mixture was stirred for 0.75 hr and the inorganic salts were filtered. The ethereal solution was dried with $MgSO_4$ and removal of the solvent gave 230 mg of *N*-methyl-1,2,3,6-tetrahydropyridine (**23**): nmr (CCl_4) τ 4.12–4.63 (m, 2 H, CH=CH), 7.08–7.27 (m, 2 H), 7.42–8.02 (m, 4 H), and 7.77 (s, 3 H, NCH_3). The nmr spectrum was identical with that prepared by the $NaBH_4$ reduction of *N*-methylpyridinium iodide.[25]

Initiating a similar reaction as above but shortening the reaction time to 10 min rather than 11 hr led to *ca.* 30% of **23** and 70% of **24** by nmr analysis. An authentic sample of *N*-methyl-1,2-dihydropyridine was prepared by the reduction of *N*-carbomethoxy-1,2-dihydropyridine (**14**)[26] and by the method of Fry.[27]

Preparation of α-Diazoacetic Acid-α-*d* Ethyl Ester. To a round-bottomed flask with magnetic stirrer was added 20.1 g of D_2O, 1.147 g of triethylamine, and 22.8 g of α-diazoacetic acid ethyl ester. The mixture was stirred for 2.5 hr and the organic material was extracted with anhydrous ether. The ether was removed by rotary evaporation and the organic phase was added to 20.7 g of D_2O and 1.14 g of triethylamine and stirring was continued for 3.5 hr, whereupon organic material was reextracted with anhydrous ether, dried over calcium sulfate, removed from the ether by rotary evaporation, and distilled (25° (0.05 mm)) to yield 16.9 g of $N_2CDCO_2C_2H_5$ (98.1% D by nmr).

Reaction of *N*-Carbomethoxypyrrole with α-Diazoacetic Acid-α-*d* Ethyl Ester. The reaction procedure was identical with that using α-diazoacetic acid ethyl ester, yielding a 17% yield of *N*-carbomethoxy-6-carbethoxy-*6-d*-2-azabicyclo[3.1.0]hex-3-ene (**33**): nmr (DMSO-d_6) τ 3.27 (d, J = 4.0 Hz), 4.25–3.25 (m, 1 H), 5.65 (d, J = 7.0 Hz, 1 H), 5.81 (q, J = 7.0 Hz, 2 H), 6.17 (s, 3 H) 7.11 (d of d, J = 7.0 Hz, J' = 3.0 Hz, 1 H), 8.74 (t, J = 7.0 Hz, 3 H).

Pyrolysis of *N*-Carbomethoxy-6-carbethoxy-*6-d*-2-azabicyclo-[3.1.0]hex-3-ene (33). The conditions of pyrolysis were identical with those for **5b** yielding upon cooling *N*-carbomethoxy-2-carbethoxy-*2-d*-1,2-dihydropyridine (**37**): nmr (DMSO-d_6, TMS external reference) τ 3.28 (d, J = 7.5 Hz, 1 H), 3.89–4.23 (m, 1 H), 4.30–4.65 (m, 1 H), 4.64 (d, J = 9.0 Hz, 1 H), 4.71–5.08 (m, 1 H), 5.98 (q, J = 7.0 Hz, 2 H), 6.38 (s, 3 H) 8.97 (t, J = 7.0 Hz, 3 H).

Acknowledgment. Financial support for this work was provided by the National Science Foundation (GP-20099) and the Research Foundation of the State University of New York. We thank Professor Robert Kerber for informative discussions and Dr. David Christman for recording the mass spectra.

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The Total Synthesis of Kasugamycin[1]

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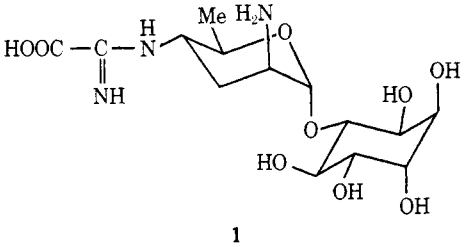
Contribution from the Institute of Microbial Chemistry, Shinagawa-ku, Tokyo, Japan, and Basic Research Laboratories, Toray Industries, Inc., Kamakura, Japan. *Received November 8, 1971*

Abstract: Kasuganobiosamine (**15d**) has stereoselectively been synthesized in ten steps, starting from 3,4-dihydro-6-methyl-2*H*-pyran-2-one (**2**). The key step involves the nitrosyl chloride addition to dihydropyran derivatives, *i.e.*, **2** → **3** and **12** → **13**, showing that the addition reaction is generally useful for the syntheses of the deoxyamino sugar moieties of kasugamycin, spiramycin, and tolypomycin Y. The displacement and resolution of **13** have been carried out by the reaction with 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol, yielding the product stereochemically conforming with natural kasuganobiosamine (D-**15d**), which is successfully crystallized in a pure state without any other procedure for the separation of the diastereoisomers. The selective α-glycosidation in the synthesis of *dl*-methylkasugaminide (**15c**) has been determined by X-ray crystallographic study.

Kasugamycin (**1**), found in 1965,[4] is an antibiotic produced by *Streptomyces kasugaensis* and is



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useful for the prevention of rice blast, being an ideal agricultural chemical with low toxicity to humans, animals, and plants. A therapeutic effect on *Pseudomonas* infection in humans has also been confirmed.[5]

The structure was established in 1966 by chemical[6] and X-ray crystallographic[7] studies which had led to assignment of the 1D-3-*O*-(2-amino-2,3,4,6-tetradeoxy-4-oxalamidino-α-D-*arabino*-hexopyranosyl)-*chiro*-inositol for kasugamycin.

The structural features characteristic of **1** include the following: (i) the 2-amino group is in an axial orientation, different from the 2-amino groups of other antibiotics such as streptomycin, kanamycin, neomycin, and paromomycin which are oriented equatorially,[8] (ii) a unique group of an amidine carboxylic acid in equatorial orientation, (iii) the presence of the α linkage between the 2-amino 2-deoxysugar residue and D-*chiro*-inositol.

In this paper, we report the stereoselective total synthesis of kasugamycin (**1**). There seem to be two main approaches to the synthesis of the amino sugar moiety of antibiotics. One is to start with carbohydrates

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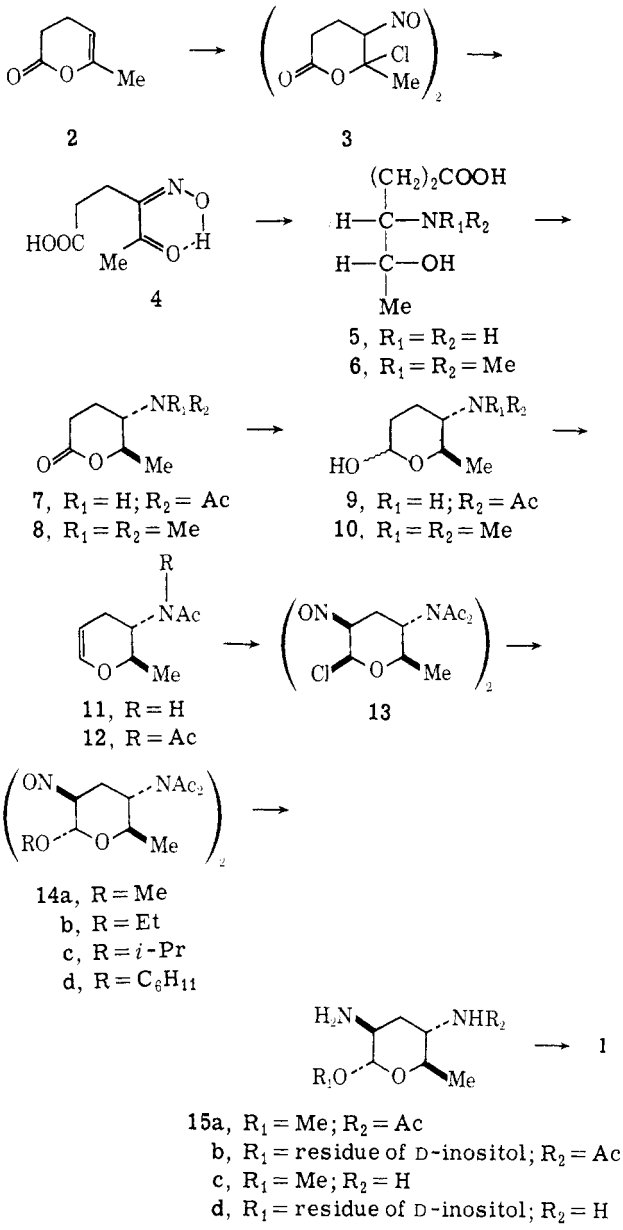
Scheme I

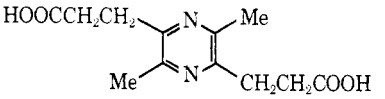


from natural sources, and the other is based on readily available chemicals.[9] In the former case, it is advantageous to use the absolute configuration of the original carbohydrates, although such syntheses require multistep chemical reactions in low overall yield as seen in the syntheses of D-galactosamine,[10] D-mannosamine,[11] D-lincosamine,[12] and paromose.[13] In the latter cases, there seem to be only a few examples in the field of amino sugars.[14]

We became interested in the latter approach to the stereoselective synthesis of 2,4-diamino-2,3,4,6-tetradeoxy-D-*arabino*-hexopyranose or the amino sugar moiety of **1**, and it was considered that the nitrosyl chloride addition to various cyclic olefins seems to be one of the best methods for fixation of nitrogen function on carbon,[15] presenting a useful synthetic method for amino sugars contained in antibiotics. Furthermore, it has been shown that the stereochemical addition reaction is very sensitive to olefin structures[16,17] and solvents.[18] It might, therefore, be possible to carry out the synthesis in a stereospecific manner, if the reaction conditions and the starting material are properly chosen.

Synthesis of DL-Methylkasugaminide (15c)

3,4-Dihydro-6-methyl-2*H*-pyran-2one[19] (**2**) was chosen as a suitable starting material (Scheme I). It was treated with nitrosyl chloride in methylene chloride at −60° to give a dimer of 6-chlorotetrahydro-6-methyl-5-nitrosopyran-2-one (**3**) in 97% yield. Direct catalytic hydrogenation of **3** was investigated with a view to reduce the nitroso group to the amino group and replace the chlorine atom with hydrogen, but it was found to be unsuccessful, affording only 3,6-dimethylpyrazine-2,5-dipropionic acid[20] (**16**) in low yield.



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However, it was shown that the chloronitroso dimer **3** was easily hydrolyzed with water at room temperature to afford 4-oximino-5-oxohexanoic acid (**4**) in quantitative yield, which might be formed through ring cleavage of the lactone **3** followed by isomerization of nitroso group to oxime. Although the stereochemistry of the nitroso and methyl groups was destroyed by ring cleavage and isomerization, the α-ketoxime **4** was considered to still be a suitable intermediate for *trans*-5-acetamidotetrahydro-6-methylpyran-2-one (**7**). The ketoxime **4** was selectively hydrogenated in the presence of platinum catalyst to give *erythro*-4-amino-5-hydroxyhexanoic acid (**5**) in 71% yield,[21] as in the case of α-methylaminopropiophenone,[22] and the proof of the stereochemistry of **5** was unambiguously made by nmr analysis of the cyclization product **18** as described later. The acid **5** was lactonized by treatment with acetic anhydride at room temperature, affording an N-acetylated lactone **7** in 95% yield. The lactone **7** was reduced with 0.5 mol equiv of lithium aluminum hydride to a hemiacetal[23] **9** in 70% yield, which by treatment with acetic anhydride and pyridine at room temperature followed by distillation gave a dihydropyran **11** in 95% yield. Furthermore, more drastic treatment of **9** with acetic anhydride and pyridine under reflux followed by distillation gave an *N*,*N*-diacetyl-

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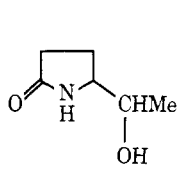
dihydropyran **12** in 70% yield. Simple heating of **5** at 150° afforded 5-(1-hydroxyethyl)pyrrolidone (**17**)



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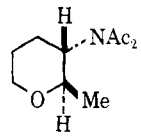

18

in 85% yield. The stereochemistry of the diacetylamino and methyl groups of **12** was confirmed to be trans by converting to the dihydro derivative **18**, showing a large coupling constant between the hydrogens in question ($J_{2,3}$ = 9.0 Hz).

Thus, it has clearly been shown that the hydrogenation product **5** has the erythro configuration. On the other hand, forosamine[24] obtained from the acid hydrolysate of spiramycin had the D erythro configuration,[25] which was considered to be easily accessible from **5** synthetically. The reductive dimethylation of **5** by Bowman's method[26] followed by lactonization with acetic anhydride gave **8** in 93% overall yield, which on reduction with 0.25 mol equiv of lithium aluminum hydride gave DL-forosamine (**10**) in 69% yield. This finding not only confirms the trans relation of the methyl and acetamido groups of **7**, but presents a new and useful method for the synthesis of a deoxyamino sugar from readily available chemicals. Furthermore, it should be mentioned here that the hemiacetal **9** is a racemic form of the *N*-acetyl derivative of tolyposamine obtained by mild acid hydrolysis of tolypomycin Y.[27] Although the dihydropyran derivatives **11** and **12** both have appropriate frameworks to the next fixation of nitrogen atom at C-2 for kasugamine (**15**, $R_1 = R_2 = H$) with the desired stereochemistry at C-4 and C-5, **12** was chosen for the following two reasons: (i) the acetamido group of **11** might undergo nitrosation with nitrosyl chloride,[28] decreasing the yield of nitrosochlorination product on the double bond; (ii) the bulky diacetylamino group of **12** might cause a steric hindrance at the transition state of nitrosyl chloride addition from α-side attack, preferring β-side attack of cis addition.[16,17]

N,N-Diacetyldihydropyran **12** was treated with nitrosyl chloride under similar conditions as in the case of **3**, affording the expected chloronitroso dimer **13** in 83% yield, but the dimeric adduct was found to be highly unstable and could not be treated above room temperature for the next step. Initially, it was thought necessary to perform the condensation of the nitrosyl chloride adduct **13** with alcohols by the application of the methods which utilize the properties characteristic of α-chloronitroso dimer[29] or α-chloroxime,[15] but the results always afforded only tarry materials. However, the condensation reaction of **13** with various alcohols was successfully carried out by using another method which utilized the property of α-chloroalkyl ether.[30] Thus, displacement of **13** with lower alcohols such as methanol, ethanol, isopropyl alcohol, and cyclohexanol in the presence of mercuric cyanide[30b] at room temperature and in a suspension state afforded the corresponding α-glycosides of nitroso dimer **14** in good yields as shown in Table I. The molecular weight

Table I. Displacement of **13** with Alcohols in the Presence of Mercuric Cyanide

Alcohol	Yields of **14**, %	Mp, °C	$J_{1,2}$ of **14**, Hz
Methanol	77	135–136	~0
Ethanol	73	139–140	~0
Isopropyl alcohol	61	129–130	~0
Cyclohexanol	44	134–136	~0

determination and ir spectra[31] of these glycosides clearly showed that they are dimeric nitroso compounds. The results are quite different from those obtained by Lemieux, *et al.*,[15b] showing no isomerization of the nitroso group to oxime. Therefore, direct reduction of the nitroso group was investigated to give the amino group at C-2 and also to establish the stereochemistry of nitrosyl chloride addition to **12**.

Hydrogenation of **14a** over Pt followed by separation using an ion-exchange resin (Dowex 50) afforded *N*-acetyl derivative **15a** in 96% yield showing that one of the acetyl groups of **14** was easily hydrolyzed. The hydrolysis of **15a** with barium hydroxide gave DL-methylkasugaminide (**15c**) in 91% yield, showing an identical nmr spectrum with that of methylkasugaminide obtained from natural kasugamycin.

The purity of **15c** was confirmed by tlc and analysis of the nmr spectrum. This evidence indicates that the nitroso group is exclusively introduced in the axial configuration at C-2 by the addition of nitrosyl chloride. The reason might be the steric hindrance of the bulky diacetylamino group at the C-4 position as described before. Furthermore, it is to be noted that the yields of various glycosides **14a–d** are decreasing with the increasing number of carbons of alcohols. This evidence may simply be due to steric hindrance. The precise mechanism of the nucleophilic attack of the alcohol at the anomeric center of dimeric 2,3,4,6-tetradeoxy-4-(diacetylamino)-2-nitroso-β-DL-*arabino*-hexopyranosyl chloride (**13**) was not determined. Nevertheless, the high degree of stereospecificity of the α-glycosidation can readily be appreciated by the consideration of transition state from the viewpoint of steric effect.

Stereochemistry of Methylkasugaminide (15c)

Confirmation of the selective α-glycosidation by the synthesis described above depends upon the extended application of nmr methods[32–34] to the synthetic prod-

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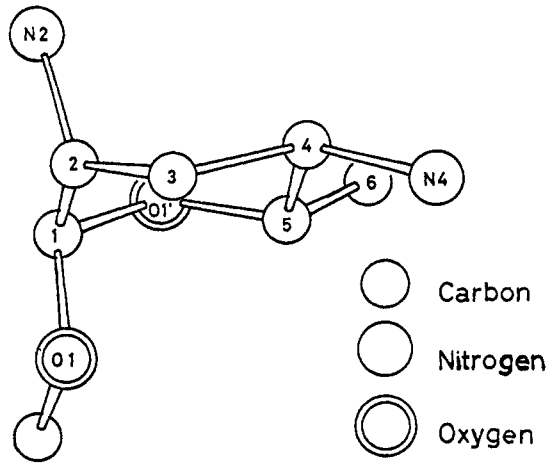

Figure 1. A perspective drawing of a molecule of **15c** (L form).

uct and natural methyl 2,4-diamino-2,3,4,6-tetradeoxy-α-D-*arabino*-hexopyranoside (D-**15c**).[35] The chemical shifts of the anomeric protons of D-**15c** and D-**15d** are located at 4.57 ppm with $J_{1,2}$ = 1.6 Hz and 5.02 ppm with $J_{1,2}$ = 1.7 Hz, respectively, suggesting that D-**15d** has an equatorial anomeric proton. The anomeric proton of D-**15c** seems to be axial from the chemical shift, but the coupling constant supports the equatorial H_1–equatorial H_2 relation. Although it seems to be more reliable to decide the stereochemistry of the anomeric proton of pyranoside ring by the coupling constant $J_{1,2}$ than by the chemical shift, it was considered to be necessary to establish the relation between the coupling constant and the configuration of **15c** by an independent method. It was of particular interest, therefore, to examine **15c** by X-ray crystallography in order to determine if the presence of an axial amino group at C-2 results in any conformational modification.

The X-ray studies on the selenate of **15c** showed that the anomeric proton is equatorially oriented and the dihedral angle ($\phi_{1,2}$) is approximately 73°, showing the pyrane ring takes the chair conformation which is somewhat flatter than an ideal cyclohexane ring (Figure 1). The results correspond to the conformation **15c** in solution[36] and clearly support the conclusion derived from Coxon's nmr method, and directly show that the nitroso group is exclusively introduced in the axial configuration at C-2 and that the α-glycosidation is highly stereospecific.

Synthesis of Kasuganobiosamine (15d)

Although the methyl glycoside **15c** was considered to be a good candidate for the synthesis of racemic **15d** according to a general method of glycoside synthesis,[37] we became interested in the direct synthesis of **15d** from **13**, which means that the optical resolution of **13** is also carried out at the stage of the reaction of the α-chloroalkyl ether moiety of **13** with D-*chiro*-inositol.

Thus, the chloronitroso dimer **13** was treated with excess 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol[38] in methylene chloride at 0° in the presence of silver carbonate, silver perchlorate, and Drielite,[30a,39,40] followed by hydrogenation over Pt in acetic acid and boiling in 50% acetic acid. The reaction product was carefully purified by chromatography using Dowex 50 (H form) to afford a crude material, $[\alpha]^{22}D$ +31° (*c* 1.3, water). It was further purified through a column of Amberlite CG-50 (ammonium form) and one of the ninhydrin positive fractions was estimated to consist of mainly **15b** from the chromatographic behavior, $[\alpha]^{27}D$ +54° (*c* 1.5, water). It was crystallized from a mixed solvent of methanol and acetone, then recrystallized three times, and further recrystallized from isopropyl alcohol to yield N^4-acetylkasuganobiosamine (**15b**), $[\alpha]^{25}D$ +108° (*c* 1.3, water).

Although the yield of **15b** thus obtained was miserable, the synthetic material **15b** was confirmed to be identical with the N^4-acetyl derivative,[6b] D-**15b**, of natural kasuganobiosamine in all respects, including nmr, ir, optical rotation, and mixture melting point. The treatment of **15b** with barium hydroxide afforded kasuganobiosamine **15d** in 96% yield. The synthesis of **15d** completes the total synthesis of kasugamycin (**1**), since D-**15d** was previously converted to kasugamycin (**1**) by treatment with the diethyl ester of oxalimidic acid and subsequent mild acid hydrolysis in our structural studies.[6]

The displacement of **13** with D-*chiro*-inositol derivative was found rather difficult affording a poor yield of **15b**, compared with lower alcohols. This may be due to the steric hindrance of reactants and the partial decomposition of **13** during the reaction time.

However, it is noteworthy that not only the displacement but also the resolution of **13** has been carried out by the reaction with 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol, yielding the product stereochemically conforming with natural kasuganobiosamine, which is successfully crystallized in a pure state without any other procedure for the separation of the diastereoisomers.

The stereoselective synthesis of the 2-amino 2-deoxysugar moiety of **1** and the selective α-glycosidation developed in this synthetic work have made possible the chemical modification of kasugamycin. Thus, a number of kasugamycin homologs have been synthesized, and the biological results of such syntheses will be published in a separate paper.

Experimental Section

General. Boiling points and melting points are uncorrected. The latter were taken on a Mettler EPI apparatus. Infrared spectra were determined with a Hitachi EPI-2 spectrophotometer. Nuclear magnetic resonance spectra were measured on Varian A-60 and HA-100 instruments, and the internal standards used in deuterium oxide and in organic solvents were sodium 2,2-dimethyl-2-silapen-

(35) All synthetic materials **5**–**15** are racemic except **15b** and **15d** (Scheme I), but only one member of the pairs is shown in the scheme. Therefore, the sign of D configuration is added to express derivatives from natural kasugamycin.

(36) Although the conformation in solid state may not always correspond to that in solution, it can be considered to hold the essentially same conformation in such a simple system as **15c**. For such examples, see J. B. Lambert, *Accounts Chem. Res.*, 4, 87 (1971).

(37) During our synthetic work on kasugamycin, a synthesis of kasuganobiosamine (**15d**) *via* methylkasugaminide (**15c**) starting from D-glucose was reported (M. Nakajima, H. Shibata, K. Kitahara, S. Takahashi, and A. Hasegawa, *Tetrahedron Lett.*, 2271 (1968)) and later a synthesis of methylkasugaminide (**15c**) starting from 2-ethoxy-3,4-dihydro-6-methyl-2*H*-pyran was reported (S. Yasuda, T. Ogawara, S. Kawabata, I. Iwataki, and T. Matsumoto, *ibid.*, 3969 (1969)).

(38) C. E. Ballon and H. O. Fischer, *J. Amer. Chem. Soc.*, 75, 3673 (1953).

(39) Helferich's method using $Hg(CN)_2$ was unsatisfactory in this reaction. Therefore, stronger reagents to abstract chlorine atom were used.

(40) Although there are two free hydroxy groups in the di-*O*-isopropylidene-*chiro*-inositol, it is apparent that the same glycoside is obtained from the reaction of either hydroxy group.

tane-5-sulfonate and tetramethylsilane, respectively. Rotations were measured on a Carl Zeiss 0.005° photoelectric polarimeter. Paper chromatography (ppc) was performed on Toyo Roshi No. 51A. Thin layer chromatography was performed on silica gel F254 (Merck) and avicel (Funakoshi Yakuhin); spots were visualized with iodine vapor or ninhydrin reagent. Solvents used for tlc were: A, butyl alcohol–acetic acid–water (4:1:5, organic phase); B, pyridine–acetone–water–acetic acid (5:4:3:2); C, 5% acetic acid–ethanol–ethyl acetate (1:1:1); D, methyl acetate–isopropyl alcohol–28% ammonia (3:7:2).

Dimeric DL-6-Chlorotetrahydro-6-methyl-5-nitroso-2*H*-pyran-2-one (3). A solution containing 10 g of 3,4-dihydro-6-methyl-2*H*-pyran-2-one (**2**) in 50 ml of anhydrous dichloromethane was cooled to −60° under nitrogen. Nitrosyl chloride (6.7 g) was passed into the solution during 30 min, keeping the temperature between −60 and −50°. The reaction mixture became green at the beginning, and then colorless crystals were precipitated. The crystals obtained after filtration were washed well with cold ether and dried in a cold place. There was obtained 15.36 g (97% yield) of **3** as colorless crystals: mp 74–75°; ir (KBr) 1758 (lactone C=O) and 1200 cm^{-1} (dimeric NO).

Anal. Calcd for $(C_6H_8NO_3Cl)_2$: C, 40.58; H, 4.54; N, 7.89; O, 27.03. Found: C, 40.36; H, 4.61; N, 7.73; O, 26.75.

Catalytic Reduction of 3. The chloronitroso dimer **3** was hydrogenated at room temperature over Pd/C. The reduction product was purified through a column of Amberlite CG-50 (H form, 2 × 50 cm). The crystals thus obtained were separated by filtration, washed with cold water, and dried. There was obtained 865 mg of colorless crystals, mp 207–208°. This material was identical in all respects with 3,6-dimethylpyrazine-2,5-dipropionic acid which was prepared by the method of Bullerwell, *et al.*[20]

4-Oximino-5-oxohexanoic Acid (4). A suspension of 1 g of **3** in a mixed solvent of dioxane (20 ml) and water (5 ml) was stirred at 20–30°, until a clear solution was obtained. To this solution was added an equivalent amount of 1 *N* sodium hydroxide solution (5.63 ml) and the mixture was evaporated under reduced pressure to a white crystalline residue. To the residue was added 30 ml of ethyl acetate. The mixture was stirred for 15 min and filtered, and the filtrate was evaporated under reduced pressure to give 900 mg (nearly quantitative yield) of crude acid **4** as a colorless crystalline mass, suitable for direct use for the next step. Recrystallization from chloroform gave colorless needles which contain chloroform as the crystal solvent. Drying the crystals *in vacuo* at 50° for 24 hr gave 750 mg (84% yield) of white amorphous acid **4**: mp 94–95.5°; ir (KBr) 3500–2500 (OH) and 1695 cm^{-1} (C=O); nmr (D_2O) δ 2.38 (s, 3, $COCH_3$) and 2.68 (m, 4, CH_2CH_2).

Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80; O, 40.22. Found: C, 45.19; H, 5.67; N, 8.84; O, 40.14.

DL-*erythro*-4-Amino-5-hydroxyhexanoic Acid (5). A solution of 12 g of **4** in 150 ml of water was hydrogenated in the presence of 0.3 g of platinic oxide at room temperature and an initial pressure of 60 psi. After 10 hr, the catalyst was removed by filtration and the filtrate was concentrated to a small volume. To this solution was added hot ethanol until precipitation began. The mixture was cooled in a refrigerator overnight and then filtered, and the crystals were washed with a small amount of ethanol to give 7.88 g (71% yield) of product **5** as colorless crystals: nmr (D_2O) δ 1.20 (d, 3, J = 6.7 Hz, CH_3), 3.28 (d of d of d, 1, $J_{4,5}$ = 3.6, $J_{4,3a}$ = 5.5, $J_{4,3b}$ = 7.8 Hz, H-4), and 4.10 (d of q, 1, $J_{5,6}$ = 6.7, $J_{5,4}$ = 3.6 Hz, H-5).

An analytical sample, mp 185–186° dec, was recrystallized from water–ethanol.

Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90; N, 9.52; O, 32.62. Found: C, 48.94; H, 8.85; N, 9.74; O, 32.86.

DL-*trans*-5-Acetamidotetrahydro-6-methylpyran-2-one (7). A suspension of 5 g of **5** in 25 ml of acetic anhydride was stirred at 20–25° until a clear solution was obtained. The solution was carefully evaporated at 35–40° (bath temperature) under reduced pressure (1 mm), and the last traces of acetic anhydride were removed by flashing off with toluene. Distillation of the oily residue gave 6.5 g (95% yield) of lactone **7** as a viscous oil, bp 165–168° (0.22 mm). Upon cooling the product solidified as very hygroscopic crystals. An analytical sample was redistilled: bp 165–167° (0.22 mm); ir (neat) 1737 (lactone C=O), 1662 (amide I), and 1554 cm^{-1} (amide II); nmr ($CDCl_3$) δ 1.04 (d, 3, J = 6.5 Hz, CH_3) and 2.20 (s, 3, $COCH_3$).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18; O, 28.04. Found: C, 56.34; H, 7.84; N, 8.21; O, 28.05.

DL-*erythro*-4-(Dimethylamino)-5-hydroxyhexanoic Acid (6). A mixture of **5** (4 g) and 37% formalin (5.1 ml) in 100 ml of water was hydrogenated in the presence of 5% Pd/C (3 g) at room temperature and an initial pressure of 50 psi for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The crystalline residue was recrystallized from methanol–ether to give 5.0 g (97.7% yield) of dimethylated product **6** as colorless platelets: mp 158–159°; nmr (D_2O) δ 2.89 (s, 6, NMe_2).

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.83; H, 9.78; N, 7.99; O, 27.39. Found: C, 54.93; H, 9.83; N, 8.26; O, 27.89.

DL-*trans*-5-(Dimethylamino)tetrahydro-6-methylpyran-2-one (8). A solution of 2 g of dimethylamino acid **6** in 20 ml of acetic anhydride was stirred at room temperature for 12 hr. The mixture was evaporated under reduced pressure, and the residue was distilled to yield 1.7 g (95% yield) of lactone **8** as a colorless oil: bp 114–115° (5 mm); ir (neat) 1743 cm^{-1} (lactone C=O); nmr ($CDCl_3$) δ 1.43 (d, 3, J = 6.5 Hz, CH_3), 2.29 (s, 6, NMe_2), and 4.46 (d of q, 1, $J_{5,4}$ = 8.9 Hz, H-5).

A sample of the product was converted to its picrate crystallized from methanol, mp 153–154°.

Anal. Calcd for $C_{14}H_{18}N_4O_9$: C, 43.52; H, 4.70; N, 14.50; O, 37.27. Found: C, 43.52; H, 4.76; N, 14.16; O, 37.29.

DL-Forosamine (10). A solution of 1.57 g of lactone **8** in 10 ml of anhydrous tetrahydrofuran was cooled to −20°. To this solution was added with stirring 4.4 ml of a 4.3% solution[41] of lithium aluminum hydride in tetrahydrofuran during 10 min at −20°. Stirring was continued for 1.5 hr at −20° and then a mixture of tetrahydrofuran (40 ml) and water (1 ml) was slowly added. The resulting slurry was filtered and the solid part was washed with tetrahydrofuran. The filtrate and washings were combined, dried over anhydrous potassium carbonate, and filtered. Removal of the solvent and fractional distillation of the residue yielded 1.1 g (69% yield) of hemiacetal **10** as a colorless oil, bp 92–94° (2 mm). The nmr spectrum of this product in deuterium oxide was identical with that of forosamine[24] obtained by degradation of spiramycins. The tlc behavior, identical with that of natural forosamine, was as follows: avicel R_f 0.41 (solvent A) and 0.72 (solvent C); silica gel R_f 0.87 (solvent D). A sample of the product was converted to its picrate crystallized from ethanol–ether–petroleum ether, mp 155.5–157°.

Anal. Calcd for $C_{14}H_{20}N_4O_9$: C, 43.30; H, 5.19; N, 14.43; O, 37.08. Found: C, 43.38; H, 5.46; N, 14.20; O, 36.98.

DL-5-Acetamidotetrahydro-6-methylpyran-2-ol (*N*-Acetyl-DL-toryposamine) (9). A solution of 9 g (5.26 mmol) of lactone **7** in 100 ml of anhydrous tetrahydrofuran was cooled to −20° while 23 ml (2.77 mmol) of a 4.57% solution[41] of lithium aluminum hydride in tetrahydrofuran was added with stirring during 30 min at −20°. After 1 hr, 50 ml of tetrahydrofuran was added, followed by addition of 4 g of ice, and the reaction mixture was brought to 0°. The resulting slurry was filtered and the solid part was washed with acetone (two 30-ml portions). The filtrate and washings were combined and evaporated under reduced pressure to give a colorless crystalline material. Recrystallization of the crude product from acetone–ether gave 6.37 g (70% yield) of hemiacetal **9** as colorless crystals: mp 139–141° dec; ir (KBr) 3400 (OH), 3300, 3090 (NH), 1645 (amide I), and 1558 cm^{-1} (amide II); nmr (CD_3COCD_3) δ 1.05 and 1.09 (two d, 3, J = 6, 6 Hz, CH_3), and 1.88 and 1.93 (two s, 3, $COCH_3$).

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; O, 27.71. Found: C, 55.43; H, 8.68; N, 7.83; O, 27.72.

A sample of **9** was converted to anomeric methyl 4-benzoylamido-2,3,4,6-tetradeoxyhexopyranosides by glycosidation (Dowex 50–methanol) followed by deacetylation (barium hydroxide) and benzoylation (benzoic anhydride). Separation by preparative tlc, followed by crystallization from ethanol–benzene, afforded the α and β anomers, whose nmr spectra were identical with those of the α and β isomers of natural methyl *N*-benzoyltoryposaminide,[30] respectively: α anomer, mp 148–149°; nmr ($CDCl_3$) δ 1.25 (d, 3, $J_{6,5}$ = 6 Hz, H-6), 3.35 (s, 3, OCH_3) and 4.69 (s with fine splitting, 1, anomeric H); β anomer, mp 169–171°; nmr ($CDCl_3$) δ 1.31 (d, 3, $J_{6,5}$ = 6 Hz, H-6), 3.48 (s, 3, OCH_3), and 4.37 (d of d, 1, $J_{1,2a}$ = 8, $J_{1,2b}$ = 3 Hz, anomeric H).

DL-*trans*-3-Acetamido-3,4-dihydro-2-methyl-2*H*-pyran (11). A mixture of hemiacetal **9** (1 g), acetic anhydride (5 ml), and pyridine (5 ml) was stirred at room temperature for 3 hr. The resulting clear solution was evaporated under reduced pressure. Distillation of the residue gave an oil, bp 125–128° (3 mm), which was crystallized from hexane to give 850 mg (95% yield) of dihydropyran **11** as

(41) The concentration of lithium aluminum hydride solution was determined by the method of J. A. Krynitsky, J. E. Johnson, and H. W. Carhart, *Anal. Chem.*, **20**, 311 (1948).

colorless crystals: mp 56–59°; nmr ($CDCl_3$) δ 4.61 (m, 1, H-5) and 6.26 (d of t, 1, $J_{6,5}$ = 6.1 Hz, H-6).

An analytical sample, mp 58–59°, was recrystallized from ether–hexane.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.12; H, 9.62; N, 8.91; O, 20.35. Found: C, 61.33; H, 9.77; N, 8.95; O, 20.40.

DL-*trans*-3-(Diacetylamino)-3,4-dihydro-2-methyl-2*H*-pyran (12). A mixture of 10 g of **9**, 50 ml of acetic anhydride, and 50 ml of pyridine was heated under reflux for 8 hr. The mixture was evaporated under reduced pressure, and the residue was distilled to give a pale yellow oil, bp 110–125° (4 mm), which was then treated with 100 ml of hexane and 60 ml of water. The mixture was shaken, and the aqueous phase was washed with 20 ml of hexane. The combined hexane extract was washed with water (two 10-ml portions), dried over anhydrous potassium carbonate, and filtered. Removal of the solvent and distillation of the residue yielded 5.24 g of product **12**: bp 110–111° (3.5 mm); $n^{25}D$ 1.4870; ir (neat) 1700 cm^{-1} (imido C=O); nmr ($CDCl_3$) δ 2.38 (s, 6, NAc_2), 3.78 (d of d of d, 1, J = 11, 9, 6 Hz, H-3), 4.5–4.9 (m, 2, H-2 and H-5), and 6.17 (d of t, 1, $J_{6,5}$ = 6 Hz).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10; O, 24.34. Found: C, 61.08; H, 7.84; N, 7.18; O, 24.05.

The combined aqueous phase which contained **11** as a major component was taken to dryness *in vacuo*, and the residue was treated with acetic anhydride and pyridine followed by isolation of the product as described above. There was obtained an additional 2.73 g of product **12**. The combined yield was 7.97 g (70% yield).

DL-*trans*-3-(Diacetylamino)tetrahydro-2-methylpyran (18). Compound **12** (0.4 g) in 30 ml of ethanol was hydrogenated over Pt at room temperature, yielding 0.31 g of **18**: bp 115–117° (4.5 mm); $n^{25}D$ 1.4746; nmr ($CDCl_3$) δ 3.25–3.60 (m, 2), 3.86 (m, 1), and 4.22 (d of q, 1, $J_{2,3}$ = 9.0 Hz, H-2).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03; O, 24.09. Found: C, 59.97; H, 8.65; N, 7.31; O, 24.30.

Dimeric 2,3,4,6-Tetradeoxy-4-(diacetylamino)-2-nitroso-β-DL-*arabino*-hexapyranosyl Chloride (13). A solution containing 3 g of **12** in 10 ml of anhydrous dichloromethane was cooled to −70°. Nitrosyl chloride was passed into the cold solution with stirring at −60°, until the solution became reddish brown. After addition of 300 ml of ether, the mixture was carefully evaporated under reduced pressure until it became pale blue. The mixture was filtered quickly in a drybox, and the solid was washed well with anhydrous ether, and dried *in vacuo* in a cold plate. There was obtained 3.33 g (83% yield) of product **13** as white amorphous powder: mp 75–76° dec; ir (KBr) 1193 cm^{-1} (dimeric NO).

Attempts to crystallize the substance led to extensive decomposition.

Anal. Calcd for $(C_{10}H_{15}N_2O_4Cl)_2$: C, 45.72; H, 5.76; N, 10.67. Found: C, 45.63; H, 5.80; N, 10.66.

Dimeric Alkyl 2,3,4,6-Tetradeoxy-4-(diacetylamino)-2-nitroso-α-DL-*arabino*-hexopyranosides 14a–c. To a stirred suspension of 0.4 g of **13** and 0.4 g of finely powdered mercuric cyanide in 20 ml of anhydrous dichloromethane was added 10 ml of methanol. The mixture was stirred at room temperature for 3 hr to give a transparent solution which was then evaporated to dryness under reduced pressure. The crystalline residue was treated with 50 ml of methanol, and the insoluble crystals were collected by filtration. Recrystallization from dichloromethane–methanol afforded 301 mg (76.5% yield) of methyl nitroso glycoside **14a** as colorless crystals: mp 135–136°; ir (KBr) 1693 (imido C=O) and 1200 cm^{-1} (dimeric NO); nmr ($CDCl_3$) δ 3.44 (s, 3, OCH_3), 4.89 (s, 1 , H-1), and 5.11 (m, 1, H-2).

Anal. Calcd for $(C_{11}H_{18}N_2O_5)_2$: C, 51.15; H, 7.03; N, 10.85; O, 30.98; mol wt, 516.5. Found: C, 51.25; H, 7.05; N, 10.73; O, 30.51; mol wt, 530.5 (by vapor pressure osmometer).

Ethyl nitroso glycoside **14b** was prepared in 73% yield in a similar manner: mp 139–140°; ir (KBr) 1200 cm^{-1} (dimeric NO).

Anal. Calcd for $(C_{12}H_{20}N_2O_5)_2$: C, 60.89; H, 7.67; N, 7.10; O, 24.34. Found: C, 61.08; H, 7.84; N, 7.18; O, 24.05.

Isopropyl nitroso glycoside **14c** was prepared in 61% yield in a similar manner: mp 129–130°; ir (KBr) 1205 cm^{-1} (dimeric NO).

Anal. Calcd for $(C_{13}H_{22}N_2O_5)_2$: C, 54.53; H, 7.75; N, 9.45; O, 27.94. Found: C, 54.57; H, 7.63; N, 9.45; O, 27.99.

Dimeric Cyclohexyl 2,3,4,6-Tetradeoxy-4-(diacetylamino)-2-nitroso-α-DL-*arabino*-hexopyranoside (14d). To a mixture of cyclohexanol (50 ml) and finely powdered mercuric cyanide (2 g) in 100 ml of anhydrous dichloromethane was added 4 g of **13**. The mixture was stirred at room temperature for 3 hr. The resulting clear solution was diluted with 150 ml of dichloromethane, then washed several times with water until the aqueous washings were neutral. The organic layer was concentrated under reduced pressure to a volume of about 70 ml. Ethanol (100 ml) was added to the solution, and the mixture was again concentrated to a volume of about 80 ml. Water was added to cause crystallization. The mixture was filtered and the crystals were washed with water–ethanol. There was obtained 2.17 g (44% yield) of product **14d** as colorless crystals: mp 134–136°; ir (KBr) 1695 (imido C=O) and 1202 cm^{-1} (dimeric NO); nmr ($CDCl_3$) δ 1.2–2.1 (m, 10), 3.66 (m, 1), and 5.18 (s, 1, anomeric H).

An analytical sample, mp 135.5–136.5°, was recrystallized from dichloromethane–hexane.

Anal. Calcd for $(C_{16}H_{26}N_2O_5)_2$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.99; H, 8.00; N, 8.14.

Methyl 4-Acetamido-2-amino-2,3,4,6-tetradeoxy-α-DL-*arabino*-hexopyranoside (15a). A suspension of 1 g (1.94 mmol) of dimeric methyl nitroso glycoside **14a** in 40 ml of 95% acetic acid was hydrogenated in the presence of 0.1 g of platinic oxide at room temperature and an initial pressure of 60 psi for 5 hr. The catalyst was removed by filtration and the filtrate was diluted with 800 ml of water. The mixture was passed through a column of Dowex 50W-X4 (H form, 100–200 mesh, 1.5 × 25 cm). The column was washed once with 300 ml of water and then eluted with 0.2 *N* ammonium hydroxide solution. The ninhydrin-positive fractions were combined and 0.804 g of a solid material was obtained after removal of the solvent. It was dissolved in a small amount of water and treated with an equivalent amount of 1 *N* hydrochloric acid (3.87 ml). Freeze-drying of the aqueous solution gave a white solid which was crystallized from ethanol–ether. There was obtained 0.887 g (96% yield) of the hydrochloride of **15a** as colorless crystals: mp 203–204° dec; ir (KBr) 1655 (amide I) and 1540 cm^{-1} (amide II); nmr (D_2O) δ 1.98 (s, 3, $COCH_3$), 3.10 (m, 1, H-2), and 4.54 (d, 1, J = 1.8 Hz, anomeric H).

Anal. Calcd for $C_9H_{18}N_2O_3 \cdot HCl$: C, 45.28; H, 8.02; N, 11.74; O, 20.11. Found: C, 45.55; H, 8.04; N, 11.54; O, 20.09.

Methyl 2,4-Diamino-2,3,4,6-tetradeoxy-α-DL-*arabino*-hexopyranoside (DL-Methylkasugaminide) (15c). A solution of 0.5 g of **15a** dissolved in 100 ml of aqueous solution saturated with barium hydroxide was refluxed for 48 hr. The solution was neutralized with carbon dioxide, from which the solid part was removed and washed well with water. The filtrate and washings were combined and concentrated to a volume of about 200 ml. The solution was passed through a column of Dowex 50W-X4 (H form, 100–200 mesh, 1.5 × 25 cm). The column was washed once with 200 ml of water and then eluted with 0.2 *N* ammonium hydroxide solution. The ninhydrin-positive fractions were combined and concentrated under reduced pressure to a volume of about 10 ml. This solution was carefully acidified to pH 4 with diluted hydrochloric acid and evaporated under reduced pressure to a hygroscopic solid which was crystallized from ethanol–ether, affording 0.541 g (90.5% yield) of the dihydrochloride–hemihydrate of **15c** as colorless crystals: mp 164–165° dec; tlc (avicel) R_f 0.48 (solvent B) and 0.53 (solvent C); nmr (D_2O) δ 1.39 (d, 3, J = 6.5 Hz, Me), 2.1–2.5 (m, 2, H-3a and H-3b), 3.49 (s, 3, OMe), 4.14 (d of q, 1, $J_{5,4}$ = 9.5 Hz, H-5), and 4.87 (d, 1, J = 2.0 Hz, anomeric H).

The tlc behavior and nmr spectrum of this product were identical with those of the dihydrochloride of methylkasugaminide (D-**15c**) obtained by degradation of kasugamycin.[6b]

Anal. Calcd for $C_7H_{16}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 34.71; H, 7.91; N, 11.57; O, 16.52. Found: C, 34.55; H, 7.87; N, 11.80; O, 16.86.

A sample of the product was converted to its selenate which crystallized from water–methanol, mp 175–200° dec. This material was employed for the X-ray crystallographic study described later.

1D-3-*O*-(4-Acetamido-2-amino-2,3,4,6-tetradeoxy-α-D-*arabino*-hexopyranosyl)-*chiro*-inositol (N^4-Acetylkasuganobiosamine) (15b). A mixture of 50 g of 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol, 15 g of freshly prepared silver carbonate, 0.1 g of silver perchlorate, and 10 g of activated Drielite was suspended in 200 ml of anhydrous dichloromethane. To the mixture was added 5.3 g of **13**, and stirring was continued at room temperature for 35 hr in the dark. The mixture was filtered and the filtrate was evaporated under reduced pressure to a solid residue which was then dissolved in 250 ml of hot benzene. Upon allowing the benzene solution to stand overnight, 38.95 g of unreacted diisopropylideneinositol was removed. The filtrate was evaporated under reduced pressure. The syrupy residue was dissolved in 130 ml of 95% acetic acid solution and the mixture was hydrogenated in the presence of 1.1 g

of platinic oxide at room temperature. The catalyst was removed by filtration. To the filtrate was added 20 ml of 1 *N* hydrochloric acid and 120 ml of water, and the mixture was heated under reflux for 5 hr. The resulting yellow solution was diluted with 1800 ml of water and the mixture was passed through a column of Dowex 50W-X4 (H form, 50–100 mesh, 2.5 × 21 cm). The column was washed with 500 ml of water and then eluted with 0.25 *N* ammonium hydroxide solution. The ninhydrin-positive fractions were combined and concentrated to a small volume. Freeze-drying of the concentrated solution gave 2.31 g of a pale yellow hygroscopic solid, $[\alpha]^{22}D$ +31° (*c* 1.3, water), which was then dissolved in 170 ml of water. The aqueous solution was again passed through a column of Amberlite CG-50 (ammonium form, type 1, 2.3 × 40 cm) and the column was eluted with water. A flow rate of 0.75 ml/min was employed and 15-ml fractions were collected. The second ninhydrin-positive fractions (fractions 83–109) were combined and concentrated under reduced pressure to a small volume. Freeze-drying of the aqueous solution afforded 515 mg of a white solid, $[\alpha]^{27}D$ +54° (*c* 1.5, water). A careful ppc examination of the freeze-dried product (*n*-butyl alcohol–pyridine–water, 3:2:2) showed that the mixture was composed of four ninhydrin positive components and that the R_f value (0.28) of the major component was identical with that of natural N^4-acetylkasuganobiosamine (D-**15b**). The crude material was dissolved in 30 ml of methanol and the solution was cooled, affording a small amount of gummy product. The methanol solution was removed by decantation and concentrated under reduced pressure to a small volume. Acetone was added and there was obtained a partly crystalline gummy material which was recrystallized three times from methanol–acetone to give 14.65 mg (0.21% yield) of colorless crystals, $[\alpha]^{26}D$ +109° (*c* 1.1, water). Further recrystallization from absolute isopropyl alcohol yielded 9.72 mg (0.14% yield) of N^4-acetylkasuganobiosamine (**15b**), identical with an authentic sample, D-**15b**, obtained by the degradation of kasugamycin with respect to mixture melting point, ir, nmr, mobilities on ppc, and optical rotation. The product showed the following properties: mp 141–142° (micro hot stage); $[\alpha]^{25}D$ +108 ± 2° (*c* 1.3, water); ir (KBr) 1660 (amide I) and 1555 cm^{-1} (amide II); nmr (D_2O) δ 1.15 (d, 3, J = 6.0 Hz, Me), 1.95 (s, 3, Ac), 3.70 (br s, 4, axial H's of inositol), 3.97 (br s, 2, equatorial H's of inositol), and 4.90 (d, 1, J = 2.0 Hz, anomeric H).

1D-3-*O*-(2,4-Diamino-2,3,4,6-tetradeoxy-α-D-*arabino*-hexopyranosyl)-*chiro*-inositol (Kasuganobiosamine) (15d). A solution of 17.0 mg of **15b** in 50 ml of aqueous solution saturated with barium hydroxide was refluxed for 48 hr. The solution was neutralized with carbon dioxide, and the deposited solid part was washed well with water. The filtrate and washings were combined and concentrated to a volume of about 50 ml. The solution was passed through a column of Amberlite CG-50 (ammonium form, type 1, 1 × 20 cm). The column was washed once with 50 ml of water and then eluted with 0.2 *N* ammonium hydroxide solution. The ninhydrin-positive fractions were combined and concentrated under reduced pressure to a volume of about 5 ml. This solution was acidified to pH 4 with diluted hydrochloric acid and evaporated under reduced pressure to a solid (19 mg). Crystallization from water–methanol–ether yielded 17.7 mg (96% yield) of the dihydrochloride **15d**, identical with an authentic sample, D-**15d**,[6b] obtained by the degradation of kasugamycin in respect to mixture melting point, ir (KBr), nmr (D_2O), mobilities on ppc, and optical rotation.

X-Ray Analysis of the Selenate of DL-Methylkasugaminide (15c). The crystals used for analysis were recrystallized from an aqueous methanol in the form of colorless prisms elongated along the *c* axis. Crystal data are: mol formula $C_7H_{16}N_2O_2 \cdot H_2SeO_4 \cdot H_2O \cdot CH_3OH$; mol weight 355.2; monoclinic, a = 25.38, b = 11.21, and c = 11.00 Å; β = 100.6°; V = 3075.5 Å^3; D_x = 1.54 g/cm^3; D_m = 1.59 g/cm^3; Z = 8; systematic absences, hkl when $h + k$ is odd, $h0l$ when l is odd, $0k0$ when k is odd; space group $C2/c$.

The crystals decomposed slowly by air exposure at room temperature. Therefore, all X-ray data were obtained with the crystals enclosed in quartz capillaries together with the recrystallizing solvent. Three-dimensional intensity data were recorded with an equi-inclination Weissenberg camera, using the multiple film technique and Ni-filtered Cu Kα radiation (λ = 1.5418 Å) for levels $hk0$ through $hk4$. The intensities were measured visually by means of a calibrated scale. The usual Lorentz and polarization corrections were applied. No corrections were made for absorption. A total of 1202 independent reflections were collected. The structure was solved by the heavy atom method and refined by several cycles of the least-squares calculation. The final R factor is 0.113 for 1202 reflections.

A perspective drawing of the molecule is shown in Figure 1. Bond distances and angles found in the molecule are very normal, except for the C(4)–N(4) bond (1.56 Å) which is significantly longer as compared with the generally accepted value. The average standard deviations for bond lengths and bond angles in the molecule are 0.02 Å and 1.4°. The pyran ring takes the chair conformation which is somewhat flatter than an ideal cyclohexane ring and this situation is well described by a series of the torsional angles around the ring bonds: $\phi_{O(1')-C(1)-C(2)-C(3)} = \mp 50.7°$,[42] $\phi_{C(1)-C(2)-C(3)-C(4)} = \pm 48.8°$, $\phi_{C(2)-C(3)-C(4)-C(5)} = \mp 53.6°$, $\phi_{C(3)-C(4)-C(5)-O(1')} = \pm 55.1°$, $\phi_{C(4)-C(5)-O(1')-C(1)} = \mp 61.8°$, $\phi_{C(5)-O(1')-C(1)-C(2)} = \pm 61.5°$. Flattening is observed markedly in the region of C(2) and C(3) and its effect is reflected on the bond distortion of the substituents. The dihedral angle between axial C(1)–O(1) and axial C(2)–N(2) bonds ($\phi_{O(1)-C(1)-C(2)-N(2)}$) is, for example, calculated to be ∓166.5°, while this value is expected to be 180° for an ideal cyclohexane ring. Consequently, the dihedral angle between equatorial H(1)–C(1) and equatorial H(2)–C(2) bonds possibly becomes larger than the normal 60°. All calculations were performed on CDC 3600 and 6600 computers at the Itoh Chu Computer Centre, Tokyo.

Acknowledgment. We are indebted to Dr. H. Naganawa for helpful consultation on the nmr data, to Miss H. Nakamura for her valuable assistance in the crystallographic study, and to Kyowa-Hakko Kogyo Co. for a generous supply of spiramycins. Deep thanks are due to Dr. T. Kishi, Takeda Chemical Industries, Ltd., for providing the spectroscopic data of natural methyl *N*-benzoyltoryposaminides.

(42) ϕ values take the upper signs in the L form and lower signs in the D form.