

SYNTHESIS OF ANTIBIOTIC FORTIMICIN B

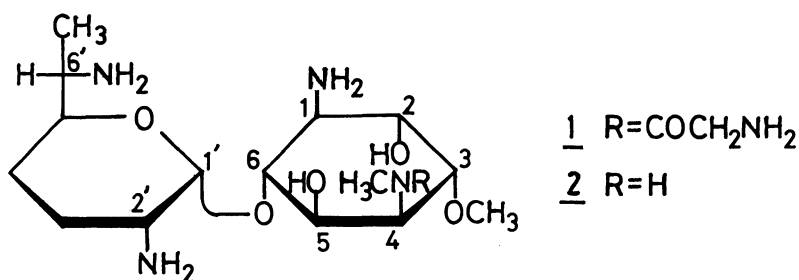
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Aminocyclitol antibiotic fortimicin B has been synthesized by condensation of 2,6-bis-N-(2,4-dinitrophenyl)- α -6-*epi*-purpurosaminyll chloride and 1,2:4,5-di-N,O-carbonylfortamine B, followed by removal of all protective groups.

Antibiotic fortimicin A (1) and B (2) are produced in a fermentation broth of *Micromonospora olivoasterospora*.^{1,2)} The structures of 1 and 2 have been established by Egan and his coworkers³⁾ 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⁾

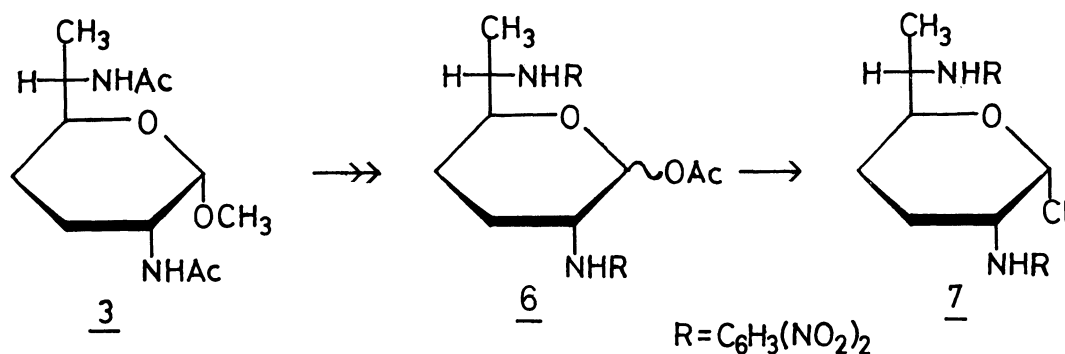
We have attempted to synthesize fortimicins by coupling a purpurosamine derivative and a fortamine derivative. Now, we wish to report a synthesis of 2, the most important key compound for a preparation of 1. Namely, 1 is readily prepared from 2 by introducing a glycyll group into the methylamino group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



Hydrolysis of methyl 2,6-di-N-acetyl-2,3,4,6-tetra-deoxy- β -1-*lyxo*-heptopyranoside^{4,5)} (3) in dilute HCl gave 6-*epi*-purpurosamine B dihydrochloride⁸⁾ (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; $^1\text{H NMR}(\text{CDCl}_3)$: 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*-purpurosaminyll chloride (7), mp 130–132°C, $[\alpha]_{\text{D}}^{20} +130^\circ$ (c 0.49, acetone), in 82% yield; $^1\text{H NMR}(\text{acetone-}d_6)$: 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).



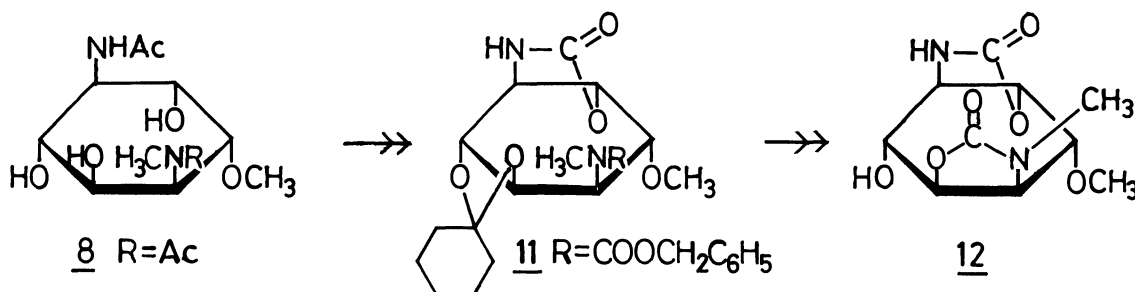
On the other hand, an aglycon was prepared as follows. Starting from di-N-acetylfortamine B⁹) (8), by successive acid hydrolysis, deionization and acylation, 1,4-bis-N-(benzyloxycarbonyl)fortamine B⁸) (9) was prepared in 50% yield, mp 135–136°C, $[\alpha]_{\text{D}}^{24} +48.7^\circ$ (c 1.1, methanol); $^1\text{H NMR}(\text{CDCl}_3)$: 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), $[\alpha]_{\text{D}}^{24} +26.1^\circ$ (c 0.98, methanol); $^1\text{H NMR}(\text{CDCl}_3)$: 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).

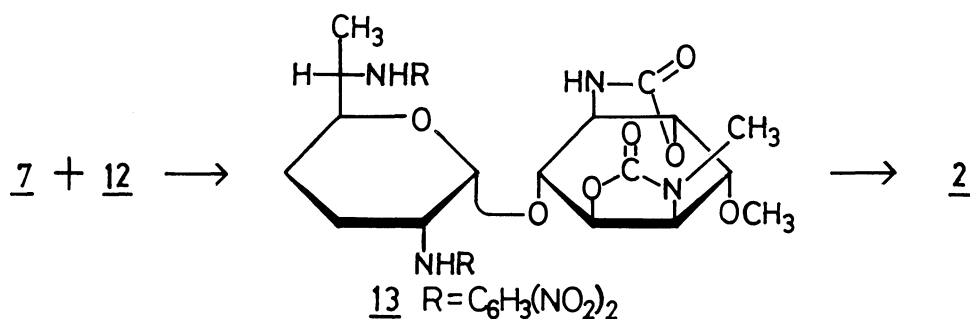
Reaction of 10 with sodium hydride in DMF gave 1,2-N,O-carbonyl-4-N-(benzyloxycarbonyl)-5,6-O-cyclohexylidene-fortamine B (11) in 91% yield, mp 71°C (dec.),

$[\alpha]_{\text{D}}^{24} -9.1^{\circ}$ (c 0.99, methanol); $^1\text{H NMR}(\text{CDCl}_3)$: 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, $[\alpha]_{\text{D}}^{16} -84.3^{\circ}$ (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, $[\alpha]_{\text{D}}^{16} +43.2^{\circ}$ (c 1.01, acetone); $^1\text{H NMR}(\text{acetone-}d_6)$: 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 $\text{C}_{29}\text{H}_{32}\text{N}_8\text{O}_{15}$ (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, $[\alpha]_{\text{D}}^{16} +25.3^{\circ}$ (c 0.65, water); $^1\text{H NMR}(\text{D}_2\text{O})$: 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⁾ $[\alpha]_{\text{D}}^{16} +22.2^{\circ}$ (c 0.1, water)].

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

References and Note

- 1) T. Nara, M. Yamamoto, I. Kawamoto, K. Takayama, R. Okachi, S. Takasawa, T. Sato, and S. Sato, *J. Antibiot.*, 30, 533 (1977).
- 2) R. Okachi, S. Takasawa, T. Sato, S. Sato, M. Yamamoto, I. Kawamoto, and T. Nara, *J. Antibiot.*, 30, 541 (1977).
- 3) R. S. Egan, R. S. Stanaszek, M. Cirovic, S. L. Mueller, J. Tadanier, J. R. Maryin, P. Collum, A. W. Goldstein, and L. A. Mitscher, *J. Antibiot.*, 30, 522 (1977).
- 4) T. Suami, Y. Honda, and T. Kato, *Chem. Lett.*, 1978, 1125.
- 5) T. Suami, Y. Honda, T. Kato, M. Masu, and K. Matsuzawa, *Bull. Chem. Soc. Jpn.*, 53, 1256 (1980).
- 6) H. Sano, K. Shirahata, and Y. Mori, Abstract paper of the Annual Meeting of the Chemical Society of Japan, 3S01, p. 1107 (1980), on April 3, 1980, Osaka, Japan.
- 7) P. Kurath, D. Grampovnik, J. Tadanier, J. R. Martin, R. S. Egan, R. S. Stanaszek, M. Cirovic, W. H. Wasburn, P. Hill, D. A. Dunnigan, J. E. Leonard, P. Johnson, and A. W. Goldstein, *J. Antibiot.*, 32, 884 (1979).
- 8) H. Sano, T. Sakaguchi, and Y. Mori, *Bull. Chem. Soc. Jpn.*, 52, 2727 (1979).
- 9) Di-N-acetylfortamine B was obtained in 73% yield by methanolysis of tetra-N-acetylfortimicin B.
- 10) T. Iida, M. Sato, I. Matsubara, Y. Mori, and K. Shirahata, *J. Antibiot.*, 32, 1273 (1979).

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