antibiotics have been published. Rinehart and collaborators[5] have tested 29 analogs of 2-deoxystreptamine (**3**) as to whether they are incorporated into antibiotics and it has been found that only two compounds (**1** and **2**) undergo bioconversion to active antibiotics. Structural features of the aminocyclitols which allow the bioconversion were limited to a minor modification of 2-deoxystreptamine; their results suggested guidelines for subsequent synthesis of 2-deoxystreptamine analogs. Along this line, we have attempted to synthesize dideoxystreptamines. In the neomycins,[7] paromomycins,[8] and ribostamycin[9] an aminohexose and D-ribose are linked to the hydroxyl groups at C-4 and C-5 of 2-deoxystreptam-

ine. Therefore, 2,4-dideoxystreptamine (**4a**) might be incorporated into these antibiotics by a bioconversion technique. Since the kanamycins[10] have two amino sugars on the C-4 and C-6 positions of 2-deoxystreptamine in α-glycosidic linkages, 2,5-dideoxystreptamine (**5a**) is an attractive compound for the bioconversion. However, none of the four possible isomers of dideoxystreptamine has been described in the literature so far. In the present paper, we wish to report the synthesis of all the predicted dideoxystreptamine isomers: 2,4- (**4a**), 2,5- (**5a**), 4,5- (**6a**), and 4,6-dideoxystreptamine (**7a**).[11] Besides the possibility of the bioconversion, these dideoxystreptamines will be used for a total chemical synthesis of hybrimycin analogs by methods extensively exploited by three research groups[12] to investigate relationships between structural features of aminocyclitols and biological activities of synthetic antibiotics.



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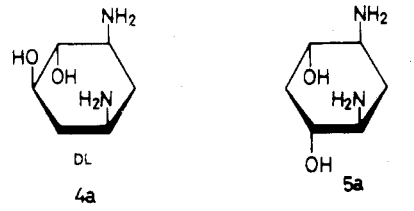

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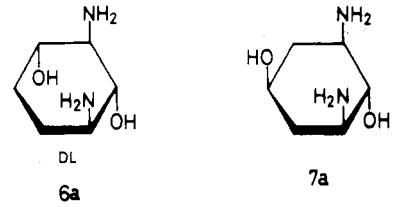

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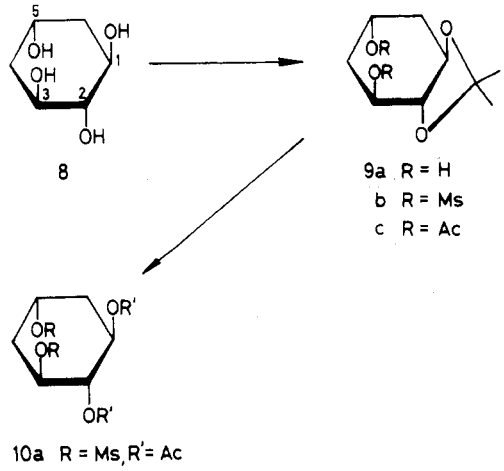
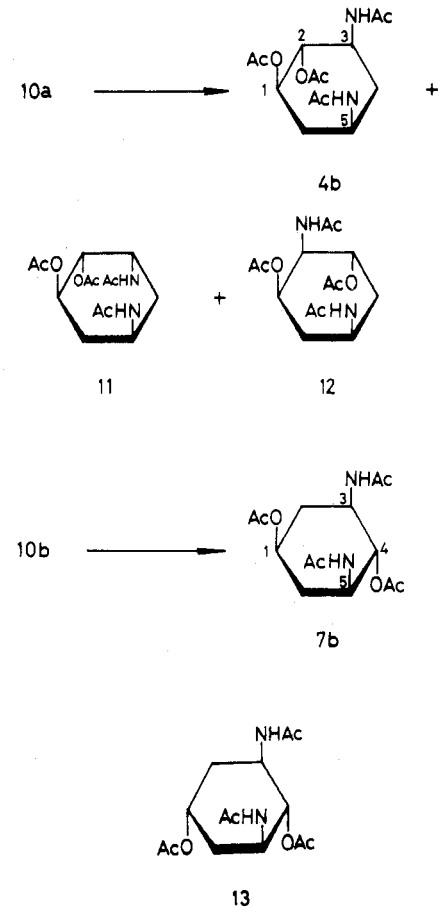
2,4- (4a) and 4,6-Dideoxystreptamines (7a). These compounds were synthesized starting from two dimesylates (**10a** and **10b**) of 1,3/2,5-cyclohexanetetrol (**8**), which was prepared by hydrogenolysis of 1,5-dibromo-1,5-dideoxy-*chiro*-inositol[13,14] in 32% yield. Treatment of **8** with 2,2-dimethoxypropane in dimethylformamide in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the 1,2-*O*-isopropylidene derivative (**9a**) as a homogeneous syrup, which was treated with mesyl chloride in pyridine yielding the dimesylate (**9b**) in 62% yield based on **8**. On hydrolysis with 50% aqueous acetic acid followed by acetylation, **9b** was converted to 1,2-di-*O*-acetyl-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (**10a**) in 89% yield. Compound **9a** was also treated with acetic anhydride in pyridine to give an oily diacetyl derivative (**9c**). Compound **9c** was hydrolyzed under mild conditions and subsequently treated with mesyl chloride in pyridine yielding 1,5-di-*O*-acetyl-2,3-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (**10b**).



8 9a R = H b R = Ms c R = Ac

10a R = Ms, R' = Ac
b R = Ac, R' = Ms

Azidolysis of **10a** with an excess amount of sodium azide in refluxing 2-methoxyethanol for 20 hr followed by acetylation gave a mixture of azido compounds. The mixture was catalytically hydrogenated and subsequently acetylated to give a mixture of tetraacetyl derivatives of three diaminocyclohexanediols which were separated by fractional crystallizations to afford **4b, 11,** and **12** in 13, 24, and 13% yields, respectively. Structural elucidations of the compounds were carried out on the basis of pmr spectroscopy and the proposed reaction mechanism. Three diazido compounds were produced from **10a** by nucleophilic substitution of its mesyloxy groups by azide ions. Thus, the axially located 5-mesyloxy group is initially replaced by an azido group by direct SN2 attack of the nucleophile with an inversion of the configuration at C-5. On the other hand, substitution of the 3-mesyloxy function is assumed to proceed either *via* neighboring-group participation or direct SN2 reaction. Therefore, the structures of the three diazido–diol acetates formed may be formulated as the acetates of (1,3,5/2)-3,5-diazido-1,2-, (1,2,5/3)-2,5-diazido-1,3-, and (1,5/2,3)-3,5-diazido-1,2-cyclohexanediols (precursors of **4b, 11,** and **12,** respectively). The pmr spectral data of the



10a → 4b + 11 + 12

10b → 7b

13

Table I
Characterization of Tetra-*N,O*-acetyldiaminocyclohexanediols

Compd	Mp,[a] °C	Chemical shifts of methyl protons[b] Acetamido Eq	Acetamido Ax	Acetoxy Eq	Acetoxy Ax	Microanalyses,[c] % C	H	N
4b	231.5–233	8.24 8.21		8.07 8.04		53.46	6.94	8.70
5b	292–293	8.22[d]		8.03[d]		53.35	6.94	8.84
6b	274–275.5	8.25[d]		8.12 8.04		53.01	6.89	8.60
7b	300–300.5	8.25[d]		8.10 8.01		53.51	7.03	8.77
11	269.5–270	8.20	8.12	8.07 8.00		53.34	7.09	8.76
12	190.5–191.5	8.17	8.10	8.02	7.95	53.52	7.03	8.63

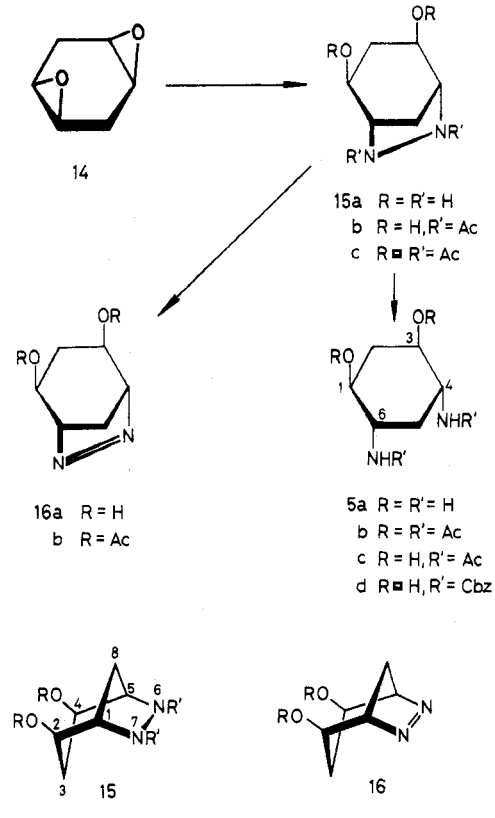
[a] Measured in a sealed capillary in a liquid bath and uncorrected. [b] Determined at 60 MHz in DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are given in τ values. [c] Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. [d] Singlet for two methyl groups.

tetra-*N,O*-acetyldiaminocyclohexanediols are listed in Table I. Assignments of the signals due to the acetyl methyl protons were based on the results of Lichtenthaler.[15] The pmr spectrum of **4b** indicated that all the substituents were in equatorial positions, and its unsymmetrical structure was demonstrated by an appearance of individual singlets due to the four acetyl groups. Consequently, structure **4b** was assigned to di-*O*-acetyl-(1,3/5/2)-3,5-diacetamido-1,2-cyclohexanediol (tetra-*N,O*-acetyl-2,4-dideoxystreptamine). The pmr spectrum of **12** showed the presence of two axial substituents, which established the structure as di-*O*-acetyl-(1,2,5/3)-2,5-diacetamido-1,3-cyclohexanediol. Compound **11** was shown by its pmr spectrum to possess one axial acetamido group in the favored conformation. Therefore, it was assigned to di-*O*-acetyl-(1,5/2,3)-3,5-diacetamido-1,2-cyclohexanediol.

On similar azidolysis followed by hydrogenation and acetylation, **10b** yielded a single crystalline tetra-*N,O*-acetyldiaminocyclohexanediol (**7b**) in 41% yield. The pmr spectral data indicated that **7b** possessed a symmetrical structure and that all the substituents were in equatorial positions, which established the structure as di-*O*-acetyl-(1,3,5/4)-3,5-diacetamido-1,4-cyclohexanediol (tetra-*N,O*-acetyl-4,6-dideoxystreptamine). The chemical shifts of the acetyl methyl protons of its epimer (**13**), (1,4/3,5)-isomer,[16] showed identical values compared with those of **7b** except for one signal of **13** at τ 7.91.[16] Mechanistically, substitutions of the two mesyloxy functions with azide ions may involve a neighboring-group participation reaction followed by direct SN2 reaction.

2,5-Dideoxystreptamine (5a). Introductions of 1,3-*cis*-diamino groups in cyclitols have been successfully carried out *via* 1,3-hydrazino derivatives by hydrazinolysis of suitable disulfonates or dideoxydihalogeno derivatives.[17] Therefore, the most promising synthetic route for **5a** was hydrazinolysis of *cis*-1,4-diepoxycyclohexane (**14**).[18] Compound **14** was prepared from 1,4-cyclohexadiene according to the directions of Craig, *et al.*[19] The separation of the stereoisomers of 1,4-diepoxycyclohexane formed was found to be most efficient by using silica gel column chromatography with 1:4 2-butanone–toluene as an eluent. The cis and trans isomers were thus obtained as pure crystals in 31 and 8% yields, respectively, based on 1,4-cyclohexadiene.

When **14** was treated with an excess amount of hydrazine in refluxing 2-methoxyethanol for 4.5 hr, the reaction proceeded smoothly to give a single crystalline 1,3-hydrazino compound (**15a**) in 85% yield, which was further characterized as the di-*N*-acetyl (**15b**) and the tetraacetyl derivatives (**15c**). Neither derivative exhibited an absorption in the amide II region in the ir spectra. Hydrogenation of **15a** in the presence of platinum catalyst or Raney nickel T-4[20] afforded a crystalline diaminocyclohexanediol (**5a**) in 88% yield, which was isolated and characterized as its dihydrochloride. Compound **5a** was converted into the tetraacetyl (**5b**), the di-*N*-acetyl (**5c**), and the di-*N*-carbobenzyloxy derivatives (**5d**) by the usual methods. On the basis of the



pmr spectral data, **5a** was assigned to di-*O*-acetyl-(1,3/4,6)-4,6-diacetamido-1,3-cyclohexanediol (tetra-*N,O*-acetyl-2,5-dideoxystreptamine). Thus, 2-proton double triplets having 4.5, 11, and 11 Hz splittings at τ 5.31 were ascribed to magnetically equivalent H-1 and H-3, indicating that all the substituents were in equatorial orientations.

Accordingly, **15a** was shown to be 6,7-diazabicyclo-[3.2.1]octane-(2*S*,4*R*)-diol ((1,3/4,6)-4,6-hydrazino-1,3-cy-

Table II
Chemical Shifts and Coupling Constants for 6,7-Diazabicyclo[3.2.1]octane-(2S,4R)-diol and -oct-6-ene-(2S,4R)-diol, and Their Derivatives[a]

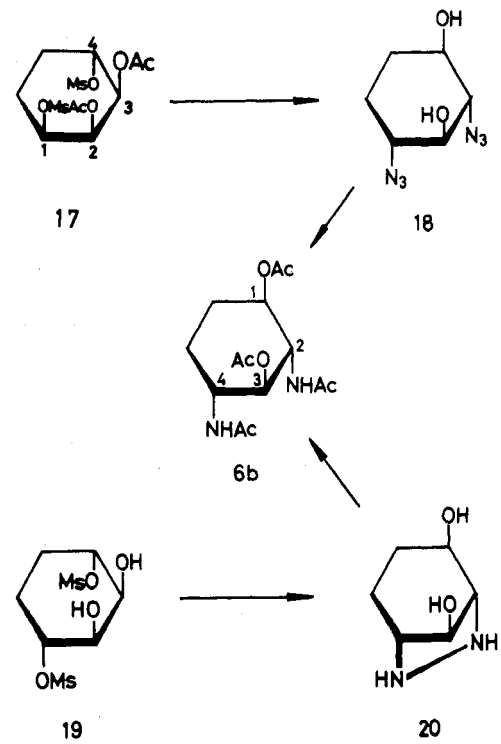
	15a (D_2O)	15b (D_2O)	15c ($CDCl_3$)	16a (D_2O)	16b ($CDCl_3$)
			Chemical Shifts[b]		
H-1,5	6.49 d	5.32 t	5.25 t	4.79 dd	4.69 dd
H-2,4	6.13 t	5.73 td	4.78 m	6.04 m	4.96 q
H-3a	7.93 dt	8.21 t	8.01 t		8.29 t
H-3e	8.43 d	8.21 t	8.01 t		8.29 t
H-8a	7.27 d	7.07 d	7.27 d	7.50 d	7.57 d
H-8e	8.48 td				8.56 td
			Coupling Constants[c]		
$J_{1,2}$ ($J_{4,5}$)	5.0	5.0	5.0	3.5	4.0
$J_{2,3a}$	5.0	3.5	3.5	6.0	4.0
$J_{2,3e}$	0	3.5	3.5	0	4.0
$J_{3a,3e}$	−17.0	0	0	−16.0	0
$J_{1,8a}$	0	0	0	0	0
$J_{1,8e}$	5.0	5.0	5.0	5.5	6.0
$J_{8a,8e}$	−12.0	−13.0	−12.5	−13.0	−12.5
$J_{2,8e}$ ($J_{4,8e}$)	1.0			1.0	1.5

[a] Measured at 60 MHz in $CDCl_3$ or D_2O with tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate as an internal standard, respectively. [b] Chemical shifts are given in τ values. Signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), td (triplet of doublet), and m (multiplet). [c] Values are first order.

clohexanediol). The pmr spectra data (Table II) of **15a** and its derivatives well supported the proposed structures. In the pmr spectrum of **15a**, the C-8 transoid proton appeared as a doublet at lower field compared with the cisoid one, attributable to the deshielding effect of the syn-diaxial two hydroxyl groups on C-2 and C-4.[18,21] The C-3 axial proton appeared also to be deshielded by the hydrazino bridge. In the pmr spectra of **15b** and **15c**, no influence owing to a restricted rotation of the secondary amido groups was observed.

Compound **15a** was comparatively stable in the pure crystalline state; however, in solution or in an impure state, it decomposed gradually by oxidation to yield a crystalline azo compound (**16a**), which was further characterized by converting into the diacetate (**16b**). The presence of the azo group in **16a** and **16b** was clearly shown by characteristic uv absorptions of λ_{max} 336 nm in water and 344 nm in methanol, respectively.[22] Their pmr spectra also supported the proposed structures. Therefore, **16a** was assigned to 6,7-diazabicyclo[3.2.1]oct-6-ene-(2S,4R)-diol. Compound **16a** was obtained from **15a** by oxidation with hydrogen peroxide in 57% yield.

4,5-Dideoxystreptamine (6a). Compound **6a** was first obtained as its tetraacetyl derivative (**6b**) in 3% yield by azidolysis, followed by hydrogenation and acetylation, of 2,3-di-*O*-acetyl-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol (**17**), which was prepared from 1,2:5,6-dianhydro-3,4-*O*-cyclohexylidene-*allo*-inositol[23] by lithium aluminum hydride reduction and successive mesylation.[24] Reaction of **17** with an azide ion is reasonably expected to proceed through initial formation of an intermediate 3,4-acetoxonium ion. Nucleophilic attack on C-3 results in formation of all-trans diazidodiol (**18**), but it seems preferable to attack on C-4.



All the substituents of **6b** were shown to be in equatorial orientations by pmr spectroscopy, and the 1-proton wide triplet at τ 5.25 and the 1-proton wide quartet at τ 6.08 were ascribed to H-2 and H-3, respectively, showing that they have trans-diaxial methine protons in the vicinal positions. Therefore, structure **6b** was assigned to di-*O*-acetyl-(1,3/2,4)-2,4-diacetamido-1,3-cyclohexanediol (tetra-*N*,*O*-acetyl-4,5-dideoxystreptamine).

In order to improve the yield of **6b**, an alternative route *via* a hydrazino compound was studied. As starting material 1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol (**19**) was used, which was readily available by lithium aluminum hydride reduction[24] of 1,2-anhydro-5,6-*O*-cyclohexylidene-3,4-di-*O*-mesyl-*chiro*-inositol[24] followed by mesylation. Treatment of **19** with an excess amount of hydrazine in refluxing 2-methoxyethanol for 6 hr, followed by hydrogenation and acetylation, afforded **6b** exclusively in 45% yield. This result was accounted for by assuming the selective formation of the 1,3-hydrazino compound (**20**).

Experimental Section[25]

1,3/2,5-Cyclohexanetetrol (8). This compound was prepared from 1,5-dibromo-1,5-dideoxy-*chiro*-inositol in 32% yield according to the directions of McCasland and Horswill,[13] mp 175–178°. Recrystallized sample melted at 178–180° (lit.[13] 179–180°). It was further characterized by preparation of the tetraacetate, mp 88–89° (lit.[14] 84–86°).

1,2-*O*-Isopropylidene-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (9b). To a solution of **8** (1.0 g) in dimethylformamide (20 ml) was added 2,2-dimethoxypropane (2.0 ml) and *p*-toluenesulfonic acid (20 mg), and the mixture was heated at 85–90° for 90 min. The mixture was cooled to 0°, neutralized with Amberlite IRA-410 (OH^-), and evaporated to yield the syrupy 1,2-*O*-isopropylidene derivative (**9a**). It was, without further purification, dissolved in pyridine (15 ml) and cooled below 0°. Mesyl chloride (2.5 ml) was added dropwise under agitation and the reaction mixture was allowed to stand in a refrigerator overnight. The mixture was then poured into ice–water (100 ml) and the resulting precipitate

was collected by filtration, giving 1.45 g (62.4%) of **9b** as needles: mp 127–132°; recrystallization from chloroform–ethanol raised its mp to 131–132°; pmr ($CDCl_3$) τ 4.73 (q, 1, H-5, J = 3 Hz), 5.08 (d of t, 1, H-3, $J_{2,3}$ = 9.5 Hz, $J_{3,4a} = J_{3,4e}$ = 5 Hz), 6.14 (d of t, 1, H-1, $J_{1,6a}$ = 11.7 Hz, $J_{1,6e}$ = 4.3 Hz), 6.51 (t, 1, H-2, $J_{1,2}$ = 9.5 Hz), 6.84 (s, 3, OMs), 6.91 (s, 3, OMs), and 8.52 (s, 6, $C(CH_3)_2$).

1,2-Di-*O*-acetyl-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (10a). A mixture of **9b** (0.97 g) and 50% aqueous acetic acid (25 ml) was heated at 75° for 80 min. The reaction mixture was then evaporated to dryness and the residue was treated with acetic anhydride (5 ml) and pyridine (7 ml) overnight at room temperature. The mixture was poured into ice–water to give 1.05 g (97%) of **10a,** mp 163–164°. Recrystallization from chloroform–ethanol gave 0.97 g (89%) of pure needles: mp 164–164.5°; pmr (DMSO-d_6) τ 6.70 (s, 3, OMs), 6.80 (s, 3, OMs), 7.96 (s, 3, OAc), and 8.01 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.11; H, 5.19; S, 16.51. Found: C, 37.02; H, 5.04; S, 16.46.

1,5-Di-*O*-acetyl-2,3-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (10b). The syrupy **9a** obtained from **8** (1.01 g) was treated with a 1:2 mixture (15 ml) of acetic anhydride and pyridine overnight at room temperature. The reaction mixture was poured into ice–water (100 ml) and extracted with ethyl acetate (30 ml), and the extract was washed successively with 10% aqueous potassium carbonate and water, dried over anhydrous sodium sulfate, and evaporated to give a syrup, which showed a single spot on tlc. The product was heated with 50% aqueous acetic acid at 70–75° for 30 min and evaporated to dryness. The resulting syrup was mesylated in the usual manner to give 1.76 g (66.5%) of **10b:** mp 168.5–171°. Recrystallization from chloroform–ethanol gave 1.52 g (57.7%) of pure needles: mp 172–173°; pmr (DMSO-d_6) τ 6.67 and 6.78 (s, 3, OMs), 7.92 and 7.95 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.11; H, 5.19; S, 16.51. Found: C, 37.12; H, 5.09; S, 16.74.

Di-*O*-acetyl-(1,3,5/2)-3,5-diacetamido-1,2-cyclohexanediol (Tetra-*N,O*-acetyl-2,4-dideoxystreptamine) (4b), -(1,5/2,3)-3,5-diacetamido-1,2-cyclohexanediol (11), and -(1,2,5/3)-2,5-diacetamido-1,3-cyclohexanediol (12). A mixture of **10a** (0.752 g), sodium azide (0.73 g), and 90% aqueous 2-methoxyethanol (30 ml) refluxed for 20 hr. The reaction mixture was then evaporated to dryness and the residue was treated with a 1:2 mixture (15 ml) of acetic anhydride and pyridine overnight at room temperature. An insoluble material was filtered and washed with acetic anhydride (5 ml) and toluene (5 ml), and the filtrate and washings were combined and evaporated to give a syrupy product, which was purified by passing through a short alumina column with ethyl acetate as an eluent. A solution of the product in ethanol (15 ml) was hydrogenated in Parr shaker apparatus in the presence of Raney nickel T-4[20] under pressure (3.4 kg/cm^2) overnight at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to give a syrupy product, which was treated with a 1:2 mixture (8 ml) of acetic anhydride and pyridine overnight at room temperature. The crystals deposited directly from the reaction mixture were collected by filtration and washed with toluene giving 139 mg (23.8%) of **11:** mp 255–260° dec. Recrystallization from ethanol–ether gave an analytically pure sample: mp 269.5–270°; pmr (DMSO-d_6) τ 1.96 (d, 1, J = 10 Hz, NHAc), 2.20 (d, 1, J = 8 Hz, NHAc).

The residual reaction mixture was concentrated to give a syrup which was dissolved in ethyl acetate (5 ml) and kept in a refrigerator overnight, affording 78 mg (13.4%) of **4b:** mp 223–225° (the slight turbidity of the melt disappeared at 240°). An analytical sample was obtained by two recrystallizations from ethyl acetate–ether: mp 231.5–233°; pmr (DMSO-d_6) τ 2.10 (d, 1, J = 8 Hz, NHAc), 2.16 (d, 1, J = 10 Hz, NHAc).

The mother liquor from **4b** was concentrated to give a syrup, which was dissolved in ether (3 ml) and kept in a refrigerator overnight to afford 74 mg (12.7%) of **12** as granular crystals: mp 126–129.5°. Recrystallization from ethanol–ether gave an analytical sample: mp 190.5–191.5°; pmr (DMSO-d_6) τ 2.17 (d, 1, J = 8.5 Hz, NHAc), 2.29 (d, 1, J = 8 Hz, NHAc), 5.79 (d of d, 1, H-2, J = 4 and 5 Hz, after deuteration).

Di-*O*-acetyl-(1,3,5/4)-3,5-diacetamido-1,4-cyclohexanediol (Tetra-*N,O*-acetyl-4,6-dideoxystreptamine) (7b). A mixture of **10b** (0.61 g), sodium azide (0.64 g), and 90% aqueous 2-methoxyethanol (30 ml) was heated at reflux for 20 hr. The reaction mixture was then evaporated to dryness and the residue was treated with acetic anhydride (5 ml) in pyridine (10 ml) overnight at room temperature, and filtered to remove an insoluble material. The filtrate was evaporated to give a syrup which was dissolved in ethanol (10 ml) and hydrogenated as described above. The product was acetylated in a similar way to give crystals, which were recrystallized from dimethyl sulfoxide–water to afford 200 mg (40.7%) of **7b** as thin needles: mp 300–300.5°; pmr (DMSO-d_6) τ 5.31 (t, 1, H-2, J = 11 Hz), 6.10 (t of d, 2, H-1 and H-3, J = 4.5, 11, and 11 Hz).

***cis*-1,4-Diepoxycyclohexane (14).** This compound was prepared from 1,4-cyclohexadiene according to the directions of Craig, *et al.*[19] Separation of a mixture of the two stereoisomers of 1,4-diepoxycyclohexane thus obtained was effected by use of a silica gel column chromatography with 1:4 2-butanone–toluene as an eluent, giving cis and trans isomers as chromatographically homogeneous crystals in 31.4 and 7.9% yields, respectively, based on 1,4-cyclohexadiene used. The cis diepoxide melted at 58–60° (lit.[19] 60–61°), and the trans one at 92–100° (lit.[19] 106–107°).

6,7-Diazabicyclo[3.2.1]octane-(2*S*,4*R*)-diol ((1,3/4,6)-4,6-Hydrazino-1,3-cyclohexanediol) (15a). A mixture of **14** (1.0 g), anhydrous hydrazine (2.5 ml), and 2-methoxyethanol (60 ml) was refluxed for 4.5 hr. The mixture was evaporated to give a crystalline residue, which was pulverized and washed with ethanol, affording 1.09 g (85%) of **15a** as granular crystals: mp 193–200°. This compound was shown to be pure enough for an elementary analysis. Attempted recrystallization from water–ethanol resulted in decomposition.

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.66; H, 8.23; N, 19.36.

Compound **15a** (0.50 g) was treated with acetic anhydride (5 ml) and pyridine (10 ml) overnight at room temperature. The mixture was evaporated to give a syrup which was crystallized from ethanol–ether affording 1.0 g (93%) of the tetraacetyl derivative (**15c**): mp 131°; ir (KBr) 1740 (OAc) and 1650 cm^{-1} (NAc).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.95; H, 6.42; N, 8.98.

Compound **15a** (0.40 g) was treated with acetic anhydride (5 ml) in methanol (40 ml) for 2 days at room temperature. The mixture was evaporated to give a crystalline residue which was pulverized with ethanol–*n*-hexane affording 0.50 g (79%) of the di-*N*-acetyl derivative (**15b**): mp 184–186°. Recrystallization from ethanol gave an analytical sample: mp 185–187°; ir (KBr) 1670 and 1620 cm^{-1} (NAc).

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.92; H, 7.04; N, 12.22.

Compound **15c** could be transformed into **15b** in the usual way.

(1,3/4,6)-4,6-Diamino-1,3-cyclohexanediol (5a) Dihydrochloride (2,5-Dideoxystreptamine Dihydrochloride). A solution of **15a** (1.2 g) in a 1:1 mixture (40 ml) of ethanol and water containing 12*M* hydrochloric acid (1.2 ml) was hydrogenated in a Parr shaker apparatus in the presence of platinum catalyst (70 mg) under hydrogen stream (3.4 kg/cm^2) for 4.5 hr at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to give a crystalline product, which was pulverized with ethanol and filtered to give 1.6 g (88%) of **5a** dihydrochloride as needles: mp 290–295° dec. An analytical sample was obtained by recrystallization from aqueous ethanol, which showed the same melting behavior and a single spot (R_f 0.21) on paper chromatography (6:4:3:1 1-butanol–pyridine–water–acetic acid).

Anal. Calcd for $C_6H_{14}N_2O_2 \cdot 2HCl$: C, 32.89; H, 7.36; N, 12.79; Cl, 32.36. Found: C, 32.76; H, 7.15; N, 12.41; Cl, 32.04.

(1,3/4,6)-4,6-Diacetamido-1,3-cyclohexanediol (5c). To a suspension of **5a** dihydrochloride (51 mg) in methanol (5 ml) was added Amberlite IRA-410 (OH^-) (*ca.* 1 ml) and the mixture was stirred until it became a clear solution. Acetic anhydride (0.5 ml) was added dropwise to the solution and the reaction mixture was settled at room temperature overnight. The mixture was evaporated and the residue was washed with ethanol to give 28 mg (49%) of **5c,** mp 297.5–301°. Recrystallization from methanol gave an analytical sample, mp 301–302°.

Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.02; H, 7.73; N, 11.90.

Di-*O*-acetyl-(1,3/4,6)-4,6-diacetamido-1,3-cyclohexanediol (Tetra-*N,O*-acetyl-2,5-dideoxystreptamine) (5b). The crude **5c** derived from **5a** dihydrochloride (81 mg) was treated with acetic anhydride (4 ml) and pyridine (6 ml) overnight at room temperature. After being heated at 100° for 30 min, the reaction mixture was filtered to remove unreacted **5c** (20 mg), and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from ethanol–ether to give 51 mg (44% based on consumed **5c**) of **5b** as needles: mp 292–293°; pmr ($CDCl_3$) τ 3.75 (d, 2, J = 9 Hz, 2NHAc), 5.13 (t of d, 2, H-1 and H-3, J = 10.5, 10.5, and 5 Hz), 7.95 (s, 6, 2 OAc), 8.07 (s, 6, 2 NHAc); (DMSO-d_6) τ 5.31 (t of d, 2, H-1 and H-3, J = 11, 11, and 4.5 Hz), 6.11 (broad q of d, 2, H-4 and H-6).

Di-*N*-Carbobenzyloxy-(1,3/4,6)-4,6-diamino-1,3-cyclohexanediol (5d). To a solution of **5a** dihydrochloride (1.7 g) in a 2:1 mixture (60 ml) of acetone and water was added sodium carbonate (3.2 g). Carbobezyloxy chloride (14.3 ml of a 35% toluene solution) was added dropwise to the stirred solution under ice cooling. Stirring was continued overnight in a refrigerator, and then the resulting precipitates were collected and washed with toluene to give 2.65 g (83%) of **5d:** mp 198–199°. Recrystallization from ethanol afforded an analytical sample: mp 201°.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.37; N, 6.76. Found: C, 63.46; H, 6.27; N, 6.74.

6,7-Diazabicyclo[3.2.1]oct-6-ene-(2*S*,4*R*)-diol (16a). To a solution of **15a** (0.30 g) in water (5 ml) was added 30% hydrogen peroxide solution (0.65 ml, 3 molar equiv) and the solution was kept for 3 days at room temperature, at which time **15a** was shown to be completely converted into the faster moving component by tlc (5:1 2-butanone–toluene). An excess amount of hydrogen peroxide was destroyed by adding a small amount of Raney nickel and the mixture was filtered and evaporated to give a crystalline residue, which was pulverized with ethanol–ether giving 0.17 g (57%) of **16a,** mp 133–138°. Recrystallization from ethanol–ether afforded an analytical sample: mp 140–145°; uv_{max} (H_2O) 336 nm (ϵ 178).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.30; H, 6.99; N, 20.06.

Compound **16a** (60 mg) was treated with acetic anhydride (1 ml) in pyridine (5 ml) overnight at room temperature, and then the mixture was evaporated to give a syrup which crystallized upon addition of ethanol to give 57 mg (60%) of the diacetyl derivative (**16b**) as needles: mp 103–104°; uv_{max} (CH_3OH) 344 nm (ϵ 238).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.39. Found: C, 52.97; H, 6.18; N, 12.96.

This compound was also obtained from the decomposed **15a** by the usual acetylation.

2,3-Di-*O*-acetyl-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol (17). A mixture of 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol[24] (4.93 g) and 80% aqueous acetic acid (100 ml) refluxed for 30 min, and the mixture was then evaporated to dryness and the residue was treated with acetic anhydride (15 ml) and pyridine (25 ml) overnight at room temperature. The reaction mixture was poured into ice–water (400 ml) and the resulting precipitate was collected by filtration, giving 3.57 g (72%) of **17** as needles: mp 152–153.5°; pmr ($CDCl_3$) τ 4.33 (t, 1, H-2, J = 2.5 Hz), 6.97 (s, 6, 2 OMs), 7.83 and 7.95 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.10; H, 5.20; S, 16.51. Found: C, 37.43; H, 5.12; S, 16.21.

1,4-Di-*O*-mesyl-1,4/2,3-cyclohexanetetrol (19). A mixture of 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol[24] (2.5 g) and 80% aqueous acetic acid (50 ml) was refluxed for 20 min. The reaction mixture was then evaporated to dryness and the residue was crystallized from ethanol to give 0.99 g (50%) of **19** as needles: mp 129–130°. The recrystallized sample melted at 131–132°.

Anal. Calcd for $C_8H_{16}O_8S_2$: C, 31.78; H, 4.66; S, 21.21. Found: C, 31.79; H, 4.88; S, 21.00.

Di-*O*-acetyl-(1,3/2,4)-2,4-diacetamido-1,3-cyclohexanediol (Tetra-*N,O*-acetyl-4,5-dideoxystreptamine) (6b). (a) A mixture of **17** (1.0 g), sodium azide (1.0 g), and 90% aqueous 2-methoxyethanol (40 ml) refluxed for 19 hr. The reaction mixture was treated according to the procedure described before for azidolysis of **10a.** The syrupy product was crystallized from ethanol–ether to give 21 mg (2.9%) of **6b:** mp 240°. An analytical sample was obtained by recrystallization from chloroform: mp 274–275.5°.

(b) A mixture of **19** (0.40 g), anhydrous hydrazine (0.5 ml), and 2-methoxyethanol (30 ml) was refluxed for 90 min. The reaction mixture was evaporated to dryness, and the syrupy residue was dissolved in water (12 ml) and treated with Amberlite IRA-410 (OH^-). The solution was hydrogenated as described above for **15a** and the product was acetylated in the usual manner to afford 188 mg (46%) of **6b:** mp 274–275.5°; pmr (DMSO-d_6) τ 2.24 (d, 2, J = 9 Hz, 2 NHAc), 5.25 (t, 1, H-3, J = 10.5 Hz), 6.08 (q, 1, H-2, J 10.5 Hz).

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Registry No.—4b, 53534-82-0; **5a** 2HCl, 53534-83-1; **5b,** 53534-84-2; **5c,** 53534-85-3; **5d,** 53534-86-4; **6b,** 53534-87-5; **7b,** 53585-07-2; **8,** 53585-08-3; **9a,** 53534-88-6; **9b,** 53534-89-7; **10a,** 53586-53-1; **10b,** 53534-90-0; **11,** 53585-09-4; **12,** 53534-91-1; **14** (cis), 16063-08-4; **14** (trans), 16063-09-5; **15a,** 53534-92-2; **15b,** 53534-93-3; **15c,** 53534-94-4; **16a,** 53534-95-5; **16b,** 53534-96-6; **17,** 53534-97-7; **19,** 53534-98-8; 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol, 53534-99-9; 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol, 53585-10-7.

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