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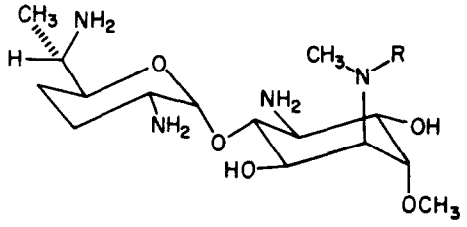
TOTAL SYNTHESIS OF FORTAMINE, THE AGLYCON OF THE MAJOR AMINOCYCLITOL ANTIBIOTICS FORTIMICIN A AND B

By C. H. Kuo and N. L. Wendler
Merck Sharp & Dohme Research Laboratories of Merck & Co., Inc.
P.O. Box 2000, Rahway, NJ 07065 USA

Summary: A total synthesis of (±) fortamine has been achieved by a 7-step sequence.

The fortimicins are a group of potent aminoglycoside antibiotics isolated from M. olivoasterosporo.[1,2] The structures of the major representatives of this group, namely, fortimicin A and B have been established as the 6-epi-purpurosamine B glycoside of the novel 1,4-diaminocyclitol fortamine and its glycylamide derivative.[3,4] We wish to report the total synthesis of fortamine via a stereospecific and substitutionally selective route.[5]

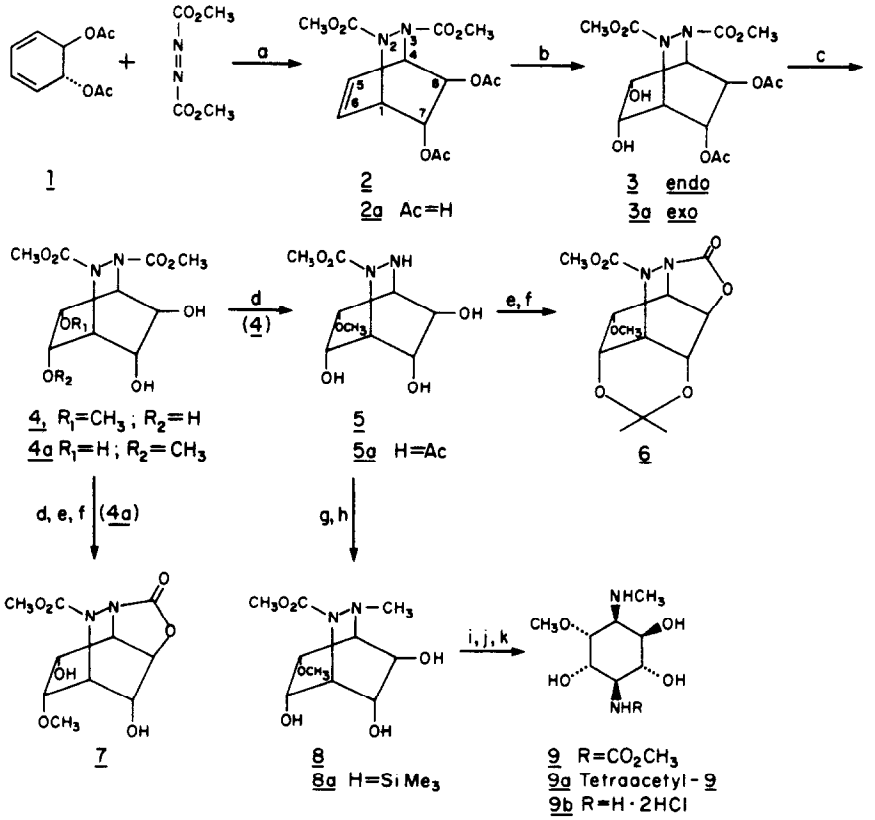


Fortimicin A R = $COCH_2NH_2$[6]
B R = H

A cyclohexane solution of equimolar amounts of trans-1,3-cyclohexadiene-5,6-diol diacetate **1**[7] and dimethyl azodicarboxylate was irradiated with a 450W Hanovia lamp 679 A36 at 46-50° for 24 hours to yield after chromatography on silica gel (8% acetone-CH_2Cl_2) 7α,8β-diacetoxy-2,3-diazabicyclo(2.2.2)-oct-5-ene-2,3-dicarboxylic acid dimethyl ester **2**[8] (75%) M^+ 342, IR($CHCl_3$) 5.73, 5.88μ; NMR ($CDCl_3$) δ 2.03 and 2.07 (OAc, 2s, 6H), 3.77 (CO_2CH_3, br. s, 6H), 4.2-5.4 (m, 4H), 6.3-6.9 (m, 2H). Deacetylation of **2** (CH_3OH, CH_3ONa) provided the corresponding diol **2a**, mp 160-162°, Calc'd for: $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.43; H, 5.53; N, 10.49. Osmylation of **2** in 1:1 pyridine-benzene with a stoichiometric amount of osmium tetroxide produced predominantly (3:1) the endo diol **3**, M^+ 376; NMR($CDCl_3$) δ 2.07 and 2.08(OAc, 2s, 6H), 3.77 (CO_2CH_3, s), 4.0-5.6 (m), together with its exo isomer **3a**, mp 163-164°, Calc'd for: $C_{14}H_{20}O_{10}N_2$: C, 44.68; H, 5.36; N, 7.44. Found: C, 44.72; H, 5.40; N, 7.41, in a total yield of 72%.[9,10] A single crystal X-ray determination on the crystalline exo isomer **3a** established its structural assignment and therewith the endo structure of **3** itself.[11]

Methylation of the endo diol **3** (CH_2N_2, silica gel, ether-CH_2Cl_2)[12] proceeded regioselectively to yield after deacetylation (CH_3ONa, CH_3OH) a 4:1 mixture respectively of the desired monomethyl ether **4** and its positional isomer **4a**[13] (75%) separable on silica gel (80% acetone-CH_2Cl_2). The structure of

4, M^+ 306; NMR ($CDCl_3$) δ 3.53 (CH_3O, s), 3.77 (CO_2CH_3, s), 3.2-4.8 (m), was ascertained inter. al. by conversion via **5** (vide infra) to the quadracyclic oxazolidone acetonide **6**, M^+ 314, IR ($CHCl_3$) 5.68, 5.99μ; NMR ($CDCl_3$) 1.37 and 1.43 (gem-dimethyl, 2s, 6H), 3.55 (OCH_3, s, 3H), 3.77 (CO_2CH_3, s). By contrast, the positional isomer **4a**, M^+ 306; NMR ($CDCl_3$) δ 3.55 (OCH_3), 3.50 (OH), 3.77 (CO_2CH_3, s), 3.2-4.8 (m), produced the oxazolidone **7**, M^+ 274 which, however, did not form the corresponding acetonide for reasons of stereochemical constraint.[14]



(a) cyclohexane, hv, 46-50°; (b) OsO_4, Py-benzene, 25°; (c) CH_2N_2, Silica gel, Ether-CH_2Cl_2; (d) KOH, CH_3OH; (e) Carbonyldiimidazole, THF, 25°; (f) $Me_2C(OMe)_2$, PTSA, Sieves 4A, 25°; (g) CH_2O, $NaBH_3CN$; (h) BSTFA,THF; (i) Na-NH_3, THF; (j) Ac_2O, Py, 25°; (k) 6N HCl, 110°, 3 hrs.

The selective decarbomethoxylation at position-3 of the nitrogen bridge in the alkaline conversion **4** →**5**, was made possible by mediation of the exo C-8 hydroxyl function. Participation of the latter provided a transfer activation process leading exclusively to **5**,[15] (98%) M^+ 248; tetra(trimethylsilyl) M^+ 536, NMR ($CDCl_3$) δ 3.48 (OCH_3, s), 3.70 (CO_2CH_3, s). This consequence was of critical significance in permitting selective methylation at the correct nitrogen position. Methylation of **5** was effected by the Borch procedure[16] to yield **8** (79%) purified on silica gel (60% acetone-CH_2Cl_2) M^+ 262; NMR $(CD_3)_2CO$ δ 2.73 (NCH_3, s, 3H), 3.23 (H_4, m, 1H), 3.47 (OCH_3, s, 3H), 3.67 (CO_2CH_3, s, 3H), 3.68-4.0 (m, 2H), 4.0-4.5 (m, 6H).

Compound **8** represents the penultimate system in which all the structural features of fortamine, both steric and substitutional, have been properly assembled. The corresponding tris-trimethylsilyl ether **8a** was reductively cleaved at the nitrogen bridge (Na-NH_3, THF)[17] to give the urethane derivative of (±) fortamine **9**. Purification of the latter was effected chromatographically (silica gel, 40% acetone-CH_2Cl_2) on the corresponding tetraacetyl derivative **9a** (60%) M^+ Calc'd: 432.1742. Found: 432.1744; IR($CHCl_3$) 2.90, 5.74, 6.09μ; NMR ($CDCl_3$) δ 2.1 (OAc, NAc, s, 12H), 2.98 (NCH_3, br. s, 3H), 3.40 (OCH_3, s, 3H), 3.68 (CO_2CH_3, s, 3H), 2.75 (m, 1H), 3.45-4.4 (m, 2H). 4.8-5.7 (m, 5H). Hydrolysis of **9a** proceeded quantitatively (6N HCl, 110°, 3 hrs) to afford (±) fortamine dihydrochloride **9b** as a microcrystalline solid mp ~ 200° dec. The 250 MHz ^1H, NMR spectrum (D_2O) of **9b** was identical with that of (+) fortamine dihydrochloride obtained from the degradation of natural (+) fortimicin B[18]. The free base, (±) fortamine **9b** itself (R=H) (aq. NaOH) also exhibited an NMR spectrum (D_2O) identical with that of natural (+) fortamine.[19]

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References and Notes

(1) T. Nara, M. Yamamoto, I. Kawamoto, K. Takayama, R. Okachi, S. Takasawa, T. Sato, and S. Sato, J. Antibiotics 30 533 (1977).

(2) R. Okachi, S. Takasawa, T. Sato, M. Yamamoto, I. Kawamoto, and T. Nara, ibid. 30 541 (1977).

(3) R. S. Egan, R. S. Stanaszek, M. Cirovic, S. L. Mueller, J. Tadanier, J. R. Martin, P. Collum, A. W. Goldstein, R. L. DeVault, A. C. Sinclair, E. E. Fager and L. A. Mitscher, ibid. 30 552 (1977).

(4) N. Hirayama, K. Shirahata, Y. Ohashi, T. Sasada and J. R. Martin, Acta Cryst. B34 2648 (1978).

(5) S. Knapp, M. J. Sebastian and H. Ramanathan, J. Org. Chem. 48 4786 (1983) recently succeeded in the total synthesis of (±) fortamine.

(6) The aminocyclitol ring in fortimicin A has the inverted chair conformation, cf. J. Tadanier, J. R. Martin, P. Kurath, A. W. Goldstein and R. Johnson, Carbohydrate Res. 79, 91 (1980).

(7) K. L. Platt and F. Oesch, Synthesis, 449 (1977).

(8) R. Askani, Chem. Ber. 98, 2551 (1965) reported the photocatalyzed Diels-Alder reaction of cyclohexadiene with diethyl azodicarboxylate.

(9) The designation endo and exo are employed with the N-N bridge as point of reference in the usual Alder-Stein convention.

(10) The catalytic osmylation procedure of V. Van Rheenen, R. L. Kelly and D. Y. Cha, Tetrahedron Letters, 1973 (1976) produced an inversion of the isomer ratio.

(11) The X-ray crystallographic determination was performed by Dr. James Springer of these laboratories. Because of the rapid equilibration (flipping) of the carbomethoxyl groups on the N-N bridge, the NMR line spectra of these and related systems were too broad to permit unequivocal structure assignments. Compare: J. E. Anderson and J. M. Lehn, J. Am. Chem. Soc. 89, 81 (1967).

(12) K. Ohno, K. Nishiyama and H. Nagase, Tetrahedron Letters 4405 (1979).

(13) The rationale for the preponderation of the methyl ether **4** is not apparent. Methylation, on the other hand, in ether-THF solution (instead of ether-CH_2Cl_2) afforded a nearly 50:50 mixutre of **4** and **4a**. Our experience further suggests that vicinal diols yield primarily monomethyl ethers. The amount of dimethyl ether formed from **4** and **4a** was small.

(14) Inspection of Dreiding models reveals that cyclic urethane formation causes skewing of the original bicyclic system to a degree inhibiting acetonide formation of the 5,7-diol.

(15) The carbomethoxyl group at position-2 remained unaffected even under refluxing conditions of saponification. **5** could be formed alternatively by initial deacetylation of **4**-$C_{7,8}$diacetate (CH_3OH, CH_3ONa) followed by treatment with NaH-DMF.

(16) R. F. Borch and A. I. Hassid, J. Org. Chem. 37, 1673 (1972).

(17) H. H. Wasserman and H. Matsuyama, J. Am. Chem. Soc. 103, 461 (1981); D. S. Kemp, M. D. Sidell and T. J. Shortridge, J. Org. Chem. 44, 4473 (1979).

(18) H. Sano, T. Sakaguchi and Y. Mori, Bull. Chem. Soc. Japan 52, 2727 (1979).

(19) Transformation of **4a** by the same sequence described for the conversion **4** → **9b**, yielded the dihydrochloride of the 2-methoxy-3-hydroxy isomer of **9b**. The latter exhibited an NMR spectrum quite different from that of natural (+) fortamine dihydrochloride.

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