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SYNTHESIS OF ANTIBIOTIC FORTIMICIN B

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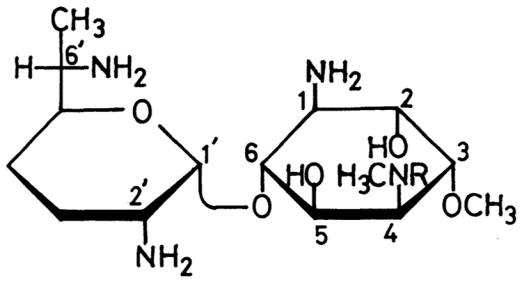
Aminocyclitol antibiotic fortimicin B has been synthesized by condensation of 2,6-bis-N-(2,4-dinitrophenyl)-α-6-*epi*-purpurosaminyl chloride and 1,2:4,5-di-N,O-carbonylfortamine B, followed by removal of all protective groups.

Antibiotic fortimicin A (1) and B (2) are produced in a fermentaion broth of *Micromonospora olivoasterospora*.[1,2] The structures of 1 and 2 have been established by Egan and his coworkers[3] by spectroscopic studies combined with chemical degradations. Both antibiotics are unique pseudodisaccharides comprising a 2,6-diaminoheptose derivative named 6-*epi*-purpurosamine B and a novel *chiro*-inosadiamine-1,4 derivative designated as fortamine B.[3] The former sugar component was synthesized in our laboratory,[4,5] and the latter aminocyclitol has been prepared very recently by Sano, Shirahata and Mori.[6]

We have attempted to synthesize fortimicins by coupling a purpurosamine derivative and a fortamine derivative. Now, we wish to report a synthesis of 2, the most important key compound for a preparation of 1. Namely, 1 is readily prepared from 2 by introducing a glycyl group into the methylamino group by a known procedure.[7]



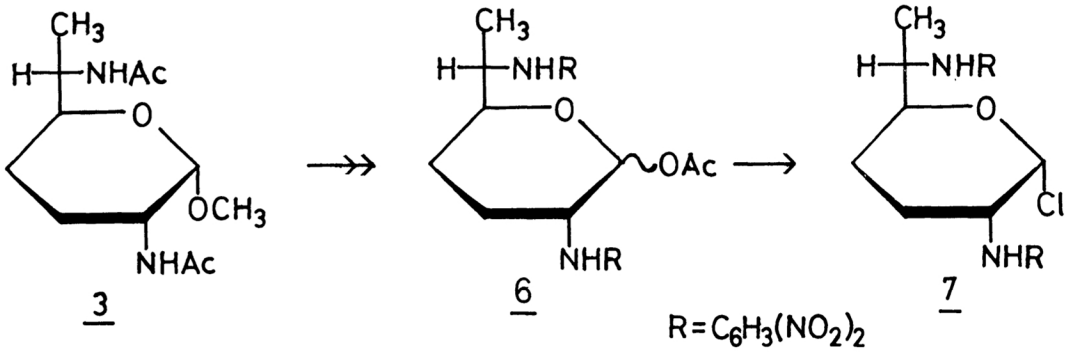
1 R=$COCH_2NH_2$

2 R=H

Hydrolysis of methyl 2,6-di-N-acetyl-2,3,4,6-tetradeoxy-β-L-*lyxo*-heptopyranoside[4,5] (3) in dilute HCl gave 6-*epi*-purpurosamine B dihydrochloride[8] (4).

Acetylation of 4 with acetic anhydride and boron trifluoride etherate afforded a salt of 1-O-acetyl-6-*epi*-purpurosamine B (5). Reaction of 5 with 2,4-dinitrofluorobenzene and triethylamine in methanol gave 1-O-acetyl-2,6-bis-N-(2,4-dinitrophenyl)-6-*epi*-purpurosamine B (6), mp 120-122°C, in 52% yield; ^{1}H NMR($CDCl_3$): δ 5.65 (d, $J_{1,2}$=8.7 Hz, axial H-1), 6.35 (d, $J_{1,2}$=3.3 Hz, equatorial H-1), a ratio of α:β was approximately 1:2.

Halogenation of 6 with acetyl chloride in dry ether containing dry hydrogen chloride gave 2,6-bis-N-(2,4-dinitrophenyl)-α-6-*epi*-purpurosaminyl chloride (7), mp 130-132°C, $[\alpha]_D^{20}$ +130° (*c* 0.49, acetone), in 82% yield; ^{1}H NMR(acetone-d_6): δ 1.45 (d, 3H, J=6.6 Hz, 6-CH_3), 6.72 (d, H, $J_{1,2}$=3.0 Hz, H-1), 8.69 (d, H, J=9.0 Hz, NH), 8.80 (d, H, J=9.9 Hz, NH).



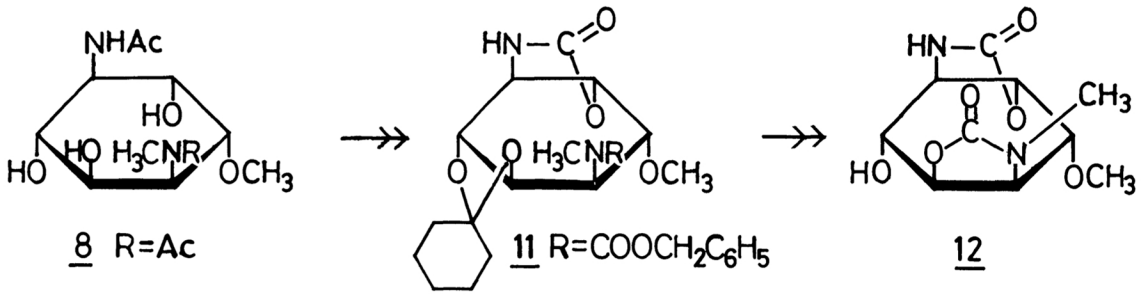
On the other hand, an aglycon was prepared as follows. Starting from di-N-acetylfortamine B[9] (8), by successive acid hydrolysis, deionization and acylation, 1,4-bis-N-(benzyloxycarbonyl)fortamine B[8] (9) was prepared in 50% yield, mp 135-136°C, $[\alpha]_D^{24}$ +48.7° (*c* 1.1, methanol); ^{1}H NMR($CDCl_3$): δ 3.06 (s, 3H, NCH_3), 3.30 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 6.46 (d, H, J=9.1 Hz, NH), 7.38 (s, 10H, phenyl).

To avoid a formation of a cyclic carbamate between an amino group on C-1 and a hydroxyl group on C-6, two hydroxyl groups on C-5 and C-6 were blocked by a cyclohexylidene group. Reaction of 9 with 1,1-dimethoxycyclohexane in N,N-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid afforded 1,4-bis-N-(benzyloxycarbonyl)-5,6-O-cyclohexylidene-fortamine B (10), $[\alpha]_D^{24}$ +26.1° (*c* 0.98, methanol); ^{1}H NMR($CDCl_3$): δ 3.07 (s, 3H, NCH_3), 3.38 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 5.63 (broad d, H, J=6.8 Hz, NH), 7.38 (s, 10H, phenyl).

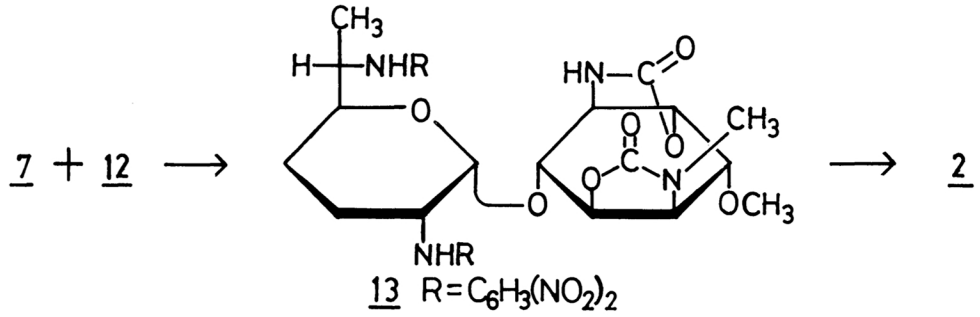
Reaction of 10 with sodium hydride in DMF gave 1,2-N,O-carbonyl-4-N-(benzyloxycarbonyl)-5,6-O-cyclohexylidene-fortamine B (11)in 91% yield, mp 71°C (dec.),

$[\alpha]_D^{24}$ -9.1° (*c* 0.99, methanol); ^{1}H NMR($CDCl_3$): δ 1.62 (broad m, 10H, cyclohexylidene), 3.14 (s, 3H, NCH_3), 3.43 (s, 3H, OCH_3), 5.17 (s, 2H, CH_2), 5.52 (broad s, H, NH).

Hydrolysis of 11 with 50% aqueous acetic acid, followed by treating with sodium hydride in DMF afforded 1,2:4,5-di-N,O-carbonylfortamine B (12) in 54% yield, mp 225-228°C, $[\alpha]_D^{16}$ -84.3° (*c* 1.06, methanol); IR(KBr) 3360, 1772, 1725 cm^{-1}.



Condensation of 7 and 12 in dioxane in the presence of silver trifluoromethanesulfonate gave 1,2:4,5-di-N,O-carbonyl-2',6'-bis-N-(2,4-dinitrophenyl)fortimicin B (13) in 37% yield, mp 226-228°C, $[\alpha]_D^{16}$ +43.2° (*c* 1.01, acetone); ^{1}H NMR(acetone-d_6): δ 1.44 (d, 3H, $J_{6',7'}$=6.3 Hz, 6'-CH_3), 2.85 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 4.67 (dd, H, J=6.0 Hz, J=7.5 Hz, H-5), 5.53 (d, H, $J_{1',2'}$=3.3 Hz, H-1'), 7.20 (broad s, H, 1-NH), 8.82 (d, 2H, J=8.1 Hz, 2' and 6'-NH). Anal. Calcd for $C_{29}H_{32}N_8O_{15}$ (732): C, 47.54; H, 4.40; N, 15.30%. Found: C, 47.50; H, 4.47; N, 14.99%. Compound 13 was identical with an authentic sample prepared from natural fortimicin B.



Treatment of 13 with Amberlite IRA-400(OH^-) resin, followed by hydrolysis in barium hydroxide solution gave fortimicin B, 2, $[\alpha]_D^{16}$ +25.3° (*c* 0.65, water); ^{1}H NMR(D_2O): δ 1.07 (d, 3H, J=6.6 Hz, 6'-CH_3), 2.40 (s, 3H, NCH_3), 3.46 (s, 3H, OCH_3), 3.98 (dd, H, $J_{4,5}$=4.5 Hz, $J_{5,6}$=9.2 Hz, H-5), 5.03 (d, H, $J_{1',2'}$=3.0 Hz, H-1'). [lit.[2] $[\alpha]_D$ +22.2° (*c* 0.1, water)].

N-Acetylation of 2 with acetic anhydride in methanol afforded tetra-N-acetylfortimicin B, mp 161-163°C, $[\alpha]_D^{20}$ +91.6° (*c* 0.6, methanol). IR and ^{1}H NMR spectra of the product were superimposable on those of an authentic sample prepared from natural fortimicin B. [lit.[10] mp 155-160°C, $[\alpha]_D^{25}$ +90.6° (*c* 0.5, water); lit.[3] $[\alpha]_D$ +92.72° (*c* 1.0, methanol)].

References and Note

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