Carbohydrate Research, 60 (1978) 289–302

A NEW METHOD FOR THE 3′-DEOXYGENATION OF BUTIROSINS A AND B

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(Received January 26th, 1977; accepted for publication in revised form, April 28th, 1977)

ABSTRACT

An aziridine ring-formation involving the reaction of adjacent amino and alcohol groups with triphenylphosphine, carbon tetrachloride, and triethylamine was applied at the 2′ and 3′ positions of butirosin A (**1a**) and B (**1b**). The amino groups at the 2′ position of **1a** and **1b** were *p*-methoxybenzylated to increase the nucleophilicity of the nitrogen atom and to avoid the formation of a P–N linkage, and the *N*-*p*-methoxybenzyl derivatives were converted into the aziridine derivatives, which were then subjected to hydrogenolysis and removal of the protecting groups to give 3′-deoxybutirosin A (**7a**) and B (**7b**), respectively. This new method is compared with the conventional *N*,*O*-protecting method that involves several complex steps.

INTRODUCTION

Although several synthetic routes to deoxy derivatives of aminoglycoside (aminocyclitol) antibiotics have been reported thus far[1], most of them require complicated steps for selective tosylation or mesylation of the hydroxyl group that is subjected to deoxygenation.

The purpose of the work reported here was to synthesize 3′-deoxybutirosin A (**7a**)[2] and B (**7b**)[1] from butirosin A (**1a**) and B (**1b**)[3], respectively, without need for complicated *O*-protection processes.

2″-Deoxygentamicin C_2 and 2″-deoxy-3″-des(methylamino)-2″-(methylamino) gentamicin C_2 have been synthesized by hydrogenation of the 2″, 3″-epimino derivative of gentamicin C_2 derived[4] from the 2″-*O*-mesyl derivative of gentamicin C_2. However, in the butirosins, selective 3′-*O*-mesylation or tosylation requires considerably more-complex processes, as compared with the selective 2″-*O*-mesylation of gentamicin C_2.

As reported by Appel[5], aziridines may be obtained in good yield by the reaction of triphenylphosphine, carbon tetrachloride, and triethylamine with *N*-substituted β-amino alcohols, whereas *N*-unsubstituted β-amino alcohols undergo mainly an

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unfavorable P–N linkage-formation and *N*-acylated *β*-amino alcohols are unreactive under these conditions. As **1a** and **1b** have only one nonglycosylated hydroxyl group (3′-OH) adjacent to a nonacylated amino group (2′-NH_2), we decided to synthesize **7a** and **7b** by way of the 2′,3′-aziridine intermediate, with subsequent hydrogenolysis to give the 3′-deoxy derivatives.

The *p*-methoxybenzyl group was used as an *N*-substituent on the *β*-amino alcohol system, because it increases the nucleophilicity of the nitrogen atom and can readily be removed after aziridine ring-closure.

RESULTS AND DISCUSSION

The reaction of tetra-*N*-(*p*-methoxybenzyl)butirosin A with triphenylphosphine, carbon tetrachloride, and triethylamine afforded a 2′,3′-(*p*-methoxybenzyl)epiminobutirosin A derivative, which was then subjected to hydrogenolysis to give **7a**. However, this procedure caused extensive side-reactions that resulted in very low yields of the desired product, and it was presumed that some of these side reactions were caused by unfavorable intra- and inter-molecular reactions[6-8] of the *p*-methoxybenzylamino groups at C-3, 6′, and 4‴ with the hydroxyl groups.

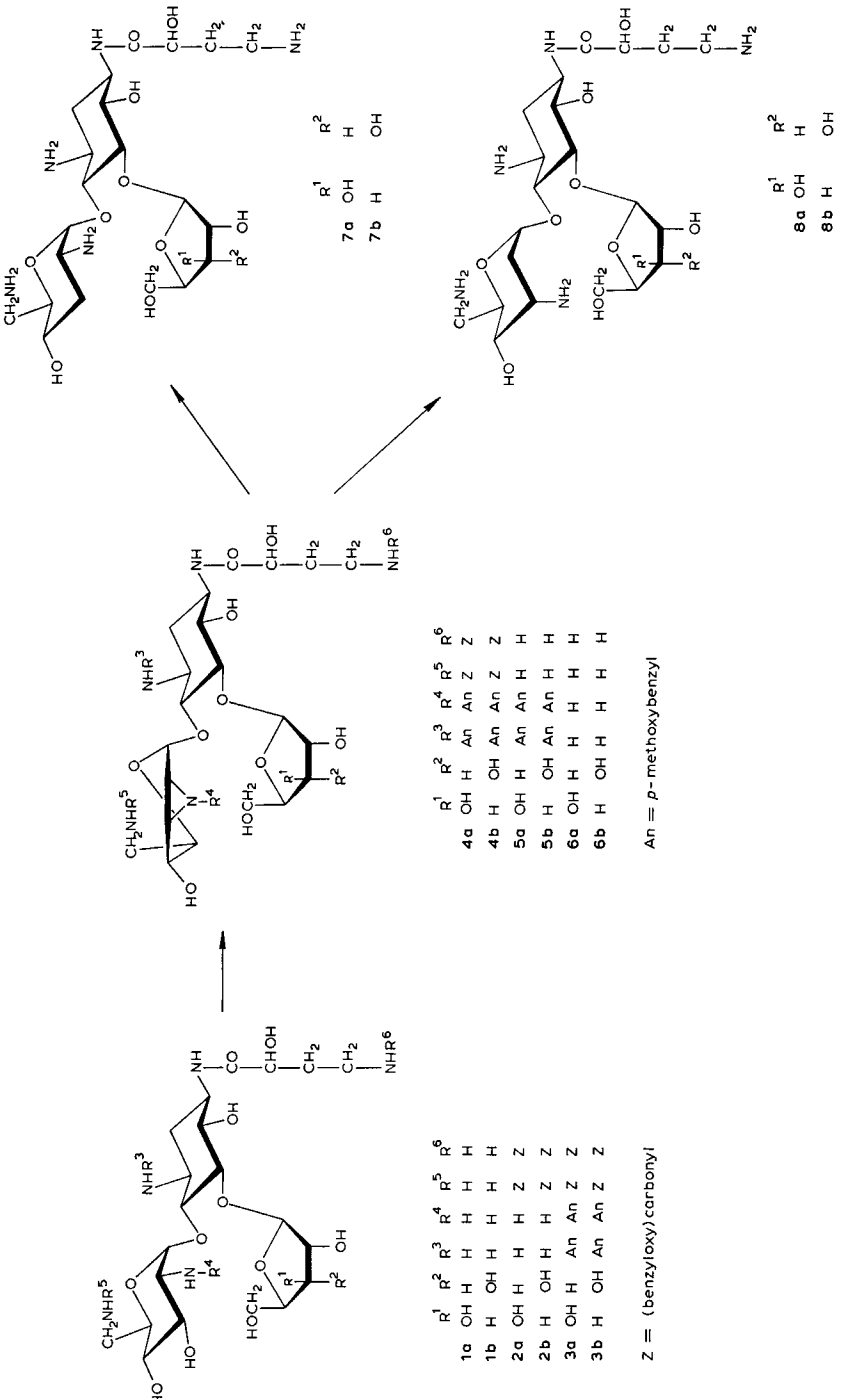
Therefore, it was considered preferable to protect the amino groups at C-3, 6′, and 4‴ with (benzyloxy)carbonyl groups before *N*-*p*-methoxybenzylation, to minimize the formation of P–N linkages (aminophosphonium chloride) at the amino groups.

When **1a** was treated with two molar equivalents of benzyl *p*-nitrophenyl carbonate, the amino groups at C-6′ and C-4‴ (-CH_2NH_2 group) were selectively protected with (benzyloxy)carbonyl groups and the amino groups at C-3 and C-2′ ($\rangle CHNH_2$ group) remained unsubstituted. The structure of the di-*N*-[(benzyloxy)carbonyl]butirosin A (**2a**) thus produced was confirmed by obtaining 1,3,2′-tri-*N*-formylxylostasin[2] via 6′-*N*-[(benzyloxy)carbonyl]xylostasin from **2a**.

Because there was only a slight difference in reactivity for *N*-(benzyloxy)carbonylation of the 3- and 2′-amino groups, we abandoned attempts to protect the 3-amino group.

After *N*-(benzyloxy)carbonylation of the 6′- and 4‴-amino groups, the 3- and 2′-amino groups were *N*-*p*-methoxybenzylated to give 6′,4‴-di-*N*-(benzyloxy)carbonyl-3,2′-di-*N*-(*p*-methoxybenzyl)butirosin A (**3a**). Compound **3a** was dissolved in tetrahydrofuran and acetonitrile, and then allowed to react with triphenylphosphine, carbon tetrachloride, and triethylamine to give 6′,4‴-di-*N*-(benzyloxy)carbonyl-2′-deamino-3′-deoxy-3-*N*-(*p*-methoxybenzyl)-2′,3′-(*p*-methoxybenzyl)epiminobutirosin A (**4a**).

Simultaneous addition of triphenylphosphine, carbon tetrachloride, and triethylamine to the reaction system also caused an increase in side reactions, because the preferential formation of the alkoxyphosphonium salt at the more-reactive hydroxyl groups (such as the 5″-hydroxyl group) than the 3′-hydroxyl group causes an undesirable, intermolecular reaction with a spatially accessible *p*-methoxybenzyl-


1a OH H H H H H
1b H OH H H H H
2a OH H H H Z Z
2b H OH H H Z Z
3a OH H An An Z Z
3b H OH An An Z Z
Z = (benzyloxy) carbonyl
4a OH H An An Z Z
4b H OH An An Z Z
5a OH H An An H H
5b H OH An An H H
6a OH H H H H H
6b H OH H H H H
An = p-methoxybenzyl
7a OH H
7b H OH
8a OH H
8b H OH

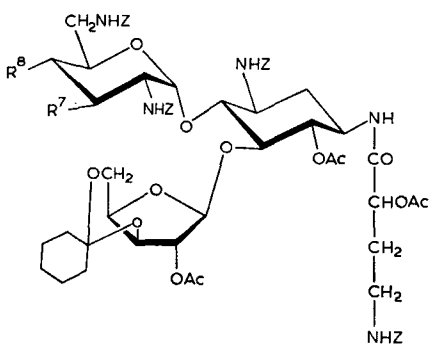
amino group (such as 2′-*p*-methoxybenzylamino) before the formation of an aziridine ring. Therefore, triethylamine was added after the formation of a triphenylphosphonium ion at the 3′-hydroxyl group had been assured. This improved procedure gave the (*p*-methoxybenzyl)epimino derivative **4a** in 70% yield. In this method, the most satisfactory results were obtained by bringing **3a** and triphenylphosphine in the molar ratio of 1:3 into the reaction system.

Compound **4a** was also synthesized from compound **3a** by using triphenylphosphine dibromide[8] and triethylamine, but the yield was low. By this method, the epimino derivative **4a** was obtained in 17% yield when triethylamine was added after the formation of triphenylphosphonium ion at the 3′-hydroxyl group. However, no isolable amount of the epimino derivative **4a** was obtained by simultaneous addition of triphenylphosphine dibromide and triethylamine.

The chemical shift (δ 2.66) and coupling constants (dd, $J_{1',2'}$ 4.5 and $J_{2',3'}$ 6.0) of H-2′ in the n.m.r. spectrum (chloroform-*d*) of **4a** showed the presence of an aziridine ring in the amino sugar moiety having the D-*allo* configuration[9].

Hydrogenolysis of **4a** with 5% palladium on carbon and a stream of hydrogen gave the *N*-de(benzyloxy)carbonylated derivative **5a**, and subsequent, carefully controlled hydrogenolysis with palladium black at 70° gave a mixture of **6a**, **7a**, and **8a**. In the n.m.r.-spectral analysis (chloroform-*d*) of **6a**, the signal at 3.08 (dd, $J_{1',2'}$ 4.5 and $J_{2',3'}$ 6.0) was assigned, by decoupling, to H-2′ in the aziridine ring. The structure of **6a** was confirmed to be 2′-deamino-3′-deoxy-2′,3′-epiminobutirosin A by comparison with an authentic sample synthesized by a combined enzymic and chemical procedure via the 3′-phosphate[10].

Further, complete hydrogenolysis of **6a** with Raney nickel afforded **7a** and **8a**



9 R^7 = OH, R^8 = OH
10 R^7 = OCSPh, R^8 = OH
11 R^7 = OTs, R^8 = OH
12 R^7 = H, R^8 = OH
13 R^7 = OBz, R^8 = OH
14 R^7 = OBz, R^8 = OMs

Z = (benzyloxy)carbonyl

in a ratio of 3.5:1. Product **7a** was identified as 3′-deoxybutirosin A by direct comparison with a sample synthesized by the following process employing the conventionally protected 3′,4′-diol[11] (**9**). The 3′,4′-diol **9** was treated with *N,N*-dimethylbenzamide, phosgene, and hydrogen sulfide[12] to give the 3′-thiobenzoate **10**, and then **10** was hydrogenolyzed with tributylstannane to give the 3′-deoxy derivative **12**. The 3′-deoxy derivative **12** was also prepared from the 3′,4′-diol **9** via the 3′-*p*-toluenesulfonate **11** and subsequently the 3′-iodo derivative. The protecting groups of **12** were cleaved successively with ammonia-saturated methanol, 70% aqueous acetic acid, and catalytic hydrogenolysis (Pd-black) to give **7a**. Although there might have remained a possibility that **12** could have the 4′-deoxy structure because **12** can be derived from a 3′,4′-diol, this possibility is ruled out by the comparison of **7a** with 4′-deoxybutirosin A (Bu-1975 C_1)[13,14]. 4′-Deoxybutirosin A was synthesized from butirosin A by the following process. The 3′, 4′-diol **9** was treated with benzoyl chloride (1.5–2 mol) and then with mesyl chloride to give the 3′-*O*-benzoyl-4′-*O*-mesyl derivative **14** via the 3′-benzoate **13**. After 4′-iodination of **14** with sodium iodide, the crude iodo derivative was subsequently hydrogenolyzed with tributylstannane[15] in the presence of α,α′-azobis(isobutyronitrile) to give the 4′-deoxy derivative. Removal of the protecting groups to give 4′-deoxybutirosin A was again conducted by successive use of ammonia-saturated methanol, 70% aqueous acetic acid, and catalytic hydrogenolysis (Pd-black).

Alkaline hydrolysis of 4′-deoxybutirosin A [which is active against *Pseudomonas aeruginosa* IFO 3080 (minimum inhibitory concentration, 1.56 μg/ml)] gave 4′-deoxy-5-β-D-xylofuranosylneamine (4′-deoxyxylostasin), which had negligible or very low

TABLE I

ANTIMICROBIAL SPECTRA OF **7a** AND **1a**

Test organisms[a]	*Minimum inhibitory concentration (μg/ml)*	
	7a	**1a**
Staphylococcus aureus FDA 209p	3.13	3.13
Escherichia coli NIHJ JC-2	1.56	3.13
Escherichia coli JR66/W677	1.56	>100
Klebsiella pneumoniae DT	0.78	0.78
Klebsiella pneumoniae 3020	3.13	>100
Pseudomonas aeruginosa U-31	12.5	>100
Pseudomonas aeruginosa TI-13	1.56	6.25
Pseudomonas aeruginosa GN 3393	6.25	100
Proteus mirabilis GN 5352	6.25	25
Proteus vulgaris GN 4413	12.5	50
Proteus morganii IFO 3168	6.25	12.5
Proteus morganii GN 4392	12.5	100
Proteus rettgeri GN 4427	6.25	100

[a]Medium: Trypticase soy agar (18 h, 37°).

activity against *Pseudomonas aeruginosa* IFO 3080 (minimum inhibitory concentration, >50 μg/ml)[14], whereas 3′-deoxyxylostasin[2], which may be derived from 3′-deoxybutirosin A by alkaline hydrolysis, is still active against *Pseudomonas aeruginosa* IFO 3080 (minimum inhibitory concentration, 0.78 μg/ml; compare 3′-deoxybutirosin A 0.78 μg/ml).

Compounds **4a** and **5a** undergo aziridine ring-opening and removal of the *N*-protecting groups by exhaustive hydrogenolysis with palladium black to give **7a** (major) and its structural isomer **8a** (minor). The minor component **8a** is presumed to be the 3′-amino-2′-deamino-3′-deoxy derivative, and the more favored cleavage of the C–3′–N bond over the C-2′–N bond is explicable on the basis that the approach of catalyst to C-3′ is stereochemically less hindered[16,17] than to C-2′. Thus it may be seen that these hydrogenolyses occur with retention of configuration at the 2′-position to give 3′-deoxybutirosins.

3′-Deoxybutirosin B (**7b**) was prepared from **1b** by a method similar to that described for the preparation of **7a** from **1a**.

The antimicrobial spectrum of the new, semisynthetic antibiotic **7a** is shown in Table I.

EXPERIMENTAL

General methods. — Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. P.m.r. spectra were recorded on a Varian HA-100 instrument; chemical shifts are reported in p.p.m. from tetramethylsilane, and coupling constants in Hz. T.l.c. was performed using glass plates precoated silica gel (Merck) in the solvent system specified. Spots were detected by spraying the plates with 5% ethanolic sulfuric acid containing 0.2% (w/v) of naphthoresorcinol, and heating. Unless otherwise indicated, compositions of solvent mixtures are given on a v/v basis.

6′,4‴-Di-N-[*(benzyloxy)carbonyl*]*butirosin A* (**2a**). — To a solution of butirosin A (**1a**, 11.1 g) in water (60 ml) and *N*,*N*-dimethylformamide (80 ml), a solution of benzyl *p*-nitrophenyl carbonate (10.9 g) in 1,4-dioxane (15 ml) was added dropwise slowly at room temperature with stirring. The mixture was further stirred overnight and then evaporated. Ethyl acetate was added to the residue, and the resulting precipitate of crude **2a** was washed with ethyl acetate and dried *in vacuo*; yield 16.5 g. The crude **2a** was purified by column chromatography on silica gel with 1:49 acetic acid–ethanol as developer to obtain pure **2a** as the acetic acid salt; yield 14.8 g (78%); $[\alpha]_D^{23}$ $+16.1°$ (*c* 1, methanol); R_F 0.48 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (methanol-*d*); δ 7.29 (10H, s, *Ph*-CH_2), 5.25 and 5.23 (2H × 2, 2s, 2 Ph-CH_2), 5.61 (1H, d, *J* 3.5, H-1′), 5.36 (1H, d, $J < 1$, H-1″), and 2.13 (6H, s, CH_3CO_2H).

Anal. Calc. for $C_{37}H_{53}N_5O_{16} \cdot 2CH_3CO_2H$: C, 52.17; H, 6.51; N, 7.42. Found: C, 51.89; H, 6.83; N, 7.33.

The acetic acid salt of **2a** (2.0 g) was dissolved in 1:1 *N*,*N*-dimethylformamide–M sodium hydroxide (800 ml), and the solution was kept for 5 days. The mixture was

brought to pH 7 with M hydrochloric acid and evaporated. The residue was dissolved in water (500 ml) and chromatographed on a column of Amberlite CG-50 resin (NH_4^+, 500 ml). The column was washed with water and eluted with 0.2% aqueous ammonia to give 6′-*N*-[(benzyloxy)carbonyl]xylostasin (410 mg, 31%), $[\alpha]_D^{23}$ +29.6° (*c* 1, water); R_F 0.27 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (D_2O): δ 7.52 (5H, s, *Ph*-CH_2), 5.18 (2H, s, Ph-CH_2), 5.30 (1H, d, *J* 3.5, H-1′), 5.20 (1H, d, $J < 1$, H-1″), 1.7–2.0 (1H, m, H-2eq), and 1.14 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{25}H_{40}N_4O_{12} \cdot 2H_2O$: C, 48.07; H, 7.10; N, 8.97. Found: C, 47.95; H, 6.86; N, 8.81.

6′-*N*-[(Benzyloxy)carbonyl]xylostasin (320 mg) and *p*-nitrophenyl formate (640 mg) were dissolved in 1:1 water—*N*,*N*-dimethylformamide (20 ml), and the solution was stirred overnight at room temperature and then evaporated. The residue was triturated with ethyl acetate, and the insoluble material was filtered off. The powder was washed with ethyl acetate, dissolved in water (10 ml), and applied to a column of Amberlite CG-50 resin (H^+, 130 ml). The column was eluted with water and appropriate fractions were concentrated and lyophilized to give 6′-*N*[(benzyloxy) carbonyl]-1,3,2′-tri-*N*-formylxylostasin (310 mg, 85%), $[\alpha]_D^{22}$ +31.8° (*c* 1, water); n.m.r. data (D_2O): δ 7.9–8.2 (total 3H, 3 formyl), 7.46 (5H, s, *Ph*-CH_2), 5.16 (2H, s, Ph-CH_2), 5.45 (1H, d, *J* 3.5, H-1′), 5.26 (1H, d, $J < 1$, H-1″), 1.8–2.2 (1H, m, H-2eq), and 1.60 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{28}H_{40}N_4O_{15} \cdot 2H_2O$: C, 47.45; H, 6.29; N, 7.91. Found: C, 47.57; H, 5.91; N, 7.74.

To a solution of 6′-*N*-(benzyloxy)carbonyl-1,3,2′-tri-*N*-formylxylostasin (200 mg) in 1:0.1:2 methanol–acetic acid–water (20 ml), palladium black (50 mg) was added. The mixture was hydrogenated for 3 h at room temperature in a stream of hydrogen. The catalyst was filtered off and washed with 1% aqueous acetic acid (100 ml), and the filtrate was evaporated. The residue was chromatographed on a column of Amberlite CG-50 resin (NH_4^+, 90 ml). The column was washed with water and eluted with 0.1% aqueous ammonia to give 1,3,2′-tri-*N*-formylxylostasin[2]; yield 148 mg (92%), $[\alpha]_D^{23}$ +38.5° (*c* 1, water); n.m.r. data (D_2O): δ 8.1–8.35 (total 3H, 3 formyl), 5.52 (1H, d, *J* 3.5, H-1′), 5.20 (1H, d, $J < 1$, H-1″), 2.0–2.4 (1H, m, H-2eq), and 1.72 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{20}H_{34}N_4O_{13} \cdot H_2O$: C, 43.16; H, 6.52; N, 10.07. Found: C, 43.25; H, 6.40; N, 10.14.

6′,4‴-Di-N-(*benzyloxy*)*carbonyl-3,2′-di*-N-(p-*methoxybenzyl*)*butirosin A* (**3a**).— To a suspension of the crude **2a** (16.4 g) in ethanol (150 ml), triethylamine (8 ml) was added. *p*-Anisaldehyde (8 ml) was added dropwise to the suspension with stirring at room temperature. The mixture was further stirred overnight, and the resulting clear solution was evaporated. Ethyl ether was added to the residue and the resulting precipitate was dissolved in methanol (60 ml), and then tetrahydrofuran (80 ml) was added. Sodium borohydride (1.6 g) was added portionwise to the solution with stirring and with cooling in an ice–water bath, and after 30 min at 0—5° the solution

was evaporated. The residue was dissolved in chloroform (100-ml) and the solution was applied to a column of silica gel (500 ml), which was eluted with chloroform–methanol (9 : 1 and then 4 : 1) to give **3a**; yield 15.4 g (69% from **1a**) as a white powder, $[\alpha]_D^{22}$ +22.1° (*c* 1, methanol); R_F 0.14 (4:1 chloroform–methanol), R_F 0.67 (105 : 45 : 50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (methanol-*d*): δ 7.28 (10H, s, *Ph*-CH_2), 5.05 and 5.00 (2H × 2, 2s, 2 Ph-CH_2), 7.19, 6.83, and 6.80 (4H, 2H, and 2H, 3d, *J* 8.5, 2 CH_3O-C_6H_4-CH_2), 3.72 and 3.68 (3H × 2, 2s, 2 CH_3O-C_6H_4-CH_2), 5.23 (1H, d, *J* 3.5, H-1′), 5.16 (1H, d, *J* < 1, H-1″), and 1.21 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{53}H_{69}N_5O_{18} \cdot CH_3OH$: C, 59.17; H, 6.71; N, 6.39. Found: C, 59.17; H, 6.64; N, 6.43.

6′,4‴-Di-N-(*benzyloxy*)*carbonyl-3,2′-di*-N-(p-*methoxybenzyl*)*butirosin B* (**3b**). — Compound **1b** (11.1 g) was treated with benzyl *p*-nitrophenyl carbonate (10.4 g) to give the di-*N*-(benzyloxy)carbonyl derivative **2b** (15.8 g), as described for the preparation of **2a**. The crude **2b** was treated with *p*-anisaldehyde (8 ml) and then sodium borohydride (1.3 g) by the procedure used for the preparation of **3a** to give **3b** (14.2 g, 67% from **1b**) as a white powder; $[\alpha]_D^{22}$ +22.7° (*c* 1, methanol); R_F 0.14 (4:1 chloroform–methanol), R_F 0.65 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (methanol-*d*): δ 7.27 (10H, s, *Ph*-CH_2), 5.04 and 5.00 (2H × 2, 2s, 2 Ph-CH_2), 7.17, 6.84, and 6.81 (4H, 2H, and 2H, 3d, *J* 8.5, 2 CH_3O-C_6H_4-CH_2), 3.73 and 3.68 (3H × 2, 2s, 2 CH_3O-C_6H_4-CH_2), 5.22 (1H, d, *J* 3.5, H-1′), and 5.12 (1H, d, *J* < 1, H-1″).

Anal. Calc. for $C_{53}H_{69}N_5O_{18} \cdot CH_3OH$: C, 59.17; H, 6.71; N, 6.39. Found: C, 59.19; H, 6.54; N, 6.78.

6′,4‴-Di-N-(*benzyloxy*)*carbonyl-2′-deamino-3′-deoxy-3*-N-p-*methoxybenzyl-2′, 3′*-(p-*methoxybenzyl*)*epiminobutirosin A* (**4a**). — *A*. To a stirred solution of **3a** (26.6 g) in 3 : 10 tetrahydrofuran–acetonitrile (650 ml), triphenylphosphine (19.7 g) was added with cooling in an ice-bath. Carbon tetrachloride (50 ml) was added to the solution below 4° under a stream of nitrogen. After stirring for an additional 5 h under the same conditions, triethylamine (25 ml) was added to the mixture. The mixture was stirred for 3 h at room temperature, water (50 ml) was added, and the mixture was stirred for an additional 3 h. The mixture was evaporated and the residue was extracted with ethyl acetate. The extract was washed with water and evaporated. The residue was dissolved in chloroform (50 ml) and the solution was applied to a column of silica gel (500 ml), which was developed with 9 : 1 chloroform–methanol. The effluent was evaporated to give **4a** (18.3 g, 70%) as a white powder, $[\alpha]_D^{22}$ +29.7° (*c* 1, methanol); R_F 0.42 (4 : 1 chloroform–methanol), R_F 0.73 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (methanol-*d*): δ 7.33 and 7.31 (5H × 2, 2s, 2 *Ph*-CH_2), 5.07 and 5.03 (2H × 2, 2s, 2 Ph-CH_2), 7.41, 7.18, and 6.79 (2H, 2H, and 4H, 3d, *J* 8.5, 2 CH_3O-C_6H_4-CH_2), 3.76 and 3.72 (3H × 2, 2s, 2 CH_3O-C_6H_4-CH_2), 5.54 (1H, d, *J* 4.5, H-1′), 5.08 (1H, d, *J* < 1, H-1″), 2.66 (1H, dd, *J* 4.5 and 6.0, H-2′), and 1.18 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{53}H_{67}N_5O_{17} \cdot CH_3OH$: C, 60.15; H, 6.64; N, 6.50. Found: C, 60.18; H, 6.40; N, 6.74.

B. To a solution of triphenylphosphine (6.6 g) in acetonitrile (70 ml), a solution of bromine (4.0 g) in acetonitrile (20 ml) was added and the mixture was stirred for 2 h at room temperature. To the resulting clear solution, a solution of **3a** (5.3 g) in tetrahydrofuran (50 ml) was added with stirring and cooling below 2° in a stream of nitrogen. After 3 h under these conditions, triethylamine (4 ml) was added dropwise to the mixture, and the temperature was kept below 4°. After stirring for an additional 5 h at 10°, the mixture was evaporated and the residue was purified to give **4a** (0.87 g, 17%) as a white powder by the procedure described in method *A*.

6′,4‴-Di-N-(*benzyloxy*)*carbonyl-2′-deamino-3′-deoxy-3*-N-p-*methoxybenzyl-2′,3′*-(p-*methoxybenzyl*)*epiminobutirosin B* (**4b**). — Compound **3b** (5.3 g) was treated with triphenylphosphine (6.6 g), carbon tetrachloride (10 ml), and triethylamine (5 ml) to give **4b** (2.9 g, 56%), as described for the preparation of **4a**; $[\alpha]_D^{22}$ +34.0° (*c* 1, methanol); R_F 0.40 (4:1 chloroform–methanol), R_F 0.72 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (methanol-*d*): δ 7.30 and 7.29 (5H × 2, 2s, 2 *Ph*-CH_2), 5.06 and 5.02 (2H × 2, 2s, 2 Ph-CH_2), 7.39, 7.16, and 6.77 (2H, 2H, and 4H, 3d, *J* 8.5, 2 CH_3O-C_6H_4-CH_2), 3.74 and 3.70 (3H × 2, 2s, 2 CH_3O-C_6H_4-CH_2), 5.47 (1H, d, *J* 4.5, H-1′), 5.07 (1H, d, *J* < 1, H-1″), and 2.64 (1H, dd, *J* 4.5 and 6.0, H-2′).

Anal. Calc. for $C_{53}H_{67}N_5O_{17}$: C, 60.85; H, 6.46; N, 6.70. Found: C, 60.80; H, 6.46; N, 6.70.

2′-Deamino-3′-deoxy-3-N-p-*methoxybenzyl-2′,3′*-(p-*methoxybenzyl*)*epiminobutirosin A* (**5a**). — To a solution of **4a** (3.0 g) in 9:10:1 water–methanol–acetic acid (200 ml), 5% palladium-on-carbon (200 mg) was added. The mixture was hydrogenated for 6 h at room temperature in a stream of hydrogen. The palladium catalyst was filtered off, and washed with 50% aqueous methanol. The filtrate and washings were evaporated and the residue was dissolved in water (100 ml), and the solution was applied to a column of Amberlite CG-50 resin (NH_4^+, 350 ml). The column was washed with water and eluted with 0.8% aqueous ammonia. The eluate was lyophilized to give **5a** (1.52 g, 68%) as a white powder, $[\alpha]_D^{22}$ +41.8° (*c* 1, water); R_F 0.54 (2:1:1 chloroform–methanol–17% aqueous ammonia), R_F 0.16 (105:45:50 1-propanol–ethyl acetate–28% aqueous ammonia); n.m.r. data (D_2O): δ 7.49, 7.36, 7.00, and 6.99 (2H × 4, 4d, 2 CH_3O-C_6H_4-CH_2), 3.88 and 3.85 (3H × 2, 2s, 2 CH_3O-C_6H_4-CH_2), 5.54 (1H, d, *J* 4.5, H-1′), and 5.03 (1H, d, *J* < 1, H-1″).

Anal. Calc. for $C_{37}H_{55}N_5O_{13} \cdot H_2CO_3$: C, 54.34; H, 6.84; N, 8.34. Found: C, 54.15; H, 6.40; N, 8.54.

2′-Deamino-3′-deoxy-2′,3′-epiminobutirosin A (**6a**). — To a solution of **5a** (1.5 g) in 9:10:1 water–ethanol–acetic acid (100 ml), palladium black (200 mg) was added and the mixture was hydrogenated for 3 h at 65–70° in a stream of hydrogen. The catalyst was filtered off and washed with 50% aqueous methanol. The filtrate and washings were combined and passed through a column of Amberlite CG-50 resin (NH_4^+, 200 ml). The column was washed with water and eluted with 0.8% aqueous

ammonia. The effluent was lyophilized to give **6a** (487 mg, 47%) as a white powder; $[\alpha]_D^{22}$ +27.2° (*c* 1, water); R_F 0.33 (2:1:1 chloroform–methanol–17% aqueous ammonia), R_F 0.59 (5:3 15% (w/v) aqueous sodium chloride–methanol); n.m.r. data (D_2O): δ 5.67 (1H, d, *J* 4.5, H-1′), 5.29 (1H, d, *J* < 1, H-1″), and 1.41 (1H, q, *J* 13, H-2ax).

Anal. Calc. for $C_{21}H_{39}N_5O_{11} \cdot 2H_2CO_3$: C, 41.75; H, 6.55; N, 10.59. Found: C, 41.78; H, 6.55; N, 10.62.

3′-Deoxybutirosin A (**7a**) *and 3′-amino-2′-deamino-3′-deoxybutirosin A* (**8a**). — *A*. Compound **4a** (3.0 g) was hydrogenolyzed in 9:10:1 water–ethanol–acetic acid (200 ml), with palladium black (600 mg) as catalyst, for 5 h at room temperature and then for 5 h at 70°. The catalyst was filtered off and washed with 10% aqueous acetic acid. The filtrate and washings were combined and evaporated. A solution of the residue in water was passed through a column of Amberlite CG-50 resin (NH_4^+, 130 ml). After washing with water, the column was eluted with 1.2% aqueous ammonia. The eluate containing **7a** and **8a** was evaporated. The residue, dissolved in water (10 ml), was adjusted to pH 5 with 0.1M sulfuric acid. The solution was concentrated to about 5 ml, and applied to a column of activated carbon (250 ml). When the column was developed with water, compound **7a** was eluted prior to **8a**. The fraction containing **7a** was passed through a column of Amberlite CG-50 resin (NH_4^+, 130 ml). The column was washed with water and eluted with 0.8% aqueous ammonia. The effluent was lyophilized to give **7a** (846 mg, 56%) as a white powder; $[\alpha]_D^{25}$ +20.4° (*c* 1, water); R_F 0.31 (2:1:1 chloroform–methanol–17% aqueous ammonia), R_F 0.48 (5:3 15% (w/v) aqueous sodium chloride–methanol); n.m.r. data (D_2O): δ 5.55 (1H, d, *J* 3.5, H-1′), 5.45 (1H, d, *J* < 1, H-1″), and 1.25–2.4 (6H, m, H-2, H-3′, and H-3‴).

Anal. Calc. for $C_{21}H_{41}N_5O_{11} \cdot 2H_2O$: C, 43.82; H, 7.88; N, 12.17. Found: C, 43.96; H, 7.74; N, 12.13.

The subsequently eluted fraction containing **8a** was passed through a column of Amberlite CG-50 resin (NH_4^+, 80 ml). The column was washed with water and eluted with 0.8% aqueous ammonia. The effluent was lyophilized to give **8a** (388 mg, 26%) as a white powder; $[\alpha]_D^{23}$ +14.4° (*c* 1, water); R_F 0.31 (2:1:1 chloroform–methanol–17% aqueous ammonia), R_F 0.41 (5:3 15% (w/v) aqueous sodium chloride–methanol); n.m.r. data (D_2O): δ 5.3–5.4 (1H, m, H-1′) and 5.27 (1H, d, *J* < 1, H-1″).

Anal. Calc. for $C_{21}H_{41}N_5O_{11} \cdot 2H_2CO_3$: C, 41.62; H, 6.84; N, 10.55. Found: C, 41.47; H, 6.86; N, 10.89.

B. A solution of **6a** (1.0 g) in water (20 ml) was hydrogenolyzed with Raney nickel (5 ml) as catalyst under pressure (100 kg/cm^2) for 12 h at 60°. The catalyst was filtered off and washed with 1% aqueous ammonia (100 ml). The filtrate and washings were combined and evaporated. A solution of the residue in water (10 ml) was adjusted to pH 5 with 0.1M sulfuric acid. The solution was chromatographed over Amberlite CG-50 resin (NH_4^+) and activated carbon to give **7a** (730 mg, 71%) and **8a** (206 mg, 20%), as described in method *A*.

3′-Deoxybutirosin B (**7b**). — Compound **4b** (500 mg) in 9:10:1 water–ethanol–acetic acid (100 ml) was hydrogenated with palladium black (200 mg) in a stream of hydrogen for 5 h at room temperature and then for an additional 5 h at 70°. Compound **7b** (130 mg, 51%) was isolated from the hydrogenolysis mixture, as described for **7a**; $[\alpha]_D^{22}$ +27.3° (*c* 1, water); R_F 0.33 (2:1:1 chloroform–methanol–17% aqueous ammonia), R_F 0.45 (5:3 15% (w/v) aqueous sodium chloride–methanol).

Anal. Calc. for $C_{21}H_{41}N_5O_{11} \cdot H_2CO_3$: C, 43.92; H, 7.20; N, 11.64. Found: C, 43.91; H, 7.50; N, 11.52.

*6,2″,2‴-Tri-*O*-acetyl-tetra-*N*-(benzyloxy)carbonyl-3″,5″-mono-*O*-cyclohexylidene-3′-*O*-thiobenzoylbutirosin A* (**10**). — *N,N*-Dimethylbenzamide (1.0 g) was dissolved in dichloromethane (25 ml) containing phosgene (1.2 g). The solution was stirred overnight and then evaporated. A solution of the residue in dichloromethane (25 ml) was added dropwise to a tetrahydrofuran solution (20 ml) of 6,2″,2‴-tri-*O*-acetyl-tetra-*N*-(benzyloxy)carbonyl-3″,5″-mono-*O*-cyclohexylidenebutirosin A (**9**, 3.9 g) and pyridine (0.62 ml). After stirring for 1 h at room temperature, pyridine (0.41 ml) was added, and then hydrogen sulfide was bubbled into the mixture for 10 min. After stirring for a further 1 h, the mixture was evaporated. The residue was applied to a column of silica gel, and the column was eluted with 8:1 chloroform–acetone to give the 3′-thiobenzoate **10**; yield 3.2 g, (75%), $[\alpha]_D^{25}$ −6.7° (*c* 1, chloroform).

Anal. Calc. for $C_{72}H_{83}N_5O_{23}S$: C, 60.96; H, 5.90; N, 4.94; S, 2.26. Found: C, 60.95; H, 5.87; N, 4.97; S, 2.27.

*6,2″,2‴-Tri-*O*-acetyl-tetra-*N*-(benzyloxy)carbonyl-3″,5″-mono-*O*-cyclohexylidene-3′-deoxybutirosin A* (**12**) *from* **10**. — The 3′-thiobenzoate **10** (1.3 g) in toluene (50 ml) was added dropwise with stirring to tributylstannane (2.3 ml) in boiling toluene (50 ml) under reflux. The solution was further boiled under reflux for 10 min and then evaporated. The residue was applied to a column of silica gel, and the column was eluted with 1:2 benzene–ethyl acetate to give the 3′-deoxy derivative **12**; yield 1.0 g (91%), $[\alpha]_D^{25}$ −6.1° (*c* 1, chloroform).

Anal. Calc. for $C_{65}H_{79}N_5O_{22}$: C, 60.88; H, 6.21; N, 5.46. Found: C, 60.40; H, 6.13; N, 5.27.

*6,2″,2‴-Tri-*O*-acetyl-tetra-*N*-(benzyloxy)carbonyl-3″,5″-mono-*O*-cyclohexylidene-3′-*O*-p-tolylsulfonylbutirosin A* (**11**). — The 3′,4′-diol **9** (1.5 g) was dissolved in dry pyridine (10 ml), and then *p*-toluenesulfonyl chloride (0.75 g) was added with cooling in an ice–water bath. The mixture was kept for 48 h at room temperature and then evaporated. The residue was taken up in chloroform, the solution was washed with water, and the chloroform extract was evaporated. The residue was applied to a column of silica gel, which was eluted with 3:7 chloroform–ethyl acetate. The effluent was evaporated to give the 3′-sulfonate **11**; yield 1.3 g (77%), $[\alpha]_D^{23}$ +1.3° (*c* 1, chloroform); n.m.r. data (chloroform-*d*): δ 2.32 (3H, s, CH_3-C_6H_4-SO_2-), 2.03, 2.06, and 2.10 (3H × 3, 3s, 3 acetyl), and 1.2–1.7 (10H, cyclohexylidene).

Anal. Calc. for $C_{72}H_{85}N_5O_{25}S$: C, 59.53; H, 5.90; N, 4.82; S, 2.21. Found: C, 59.18; H, 5.98; N, 4.71; S, 2.26.

*6,2″,2‴-Tri-*O*-acetyl-tetra-*N*-(benzyloxy)carbonyl-3″,5″-mono-*O*-cyclohexyli-*

dene-3'-deoxybutirosin A (**12**) *from* **11**. — The 3'-*p*-toluenesulfonate **11** (5.0 g) in acetone (300 ml) was heated with sodium iodide (50 g) in a sealed tube for 48 h at 110°. Insoluble material was filtered off and washed with acetone. The combined filtrate and washings were then evaporated to a syrup. The syrup was partitioned between chloroform and saturated aqueous sodium thiosulfate. The organic phase was washed with water and evaporated. The residue was dissolved in dry toluene (100 ml) and the solution was boiled under reflux with tributylstannane (5.5 ml) and α,α'-azobis(isobutyronitrile) (30 mg) for 1.5 h under nitrogen. The mixture was concentrated and then purified by chromatography on silica gel with 1:2 benzene–ethyl acetate. The effluent was evaporated to give the 3'-deoxy derivative **12**; yield 1.5 g (34%), $[\alpha]_D^{23}$ −6.1° (*c* 1, chloroform).

Anal. Calc. for $C_{65}H_{79}N_5O_{22}$: C, 60.88; H, 6.21; N, 5.46. Found: C, 60.40; H, 6.13; N, 5.27.

3'-Deoxybutirosin A (**7a**) *from* **12**. — A solution of **12** (0.1 g) in ammonia-saturated methanol (30 ml) was kept overnight at room temperature and then evaporated. The residue was dissolved in 70% aqueous acetic acid (30 ml) and the solution was heated for 2 h at 50°, and then hydrogenated in the presence of palladium black (40 mg) for 3 h. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was adsorbed on a column of CM-Sephadex (NH_4^+, 50 ml) and the column was eluted with 0.8% aqueous ammonia to give **7a**; yield 31 mg (60%).

6,2",2"'-Tri-O-*acetyl-3'*-O-*benzoyl-tetra*-N-(*benzyloxy*)*carbonyl-3",5"-mono*-O-*cyclohexylidenebutirosin A* (**13**). — The 3',4'-diol **9** (43 g) was dissolved in pyridine (350 ml), and then benzoyl chloride (9.3 ml) was added with cooling in an ice-water bath. After stirring for 1 h at 0—5° and a further 6 h at room temperature, the mixture was poured into ice–water and the product extracted with chloroform. The extract was evaporated and the residue applied to a column of silica gel. The column was eluted with 1:1 chloroform–ethyl acetate to give the 3'-benzoate **13**; yield 26 g (57%), $[\alpha]_D^{22}$ +18.0° (*c* 1, chloroform); n.m.r. data (chloroform-*d*): δ 7.38 and 7.88 (2H × 2, 2d, *J* 8, benzoyl), 2.09 and 2.12 (6H and 3H, 2s, 3 acetyl), and 1.2–1.7 (10H, cyclohexylidene).

Anal. Calc. for $C_{72}H_{83}N_5O_{24}$: C, 61.66; H, 5.97; N, 4.99. Found: C, 61.50; H, 5.94; N, 5.00.

6,2",2"'-Tri-O-*acetyl-3'*-O-*benzoyl-tetra*-N-(*benzyloxy*)*carbonyl-3",5"-mono*-O-*cyclohexylidene-4'*-O-*mesylbutirosin A* (**14**). — To a solution of the 3'-benzoate **13** (26 g) in dry pyridine (100 ml), mesyl chloride (8.1 ml) was added with cooling in an ice–water bath. The solution was kept overnight at room temperature, and then poured into ice–water. The mixture was extracted with chloroform, and the extract was washed with water and then evaporated. The residue was applied to a column of silica gel, and the column was eluted with 25:1 chloroform–methanol to give the 3'-*O*-benzoyl-4'-*O*-mesyl derivative **14** (27 g, almost quantitative); $[\alpha]_D^{22}$ +1.3° (*c* 1, chloroform); n.m.r. data (chloroform-*d*): δ 2.64 (3H, s, CH_3-SO_2), 2.07 and 2.10 (6H and 3H, 2s, 3 acetyl), and 1.2–1.7 (10H, cyclohexylidene).

Anal. Calc. for $C_{73}H_{85}N_5O_{26}S$: C, 59.22; H, 5.79; N, 4.73; S, 2.17. Found: C, 58.98; H, 5.98; N, 4.61; S, 2.37.

Tetra-N-(*benzyloxy*)*carbonyl-4′-deoxybutirosin A.* — The 3′-*O*-benzoyl-4′-*O*-mesyl derivative **14** (2.0 g) in acetone (200 ml) was heated with sodium iodide (20 g) in a sealed tube at 110°. After 48 h, insoluble material was filtered off and washed with acetone. The filtrate and washings were concentrated to syrup, which was partitioned between chloroform and saturated aqueous sodium thiosulfate. The organic phase was washed with water and evaporated. The residue was dissolved in dry toluene (50 ml) and the solution was boiled under reflux with tributylstannane (0.5 ml) and α,α′-azobis(isobutyronitrile) (20 mg) for 1.5 h under nitrogen. The solution was evaporated and the residue was dissolved in ammonia-saturated methanol (30 ml), and the solution was kept overnight at room temperature. The solution was evaporated, and the residue was dissolved in 70% aqueous acetic acid (30 ml). After heating for 2 h at 50°, the mixture was evaporated and the residue was applied to a column of silica gel. The column was eluted with 9:1 chloroform–methanol to give tetra-*N*-(benzyloxy)carbonyl-4′-deoxybutirosin A; yield 0.28 g (19%), $[\alpha]_D^{26}$ +27.7° (*c* 1, methanol).

Anal. Calc. for $C_{53}H_{65}N_5O_{19}$: C, 59.15; H, 6.09; N, 6.51. Found: C, 58.79; H, 5.97; N, 6.44.

4′-Deoxybutirosin A. — Tetra-*N*-(benzyloxy)carbonyl-4′-deoxybutirosin A (200 mg) was dissolved in 1:3 methanol–water (40 ml), and then acetic acid (0.5 ml) was added. The solution was hydrogenated in the presence of palladium black (40 mg) for 3 h. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was adsorbed onto a column of Amberlite CG-50 resin (NH_4^+) and the column was eluted with 0.9% aqueous ammonia to give 4′-deoxybutirosin A (93 mg, 77%); $[\alpha]_D^{26}$ +27.6° (*c* 1, water); R_F 0.20 (1:3:2 chloroform–methanol–28% aqueous ammonia), R_F 0.36 (3:4:4 chloroform–methanol–28% aqueous ammonia, upper layer; compare butirosin A R_F 0.28, 3′-deoxybutirosin A R_F 0.33); n.m.r. data (D_2O): δ 5.74 (1H, d, *J* 3.5, H-1′), 5.33 (1H, d, $J < 1$, H-1″), 1.72–2.22 (4H, m, H-2eq, H-4′eq, and H-3‴), 1.41 (1H, q, *J* 12, H-4′ax), and 1.29 (1H, q, *J* 12, H-2ax).

Anal. Calc. for $C_{21}H_{41}N_5O_{11} \cdot H_2CO_3$: C, 43.92; H, 7.20; N, 11.64. Found: C, 43.86; H, 7.23; N, 12.11.

4′-Deoxybutirosin A (50 mg) was dissolved in water (5 ml), and then 0.1M sulfuric acid (0.83 ml) was added. The solution was lyophilized to give 4′-deoxybutirosin A monosulfate[13] (54 mg, nearly quantitative), $[\alpha]_D^{23}$ +24.3° (*c* 1, water), n.m.r. data (D_2O, pH 2): δ 6.11 (1H, d, *J* 3.5, H-1′), 5.30 (1H, d, $J < 1$, H-1″), and 1.2–2.4 (6H, m, H-2, H-4′, and H-3‴).

Anal. Calc. for $C_{21}H_{41}N_5O_{11} \cdot H_2SO_4 \cdot 2H_2O$: C, 37.44; H, 7.03; N, 10.40; S, 4.76. Found: C, 37.65; H, 7.33; N, 10.48; S, 4.65.

4′-Deoxybutirosin A (30 mg) was dissolved in 0.5M sodium hydroxide (10 ml), and the solution was boiled under reflux for 1 h. The solution was brought to pH 7 with M hydrochloric acid and passed through a column of CM-Sephadex (NH_4^+, 60 ml). The column was washed with water and eluted with 0.4% aqueous ammonia.

The effluent was concentrated and lyphilized to give 4′-deoxy-5-β-D-xylofuranosylneamine[14] (4′-deoxyxylostasin, 21 mg, 89%), $[\alpha]_D^{26}$ +63.5° (*c* 0.5, water); R_F 0.58 (3:4:4 chloroform–methanol–28% aqueous ammonia, upper layer); n.m.r. data (D_2O, pH 2): δ 6.09 (1H, d, *J* 3.5, H-1′) and 5.35 (1H, d, *J* < 1, H-1″).

Anal. Calc. for $C_{17}H_{34}N_4O_9 \cdot 2H_2O$: C, 40.71; H, 6.47; N, 10.00. Found: C, 40.71; H, 6.51; N, 10.30.

ACKNOWLEDGMENTS

We thank Drs. S. Tatsuoka, E. Ohmura, K. Morita, K. Mizuno, and M. Yoneda, Central Research Division of our company for their support and encouragement throughout this study. Grateful acknowledgment is extended to Mr. M. Kida for the antimicrobial spectrum of 3′-deoxybutirosin A, to Drs. K. Hiraga and T. Okutani for conveying the information on 2′-deamino-3′-deoxy-2′,3′-epiminobutirosin A to us prior to publication, and to Messrs. Y. Yasumura, K. Kawahara, and T. Matsuyama for their technical assistance.

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