Synthesis of 1,4-Diaminocyclitols From L-Serine Methyl Ester

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Received April 16, 1996[⊗]

L-Serine methyl ester hydrochloride was converted to (*S*)-2-[*N*-(benzyloxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)propanal (**6**). Homocoupling of **6** promoted by $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**) gave C_2-symmetric diol (**7**). After manipulation of protecting groups and Swern oxidation, **7** was converted to a 1,6-dialdehyde **10**. Intramolecular pinacol coupling of **10** with **1** gave a selectively protected 1,4-diamino-2,3,5,6-tetrahydroxycyclohexane, which is the key skeleton of Fortimicin AM and AK.

Introduction

The fortimicins are a family of broad-spectrum antibiotics first isolated from the culture broths of a soil mold, *Micromonospora olivoasterospora*.[1] Several racemic and enantioselective syntheses of fortamine and *epi*-fortamine and the diaminocyclitol portions of many of the fortimicins have been described.[2] The majority of these syntheses have relied on functional group manipulation of existing six-membered rings. We felt that *epi*-fortamine, the aglycon core of two minor fortimicins, namely fortimicin AM and AK (Figure 1), could be constructed from two pinacol coupling reactions as depicted in Figure 2.[3] This approach would involve an intermolecular, homocoupling reaction to set the *trans*-diol unit, followed by an intramolecular coupling to give the *cis*-diol. Formally, this would involve coupling the dialdehyde shown in Figure 2. However, this substrate lacks a stereogenic center and would exist in its tautomeric enol form. We therefore turned our attention to a synthon of this dialdehyde, namely a suitably protected serinal derivative. Herein, we describe the details of this approach and the synthesis of a protected, *N*-demethyl-*epi*-fortamine core.

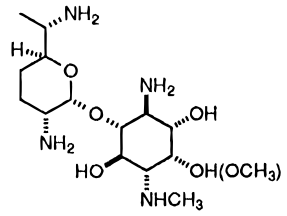


Figure 1. Fortimicin AM (AK).

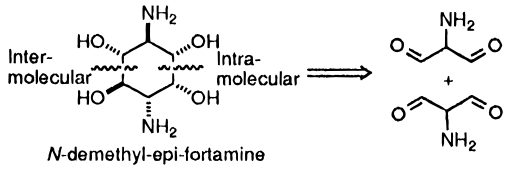
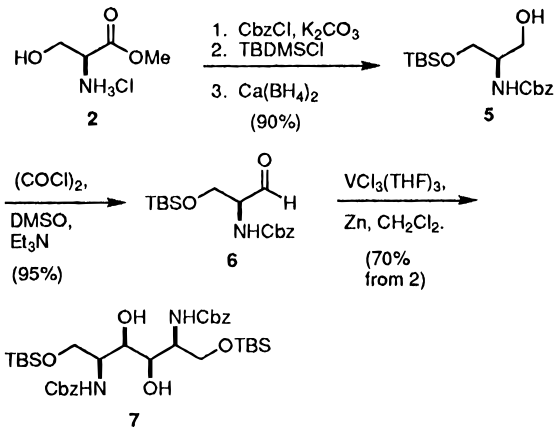


Figure 2.

Results and Discussion

The synthesis of (*S*)-2-[*N*-(benzyloxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)propanal (*N*-Cbz-*O*-TBS-L-serinal) **6**, the protected serinal chosen for this route, is illustrated in Scheme 1.[4] It is worth mentioning that all steps leading to **6** proceeded in high yield and, for the purposes of this synthesis, did not require any purification steps. Aldehyde **6** was then added to $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**), prepared in situ from $VCl_3(THF)_3$ and zinc dust. After stirring for 4 h, the reaction mixture was worked up with 10% aqueous sodium tartrate. ^1H and ^{13}C NMR spectroscopy of the product were consistent with the desired, C_2-symmetric, diamino diol **7** (Scheme 1). The 3,4-diol unit in **7** was protected with cyclohexanone diethyl ketal followed by removal of the *tert*-butyldimethysilyl groups using tetrabutylammonium fluoride to yield diol **9** (Scheme 2). Swern oxidation of **9** gave dialdehyde (**10**) in 95% mass recovery.

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) (a) Nara, T.; Yamamoto, M.; Kawamoto, I.; Takayama, K.; Okachi, R.; Takasawa, S.; Sato, T.; Sato, S. *J. Antibiot.* **1977**, *30*, 533. (b) Okachi, R.; Takasawa, S.; Sato, T.; Sato, S.; Yamamoto, M.; Kawamoto, I.; Nara, T. *J. Antibiot.* **1977**, *30*, 541. (c) Egan, R. S.; Stanaszek, R. S.; Cirovic, M.; Mueller, S. L.; Tadanier, J.; Martin, J. R.; Collum, P.; Goldstein, A. W.; De Vault, R. L.; Sinclair, A. C.; Fager, E. E.; Mitscher, L. A. *J. Antibiot.* **1977**, *30*, 552.

(2) (a) Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.* **1983**, *48*, 4786. (b) Knapp, S.; Sebastian, M. J.; Ramanathan, H.; Bharadwaj, P.; Potenza, J. A. *Tetrahedron* **1986**, *42*, 3405. (c) Kuo, C. H.; Wendler, N. L. *Tetrahedron Lett.* **1984**, *25*, 3429. (d) Kobayashi, S.; Kamiyama, K.; Ohno, M. *J. Org. Chem.* **1990**, *55*, 1169. (e) Sakairi, N.; Hayashida, M.; Amanl, A.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1301. (f) Liu, P.; Vandewalle, M. *Tetrahedron Lett.* **1993**, 34, 3625.

(3) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177. (c) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 4506. (d) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924. (e) Raw, A. S.; Pedersen, S. F. *J. Org. Chem.* **1991**, *56*, 830. (f) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, 57, 28. (g) Park, J.; Pedersen, S. F. *Tetrahedron* **1992**, *48*, 2069. (h) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

(4) The optical purity of the aldehyde (**6**) was confirmed as follows. A sample of the aldehyde (**6**) was reduced with $NaBH_4$, giving another sample of the alcohol **5b**. A racemic sample of the alcohol **5c** was prepared by partial protection of *N*-Cbz-2-amino-1,3-propanediol with *tert*-butyldimethylchlorosilane. The Mosher esters of **5a**, **5b**, and **5c** were compared by ^1H NMR spectroscopy and gas chromatography.

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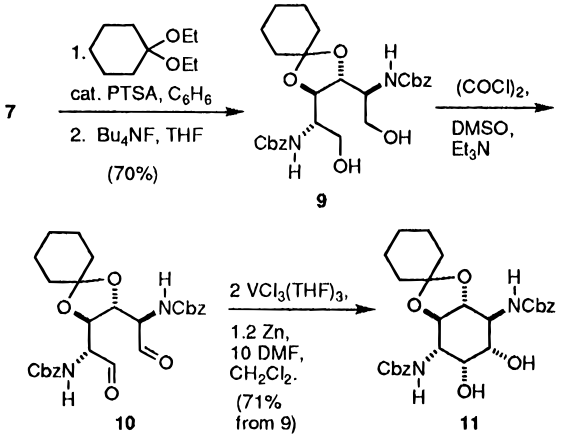
Scheme 2



Several conditions were explored for affecting the intramolecular pinacol coupling of **10**. We eventually found that it is crucial for **10** to be added slowly (3 h) to a solution of **1** in the presence of 10 equiv of dimethylformamide.[5] One role that dimethylformamide was expected to play in this reaction was competing with binding of the benzyloxy carbonyl groups in the substrate (i.e. the Cbz groups). If binding of one of these groups were to take place (forming a chelate with a vanadium(II) ion that included one of the aldehyde oxygens), then the resulting transition state required to bring the second aldehyde into the coordination sphere of the vanadium ion would be quite strained (i.e. "boat like"). As can be seen in Figure 3, if the benzyloxy carbonyl groups are not involved in binding, then a chair-like transition state would be available for coupling. The overall yield of **11** from **9** was 71%. The expected *cis*-diol stereochemistry of **11** was confirmed by X-ray analysis of a derivative.[6]

In conclusion, we have accomplished the synthesis of *N*-demethyl-*epi*-fortamine, a 1,4-diaminocyclitol, from commercially available L-serine methyl ester hydrochloride (**2**) in nine steps and an overall yield of 36%. Furthermore, in only two steps was purification by chromatography required (one of these being of the final product). Our approach utilizes two stereoselective pinacol coupling reactions to generate the cyclitol skeleton and can conceivably be used to generate other cyclitols starting from simple, acyclic aldehydes.

Experimental Section

See ref 3e for general experimental details.

(2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-hydroxypropanoic Acid, Methyl Ester (3). To a 0 °C solution of 5.00 g (32.1 mmol) of L-serine methyl ester hydrochloride (**2**) and 15.9 g (96.4 mmol) of $K_2CO_3 \cdot 1.5\ H_2O$ in 25 mL of H_2O was added a solution of 5.05 mL (6.03 g, 35.4 mmol) of benzyl chloroformate in 25 mL of THF. The two phases were stirred vigorously for 4 h while warming to rt, and then 25 mL of hexanes was added. The aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with 5% citric acid (25 mL) and saturated NaCl (25 mL), dried with $MgSO_4$, and evaporated to give 8.17 g (mass recovery 100%) of a clear oil. On the basis of TLC and ^{1}H NMR spectroscopy, the crude product was judged pure enough for use in the next step without purification. An analytical sample was purified by flash chromatography on silica gel using EtOAc/hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 5.79 (d, J = 6.7, 1H), 5.10 (s, 2H), 4.43 (t, J = 3.7, 1H), 3.97 (dd, J = 2.7, J = 10.9, 1H), 3.89 (dd, J = 2.5, J = 11.0, 1H), 3.75 (s, 3H), 2.03 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.2, 136.0, 128.5, 128.2, 128.1, 67.2, 63.2, 56.0, 52.7; $[\alpha]_D$ +7.4° (*c* 0.0199, $CHCl_3$). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.23; H, 5.92; N, 5.28.

(2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)propanoic Acid, Methyl Ester (4). To a solution of 7.97 g (31.3 mmol) of crude **3** and 2.62 g (38.5 mmol) of imidazole in 30 mL of DMF was added 5.32 g (35.3 mmol) of *tert*-butyldimethylchlorosilane. The mixture was stirred under an atmosphere of N_2 for 8 h, during which time a solid precipitate formed. The reaction mixture was poured into 150 mL of ice−water, and the resulting suspension was sequentially extracted with Et_2O (150 mL) and hexanes (150 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and saturated NaCl (100 mL), dried with $MgSO_4$, and evaporated to give 11.00 g (mass recovery 96% from **3**) of a clear oil. On the basis of TLC and ^{1}H NMR spectroscopy, the crude product was judged pure enough for use in the next step without purification. An analytical sample was purified by flash chromatography on silica gel using EtOAc/hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 5.60 (d, J = 8.1, 1H), 5.14 (d, J = 12.2, 1H), 5.10 (d, J = 12.2, 1H), 4.42 (m, 1H), 4.06 (dd, J = 2.4, J = 10.0, 1H), 3.83 (dd, J = 2.9, J = 10.0, 1H), 3.73 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.9, 136.2, 128.5, 128.15, 128.11, 67.0, 63.6, 55.9, 52.3, 25.6, 18.1, −5.6, −5.7; $[\alpha]_D$ +18.6° (*c* 0.0227, $CHCl_3$). Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.83; H, 7.95; N, 3.81. Found: C, 58.50; H, 7.90; N, 4.03.

(2*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)-1-propanol (5). To a 0 °C solution of 10.80 g (30.3 mmol) of crude **4** and 7.13 g (64.2 mmol) of $CaCl_2$ in THF (40 mL) and absolute ethanol (60 mL) was added 4.86 g (128.4 mmol) of $NaBH_4$. The mixture was stirred under an atmosphere of N_2 for 3 h while warming to rt and then poured into 5% citric acid (200 mL) at 0 °C, causing the evolution of gas. The resulting suspension was extracted with Et_2O (2 × 150 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 75 mL), H_2O (2 × 75 mL), and saturated NaCl (75 mL); dried with $MgSO_4$; and evaporated to give 9.43 g (mass recovery 94% from **4**) of a clear oil. On the basis of TLC and ^{1}H NMR spectroscopy, the crude product was judged pure enough for use in the next step without purification. An analytical sample was purified by flash chromatography on silica gel using EtOAc/hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.31 (m, 5H), 5.39 (d, J = 6.0, 1H), 5.10 (s, 2H), 3.84 (dd, J = 10.6, J = 2.7, 1H), 3.81 (dd, J = 10.2, J = 2.7, 1H), 3.77 (dd, J = 10.8, J = 3.0, 1H), 3.72 (m, 1H), 3.69 (dd, J = 10.8, J = 4.3, 1H), 2.27 (bs, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 136.3, 128.5, 128.14, 128.10, 66.8, 63.9, 63.8, 52.9, 25.8,

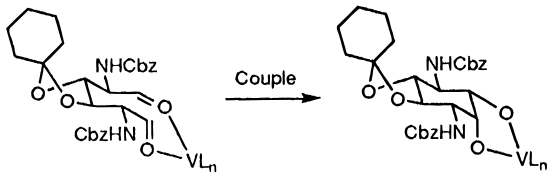
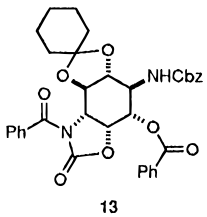


Figure 3.

(5) For the intramolecular pinacol coupling reaction of 1,4-ketoaldehydes, we found that the addition of 5 equiv of DMF increases the yield of cyclized product. See ref 3e.

(6) The stereochemistry of **11** was confirmed by X-ray analysis of a derivative, **13**. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.



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18.1, −5.61, −5.63; $[\alpha]_D$ +14.9° (*c* 0.0215, $CHCl_3$). Anal. Calcd for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.13. Found: C, 59.92; H, 8.59; N, 4.11.

(2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)propanal (6). To a stirred solution of 2.05 mL (23.5 mmol) of oxalyl chloride in 50 mL of dry CH_2Cl_2 at −63 °C (dry ice/$CHCl_3$) was added a solution of 2.22 mL (31.3 mmol) of dry DMSO in 50 mL of CH_2Cl_2 over 15 min. After 5 min of stirring, a solution of 5.32 g (15.7 mmol) of crude **5** in 50 mL of CH_2Cl_2 was added over 15 min, resulting in a cloudy solution which was stirred for 30 min. Neat triethylamine (8.73 mL, 62.6 mmol) was then added over 10 min, generating first a clear solution and later a solid precipitate after stirring for 30 min at −63 °C. TLC of the reaction mixture at this point showed no starting material. After the cooling bath was removed, 20% saturated $KHSO_4$ (80 mL) and hexanes (200 mL) were added to the reaction mixture, which was stirred vigorously while warming, generating two phases. The phases were separated, and the aqueous layer was extracted with Et_2O (200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (80 mL × 2), H_2O (80 mL × 3), saturated NaCl (80 mL × 2), then dried over $MgSO_4$, and evaporated *in vacuo*, at or below rt, giving 5.05 g (mass recovery 95% from **5**) of a clear oil. To minimize racemization, the crude product was used immediately in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.37−7.31 (m, 5H), 5.62 (bd, J = 6.6, 1H), 5.13 (s, 2H), 4.31 (pent, J = 3.6, 1H), 4.21 (dd, J = 2.9, J = 10.4, 1H), 3.87 (dd, J = 4.1, J = 10.4, 1H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 156.0, 128.5, 128.2, 128.1, 67.0, 61.8, 61.2, 25.6, 18.1, −5.69, −5.71.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-bis(*tert*-butyldimethylsiloxy)-3,4-hexanediol (7). Under an atmosphere of N_2, a mixture of 6.05 g (16.2 mmol) of $VCl_3(THF)_3$, 578 mg (8.84 g atoms) of zinc dust, and 30 mL of dry CH_2Cl_2 was stirred vigorously for 30 min, giving a green solution. A solution of 4.72 g (14.0 mmol) of crude **6** in 50 mL of CH_2Cl_2 was added rapidly, generating a dark brown solution. After 4 h of stirring, the reaction mixture was opened to the air and poured into 10% aqueous sodium tartrate (150 mL). The two phases were stirred vigorously for 12 h, giving a green aqueous layer and a pale yellow CH_2Cl_2 layer. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with $MgSO_4$, filtered through Celite, and evaporated to give 4.60 g (mass recovery 97% from **6**) of a white solid. On the basis of TLC and ^{1}H NMR spectroscopy, the crude product was judged pure enough for use in the next step without purification. An analytical sample was purified by flash chromatography on silica gel using EtOAc/hexanes to give a white solid: mp 92−93 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.39−7.27 (m, 5H), 6.56 (d, J = 9.0, 1H), 5.03 (d, J = 12.6, 1H), 4.93 (d, J = 12.6, 1H), 4.41 (bs, 1H), 3.70 (q, J = 7.3, 1H), 3.59−3.55 (m, 2H), 3.47 (dd, J = 6.3, J = 9.4, 1H), 0.82 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 155.9, 137.1, 128.2, 127.7, 127.5, 68.7, 65.2, 62.2, 53.7, 25.7, 17.8, −5.4, −5.5; $[\alpha]_D$ +22.0° (*c* 0.0126, $CHCl_3$). Anal. Calcd for $C_{34}H_{56}N_2O_8Si_2$: C, 60.32; H, 8.34; N, 4.14. Found: C, 60.32; H, 8.09; N, 4.30.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-bis(*tert*-butyldimethylsiloxy)-3,4-cyclohexylidene-3,4-hexanediol (8). To a stirred solution of **7** (3.55 g, 5.24 mmol) in 60 mL of benzene were added cyclohexanone diethyl ketal (1.35 g, 7.84 mmol) and a catalytic amount of *p*-toluenesulfonic acid (16 mg). After refluxing for 30 min, TLC showed no starting material. Benzene (40 mL) was removed by distillation. The remaining solution was cooled to rt and partitioned between aqueous saturated $NaHCO_3$ (150 mL) solution and ether (300 mL). The aqueous layer was separated and extracted with ether (300 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated to give 3.97 g of an oil (mass recovery 99%). On the basis of TLC and ^{1}H NMR spectroscopy, the crude product was judged pure enough for use in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 10H), 5.13 (m, 2H), 5.02 (m, 4H), 4.05 (s, 2H, N*H*), 3.82 (m, 2H), 3.68 (m, 2H), 3.57 (m, 2H), 1.54 (m, 8H), 1.35 (m, 2H), 0.86 (s, 18H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.5, 128.5, 128.11, 128.08, 109.4, 74.9, 66.8, 63.0, 51.3, 36.6, 25.8, 25.0, 23.8, 18.1, −5.4, −5.6; TLC (30% ethylacetate in hexane) R_f 0.77.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-3,4-cyclohexylidene-1,3,4,6-hexanetetrol (9). The crude product **8** was dissolved in THF (20 mL) and treated with 18.9 mL of TBAF (1.0 M, THF solution) for 15 min. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to give an oil. The product was purified by flash chromatography on silica gel using ethyl acetate/hexanes to give 1.93 g (70% from **7**) of a white oily foam: IR (CH_2Cl_2, cm^{-1}) ν 3533, 3429, 2941, 1718, 1510, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 10H), 5.44 (d, J = 9.2, 2H), 5.08 (s, 4H), 3.93 (m, 4H), 3.75 (dd, J = 11.3, 3.4, 2H), 3.65 (dd, J = 11.2, 5.3, 2H), 2.59 (bs, 2H, O*H*), 1.53 (m, 8H), 1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (C), 136.1 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 109.8 (C), 76.8 (CH), 67.0 (CH_2), 63.7 (CH_2), 51.0 (CH), 36.2 (CH_2), 24.8 (CH_2), 23.7 (CH_2); $[\alpha]_D$ = −15.1° (*c* 0.0075, CH_2Cl_2); TLC (100% ethyl acetate) R_f 0.61; Anal. Calcd for $C_{28}H_{36}N_2O_8$: C, 63.62; H, 6.86; N, 5.30. Found: C, 63.28; H, 6.94; N, 5.21.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-3,4-cyclohexylidene-3,4-dihydroxy-1,6-hexanedial (10). This dialdehyde was synthesized using the procedure described for synthesis of **6**. A white foam was obtained whose ^{1}H NMR was consistent with the desired product (95% mass recovery). To minimize racemization, the crude product was used immediately in the next step without purification.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*R*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-3,4-cyclohexylidene-1,3,4,6-cyclohexanetetrol (11). Under an atmosphere of N_2, a mixture of 1.58 g (4.22 mmol) of $VCl_3(THF)_3$, 0.17 g (2.53 g atoms) of zinc dust, and 15 mL of dry CH_2Cl_2 was stirred vigorously for 30 min, giving a green solution. DMF (1.54 g, 21.1 mmol) was added. A solution of 1.01 g (1.92 mmol) of crude **10** in 5 mL of CH_2Cl_2 was added over 3 h by syringe pump. After stirring for an additional 3 h, the reaction mixture was opened to air and poured into 10% aqueous sodium tartrate solution (40 mL) and CH_2Cl_2 (50 mL). The two phases were stirred vigorously together for 12 h, giving a green aqueous layer and a pale yellow CH_2Cl_2 layer. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered through Celite, and evaporated, to give a yellowish foam. The residue was purified by flash chromatography on silica gel using EtOAc/hexanes to give 0.71 g (71% from **9**) of a white solid: mp 176−179 °C; IR (CH_2Cl_2, cm^{-1}) ν 3423, 3087, 2941, 1722, 1514, 1274; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, at 105 °C) δ 7.27−7.26 (m, 10H), 6.71 (d, J = 9.3, 1H, N*H*), 6.58 (bs, 1H, N*H*), 5.06 (d, J = 4.1, 4H), 3.86 (t, J = 2.9, 1H), 3.75 (m, 2H), 3.64 (m, 1H), 3.46 (dd, J = 9.4, 3.0, 1H), 3.39 (t, J = 9.9, 1H), 2.96 (bs, 2H, O*H*), 1.56 (m, 8H), 1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1 (C), 136.2 (C), 128.44 (CH), 128.38 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 112.6 (C), 75.9 (CH), 72.3 (CH), 67.5 (CH), 66.9 (CH), 54.0 (CH), 52.0 (CH), 36.2 (CH_2), 36.1 (CH_2), 24.9 (CH_2), 23.5 (CH_2); high resolution FAB MS calcd for $C_{28}H_{35}N_2O_8$ (MH^+) 527.2393, found 527.2389; TLC (5% methanol in dichloromethane) R_f 0.13.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*R*)-5-Amino-2-[*N*-(benzyloxycarbonyl)amino]-5-*N*,6-*O*-carbonyl-3,4-cyclohexylidene-1,3,4,6-cyclohexanetetrol (12). To a solution of 0.81 g (1.53 mmol) of **11** in 25 mL of 60% aqueous 1,3-dioxane was added 0.16 g (1.53 mmol) of Na_2CO_3. After stirring overnight, water (40 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a foam. The product was purified by flash chromatography on silica gel using methanol/CH_2Cl_2 (2%) to give 0.24 g, (30%) of **11** and 0.33 g (51%) of a white foam: IR (CH_2Cl_2, cm^{-1}) ν 3433, 3340, 3062, 1765, 1724, 1516, 1132, 1070; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, at 100 °C) δ 7.78 (s, 1H, N*H*), 7.37−7.28 (m, 5H), 7.22 (d, J = 7.9, 1H, N*H*), 5.06 (d, J = 1.3, 2H), 4.79 (dd, J = 8.7, 3.1, 1H), 4.06 (dd, J = 10.2, 8.1, 1H), 3.87 (t, J = 8.4, 1H), 3.76 (m, 2H), 3.52 (t, J = 9.8, 1H), 2.49 (bs, 1H, O*H*), 1.57 (m, 8H), 1.37 (m, 2H); high resolution FAB MS calcd for $C_{21}H_{27}N_2O_7$

(MH^+) 419.1818, found 419.1818; TLC (5% methanol in dichloromethane) R_f 0.16.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*R*)-5-amino-2-[*N*-(benzyloxycarbonyl)amino]-5-*N*,6-*O*-carbonyl-3,4-cyclohexylidene-1-*O*,5-*N*-dibenzoyl-1,3,4,6-cyclohexanetetrol (13). To a solution of 80 mg (0.19 mmol) of oxazolidinone **12** in 3 mL of dichloromethane were added DMAP (46 mg, 0.38 mmol) and triethylamine (38 mg, 0.38 mmol) followed by benzoyl chloride (53 mg, 0.38 mmol). After the mixture was stirred for 5 min, ether (20 mL) was added and the mixture was washed with 5% aqueous citric acid (8 mL), saturated $NaHCO_3$ (8 mL), brine (8 mL), then dried over Na_2SO_4, and concentrated to give a solid. The product was purified by flash chromatography on silica gel using ethyl acetate/hexanes. The first fraction gave 99 mg (83%) of a white solid. An analytical sample was recrystalized from ethyl acetate: mp 245−246 °C; IR (CH_2Cl_2, cm^{-1}) ν 3434, 1794, 1728, 1699, 1095; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.69−7.65 (m, 3H), 7.54−7.50 (m, 3H), 7.35−7.31 (m, 7H), 5.60 (m, 3H), 5.12 (s, 2H), 5.02 (t, J = 7.2, 1H), 4.15 (m, 2H), 3.69 (bs, 1H), 1.79−1.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (C), 165.2 (C), 155.9 (C), 152.8 (C), 135.7 (C), 133.9 (CH), 132.8 (CH), 132.5 (C), 129.9 (CH), 129.6 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 113.8 (C), 78.4 (CH), 75.0 (CH), 73.5 (CH), 71.7 (CH), 69.3 (CH_2), 57.7 (CH), 55.9 (CH), 36.6 (CH_2), 36.3 (CH_2), 24.8 (CH_2), 23.7 (CH_2), 23.6 (CH_2); high resolution FAB MS calcd for $C_{35}H_{35}N_2O_9$ (MH^+) 627.2343, found 627.2333; TLC (50% ethyl acetate in hexane) R_f 0.42.

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735) for support of this research.

Supporting Information Available: An ORTEP drawing and details of data aquisition for compound **13** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960691A