Improved Syntheses of 3′-Deoxybutirosin A and B

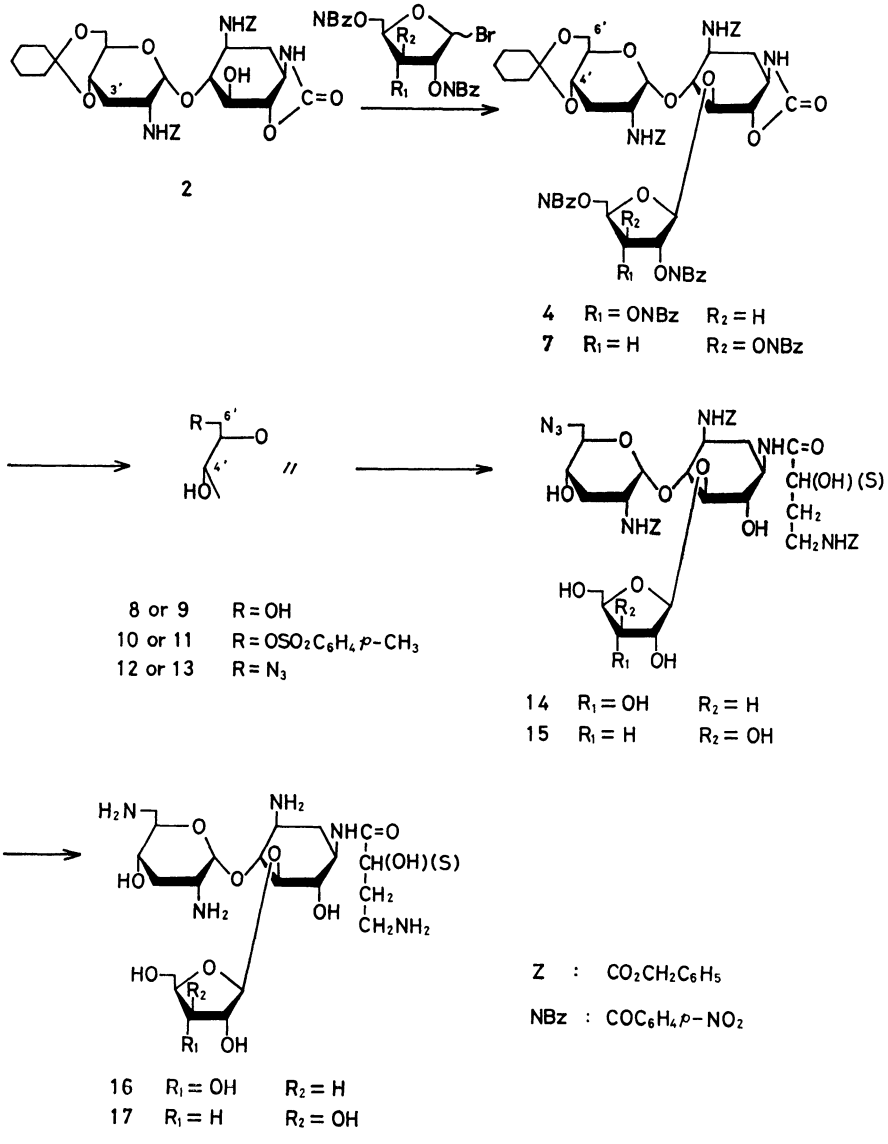
Isamu WATANABE, Tsutomu TSUCHIYA, and Sumio UMEZAWA
Institute of Bioorganic Chemistry, 1614, Ida, Nakahara-ku, Kawasaki 211

(Received September 9, 1976)

3′-Deoxybutirosin B and A (**16**, **17**) were synthesized *via* condensation of 3,2′-bis-*N*-benzyloxycarbonyl-4′,6′-*O*-cyclohexylidene-3′-deoxyparomamine 1,6-carbamate (**2**) with tris-*O*-(*p*-nitrobenzoyl)-D-ribofuranosyl and -D-xylofuranosyl bromide, respectively, followed by 6′-*O*-tosylation of the decyclohexylidene derivative (**8** and **9**), cyclic 1,6-carbamate opening and amidation with (*S*)-4-benzyloxycarbonylamino-2-hydroxybutyric acid at the free C-1 amino group.

In a previous paper,[1] we described a synthesis of 3′-deoxybutirosin B starting from 3′-deoxyparomamine. Here we describe another synthesis of 3′-deoxybutirosin B as well as A by an alternative route. In the previous synthesis[1] there have been found the following disadvantages: 1) regioselective 6′-*O*-tosylation and 4′-*O*-α-naphthoylation gave unsatisfactory yields owing to the presence of other similarly reactive hydroxyl groups, 2) low solubilities of the 6′-*O*-tosyl and other related derivatives (compound **2**, **3**, **4**, and **5** in the previous paper[1]) in organic solvents render the column-chromatographical purification difficult, 3) the 4′-*O*-naphthoyl group unexpectedly resisted to the basic hydrolysis, and the removal of this group was forced to be incomplete in order to prevent the removal of the *N*-benzyloxycarbonyl groups. One device to overcome this disadvantage was the use of sodium *p*-methoxybenzylate, a stronger base.[1]

The condensing partner adopted in this paper is 4′,6′-*O*-cyclohexylidene-1,6-carbamate (**2**), prepared



from tris-*N*-benzyloxycarbonyl-3′-deoxyparomamine[1] (**1**). The compound **2** has a free hydroxyl group only at C-5 and suitable solubilities in organic solvents. The condensation of **2** with tris-*O*-(*p*-nitrobenzoyl)-α,β-D-ribofuranosyl bromide[1] (**3**) or α,β-D-xylofuranosyl bromide[2] was successfully carried out to give **4** or **7**. The latter bromide was prepared from 1,2-*O*-isopropylidene-3,5-bis-*O*-(*p*-nitrobenzoyl)-α-D-xylofuranose (**5**) *via* methyl 2,3,5-tris-*O*-(*p*-nitrobenzoyl)-α,β-D-xylofuranoside[2] (**6**). The cyclohexylidene group of the condensation product (**4** or **7**) was then selectively hydrolyzed and the 6′-hydroxyl group of the resulting diol derivative (**8** or **9**) was tosylated to give **10** or **11**.

Treatment of **10** or **11** with sodium azide gave a 6′-azido derivative (**12** or **13**). Treatment with aqueous barium hydroxide cleaved their ester groups as well as cyclic carbamate smoothly in comparison to the *O*-α-naphthoyl group described in the previous paper.[1] Introduction of (*S*)-4-benzyloxycarbonylamino-2-hydroxybutyryl group to the amino group at C-1 gave **14** or **15** and catalytic hydrogenolysis of the *N*-benzyloxycarbonyl and azido groups gave 3′-deoxybutirosin B (**16**) or A (**17**). By taking this synthetic route, the aforementioned disadvantages were substantially avoided and the overall yields based on **1** were 10—15%.

Experimental

General procedures were the same as described in a previous paper.[1]

3,2′-Bis-N-benzyloxycarbonyl-4′,6′-O-cyclohexylidene-3′-deoxyparomamine 1,6-Carbamate (2). To an ice-cold solution of tris-*N*-benzyloxycarbonyl-3′-deoxyparomamine[1] (**1**) (9.60 g) in DMF (190 ml), 50% oily sodium hydride (1.92 g) was added and the mixture was vigorously stirred for 2 h in the cold. Acetic acid (5 ml) was added and the mixture was poured into ice–water (3 1). Precipitates were collected by filtration and dried. To a solution of the solid (7.53 g) in dry DMF (150 ml), 1,1-dimethoxycyclohexane (15 ml) and anhydrous *p*-toluenesulfonic acid (430 mg) were added and the solution was stirred for 2.5 h at 30 °C under reduced pressure (≈15 Torr). The solution was poured into aqueous acetic acid–sodium acetate buffer (0.2 M, pH 4.5, 2 1) and the precipitates were collected by filtration and thoroughly washed with hexane and then with water to give a solid, 8.1 g (89%). It was reprecipitated from dioxane–acetone–hexane, mp 264—265 °C, $[\alpha]_D^{20}$ +52° (*c* 1, C_5H_5N); IR (KBr): 2930, 1775, 1700 cm^{-1}.

Found: C, 61.47; H, 6.38; N, 5.97%. Calcd for $C_{35}H_{43}N_3O_{11}$: C, 61.66; H, 6.36; N, 6.16%.

3,2′-Bis-N-benzyloxycarbonyl-4′,6′-O-cyclohexylidene-3′-deoxy-5-O-[2,3,5-tris-O-(p-nitrobenzoyl)-β-D-ribofuranosyl]paromamine 1,6-Carbamate (4). A mixture of **2** (5.0 g), **3**[1] (20.5 g), mercuric cyanide (9 g), and calcium sulfate (Drierite, 18 g) in dichloromethane (115 ml) was vigorously stirred at room temperature overnight. After addition of methanol (20 ml) and pyridine (10 ml) followed by agitation for a while, the mixture was filtered and the solid was washed with dichloromethane (≈50 ml). The filtrate and the washings combined were washed with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The resulting solid was chromatographed over silica gel with chloroform–ethanol–triethylamine (30: 1: 0.1) to give a solid of **4**, 5.8 g, $[\alpha]_D^{23}$ +10° (*c* 1, $CHCl_3$); Though the solid still contained 1—2% ash, it was used without purification to the next step.

1,2-O-Isopropylidene-3,5-bis-O-(p-nitrobenzoyl)-α-D-xylofuranose (5). 1,2-*O*-Isopropylidene-α-D-xylofuranose[4] was treated with *p*-nitrobenzoyl chloride in pyridine in a usual manner to give a solid of **5**, which was recrystallized from ethyl acetate–hexane to give needles in a yield of 76%, mp 149—150 °C, $[\alpha]_D^{23}$ −70° (*c* 1, $CHCl_3$).

Found: C, 53.84; H, 4.11; N, 5.53%. Calcd for $C_{22}H_{20}N_2O_{11}$: C, 54.10; H, 4.13; N, 5.74%.

Methyl 2,3,5-Tris-O-(p-nitrobenzoyl)-α,β-D-xylofuranoside (6). To a solution of **5** (2.5 g) in dichloromethane (40 ml), 0.5 M methanolic hydrogen chloride (45 ml) was added and the solution was kept at room temperature for 60 h. Pyridine (10 ml) and toluene (20 ml) were added and the solution was concentrated. The residue was dissolved in pyridine (50 ml) and the solution was treated with *p*-nitrobenzoyl chloride in a usual manner to give a syrup of **6**, 3.1 g; PMR ($CDCl_3$) δ: 5.20 (≈0.6H s, β-H-1); the peaks corresponding to α-H-1 could not be discerned by overlapping with other signals. The syrup was used without purification to bromination followed by glycosylation (The crystalline β-anomer of **6** was described by El Khadem *et al.*[2]).

3,2′-Bis-N-benzyloxycarbonyl-4′,6′-O-cyclohexylidene-3′-deoxy-5-O-[2,3,5-tris-O-(p-nitrobenzoyl)-β-D-xylofuranosyl]paromamine 1,6-Carbamate (7). To a cold (≈10 °C) solution of **6** (2.02 g) in dry dichloromethane (40 ml), hydrogen bromide was introduced until saturation and the solution was kept at 0 °C overnight. Removal of the solvent and the excess hydrogen bromide by coevaporation with toluene gave a syrup, which was dissolved in dichloromethane (21 ml). To the solution, **2** (750 mg), mercuric cyanide (1.0 g), and calcium sulfate (Drierite, 2.0 g) were added and the mixture was vigorously stirred at room temperature overnight. The reaction mixture was then treated similarly as described for **4** to give a solid of **7**, 583 mg (42%), $[\alpha]_D^{23}$ +53° (*c* 1, $CHCl_3$).

Found: C, 57.66; H, 4.82; N, 6.51%. Calcd for $C_{61}H_{60}N_6O_{24}$: C, 58.09; H, 4.80; N, 6.66%.

3,2′-Bis-N-benzyloxycarbonyl-3′-deoxy-5-O-[2,3,5-tris-O-(p-nitrobenzoyl)-β-D-ribo- and -β-D-xylofuranosyl]paromamine 1,6-Carbamates (8 and 9). To a solution of crude **4** (350 mg) in acetone (3.5 ml), acetic acid (7 ml) and water (3.5 ml) were added and the mixture was heated at 60 °C for 6 h. The solution was concentrated and the residue was dissolved in chloroform. The solution was washed with aqueous hydrogencarbonate and water, dried (Na_2SO_4), and concentrated to give a solid of **8**, 230 mg (≈70%). Since the solid contained slight impurities, it was further purified by chroma tography over silica gel with chloroform–ethanol (20: 1) (30: 1, in the case of **9**), $[\alpha]_D^{22}$ +10° (*c* 1, $CHCl_3$); IR (KBr): 1775, 1720, 1525 cm^{-1}.

Found: C, 55.68; H, 4.51; N, 6.85%. Calcd for $C_{55}H_{52}N_6O_{24}$: C, 55.93; H, 4.44; N, 7.12%.

Compound **9**: Compound **7** (440 mg) was treated similarly as described for **8** to give a solid of **9**, 237 mg (57.5%); $[\alpha]_D^{23}$ +57° (*c* 1, $CHCl_3$); IR (KBr); 1780, 1725, 1530 cm^{-1};

Found: C, 55.71; H, 4.44; N, 6.92%.

3,2′-Bis-N-benzyloxycarbonyl-3′-deoxy-5-O-[2,3,5-tris-O-(p-nitrobenzoyl)-β-D-ribo- and -β-D-xylofuranosyl]-6′-O-tosylparomamine 1,6-Carbamates (10 and 11). To a solution of **8** (360 mg) in pyridine (10 ml), *p*-toluenesulfonyl chloride (230 mg) was added and the solution was kept at −10 °C for 40 h. Water (0.1 ml) was added and the solution was concentrated. A solution of the residue in chloroform was washed with aqueous potassium hydrogensulfate. aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated to give a solid, which was chromatographed over silica gel with chloroform–ethanol (40: 1), giving a solid of **10**, 320 mg (79%), $[\alpha]_D^{22}$ +4° (*c* 0.4, $CHCl_3$); IR (KBr):

1770, 1725, 1525, 1175 cm^{-1} (Ts); PMR ($CDCl_3$) δ: 2.37 (3H, s, CH_3 (Ts)).

Found: C, 55.85; H, 4.54; N, 6.28; S, 2.35%. Calcd for $C_{62}H_{58}N_6O_{26}S$: C, 55.77; H, 4.38; N, 6.29; S, 2.40%.

Compound 11: Compound **9** (335 mg) was treated similarly as described for **10** to give a solid of **11**, 298 mg (79%); $[\alpha]_D^{23}$ +70° (*c* 0.6, $CHCl_3$); IR (KBr): 1775, 1725, 1530, 1180 cm^{-1} (Ts); PMR ($CDCl_3$ δ: 2.35 (3H, s, CH_3 (Ts)).

Found: C, 55.48; H, 4.48; N, 5.99; S, 2.36%.

6'-Azido-3,2'-bis-N-*benzyloxycarbonyl-3',6'-dideoxy-5*-O-[*2,3,5-tris*-O-(p-*nitrobenzoyl*)-*β*-D-*ribo- and* -*β*-D-*xylofuranosyl*]*paromamine 1,6-Carbamates (12 and 13)*. To a solution of **10** (160 mg) in DMF (3.2 ml), sodium azide (80 mg) was added and the mixture was stirred at 60 °C for 4 h. Chloroform (30 ml) was added and the reaction mixture was washed with saturated sodium chloride solution (30 ml × 3) and then with water (30 ml). The solution was concentrated and the residue was washed with water to remove trace of DMF accompanied, and dried to give a solid of **12**, 142 mg (96%), $[\alpha]_D^{22}$ +6.5° (*c* 0.8, $CHCl_3$); IR (KBr): 2100 (N_3), 1775, 1720, 1525 cm^{-1}.

Found: C, 54.57; H, 4.34; N, 10.52%. Calcd for $C_{55}H_{51}N_9O_{23}$: C, 54.77; H, 4.26; N, 10.45%.

Compound 13: Compound **11** (130 mg) was treated similarly as described for **12** to give a solid of **13**, 115 mg (98%); $[\alpha]_D^{23}$ +54° (*c* 1, $CHCl_3$); IR (KBr): 2100 (N_3), 1775, 1720, 1525 cm^{-1}.

Found: C, 54.44; H, 4.36; N, 10.30%.

6'-Azido-3,2'-bis-N-*benzyloxycarbonyl-1*-N-[(S)-*4-benzyloxycarbonylamino-2-hydroxybutyryl*]-*3',6'-dideoxy-5*-O-(*β*-D-*ribo- and* -*β*-D-*xylofuranosyl*)*paromamines (14 and 15)*. To a solution of **13** (260 mg) in dioxane (13 ml), 0.05 M aqueous barium hydroxide (5.8 ml) 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 (5.0 and 2.1 ml) were added at intervals and the mixture was treated as stated above. Carbon dioxide was introduced, and, after filtration, the solution was concentrated to give a residue, which was again dissolved in dioxane. After filtration, the solution was concentrated to give a solid.

To a solution of the solid in THF (2.7 ml), *N*-hydroxysuccinimide ester[3] (115 mg) of (*S*)-4-benzyloxycarbonylamino-2-hydroxybutyric acid and triethylamine (0.1 ml) were added and the solution was stirred at 0 °C for 1 h and then kept at room temperature overnight. The solution was concentrated and the residue was chromatographed over silica gel with chloroform–ethanol (7: 1) to give a solid of **15**, 142 mg (68%), mp 86—90 °C, $[\alpha]_D^{23}$ +23° (*c* 1, CH_3OH); IR (KBr): 2100, 1700, 1530 cm^{-1}.

Found: C, 55.47; H, 5.83; N, 9.77%. Calcd for $C_{45}H_{57}N_7O_{17}$: C, 55.84; H, 5.94; N, 10.13%.

Compound 14: Compound **12** (95 mg) was treated similarly as described for **15** to give a solid of **14**, 50 mg (66%); mp 94—96 °C, $[\alpha]_D^{22}$ +20° (*c*, 1 $CHCl_3$) (lit,[1] +19°); IR (KBr): 2100 (N_3), 1695, 1525 cm^{-1}.

Found: C, 55.67; H, 6.07; N, 9.87%.

3'-Deoxybutirosin B (16). Compound **14** (115 mg) was catalytically hydrogenated as described in the foregoing paper[1] to give a solid of **16**, 55 mg (77%), $[\alpha]_D^{22}$ +32° (*c* 1, H_2O) (lit,[1] +29°).

Found: C, 44.08; H, 7.37; N, 11.57%. Calcd for $C_{21}H_{41}N_5O_{11}\cdot H_2CO_3$: C, 43.92; H, 7.20; N, 11.64%.

3'-Deoxybutirosin A (17). Compound **15** (126 mg) was catalytically hydrogenated as described for the preparation of 3'-deoxybutirosin B in the foregoing paper[1] to give a solid of **17**, 55 mg (74%), $[\alpha]_D^{23}$ +23° (*c* 1, H_2O).

Found: C, 45.33; H, 7.49; N, 12.29%. Calcd for $C_{21}H_{41}N_5O_{11}\cdot 1/2H_2CO_3$: C, 45.26; H, 7.42; N, 12.27%.

The authors are grateful to Professor Hamao Umezawa, Director of Institute of Microbial Chemistry, for his support and encouragement.

References

1) I. Watanabe, A. Ejima, T. Tsuchiya, D. Ikeda, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **50**, 487 (1977).

2) H. S. El Kkadem, T. D. Audichya, D. A. Niemeyer, and J. Kloss, *Carbohydr. Res.*, **47**, 233 (1976).

3) H. Kawaguchi, T. Naito, S. Nakagawa, and K. Fujisawa, *J. Antibiot.*, **25**, 695 (1972).

4) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, **1928**, 611.