80041-97-0; **7**, 67435-25-0; **7** oxalate, 80041-98-1; **8**, 80041-99-2; **9**, 38945-22-1; **10**, 80042-00-8; **11a**, 80042-01-9; **11b**, 80042-02-0; **12**, 80042-03-1; **13**, 80042-04-2; **15**, 80042-05-3; **16**, 80042-06-4; **17**, 80042-07-5; **18**, 80042-08-6; **19**, 80042-09-7; **20**, 80042-10-0; **21**, 80042-11-1; **22**, 80042-12-2; **23**, 80042-13-3; (*E*)-**24**, 80042-15-5; (*Z*)-**24**, 80042-16-6; **25**, 80042-14-4; epibromohydrin, 3132-64-7; *N*-hydroxyphthalimide, 524-38-9; *N*-hydroxy-5-norborene-2,3-dicarboximide, 21715-90-2; *tert*-butyl amine, 75-64-9; potassium benzohydroxamate, 32685-16-8; *N*-amino-5-norbornene-2,3-dicarboximide, 4180-86-3; 1-chloro-2-butene, 591-97-9; *N*-(3-butenoxy)phthalimide, 80042-17-7; 1-bromo-4-pentene, 1119-51-3.

Supplementary Material Available: Tables III–VI containing fractional coordinates, anisotropic thermal parameters, bond lengths and bond angles for **4a** (4 pages). Ordering information is given on any current masthead page.

Acyl Nitrene Cyclizations in Antibiotics. Synthesis of 6″-Aminogentamicin C_2†

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The insertion reaction of an acyl nitrene has been used to functionalize the branched-chain sugar moiety, garosamine, of the antibiotic gentamicin C_2. Contrary to expectations based on intermolecular reactions in simple systems, insertion into the branched-chain methyl group was found to be competitive with insertion into the neighboring methylene group. A new approach is described for the preparation of azidocarbonates from hindered alcohols. The first example of the insertion of an acyl nitrene into a carbamate is described.

As part of a program directed toward the modification of aminocyclitol antibiotics[1,2] it was considered desirable to develop a method to functionalize the branched-chain methyl group of the garosamine moiety of gentamicin C_2 (**1**, Chart I). Our previous success in functionalizing the 4-α-methyl group of 3-β-lanostenol via nitrene insertion reactions[3] led us to explore the chemistry of the 4-oxycarbonyl nitrene species **2** with the ultimate intention of introducing an extra amino group into the gentamicin molecule.

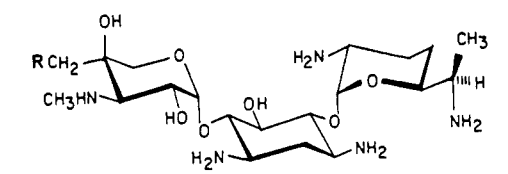
A number of competing reaction pathways were possible in principle, including insertion into the C–H bonds at C-2 and C-5 as well as the desired insertion into the *C*-methyl group.

Two factors suggested that unwelcome insertion into C-5 might predominate over insertion into the *C*-methyl group. First was the greater reactivity of secondary compared to primary hydrogen toward nitrenes. This preference has been shown to be approximately tenfold in the thermolytic reactions of ethyl azidoformate with 2-methylbutane.[4] Second, it has been amply demonstrated in intermolecular reactions that ether oxygens promote insertion of nitrenes into the C–H bonds α to the oxygen atom. This has been explained in terms of a hydrogen extraction–recombination process involving radicals or the intermediacy of an O–N ylide intermediate, **3**.[5] A priori the ring oxygen of **2** is suitably disposed to influence the course of reaction of the generated nitrene, possibly involving the ylide intermediate **3**.

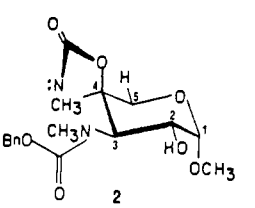
However, we[3] and others[6] have shown that in *intra*molecular reactions of this type, conformational factors are of primary importance. Our prediction that, in the present case, insertion into the methyl group would be competitive with insertion at C-5 has been realized.

Preliminary studies were conducted on methyl β-garosaminide obtained from gentamicin by methanolysis and synthesized recently in these laboratories.[7] Methyl 3-*N*-(benzyloxycarbonyl)-β-garosaminide **4** was benzoylated in pyridine to give **5** in high yield. The lack of reactivity

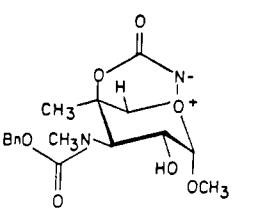
Chart I



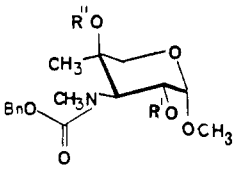
1 R = H
28 R = NH_2



2



3



4	R′ = H	R″ = H
5	R′ = COC_6H_5	R″ = H
6	R′ = H	R″ = $CONHNH_2$
7	R′ = COC_6H_5	R″ = $CONHSO_2Tol$
8	R′ = COC_6H_5	R″ = $CONCH_3SO_2Tol$
9	R′ = H	R″ = CON_3

of the tertiary hydroxyl group in this molecule is well established[8] and precluded the preparation of an azidocarbonate by standard methods. In our hands neither

† This work was presented at the International Carbohydrate Conference in Sydney, Australia, July 1980.

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(4) N. Torimoto, T. Shingaki, and T. Nagai, *Bull. Chem. Soc. Jpn.*, **49**, 2572 (1976), and references therein.
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(6) O. E. Edwards and Z. Paryzek, *Can. J. Chem.*, 3866 (1973).
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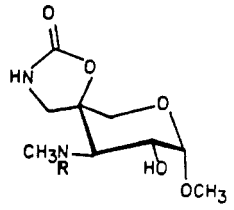
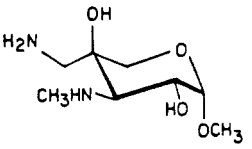
0022-3263/82/1947-0523$01.25/0

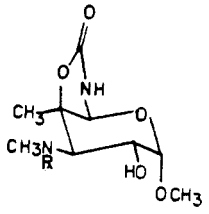
Chart II



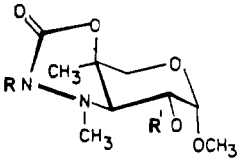
10 R = CO_2Bn
11 R = H



12

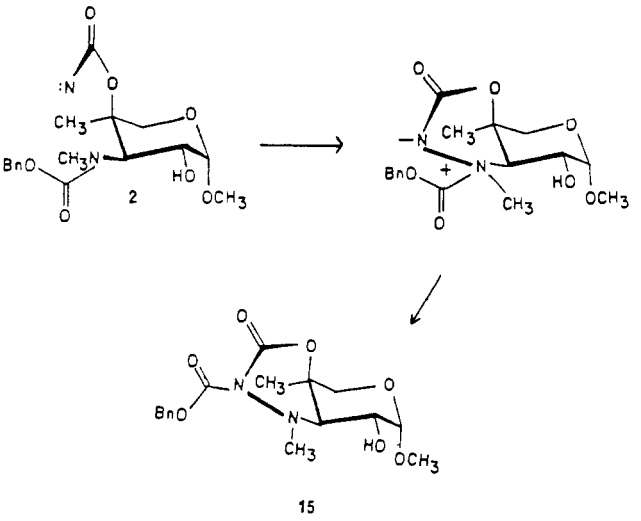


13 R = CO_2Bn
14 R = H



15 R = CO_2Bn R' = H
16 R = H R' = H
17 R = Ac R' = Ac

Scheme I



2

15

phenyl chloroformate nor methyl chlorothioformate reacted with **5** under the reaction conditions employed in the synthesis of *tert*-butylazidocarbonate.[9,10] However, tosyl isocyanate was found to react rapidly and completely with **5** at room temperature to furnish the tosyl urethane **7**. Treatment of **7** with hydrazine regenerated the alcohol **4**. However, after replacement of the acidic hydrogen by a methyl group to give **8** (methyl iodide and potassium carbonate in acetone at room temperature, 86% yield), exposure to ethanolic hydrazine led exclusively to cleavage in the desired manner to furnish the carbazate **6** in essentially quantitative yield. Conversion of **6** into the azidocarbonate **9** proceeded smoothly with sodium nitrite in aqueous acetic acid in 79% yield (from compound **8**). The infrared spectrum of **9** in chloroform contained a doublet at 2200 and 2140 cm^{-1} corresponding to the azide group. Carbonyl absorptions appeared at 1725 and 1700 cm^{-1}.

Thermolysis of **9** was conducted at 130 °C in a Teflon-lined Parr bomb in dichloromethane, a solvent which has been shown to stabilize the singlet state of the nitrene[11,12] while being essentially inert to C–H insertion or hydrogen extraction reactions. Three products were obtained, each in approximately 20% yield. These were separated by chromatography and shown by analysis to be isomers of the formula $C_{17}H_{22}N_2O_7$.

The most polar compound proved to be the desired oxazolidinone **10** (Chart II). There were no resonances in the ^1H NMR spectrum of **10** corresponding to a *C*-methyl group, while an absorption characteristic of an oxazolidinone was present in the infrared spectrum at 1776 cm^{-1}. Catalytic hydrogenolysis of **10** gave **11** which when treated with strong base gave the methyl glycoside (**12**) of the new amino sugar 3-(methylamino)-3-deoxy-4-(aminomethyl)-β-L-arabinopyranose. The chemical shifts and coupling constants of H-1, H-2, and H-3 in the ^1H NMR spectrum of **12** were very similar to those of methyl β-garosamide, while the resonance corresponding to the *C*-methyl group of methyl β-garosaminide had been replaced by a low-field multiplet corresponding to the newly formed aminomethylene group. The ^{13}C NMR spectrum of **12** was also entirely in accord with its structure.

The thermolysis product (**13**) of intermediate polarity proved to be the product of insertion into the C-5 methylene group. Carbonyl absorptions appeared in the infrared spectrum of **13** at 1776 and 1692 cm^{-1}. Catalytic hydrogenolysis of **13** gave the methyl glycoside **14**. The only carbonyl absorption in the infrared spectrum of **14** occurred at 1765 cm^{-1} and corresponded to the oxazolidinone group. In the ^1H NMR spectra of **13** and **14**, the chemical shifts and coupling constants of H-1, H-2, and H-3 were again very similar to those of methyl β-garosaminide, and three-proton singlets at δ 1.4 (**13**) and 1.6 (**14**) confirmed the presence in these molecules of the *C*-methyl group. A singlet at δ 4.9 in the spectrum of **14** could be assigned to the C-5 hydrogen. The stereochemistry at C-5 is as shown in **14** because formation of the *trans*-oxazolidinone would have locked the pyranoside ring into a boat conformation or the alternate chair conformation. The chemical shift (δ 4.8) and coupling constant (4 Hz) of the anomeric hydrogen of **14** is consistent only with the chair conformation shown. Compound **14** underwent conversion into a number of unidentified products in the presence of base, a result presumably of ring opening at C-5.

The least polar of the thermolysis products has been assigned the novel structure **15**. It is considered to arise from initial attack of the nitrene on the urethane nitrogen atom to give an intermediate ylide which undergoes intramolecular transacylation (Scheme I). The structure of **15** was deduced from its spectroscopic properties and its subsequent reactions. Two carbonyl absorptions were present in the infrared spectrum at 1802 and 1748 cm^{-1}. Upon catalytic hydrogenation a quantitative yield of an isomer of **11** and **14** was produced in which the remaining carbonyl group was associated with an absorption at 1695 cm^{-1}. This product was assigned structure **16**. Acetylation of **16** in pyridine gave only (**17**) having carbonyl absorptions at 1800 and 1750 cm^{-1} in its infrared spectrum resulting from acetylation of both the 2-hydroxyl group and the hydrazidic nitrogen.

Proof of structure **15** was obtained by reductive cleavage of the N–N bond in compound **16**. Treatment of **16** with

(9) L. A. Carpino, D. Collins, S. Goweke, J. Mayo, S. D. Thatte, and F. Tibetts, *Org. Synth.*, **44**, 20 (1964).
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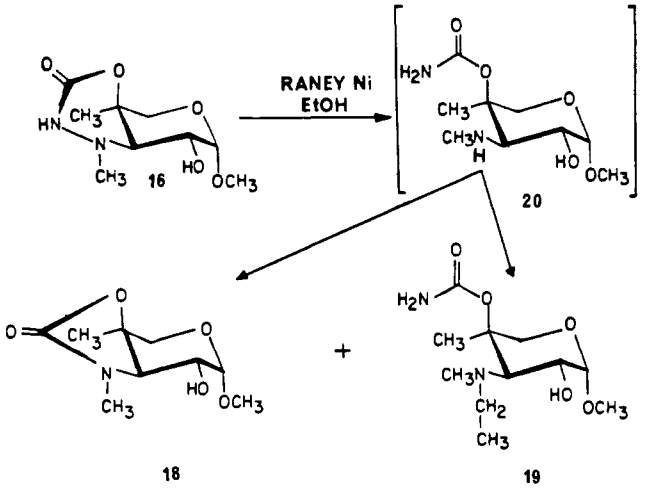
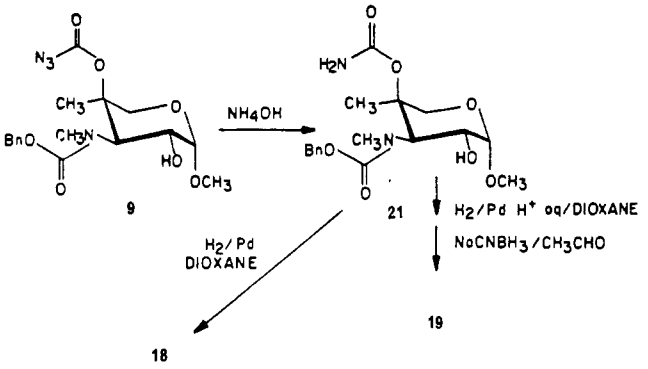
Scheme II



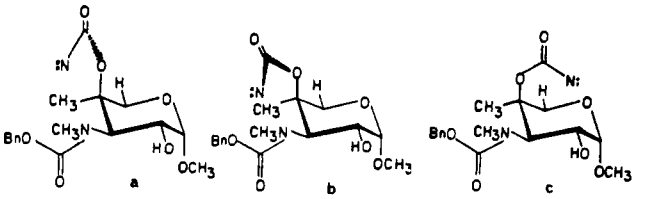
Scheme III



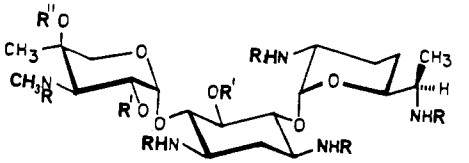
Raney nickel in ethanol gave two products **18** and **19** (Scheme II). The oxazolidinone **18** was formed from the initial product (**20**) of the reductive cleavage of **16**, by in situ cyclization. Fortuitous reductive alkylation of **20** under the conditions of the reaction in ethanol led to the formation of **19**. These processes were examined by independent syntheses of **18** and **19** (Scheme III). Treatment of the azidocarbonate **9** with methanolic ammonia gave the urethane **21**, which upon catalytic hydrogenolysis in dioxane gave a compound identical in all respects with **18** in 87% yield. When the hydrogenolysis was conducted in the presence of acid in order to trap the initially formed urethane **20** as its salt and the reaction mixture was treated with sodium cyanoborohydride and acetaldehyde, the 3-*N*-ethylurethane **19** was produced. This material was identical in all respects with that produced in the treatment of **16** with Raney nickel. These experiments allow structure **15** to be unambiguously assigned to the least polar product of the azidocarbonate thermolysis.

Photolysis of **9** gave the same products in essentially the same relative proportions as those produced by the thermolysis experiments. In both cases, insertion into the *C*-methyl group and the C-5 methylene group took place with essentially equal readiness. The ring oxygen was clearly not participating by facilitating overall insertion into the α-C–H bond as has been observed in intermolecular reactions.

These results may arise from either or both the following conformational factors. The conformational preferences of the acyl nitrene may be playing a determining role in the choice of the ultimate site of reaction, implying that of the three gauche conformations a–c, a and b are greatly favored over c. Second, the ability of the hydrogens of the conformationally mobile methyl group to adopt the optimum orientation for reaction with the nitrene intermediate could overcome the intrinsically greater activity of secondary vs. primary hydrogens in nitrene reactions. Studies in simpler systems are required in order to evaluate the relative importance of these factors as well as the influence of neighboring heteroatoms in intramolecular nitrene chemistry.



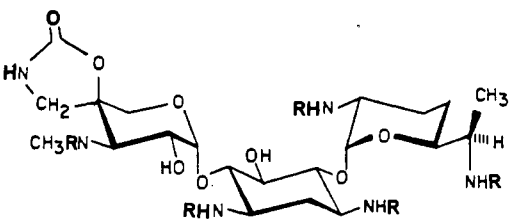
For application of this synthetic procedure to the gentamicin C_2 molecule, the partially blocked substrate **23** was



22	R = CO_2Bn	R' = H	R'' = H
23	R = CO_2Bn	R' = Ac	R'' = H
24	R = CO_2Bn	R' = Ac	R'' = $CONCH_3SO_2Tol$
25	R = CO_2Bn	R' = H	R'' = $CONHNH_2$
26	R = CO_2Bn	R' = H	R'' = CON_3

required. This was prepared easily by acetylation in pyridine of the readily available percarbobenzyloxy derivative of gentamicin C_2 (**22**). The *N*-methyl-*N*-tosylurethane **24** was prepared as before and reacted with ethanolic hydrazine hydrate under modified conditions to provide the desired carbazate (**25**) in which both acetate groups had been removed by hydrazinolysis. Oxidation with nitrous acid led to the azidocarbonate **26**.

Thermolysis of **26** led to the formation of three major products of which the most polar was separated by chromatography and which proved to be the desired oxazolidinone **27**. Removal of the carbobenzyloxy groups by



27 R = CO_2Bn

catalytic hydrogenolysis was followed by treatment of the product with alkali under reflux to give the desired compound, 6″-aminogentamicin C_2 (**28**). The structure was assigned by comparison of its ^1H NMR and ^{13}C NMR spectral data with those of compound **12** and of gentamicin C_2 itself. The 6″-aminogentamicin C_2 prepared in this way proved to be equal in potency and spectrum to the parent compound. The second major product, produced in a yield equal to that of **28**, proved to be the product of insertion into C-5. Catalytic hydrogenolysis of this compound followed by treatment with base led to the ψ-disaccharide gentamine C_2 by cleavage of the garosamine ring at the newly formed amidoacetal moiety.

In summary, this synthesis constitutes a successful attempt to exploit the insertion reactions of *O*-acyl nitrenes to functionalize unactivated positions in a complex anti-

biotic. In addition, synthetic procedures developed in the course of this work for the preparation of azidocarbonates from sterically hindered alcohols should prove generally applicable.

Experimental Section

^{1}H NMR spectra were obtained at 60 MHz by using a Varian A60A spectrometer. Chemical shifts in $CDCl_3$ are reported in parts per million downfield from internal Me_4Si. IR spectra were recorded with either a Perkin-Elmer 221 or an Infracord 137 spectrometer. Mass spectra were recorded with a Varian CH5 spectrometer. CD spectra were recorded on a Cary 61 spectrometer. Rotations were determined at 0.3% concentration by using a Bendix Model 143 automatic polarimeter. The silica gel used was from Baker (60–200 mesh).

Methyl 2-*O*-Benzoyl-3-*N*-(benzyloxycarbonyl)-β-garosaminide (5). A mixture of methyl 3-[methyl(benzyloxycarbonyl)amino]-3-deoxy-4-methyl-β-L-arabinopyranoside (4, 17.2 g) and benzoyl chloride (9.4 mL) in pyridine (65 mL) was prepared at 10 °C and allowed to warm to room temperature. After 18 h the solution was filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in chloroform, and the solution was extracted with 5% HCl followed by saturated aqueous $NaHCO_3$ and brine. Drying, ($MgSO_4$), filtration, and removal of the solvent gave the title compound as a glass of sufficient purity for further transformations. A sample (1.1 g) was chromatographed on silica gel in 1% methanol in chloroform to give 0.9 g of product for characterization: $[\alpha]^{26}$ + 116° (ethanol); IR 1690, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 3 H, CMe, rotamers), 3.0 (s, 3 H, NMe), 3.6 (s, 3 H, OMe), 5.25 (br s, 2 H, $ArCH_2$), 5.30 (d, 2 H, H-1, J = 4 Hz), 5.55 (dd, 1 H, H-2, J = 4, 10 Hz), 7.2–8.0 (m, 10 H, Ar). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.3; H, 6.3; N, 3.3. Found: C, 64.2; H, 6.4; N, 3.4.

Methyl 2-*O*-Benzoyl-3-*N*-(benzyloxycarbonyl)-4-*O*-(*N*-methyltoluenesulfonylcarbamoyl)-β-garosaminide (8). A solution of 7.3 g of benzoate 5 in dry acetonitrile (75 mL) was treated with tosyl isocyanate (5.04 g) in portions until the reaction was complete (by TLC). Addition of water (0.25 mL) was followed by evaporation of the solvent. The residue was dissolved in acetone (175 mL) and treated with methyl iodide (10.5 mL) and anhydrous potassium carbonate powder (8.5 g), and the whole was stirred for 40 h at room temperature. Filtration and removal of the solvent gave a crude product which was chromatographed on silica gel. Elution with 20% benzene in chloroform gave 9.35 g of the title compound: mp 155–156 °C (ethanol); $[\alpha]^{26}$ +156° (ethanol); IR (KBr) 1695, 1715 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.5 (s, 3 H, CMe), 2.43 (s, 3 H, ArMe), 2.93 (s, 3 H, C-3 NMe); 3.4 (s, 3 H, OMe), 3.5 (s, 3 H, NTos Me), 3.78, 4.32 (two 1 H d, J = 18 Hz, H-5$_{ax}$ and H-5$_{eq}$), 5.3 (m, 4 H, Ar CH_2, H-1 and H-3), 5.5 (dd, 1 H, J = 4, 12 Hz, H-2), 7.17, 7.95 (m, 14 H, aromatic). Anal. Calcd for $C_{32}H_{36}O_{10}N_2S$: C, 60.0; H, 5.7; N, 4.4; S, 5.0. Found: C, 59.9, H, 5.5; N, 4.4; S, 5.4.

Methyl 3-*N*-(Benzyloxycarbonyl)-4-*O*-(hydrazidocarbonyl)-β-garosaminide (6). A solution of the *N*-methyltosylurethane 8 (9.65 g) in anhydrous ethanol (250 mL) was treated with anhydrous hydrazine (7.2 mL), and the solution was left at room temperature for 30 h. Water (2 mL) was added, and the solvent was removed under vacuum. The residue was chromatographed on silica gel. Elution with 4% methanol in chloroform gave the title compound: 5.7 g; $[\alpha]^{26}$ +188° (ethanol); IR 1720, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3 H, CMe), 3.0 (s, 3 H, C-3 NMe), 3.4 (s, 3 H, OMe), 3.5–4.6 (m, 3 H, H-3, H-5), 4.8 (d, J = 4 Hz, H-1), 5.1 (s, 2 H, Ar CH_2), 7.4 (m, aromatic). Anal. Calcd for $C_{17}H_{25}N_3O_7$: C, 53.25; H, 6.6; N, 11.0. Found: C, 53.15; H, 6.55; N, 11.0.

Methyl 3-*N*-(Benzyloxycarbonyl)-4-(azidocarbonyl)-β-garosaminide (9). To a solution of methyl 3-*N*-(benzyloxycarbonyl)-4-*O*-(hydrazidocarbonyl)-β-garosaminide (8, 5.28 g) in acetic acid (50 mL) and water (10 mL) at 5 °C was added dropwise a solution of sodium nitrite (2.58 g) in water (10 mL). After 0.5 h the reaction mixture was poured into saturated sodium bicarbonate solution and extracted twice with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated to give an oily residue (4.9 g). Chromatography on silica gel and elution with chloroform gave the title product: 4.3 g; $[\alpha]^{26}$ +184° (ethano); IR ($CHCl_3$) 2200, 2140, 1725, 1700 cm^{-1}; ^{1}H NMR δ 1.4 (s, 3 H, CMe), 3.0 (s, 3 H, NMe), 3.4 (s, 3 H, OMe), 3.6 (d, 1 H, J = 13 Hz, H-5), 4.1 (dd, 1 H, J = 3.5, 10 Hz, H-2), 4.4 (d, 1 H, J = 13 Hz, H-5), 4.82 (d, 1 H, J = 3.5 Hz, H-1), 5.2 (s, 2 H, Ar CH_2). Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.8; H, 5.6; N, 14.2. Found: C, 55.2; H, 5.5; N, 14.3.

Pyrolysis of 9. The azidocarbonate 9 (2.25 g) was dissolved in dichlormethane (60 mL) and, in three separate experiments involving 20 mL each, was heated in a Teflon-lined bomb at 130 °C for 4 h. The residue obtained on removal of the solvent was chromatographed on silica gel, and elution with 25% acetone in benzene gave three products. That eluted first was the cyclic hydrazide 15: 22%; $[\alpha]^{26}$ +138° (ethanol); IR 1802, 1748 cm^{-1}; ^{1}H NMR δ 1.52 (s, 3 H, CMe), 3.0 (s, 3 H, NMe), 3.32 (m, 4 H, OMe, H-3), 3.7 (m, 3 H, H-5 and H-2), 4.55 (d, J = 4 Hz, H-1), 5.3 (s, 2 H, $ArCH_2$), 7.4 (m, 5 H, aryl). Anal. Calcd for $C_{17}H_{22}H_2O_7$: C, 55.7; H, 6.1; N, 7.7. Found: C, 55.7; H 6.1, N, 7.9.

The product of intermediate polarity was compound 13: 23%; $[\alpha]^{26}$ +152° (ethanol); IR 1776, 1692 cm^{-1}; ^{1}H NMR δ 1.4 (s, 3 H, CMe), 3.0 (s, 3 H, NMe), 3.5 (s, 3 H, OMe), 5.15 (s, 2 H, $ArCH_2$); 7.3 (s, 3 H, aryl). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.7; H, 6.1; N, 7.7. Found: C, 55.7; H, 6.1; N, 7.7.

The most polar isomer was compound 10, its isolated yield being 12%. Some material remained in overlaps. Careful TLC studies led to an estimated yield of 20%. The compound had the following: [α] +175° (ethanol); IR 1776, 1695 cm^{-1}; ^{1}H NMR δ 3.1 (s, 3 H, N-Me), 3.45 (s, 3 H, OMe), 3.72 (br s, 2 H, H-5), 4.2 (dd, 1 H, J = 4, 10 Hz, H-2), 4.9 (d, J = 4 Hz, H-1), 5.2 (s, 2 H, $ArCH_2$), 7.4 (s, 5 H, aryl). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.7; H, 6.1; N, 7.7. Found: C, 55.3; H, 6.4; N, 7.0.

Hydrogenolysis of Cyclic Hydrazide (15). A solution of 15 (130 mg) in ethanol (20 mL) was hydrogenated in the presence of 5% palladium on carbon at 50 psi of H_2 for 8 h. Chromatography of the residue, obtained on evaporation of the filtered solution, on silica gel gave compound 16 as a glass: 82 mg; $[\alpha]^{26}$ +124°; IR ($CHCl_3$) 1695 cm^{-1}; ^{1}H NMR (80 MHz) δ 1.48 (s, 3 H, CMe), 2.97 (s, 3 H, NMe), 3.05 (d, 1 H, H-3), 3.44 (s, 3 H, OMe), 3.6 (m, 2 H, H-5), 4.78 (d, J = 4 Hz, H-1), 7.54 (s, 1 H, NH); mass spectrum, m/e 232.1052 (M$^+$, 0.5 mmu, 26.6%).

Acetylation of Compound 16. The cyclic hydrazide 16 (35 mg) was treated with acetic anhydride (0.3 mL) and pyridine (2 mL) at room temperature overnight. Evaporation gave a residue which was chromatographed on silica gel, elution with 10% acetone–benzene giving the *N*,*O*-diactate 17: IR 1800, 1750 cm^{-1}; ^{1}H NMR δ 1.6 (s, 3 H, CMe), 2.15 (s, 3 H, OCOMe), 2.5 (s, 3 H, NCOMe), 3.08 (s, 3 H, NMe), 3.4 (d, 1 H, J = 10 Hz, H-3), 3.5 (s, 3 H, OMe), 3.75 (s, 2 H, H-5), 4.8 (d, J = 4 Hz, H-1), 5.0 (dd, 1 H, J = 4, 10 Hz, H-2).

Raney Nickel Hydrogenolysis of 16. A solution of the hydrazide 16 (221 mg) was dissolved in absolute ethanol, and the mixture was heated under reflux overnight with Raney nickel. Filtration and removal of the solvent in vacuo gave an oil (202 mg). Chromatography on silica gel in 5% methanol in chloroform gave two products. The less polar was 18, the 3,4-oxazolidinone of methyl β-garosaminide: 10%; $[\alpha]^{26}$ +136° (ethanol); IR 1740 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3 H, CMe), 2.95 (s, 3 H, NMe), 3.18 (m, 1 H, H-3), 3.5 (s, 3 H, OMe), 4.05 (m, 1 H, H-2), 4.68 (d, 1 H, J = 4 Hz, H-1); mass spectrum, m/e 217.0939 (M$^+$, 1.0 mmu).

Next eluted was the *N*-ethylurea 19: 24%; $[\alpha]^{26}$ +183.4°; IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR (80 MHz) 1.08 (t, 3 H, J = 7 Hz), CH_2CH_3), 1.54 (s, 3 H, CMe), 2.52 (s, 3 H, NMe), 2.62 (d, 1 H, J = 10 Hz, H-3), 2.8 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.45 (s, 3 H, OMe), 3.45 (d, 1 H, J = 12 Hz, H-5$_{ax}$), 4.1 (dd, 1 H, J = 4, 10 Hz, H-2), 4.4 (d, 1 H, J = 12 Hz, H-5$_{eq}$), 4.85 (d, 1 H, J = 4 Hz, H-1); mass spectrum, m/e 262.1535 (M$^+$, –0.8 mmu).

Hydrogenation of Oxazolidinone 13. A solution of 13 (120 mg) in ethanol (20 mL) was hydrogenated with 5% palladium on carbon at 50 psi of H_2 for 18 h. Filtration and evaporation of the filtrate gave a glass which was chromatographed on silica gel. Elution with the lower phase of a mixture of chloroform, methanol, and concentrated ammonium hydroxide (50:10:1) gave the oxazolidinone 14 (15 mg). Decomposition of much of the reaction product on the column was observed. The product 14 had the following: $[\alpha]^{26}$ +153°; IR (KBr) 1765 cm^{-1}; ^{1}H NMR δ 1.6 (s, 3 H, CMe), 2.7 (s, 3 H, NMe), 2.9 (d, 1 H, J = 10 Hz, H-3), 3.5 (s, 3 H, OMe), 3.65 (dd, 1 H, J = 4, 10 Hz, H-2), 4.8 (d, 1 H,

J = 4 Hz, H-1), 4.9 (s, 2 H, H-5), mass spectrum, m/e 232.1068 (M^+, −0.9 mmu).

Hydrogenation of Oxazolidinone 10. A solution of 10 (210 mg) in ethanol (50 mL) was treated with 5% palladium on carbon in a atmosphere of hydrogen (50 psi) for 18 h. Chromatography of the residue obtained after filtration and removal of the solvent gave 11: $[\alpha]^{26}$ +159°; IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 2.6 (d, 1 H, J = 10 Hz, H-3), 2.7 (s, 3 H, NMe), 3.1 (d, 1 H, J = 8 Hz, H-5_{ax}), 3.4 (s, 3 H, OMe), 3.7 (m, 3 H, H-5_{eq}, CH_2N), 3.8 (dd, 1 H, J = 4, 10 Hz, H-2), 4.8 (d, 1 H, J = 4 Hz, H-1); mass spectrum, m/e 232.1063 (M^+, −0.6 mmu).

Methyl 6-Amino-β-garosaminide (12). A solution of the oxazolidinone 11 (165 mg) in 10 mL of 1 N potassium hydroxide was heated under reflux for 23 h. The cooled solution was adjusted to pH 10 and evaporated to dryness in vacuo. The residue was taken up in methanol, filtered, and evaporated to leave a tan solid which was chromatographed on silica gel. Elution with the lower phase of a mixture of chloroform, methanol, and ammonium hydroxide (10%, 2:1:1) gave the title compound: 64 mg; $[\alpha]^{26}$ +157°; IR ($CHCl_3$) 3640, 3450, 3040, 2960, 2860, 1070, 1030 cm^{-1}; ^{13}C NMR 100.25, 75.1 69.8, 65.0, 61.4, 56.0, 45.85, 37.3 ppm; mass spectrum, m/e 206.1280 (M^+, −1.4 mmu).

Methyl 3-*N*-(Benzyloxycarbonyl)-4-*O*-carbamoyl-β-garosaminide (21). Methyl 3-*N*-(benzyloxycarbonyl)-4-*O*-(azidocarbonyl)-β-garosaminide (79 mg) was treated with dimethylformamide–concentrated ammonium hydroxide (1:1, 6 mL) for 1 h at room temperature. The solution was evaporated in vacuo, and the residue was chromatographed on silica gel to provide the title compound as a foam (80%). This material was homogeneous by TLC and was not characterized further but was used as such in the subsequent hydrogenolysis experiment.

Methyl 3-*N*,4-*O*-Carbonyl-β-garosaminide (18) from Hydrogenolysis of 21. A solution of 21 (315 mg) in dioxane (15 mL) was shaken with 10% palladium on carbon at 50 psi of H_2 for 18 h. Filtration and evaporation gave an oil which on chromatography gave the title compound identical in all respects with product 18 isolated from the Raney nickel reduction of 16.

Methyl 3-*N*-Ethyl-4-*O*-carbamoyl-β-garosaminide (19) from Hydrogenation of 21. The *O*-carbamate 21 (100 mg) in 20% water in dioxane (10 mL) was treated with 1 N hydrochloric acid (0.85 mL) and hydrogenated in the presence of 10% palldium on carbon (50 mg) for 18 h. The mixture was filtered, and the pH was adjusted to 4.0 with 0.1 N sodium hydroxide. Acetaldehyde (0.6 mL) and sodium cyanoborohydride (80 mg) were added, and the solution was left overnight. The pH was readjusted to pH 8.5 with 0.1 N sodium hydroxide, and the solution was evaporated. The residue was partitioned between ethyl acetate and brine. Drying ($MgSO_4$), filtration, and evaporation followed by chromatography on silica gel in 5% methanol in chloroform gave the title compound (28 mg) identical in all respects with the major product obtained by Raney nickel hydrogenolysis of 16.

2″,5-Di-*O*-acetyl-1,3,2′,6′,3″-penta-*N*-(benzyloxycarbonyl)gentamicin (23). A solution of 68.7 g of the penta-*N*-(benzyloxycarbonyl)gentamicin C_2 in pyridine (550 mL) and acetic anhydride (352 mL) was heated under nitrogen at 60 °C for 3 days. Conversion, as monitored by thin-layer chromatography, was complete. The excess pyridine and acetic anhydride were removed by evaporation, and the residue was chromatographed rapidly on silica gel (0.8 kg) in 2% methanol in chloroform to give the title compound: 62.4 g; $[\alpha]^{26}$ +85°. Anal. Calcd for $C_{64}H_{75}N_5O_{19}$: C, 63.10; H, 6.2; N, 5.75. Found: C 62.9; H, 6.1; N, 5.6.

2″,5-Di-*O*-acetyl-4″-(*N*-methyltoluenesulfonylcarbamoyl)-1,3,2′,6′,3″-penta-*N*-(benzyloxycarbonyl)gentamicin C_2 (24). To a solution of 23 (61 g) in dry acetonitrile (600 mL) was added a solution of toluenesulfonyl isocyanate (15.0 g) in acetonitrile (20 mL), and the whole was left at room temperature for 18 h. Water (0.5 mL) was added, and stirring was continued for 1 h. The solvent was evaporated to leave a residue which was dissolved in acetone, treated with methyl iodide (40 mL) and powdered anhydrous potassium carbonate (50 g), and stirred at room temperature for 18 h. Filtration and evaporation gave a crude product. High-pressure chromatography on silica gel (1.5 kg, Merck) gave the title compound: 29 g; $[\alpha]^{26}$ +99°. Anal. Calcd for $C_{73}H_{84}N_6O_{22}S$: C, 61.4; H, 5.9; N, 5.9; S, 2.2. Found: C, 61.2; H, 5.9; N, 5.5; S, 2.1.

4″-*O*-(Hydrazidocarbonyl)-1,3,2′,6′,3″-penta-*N*-(benzyloxycarbonyl)gentamicin C_2 (25). The *N*-methyltoluenesulfonylurethane (27, 14 g) in ethanol (400 mL) was treated with 90% hydrazine in water (150 mL), and the whole was left overnight at room temperature. The reaction mixture was added to ice–water. Extraction with chloroform and combination and drying of the organic extracts followed by evaporation of the solvent gave the crude title compound (27). This material was sufficiently homogeneous to be used directly in the preparation of compound 28.

1,3,2′,6′,3″-Penta-*N*-(benzyloxycarbonyl)-4″-*O*-(azidocarbonyl)gentamicin C_2 (26). The carbazate 27 (13 g) in acetic acid (55 mL) and water (7 mL) was treated at 5 °C with sodium nitrite (1.68 g) in water (13 mL). After the mixture was allowed to stand at room temperature for 40 min, the solution was partitioned between ether and water. The ether layer was washed with saturated sodium bicarbonate and water and dried ($MgSO_4$). Evaporation gave a residue (10.1 g) which was chromatographed on silica gel. Elution with 2% methanol in chloroform gave the title compound: 5.3 g; $[\alpha]^{26}$ +112° (methanol); IR ($CHCl_3$) 2165 cm^{-1}. Anal. Calcd for $C_{61}H_{70}N_8O_{18}$: C, 60.9; 5.8. Found: C, 60.7; H, 5.8.

6″-Aminogentamicin C_2 (28). Azidocarbonate 28 (1.2 g) in dichlormethane was heated at 130 °C in a Paar bomb for 4 h. The crude products of four such reactions were combined and chromatographed on silica gel. Elution with silica gel gave three fractions: 1.7, 0.76, and 0.75 g in the order of elution. The most polar compound was that derived from insertion into the garosaminyl *C*-methyl group. This material (0.74 g) was dissolved in 20% aqueous dioxane (35 mL). Hydrochloric acid (1 N, 3.15 mL) was added, and the whole was hydrogenated at 55 psi of H_2 for 4 h in the presence of 10% palladium on carbon (100 mg). The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in 1 N NaOH (10 mL) and heated under reflux for 24 h under argon. The pH of the solution was adjusted to 10 with 1 N sodium hydroxide solution, and most of the solvent was removed by evaporation. The concentrated solution was added dropwise to absolute ethanol and the precipitate collected by filtration. Evaporation of the filtrate and chromatography of the residue on silica gel in the lower phase of a mixture of chloroform, methanol, and concentrated ammonium hydroxide (1:1:1) gave 6-aminogentamicin C_2: 52 mg; $[\alpha]$ +136° (ethanol); CD (TaCu) $[\theta]^{282}$ −4100; ^1H NMR δ 1.1 (d, 3 H, J = 7 Hz, 6′-CCH_3), 2.5 (s, 3 H, NCH_3), 3.9 (dd, 1 H, J = 4, 12 Hz, H-2″), 4.15 (d, 1 H, J = 12 Hz, H-5″$_{eq}$, 5.15 (m, 2 H, H-1′ and H-1″). The yield the this reaction was low due largely to difficult chromatographic separations.

Registry No. 4, 80010-07-7; 5, 79991-74-5; 6, 79991-75-6; 8, 79991-76-7; 9, 79991-77-8; 10, 79991-78-9; 11, 79991-79-0; 12, 79991-80-3; 13, 79991-81-4; 14, 80010-08-8; 15, 79991-82-5; 16, 79991-83-6; 17, 79991-84-7; 18, 80040-34-2; 19, 79991-85-8; 21, 79991-86-9; 22, 53958-54-6; 23, 78518-52-2; 24, 78518-53-3; 25, 78518-54-4; 26, 78518-55-5; 27, 78518-57-7; 28, 78518-56-6.