Synthesis on 1,4-Diaminocyclitol Antibiotics. III. Synthesis of 4-Hydroxypurpurosamine B Derivatives

Kazuaki KANAI, Itsuki SAKAMOTO, Seiichiro OGAWA,* and Tetsuo SUAMI†
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223
(Received September 13, 1986)

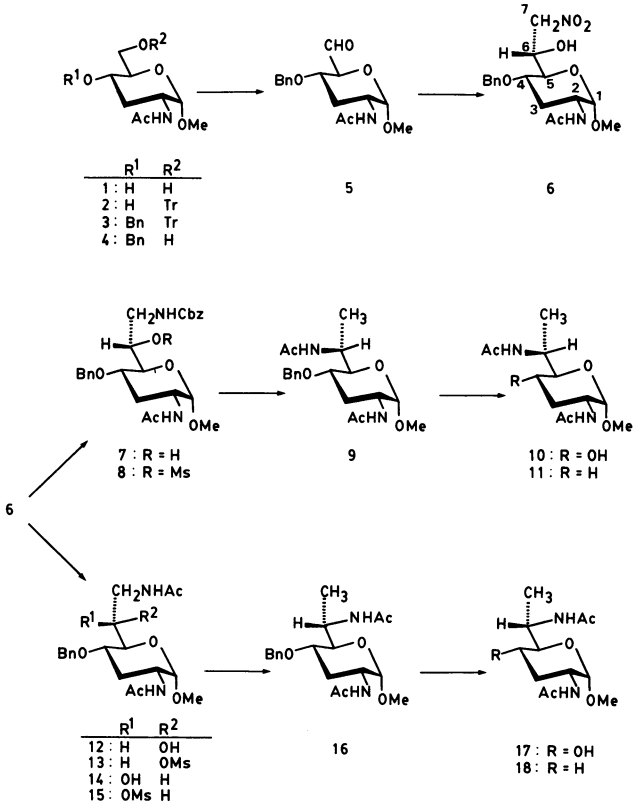
Synopsis. Methyl 2,6-di-*N*-acetyl-4-hydroxy-6-epi-α-purpurosaminide B and -4-hydroxy-α-purpurosaminide B have been prepared from D-glucosamine by sequence of reactions including stereoselective nitro aldol reaction.

In connection with synthetic studies on 4′-hydroxyfortimicins,[1] synthesis of 4-hydroxy-6-epipurpurosamine B has been carried out.

One of the authors reported that nitro aldol reaction of methyl 2-acetamido-2,3,4-trideoxy-α-*erythro*-hexodialdo-1,5-pyranoside with nitromethane gave the heptose derivative with D-ribo configuration in 52% yield.[2] In contrast the present work has shown that similar reaction of the corresponding 4-*O*-benzyl compound **5** gives selectively single condensate **6** with L-talo configuration in good yield. The C-4 benzyloxy group seems to control the direction of nucleophilic attack of aci-nitronium salt. We now describe syntheses of 4-hydroxypurpurosamine derivatives (**10**) and (**17**) starting from **6**.

Methyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**1**)[3] was converted into the 4-*O*-benzyl derivative (**4**) (84% in three steps). Oxidation of **4** with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of pyridinium phosphate gave aldehyde **5**, which reacted with nitromethane in the presence of sodium methoxide to give the nitro compound **6** (84% based on **4**). The stereochemistry of **6** was determined finally by converting it to the known α-purpurosamine B derivative (**11**).[4] Catalytic hydrogenation of **6** in the presence of Raney nickel, followed by *N*-benzyloxycarbonylation, gave **7** in 86% yield. Treatment of **7** with methanesulfonyl chloride in pyridine afforded **8** in 95% yield. Treatment of **8** with sodium isopropoxide in 1,4-dioxane gave an epimino intermediate, which was hydrogenated in the presence of Raney nickel, followed by *N*-acetylation, to give 60% yield of **9**. The ^{1}H NMR spectrum of **9** revealed the presence of a terminal methyl group. Catalytic hydrogenation of **9** in the presence of 10% palladium on charcoal gave **10** in a quantitative yield. Deoxygenation at C-4 was carried out by Barton's method[5] to give **11** identical to an authentic sample[4] in all respects.

Inversion of the 6-hydroxyl group of **6** was attempted in order to obtain the 4-hydroxy-6-epipurpurosamine B derivative. Catalytic hydrogenation of **6** in the presence of Raney nickel, followed by *N*-acetylation, gave the 2,7-di-*N*-acetyl derivative (**12**) in 83% yield. Compound **12** was converted to the mesylate (**13**, 96%), which was then treated with sodium acetate in water, followed by *N*-acetylation, to give 83% yield of the D-allo derivative (**14**). This compound was similarly transformed into **17**. The proposed structure of **17** was determined by converting it to the 6-epipurpurosamine B derivative (**18**)[2,4] as described for the preparation of **11**.



Experimental[6]

Methyl 2-Acetamido-2,3-dideoxy-6-*O*-trityl-α-D-*ribo*-hexopyranoside (2). Compound **1**[3] (6.0 g) was treated with trityl chloride (19.1 g) and 4-dimethylaminopyridine (1.10 g) in pyridine (120 ml) at 60 °C overnight. The mixture was concentrated after addition of triethylamine (1.2 ml). The residue was chromatographed on silica gel with toluene-ethanol (10:1) to give **2** (12.6 g, quant.): mp 162—163.5 °C; $[\alpha]_D^{24}$ +35.1° (*c* 1.06, $CHCl_3$).

Found: C, 72.61; H, 6.99; N, 2.88%. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03%.

Methyl 2-Acetamido-4-*O*-benzyl-2,3-dideoxy-6-*O*-trityl-α-D-*ribo*-hexopyranoside (3). Compound **2** (12.1 g) in *N*,*N*-dimethylformamide (200 ml) was treated with 60% sodium hydride (1.32 g), benzyl bromide (6.44 ml) and tetrabutylammonium iodide (0.11 g) for 1.5 h at room temperature. The product was purified by chromatography on silica gel with toluene-ethanol (20:1) to give **3** (14.0 g, 99%): mp 70—76 °C; $[\alpha]_D^{24}$ +39.4° (*c* 0.64, $CHCl_3$).

Found: C, 76.03; H, 6.79; N, 2.46%. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54%.

Methyl 2-Acetamido-4-*O*-benzyl-2,3-dideoxy-α-D-*ribo*-

†Present address: Department of Chemistry, Faculty of Science and Technology, Meisei University, Hodokubo, Hino, Tokyo 191.

hexopyranoside (4). Compound **3** (14.0 g) was treated with *p*-toluenesulfonic acid monohydrate (9.97 g) in methanol (300 ml). After stirring for 1 h, the mixture was neutralized with $NaHCO_3$ and concentrated. The residue was chromatographed on silica gel with toluene-ethanol (8 : 1) to give **4** (6.90 g, 85%): mp 167—168 °C; $[\alpha]_D^{24}$ +111° (*c* 0.92, MeOH).

Found: C, 62.35; H, 7.38; N, 4.30%. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53%.

Methyl 2-Acetamido-4-*O*-benzyl-7-nitro-2,3,7-trideoxy-β-L-*talo*-hexopyranoside (6). To a stirred solution of **4** (1.84 g) in dimethyl sulfoxide (8 ml) and benzene (3.4 ml), pyridine (0.47 ml), phosphoric acid (0.16 ml) and dicyclohexylcarbodiimide (3.67 g) were added successively under ice cooling. The stirring was continued for 2 h at room temperature and then oxalic acid (2.20 g) in methanol (20 ml) was added. Dicyclohexylurea precipitated was removed by filtration and the filtrate was extracted with ethyl acetate (200 ml). The extract was successively washed with saturated aqueous $NaHCO_3$ and water, dried, and evaporated to give aldehyde **5**. It was dissolved in methanol (7.4 ml), and nitromethane (6.0 ml) and methanolic 1M sodium methoxide (7.4 ml) were then added under ice cooling. After stirring overnight in a refregirator, the mixture was acidified with Amberlite IR-120 (H^+) resin and concentrated. The product was purified by chromatography on silica gel with toluene-ethanol (14 : 1), and recrystallized from ethanol to give **6** (1.54 g, 84%): mp 150—151 °C; $[\alpha]_D^{26}$ +87.8° (*c* 1.19, MeOH); IR (KBr) 1550, 1370 (NO_2) cm^{-1}.

Found: C, 63.54; H, 6.83; N, 5.93%. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.27; H, 6.72; N, 5.74%.

Methyl 2-Acetamido-4-*O*-benzyl-7-benzyloxycarbonylamino-2,3,7-trideoxy-β-L-*talo*-heptopyranoside (7). Compound **6** (288 mg) was hydrogenated in methanol (3 ml) in the presence of Raney nickel in an initial hydrogen pressure of 3.4 $kg\,cm^{-2}$ overnight to give the corresponding 7-amino derivative (351 mg). To a solution of the amino-derivative in methanol (6 ml) and water (2 ml), *N*-(benzyloxycarbonyloxy)succinimide (195 mg) and triethylamine (0.06 ml) were added. After stirring for 0.5 h, the mixture was extracted, dried, and concentrated. The residue was chromatographed on silica gel with toluene-ethanol (15 : 1) to give **7** (318 mg, 86%): mp 156—157 °C; $[\alpha]_D^{22}$ +70.9° (*c* 0.17, $CHCl_3$).

Found: C, 63.54; H, 6.83; N, 5.93%. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.27; H, 6.72; N, 5.74%.

Methyl 2-Acetamido-4-*O*-benzyl-7-benzyloxycarbonylamino-2,3,7-trideoxy-6-*O*-mesyl-β-L-*talo*-heptopyranoside (8). Compound **7** (33 mg) was treated with methanesulfonyl chloride (0.01 ml) in pyridine (1 ml) at 0 °C for 1.5 h. The product was purified by chromatography on silica gel with toluene-ethanol (10 : 1) to give **8** as a solid (37 mg, 95%): $[\alpha]_D^{23}$ +29.8° (*c* 1.79, $CHCl_3$).

Found: C, 56.44; H, 6.19; N, 4.90%. Calcd for $C_{26}H_{34}N_2O_9S$: C, 56.72; H, 6.22; N, 5.09%.

Methyl 2,6-Diacetamido-4-*O*-benzyl-2,3,6,7-tetradeoxy-α-D-*allo*-heptopyranoside (9). To a solution of **8** (331 mg) in dioxane (3 ml), a solution of sodium (35 mg) in isopropyl alcohol (6 ml) was added at 95 °C. After stirring for 1 h, an insoluble material was filtered and the filtrate was concentrated to give the epimino derivative, which was hydrogenated as described for the preparation of **7** and then *N*-acetylated with acetic anhydride (0.5 ml) in methanol (5 ml). The product was purified by chromatography on silica gel with toluene-ethanol (10 : 1) to give **9** (132 mg, 60%): mp 196—197 °C; $[\alpha]_D^{22}$ +118° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$), δ=0.94 (3H, d, *J*=8 Hz, H-7), 1.89, 1.95 (each 3H, s, NAc), 3.37 (3H, s, OMe), 4.27—4.70 (3H, m, H-1 and benzyl), 7.29 (5H, s, phenyl).

Found: C, 62.35; H, 7.60; N, 7.43%. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69%.

Methyl 2,6-Di-*N*-acetyl-4-hydroxy-α-purpurosaminide B (10). Compound **9** (105 mg) was hydrogenated in ethanol (10 ml) containing 1M hydrochloric acid (0.5 ml) (1 M=1 mol dm^{-3}) in the presence of 10% palladium on charcoal (50 mg) in an initial hydrogen pressure of 3.4 $kg\,cm^{-2}$ overnight. The product was purified by chromatography on silica gel with toluene-ethanol (3 : 1) to give **10** (90 mg, quant.): mp gradually melt over than 135 °C; $[\alpha]_D^{26}$ +159° (*c* 1.0, MeOH); ^1H NMR (CD_3OD) δ=1.14 (3H, d, *J*=7 Hz, H-7), 1.95 (6H, s, NAc×2), 3.40 (3H, s, OMe), 4.60 (1H, d, *J*=3.8 Hz, H-1).

Found: *m/z*, 275.1622. Calcd for $C_{12}H_{23}N_2O_5$: M+1, 275.1606.

Methyl 2,6-Di-*N*-acetyl-α-purpurosaminide B (11). Compound **10** (50 mg) was converted into the xanthate derivative (44 mg), which was treated with *n*-Bu_3SnH (0.1 ml) and α,α′-azobisisobutyronitrile in toluene (4 ml) to give **11** (17 mg, 56%) by the method described in the preceding paper:[1] mp 256—257 °C; $[\alpha]_D^{19}$ +178° (*c* 0.48, MeOH). Lit,[4] mp 261—262 °C, $[\alpha]_D^{20}$ +185.7° (*c* 0.7, MeOH). ^1H NMR and IR spectra were superimposable on those of an authentic sample.[4]

Methyl 2,7-Diacetamido-4-*O*-benzyl-2,3,7-trideoxy-β-L-*talo*-heptopyranoside (12). Compound **6** (1.54 g) in methanol (10 ml) was hydrogenated as described for the preparation of **7**. The amine was *N*-acetylated and the product was crystallized from ethanol to give **12** (1.37 g, 83%): mp 233—234 °C; $[\alpha]_D^{17}$ +62.4° (*c* 1.0, MeOH).

Found: C, 59.76; H, 7.38; N, 7.31%. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.99; H, 7.41; N, 7.36%.

Methyl 2,7-Diacetamido-4-*O*-benzyl-2,3,7-trideoxy-6-*O*-mesyl-β-L-*talo*-heptopyranoside (13). Compound **12** (916 mg) was treated with methanesulfonyl chloride in pyridine, and the product was purified as described for the preparation of **8** to give **13** (1.01 g, 96%): $[\alpha]_D^{26}$ +25.8° (*c* 0.95, $CHCl_3$); IR (KBr) 1370, 1195 (SO_2) cm^{-1}.

Methyl 2,7-Diacetamido-4-*O*-benzyl-2,3,7-trideoxy-α-D-*allo*-heptopyranoside (14). A suspension of **13** (6.5 g) and sodium acetate (1.2 g) in water (200 mg) was refluxed for 15 h, and then concentrated. The residue was treated with acetic anhydride (1.0 ml) in methanol (10 ml) for 1 h. The product was purified by chromatography on silica gel with toluene-ethanol (5 : 1) and crystallized from methanol-ethyl acetate to give **14** (4.47 g, 83%): mp 173—174 °C; $[\alpha]_D^{20}$ +119° (*c* 1.0, MeOH).

Found: C, 60.25; H, 7.51; N, 7.20%.

Methyl 2,7-Diacetamido-4-*O*-benzyl-2,3,7-trideoxy-6-*O*-mesyl-α-D-*allo*-heptopyranoside (15). Compound **14** (3.92 g) was treated with methanesulfonyl chloride in pyridine, and the product was purified as described for the preparation of **8** to give **15** (4.26 g, 90%): $[\alpha]_D^{26}$ +104° (*c* 0.88, $CHCl_3$); IR (KBr) 1370, 1195 (SO_2) cm^{-1}.

Methyl 2,6-Diacetamido-4-*O*-benzyl-2,3,6,7-tetradeoxy-β-L-*talo*-heptopyranoside (16). Compound **15** (1.60 g) was converted into the epimino derivative, which was hydrogenated, and then acetylated as described for the preparation of **9** to give **16** (698 mg, 55%): mp 144—145 °C; $[\alpha]_D^{18}$ +83.3° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.18 (3H, d, *J*=6 Hz, H-7), 1.95, 1.99 (each 3H, s, NAc), 3.38 (3H, s, OMe), 4.59 (1H, d, *J*=3 Hz, H-1), 5.81 (2H, d, *J*=9 Hz, NH-2,6), 7.34 (5H, s, phenyl).

Found: C, 62.76; H, 7.70; N, 7.80%.

Methyl 2,6-Di-*N*-acetyl-4-hydroxy-6-epi-α-purpurosaminide B (17). Compound **16** (50 mg) was hydrogenated as described for the preparation of **10** to give **17** (37 mg, 99%): mp 221—222 °C; $[\alpha]_D^{19}$ +42.3° (*c* 0.70, MeOH); ^1H NMR δ=1.26 (3H, d, *J*=6.5 Hz, H-7), 1.99, 2.11 (each 3H, s, NAc), 3.34 (3H, s, OMe), 4.57 (1H, d, *J*=3 Hz, H-1).

Found: C, 52.44; H, 7.95; N, 10.02%. Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.08; N, 10.21%.

Methyl 2,6-Di-*N*-acetyl-6-epi-α-purpurosaminide B (18).

Compound **17** (75 mg) was converted into the xanthate derivative (97 mg, 97%), which was treated *n*-Bu_3SnH (0.2 ml) and α,α'-azobisisobutyronitrile as described for the preparation of **11** to give **18** (24 mg, 34%): mp 208—209 °C; $[\alpha]_D^{19}$ +70.3° (*c* 0.45, MeOH). Lit,[2] mp 212—213 °C, $[\alpha]_D^{20}$ +63.3° (*c* 1.0, MeOH). ^1H NMR and IR spectra were superimposable on those of an authentic sample.[2]

The authors wish to thank Mr. Saburo Nakada for elemental analyses.

References

1) K. Kanai, I. Sakamoto, Y. Miyamoto, S. Ogawa, and T. Suami, *Bull. Chem. Soc. Jpn.*, **60**, 255 (1987).

2) T. Suami, Y. Honda, T. Kato, M. Masu, and K. Matsuzawa, *Bull. Chem. Soc. Jpn.*, **53**, 1373 (1980).

3) Compound **1** was accessible from methyl 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside[1] in 99% yield by acid hydrolysis; see also, T. F. Gallagher, and D. Horton, *Carbohydr. Res.*, **116**, 227 (1983).

4) Y. Honda and T. Suami, *Bull. Chem. Soc. Jpn.*, **54**, 2825 (1981).

5) D. H. Barton, and W. B. Motherwell, "Organic Synthesis Today and Tomorrow" ed by B. M. Trost and C. R. Hutchinson, Pergamon Press, (1981), pp. 1—7.

6) The general methods used in the present work have been described in the preceding paper.[1]