A Synthesis of 3′-Deoxybutirosin B

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3′-Deoxybutirosin B (**13**) was prepared from 3′-deoxyparomamine (**1**), D-ribose and (*S*)-4-amino-2-hydroxybutyric acid (AHBA). The synthesis involves replacement of the 6′-hydroxyl group of 3′-deoxyparomamine with azido group, 1,6-carbamate ring formation, condensation with tri-*O*-(*p*-nitrobenzoyl)-α,β-D-ribofuranosyl bromide, selective cleavage of the carbamate ring, and acylation of the free amino group at C-1 with AHBA.

In a previous paper,[1] we described the synthesis of 3′-deoxybutirosin B (**13**), a compound having a remarkable activity against resistant bacteria, starting from ribostamycin. In this paper we describe a second synthesis of **13** by condensation of a 3′-deoxyparomamine derivative with a protected ribosyl bromide. The starting material 3′-deoxyparomamine[2] (**1**) is conveniently obtained by hydrolysis of lividomycins,[3] an antibiotic complex produced by *streptomyces lividus*.

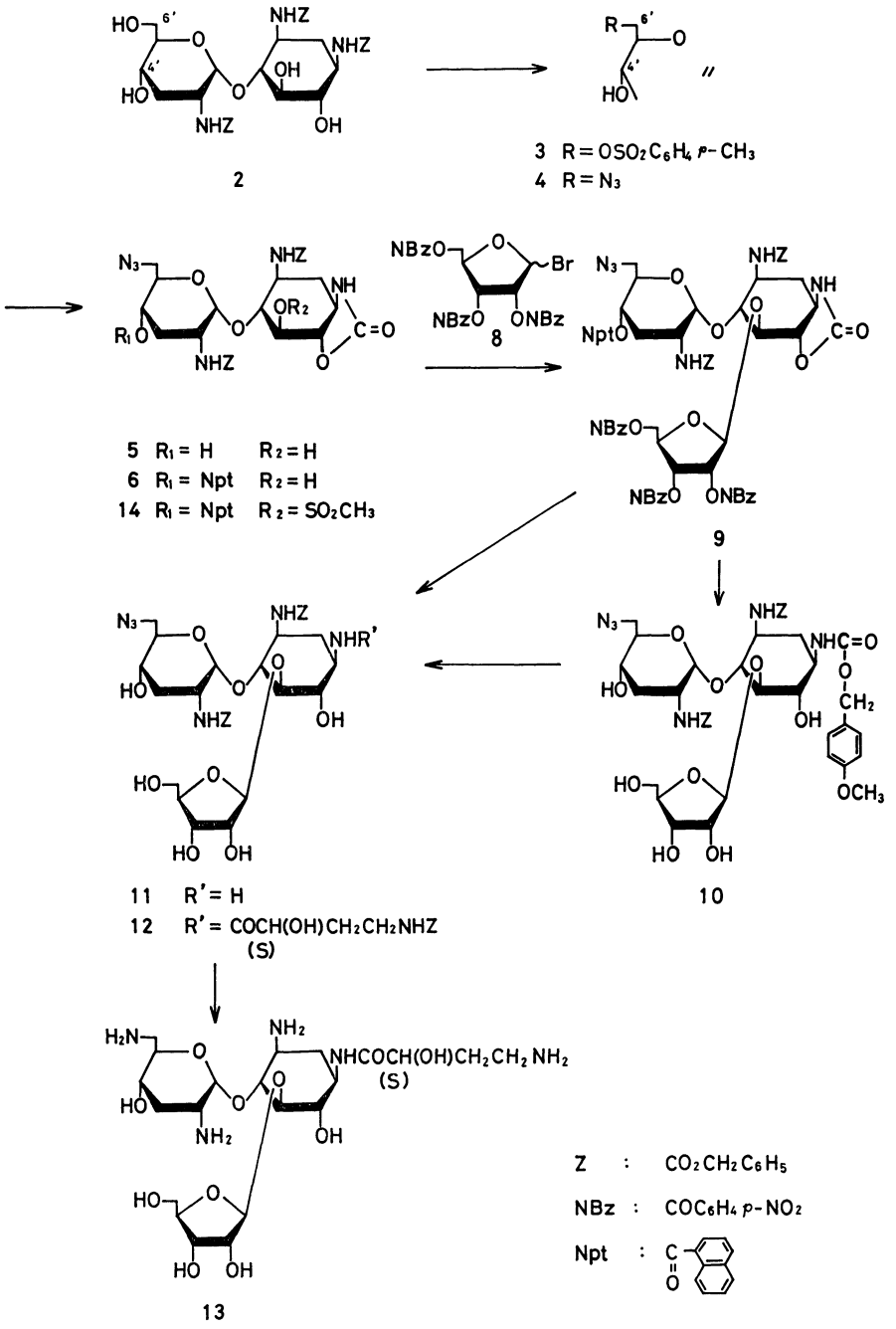
For attaining the synthesis, three key steps were required: 1) replacement of the 6′-hydroxyl group with an amino group, 2) selective ribosylation of the 5-hydroxyl group, and 3) selective amidation of the 1-amino group with (*S*)-4-amino-2-hydroxybutyric acid. The step (1) was performed by selective 6′-*O*-tosylation of a paromamine derivative followed by azidation and hydrogenation. For the step (2) the preparation of a 3′-deoxyparomamine derivative having a free hydroxyl group only at C-5 was required. For this purpose cyclic 1,6-carbamate[4] formation was utilized. Ito *et al.*[5] have reported the synthesis of ribostamycin by condensation of an *O*-benzoylribosyl chloride with a neamine derivative bearing two free hydroxyl groups at C-5 and C-6 to give 5-*O*-ribosyl glycoside as the major product. On the other hand, Hanessian *et al.*[6] have obtained a 6-*O*-ribosyl glycoside almost quantitatively by condensation of the ribosyl chloride with a protected paromamine derivative having two free hydroxyl groups at C-5 and C-6. In our experiences,[13] the 6-hydroxyl group is observed to be more reactive than the 5-hydroxyl group, therefore, we designed to protect the 6-hydroxyl group by cyclic 1,6-carbamate formation. The 1,6-carbamate suggested another advantage that the space around the 5-hydroxyl group is extended by the formation of the cyclic carbamate, favouring the 5-*O*-glycosylation, while commonly used 6-*O*-acyl groups may exert steric hindrance on the 5-hydroxyl group. For the step (3), the cyclic 1,6-carbamate was again useful because it is preferentially cleaved[4] to give the free amino group at C-1.

Tri-*N*-benzyloxycarbonyl-3′-deoxyparomamine (**2**) obtained by treatment of 3′-deoxyparomamine[2] (**1**) with benzyl chloroformate was tosylated. In spite of the presence of four hydroxyl groups in **2**, the 6′-*O*-tosyl derivative (**3**) was isolated in a yield of 68%. The position of the group was indicated by the difficulty of tritylation of **3**. Treatment of **3** with sodium azide in *N*,*N*-dimethylformamide (DMF) gave the 6′-azido derivative (**4**) quantitatively. Reaction of **4** with sodium hydride in DMF in a manner as described in previous papers[1,4,7] gave the cyclic carbamate derivative (**5**) in a yield of 80%. The presence of a carbamate group was confirmed by its IR spectrum.[8] Since **5** has two hydroxyl groups at C-5 and 4′, the hydroxyl group at C-4′ was protected in advance. For the purpose we utilized α-naphthoyl group, a bulky one, expecting its regioselective effect. The 4′-*O*-(α-naphthoyl) derivative (**6**) was obtained in a yield of 65%. The structure of **6** was confirmed by acidic hydrolysis of the mesyl derivative (**14**) of **6**. Hydrolysis of **6** gave 2-deoxystreptamine, whereas hydrolysis of **14** did not give 2-deoxystreptamine, indicating that the hydroxyl at C-5 of 2-deoxystreptamine moiety was mesylated.

The 5-*O*-ribosylation of **6** was next studied. Among the protected ribosyl halogenides tested, the anomeric mixture (*ca.* 1 : 1) of 2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranosyl bromide (**8**), which was prepared *via* methyl 2,3,5-tri-*O*-(*p*-nitrobenzoyl)-β-D-ribofuranoside (**7**), was found suitable for the coupling partner to **6**, because **8** is stable to recrystallization from benzene and can be kept for months. The corresponding *O*-acetyl and *O*-benzoyl bromide were less stable. In addition, the presence of the *p*-nitrobenzoyl group at C-2 may be convenient in the glycoside formation in preventing[9] the formation of undesirable orthoester. After completion of our work, Khadem *et al.*[12] have reported the syntheses of **7** and **8** in the β-anomeric form by a method similar to ours. Condensation of **6** with **8** was carried out in dichloromethane in the presence of mercuric cyanide. In this reaction, the use of fairly decreased amount of dichloromethane (7—10 times v/w for **8**) was required to raise the yield of the condensation product (**9**). The use of benzene–dioxane, or nitromethane as the solvent or the use of Ag_2CO_3–$AgClO_4$ as the catalyst also decreased the yield.

Cleavage of the 1,6-carbamate as well as that of *O*-acyl groups was performed by use of a limited amount of barium hydroxide in dioxane, as reported in previous papers,[1,4,7] to give **11**. When, sodium *p*-methoxybenzylate was used as the base in this reaction, the 1,6-carbamate was cleaved to give the 1-*N*-(*p*-methoxybenzyloxycarbonyl) derivative (**10**). The 1-*N*-protecting group was selectively removed by the action of trifluoroacetic acid[10] in methoxybenzene to give **11** in high yield. The use of boiling acetic acid[10] decreased the yield of **11**.

(*S*)-4-Benzyloxycarbonylamido-2-hydroxybutyryl[11] group was then introduced to the free amino group at C-1 by *N*-hydroxysuccinimide ester method. Catalytic hydrogenolysis of the *N*-benzyloxycarbonyl groups



and the 6'-azido group of the amide (**12**) gave the 3'-deoxybutirosin B (**13**) in overall yield of *ca.* 6% based on **1**. The PMR spectrum of **13** was superimposable with that of 3'-deoxybutirosin B prepared[1] from ribostamycin.

Experimental

Thin-layer chromatography (TLC) was carried out on Wakogel B-5 with sulfuric acid spray for detection. For column chromatography, silica gel (Wakogel C-200) was used.

1,3,2'-Tri-N-*benzyloxycarbonyl-3'-deoxyparomamine (2).* A sample of 3'-deoxyparomamine[2] (**1**) was treated with benzyl chloroformate in a similar manner as reported[7] in benzyloxycarbonylation of lividomycin A to give a solid of **2** almost quantitatively, $[\alpha]_D^{22}$ +43° (*c* 0.5, dioxane).

Found: C, 60.70; H, 6.06; N, 5.63%. Calcd for $C_{36}H_{43}N_3O_{12}$: C, 60.92; H, 6.11; N, 5.92%.

1,3,2'-Tri-N-*benzyloxycarbonyl-3'-deoxy-6'-O-tosylparomamine (3).* To an ice-cold solution of **2** (9.78 g) in pyridine (200 ml), anhydrous *p*-toluenesulfonyl chloride (12.7 g, 5 mol equivalent for **2**) was added and the solution was kept at −10 °C overnight. The solution showed, on TLC with chloroform–ethanol (12 : 1), a major spot at R_f 0.53 and other several slight spots. After addition of water (2.5 ml), the solution was concentrated to give a yellow syrup. The chloroform solution (500 ml) of the syrup was washed with aqueous potassium hydrogensulfate, aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated to give a slightly yellow syrup, which was recrystallized from hot dioxane–hexane to give colorless needles, 8.04 g (68%), mp 185—186 °C, $[\alpha]_D^{21}$ +33° (*c* 1, dioxane); PMR ($CDCl_3$–pyridine-d_5) δ: 2.33 (3H s, CH_3(Ts)).

Found: C, 59.89; H, 5.70; N, 4.87; S, 3.72%. Calcd

for $C_{43}H_{49}N_3O_{14}S$: C, 59.78; H, 5.72; N, 4.86; S, 3.71%.

6'-Azido-1,3,2'-tri-N-*benzyloxycarbonyl-3',6'-dideoxyparomamine (4).* A mixture of **3** (5.46 g) and sodium azide (4.2 g) in DMF (100 ml) was agitated at 60 °C for 7 h. Either prolonged or shorter reaction at that temperature decreased the yield of **4**. The solution showed, on TLC with chloroform–ethanol (12 : 1), a single spot at R_f 0.50. Filtration followed by concentration of the filtrate with additions of toluene gave a solid, which was dissolved in dioxane and, after filtration, the solution was concentrated to give a solid, 4.51 g (97%), $[\alpha]_D^{22}$ +90° (*c* 0.5, dioxane); IR (KBr): 2100 (N_3), 1690 cm^{-1} (carbamate).

Found: C, 58.87; H, 5.78; N, 11.20%. Calcd for $C_{36}H_{42}N_6O_{11}$: C, 58.85; H, 5.76; N, 11.44%.

6'-Azido-3,2'-di-N-*benzyloxycarbonyl-3',6'-dideoxyparomamine 1,6-Carbamate (5).* To an ice-cold solution of **4** (1.11 g) in DMF (22 ml), 50% oily sodium hydride (240 mg) was added and the mixture was vigorously stirred for 2.5 h in the cold under the atmosphere of nitrogen. The solution showed, on TLC with chloroform–ethanol (15 : 1), a single spot at R_f 0.2. After addition of acetic acid (0.35 ml), the resulting pale-brown gelatinous mixture was poured into water (400 ml). After the mixture had been kept in a refrigerator overnight, it was filtered, and the solid was washed with water. After drying, the solid was reprecipitated from dioxane–hexane to give a solid, 0.75 g (80%). $[\alpha]_D^{20}$ +73° (*c* 1, dioxane); IR (KBr): 2100, 1760 (cyclic carbamate), 1700 cm^{-1}.

Found: C, 55.67; H, 5.50; N, 12.91%. Calcd for $C_{29}H_{34}N_6O_{10}$: C, 55.59; H, 5.47; N, 13.41%.

6'-Azido-3,2'-di-N-*benzyloxycarbonyl-3',6'-dideoxy-4'*-O-*(α-naphthoyl)paromamine 1,6-Carbamate (6).* To a cold solution of **5** (1.03 g) in dry pyridine (20 ml) in ice–salt bath, α-naphthoyl chloride (370 mg, 1.2 mol equivalent for **5**) was added and the solution was kept at −10 °C overnight. On TLC with chloroform–ethanol (20 : 1), the solution showed spots at R_f 0.12 (slight, **5**), 0.33 (major, **6**), 0.40 (slight, 5-*O*-α-naphthoyl isomer?) and 0.57 (slight, di-*O*-α-naphthoyl isomer?). Working up in a usual manner gave a crude solid, which was chromatographed over silica gel with benzene–ethyl acetate (3 : 2, gradually changed to 1 : 1) to give a solid of **6**, 826 mg (65%), $[\alpha]_D^{23}$ +98° (*c* 1, dioxane); IR (KBr): 2100, 1750, 1730 cm^{-1}.

Found: C, 61.42; H, 5.24; N, 10.49%. Calcd for $C_{40}H_{40}N_6O_{11}$: C, 61.53; H, 5.17; N, 10.76%.

6'-Azido-3,2'-di-N-*benzyloxycarbonyl-3',6'-dideoxy-4'*-O-*(α-naphthoyl)-5*-O-[*2,3,5-tri*-O-(p-*nitrobenzoyl)-β*-D-*ribofuranosyl]paromamine 1,6-Carbamate (9).* To a suspension of **6** (108 mg) in dichloromethane (2.0 ml), calcium sulfate (Drierite, 600 mg, reactivated at 250 °C), mercuric cyanide (350 mg, dried at 90 °C *in vacuo*) and **8** (330 mg, 3.85 mol. equivalent for **6**) were added and the mixture was vigorously stirred at room temperature overnight. On TLC with chloroform–ethanol (30 : 1), the solution showed spots of R_f 0.27 (major), 0.23 (slight), and 0.19 (minor, α-anomeric isomer?), which were of all non-reducing ability (checked by triphenyltetrazolium chloride reagent). After filtration, the solution was washed with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The resulting solid was chromatographed over silica gel with chloroform–ethyl acetate (3 : 2) to give a solid of **9**, 119 mg (66%), mp 136—138 °C, $[\alpha]_D^{22}$ +25° (*c* 1, chloroform); IR (KBr): 2100, 1770 (cyclic carbamate), 1730, 1530, and 1350 cm^{-1} (NO_2).

Found: C, 58.04; H, 4.32; N, 8.99%. Calcd for $C_{66}H_{57}N_9O_{24}$: C, 58.28; H, 4.22; N, 9.27%.

6'-Azido-3,2'-di-N-*benzyloxycarbonyl-3',6'-dideoxy-1*-N-*(p-methoxybenzyloxycarbonyl)-5*-O-*(β*-D-*ribofuranosyl)paromamine (10).* To a solution of **9** (444 mg) in dioxane (40 ml) containing *p*-methoxybenzylalcohol (8.8 ml dried over Molecular Sieves 4A), 1 M sodium *p*-methoxybenzylate in the same alcohol (1.6 ml) was added and the solution was kept overnight at room temperature. On TLC with chloroform–ethanol (10 : 1), the solution showed a single spot at R_f 0.26. After addition of acetic acid (0.1 ml), the solution was concentrated and the syrup was dissolved in chloroform (150 ml). The solution was washed several times with water and concentrated to give a syrup. Evaporation (110 °C, 0.02 Torr) of the *p*-methoxybenzylalcohol remained in the syrup gave a thick syrup, which was chromatographed over silica gel firstly with chloroform (to elute the alcohol remained) and then with chloroform–ehtanol (12 : 1) to give a colorless solid of **10**, 175 mg (60%), mp 96—98 °C, $[\alpha]_D^{23}$ +38° (*c* 1, chloroform); IR (KBr): 2100, 1695, 1520 cm^{-1}; PMR ($CDCl_3$) δ: 3.69 (3H s, $CH_3O \cdot C_6H_4$).

Found: C, 56.12; H, 5.76; N, 9.08%. Calcd for $C_{42}H_{52}N_6O_{16}$: C, 56.24; H, 5.84; N, 9.37%.

6'-Azido-3,2'-di-N-*benzyloxycarbonyl-1*-N-*[(S)-4-benzyloxycarbonylamido-2-hydroxybutyryl]-3',6'-dideoxy-5*-O-*(β*-D-*ribofuranosyl)paromamine (12).* *A. From 9.* To a solution of **9** (94 mg) in dioxane (4.4 ml), 0.05 M barium hydroxide solution (1.5 ml, 1 mol equivalent for **9**) was added and the mixture was stirred at 60 °C for 30 min. To the resulting neutral solution, additional aliquots of the barium hydroxide solution (1.5 ml × 2) were added at intervals and the mixture was treated as above. On TLC with chloroform–ethanol (7 : 2), the solution showed a major spot at R_f 0.15. Introduction of carbon dioxide followed by filtration and concentration of the filtrate gave a residue, which was extracted with dioxane and the dioxane-soluble product (crude **11**, 65 mg) was isolated.

To a solution of the crude **11** in THF (0.8 ml), *N*-hydroxysuccinimide ester[11] (32 mg) of (*S*)-4-benzyloxycarbonylamido-2-hydroxybutyric acid and triethylamine (*ca.* 11 mg) were added and the solution was stirred at 0 °C for 1 h and then kept at room temperature overnight. On TLC with chloroform–methanol (7 : 1), the solution showed a major spot at R_f 0.31 and the spot at R_f 0.05 (**11**) almost disappeared. The solution was concentrated and the chloroform solution of the residue was washed successively with aqueous potassium hydrogensulfate, aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The residue was then chromatographed over silica gel with chloroform–methanol (20 : 1) to give **12**, 24 mg (36% based on **9**), mp 94—96 °C, $[\alpha]_D^{22}$ +19° (*c* 0.25, chloroform); IR (KBr): 2100, 1700, 1530 cm^{-1}.

Found: C, 55.62; H, 5.81; N, 9.95%. Calcd for $C_{45}H_{57}N_7O_{17}$: C, 55.84; H, 5.94; N, 10.13%.

B. From 10. To a cold suspension (in ice–salt bath) of **10** (142 mg) in methoxybenzene (0.13 mg), trifluoroacetic acid (0.8 ml) was added and the mixture was stirred in the cold for a while. The resulting clear solution was kept in the cold for further 30 min. On TLC with chloroform–ethanol (7 : 2), the solution showed majorly a ninhydrin-positive spot (**11**, R_f 0.15). Concentration of the solution *in vacuo* followed by addition of methanolic ammonia to the concentrate until weakly alkaline gave a gelatinous mixture, which was chromatographed over silica gel with chloroform–ethanol (10 : 1) to give a solid of **11**, 102 mg (88%). Reaction of the solid with the active ester in a similar manner as described in A gave **12**, 71 mg (58%).

3'-Deoxybutirosin B (13). To a solution of **12** (64 mg) in dioxane (1.2 ml), water (1.0 ml) and a drop of acetic acid was added and the mixture was hydrogenated with

palladium black under an atmospheric pressure of hydrogen. Concentration of the solution gave a solid, which was chromatographed over CM-Sephadex C-25 (NH_4 form) with 0—0.4 M ammonia with gradient increase in concentration to give **13** as monocarbonate, 25 mg (63%), mp 147—149 °C, $[\alpha]_D^{23}$ +29° (*c* 1, water); IR (KBr): 1640, 1565 cm^{-1}.

Found: C, 44.22; H, 7.27; N, 11.71%. Calcd for $C_{21}H_{41}N_5O_{11}\cdot H_2CO_3$: C, 43.92; H, 7.20; H, 11.64%.

Methyl 2,3,5-Tri-O-(p-nitrobenzoyl)-β-D-ribofuranoside (7). To an ice-cold solution of D-ribose (2.0 g) in dry methanol (40 ml), 1 M methanolic hydrogen chloride (4.5 ml) was gradually added and the solution was kept at room temperature for 1 h. On TLC with benzene–ethanol (1 : 1), the solution showed spots at R_f 0.63 (major, β-riboside) and 0.44 (slight) (*cf.* D-ribose, R_f 0.54). Pyridine (12 ml) was added and the solution was concentrated with additions of toluene to give a syrup. To the solution of the syrup in pyridine (44 ml), *p*-nitrobenzoyl chloride (8.15 g) was added and the solution was kept at room temperature overnight. Water (1 ml) was added and the solution was concentrated. The chloroform solution of the syrup was successively washed with aqueous potassium hydrogensulfate, aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. Recrystallization of the solid from acetone gave pale-yellow needles, 4.9 g (60%), mp 169—170.5 °C, $[\alpha]_D^{27}$ +80° (*c* 1, choroform) [lit,[12]: mp 169.5—170 °C (from acetone–petroleum ether), $[\alpha]_D^{20}$ +79.7° (*c* 1.38, $CHCl_3$)]; IR (KBr): 1735, 1525, 1350 (NO_2) cm^{-1}; PMR ($CDCl_3$) δ: 3.53 (3H s, OCH_3), 5.32 (1H s, H-1).

Found: C, 53.23; H, 3.56; N, 7.03%. Calcd for $C_{27}H_{21}N_3O_{14}$: C, 53.03; H, 3.46; N, 6.87%.

2,3,5-Tri-O-(p-nitrobenzoyl)-α,β-ribofuranosyl Bromide (8). To an ice-cold solution of **7** (210 mg) in dichloromethane (1.1 ml), hydrogen bromide saturated in acetic acid (1.1 ml) was added and the solution was kept at room temperature for 1 h in the dark place. The solution was concentrated *in vacuo* and the resulting syrup was again dissolved in dichloromethane (20 ml). The solution was successively washed, as fast as possible, with water, aqueous sodium hydrogen carbonate, water again, dried (Na_2SO_4) and concentrated to give a pale-yellow solid. Recrystallization from benzene gave almost colorless needles, 170 mg (75%), mp 105—112 °C, $[\alpha]_D^{23}$ +61° (*c* 1, chloroform) [β-anomer:[12] mp 100—105 °C (from CH_2Cl_2), $[\alpha]_D^{20}$ +55.4° (*c* 1.58, $CHCl_3$)]; PMR ($CDCl_3$) δ: 6.56 (*ca.* 0.5 H s, β-H-1), 6.94 (*ca.* 0.5 H d, J= 4.5 Hz, α-H-1), 6.32 (*ca.* 3H s, C_6H_6).

Found: C, 49.85; H, 3.17; N, 5.87; Br, 10.88%. Calcd for $C_{26}H_{18}BrN_3O_{13}\cdot 1/2C_6H_6$: C, 49.80; H, 3.03; N, 6.01; Br, 11.43%.

6'-Azido-3,2'-di-N-benzyloxycarbonyl-3',6'-dideoxy-5-O-mesyl-4'-O-(α-naphthoyl)paromamine 1,6-Carbamate (14). To a solution of **6** (60 mg) in dry pyridine (2 ml), methanesulfonyl chloride (60 mg) was added and the solution was kept at room temperature for 4 h. The solution showed on TLC with chloroform–methanol (30 : 1) an single spot at R_f 0.48. Isolation of the product in a usual manner gave a solid of **14**, 58 mg (88%); $[\alpha]_D^{24}$ +86 ° (*c* 0.5, chlorofrom); IR (KBr): 1180 ($\nu_s SO_2$), 1350 ($\nu_{as} SO_2$), 1770 cm^{-1}; PMR, δ of SO_2-CH_3: 3.10 ($CDCl_3$), 3.21 ($CDCl_3$–CD_3OD=1 : 1), 3.39 (C_5D_5N).

Found: C, 57.11; H, 5.00; N, 9.57; S, 3.44%. Calcd for $C_{41}H_{42}N_6O_{13}S$: C, 57.33; H, 4.93; N, 9.79; S, 3.73%.

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