CHEMISTRY LETTERS, pp. 29-32, 1987.

An Enantioselective Synthesis of (-)-Fortamine[1)†]

Keiji KAMIYAMA, Susumu KOBAYASHI, and Masaji OHNO*
Faculty of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113

The aminocyclitol moiety of fortimicin A, (-)-fortamine, was synthesized in an enantioselective manner starting from the chiral half ester, easily available by the enantioselective hydrolysis of a symmetrical diester with pig liver esterase. The present approach provides a general and efficient route to variously substituted 1,4-diaminocyclitol-derivatives.

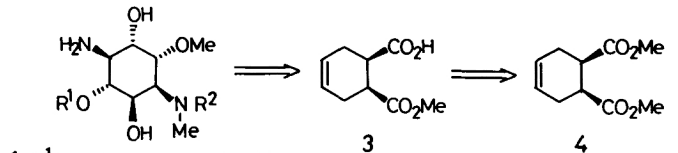
Since the discovery of fortimicin A (**1**) in 1977, a number of the related antibiotics[2)] have been isolated and characterized as pseudodisaccharide antibiotics possessing 4-N-glycyl moiety. In addition to the medicinal importance,[3)] these antibiotics are of great interest because of the unique 1,4- diaminocyclitol skeleton instead of the usual 1,3-diaminocyclitol skeleton seen in the classical aminoglycoside antibiotics such as streptomycin and kanamycin. Therefore, a great deal of synthetic study has been focused on the unique polyfunctional structure of fortamine **2**, all six carbons of which are asymmetric, and diastereoselective syntheses of fortamine were already reported by several groups,[4)] but optically pure fortamine has been obtained only by resolution of racemic intermediates.[4c)] These facts clearly show that the introduction of the chiral center into cyclohexane ring is not well developed. The requirements for a general and efficient synthesis of variously substituted 1,4-diaminocyclitols are indeed demanding in the exploitation of such highly potential antibiotics.[5)] We wish to report here an enantioselective synthesis of (-)-fortamine (**2**) under complete stereo- and regiochemical control starting from a symmetrical diester **4**.

The key feature of the present approach is that the meso-diester **4** was generated by a retrosynthetic analysis based on symmetrization-asymmetrization concept[6)] (Scheme 1). Purified chiral half ester[8)] **3** was subjected to the formal enantiomer conversion by treatment with isobutene in the presence of a catalytic amount of sulfuric acid, followed by alkaline hydrolysis with sodium hydroxide to afford the half ester **5** in 88% yield (Scheme 2). The carboxyl group of **5** was converted to the amino group with retention of the configuration through Curtius rearrangement[7)] (92% yield). Then, t-butyl ester was hydrolyzed with TFA and the resultant β-amino acid was subjected to iodolactonization followed by DBU

† Dedicated to Professor Teruaki Mukaiyama of the University of Tokyo on the occasion of his 60th birthday.

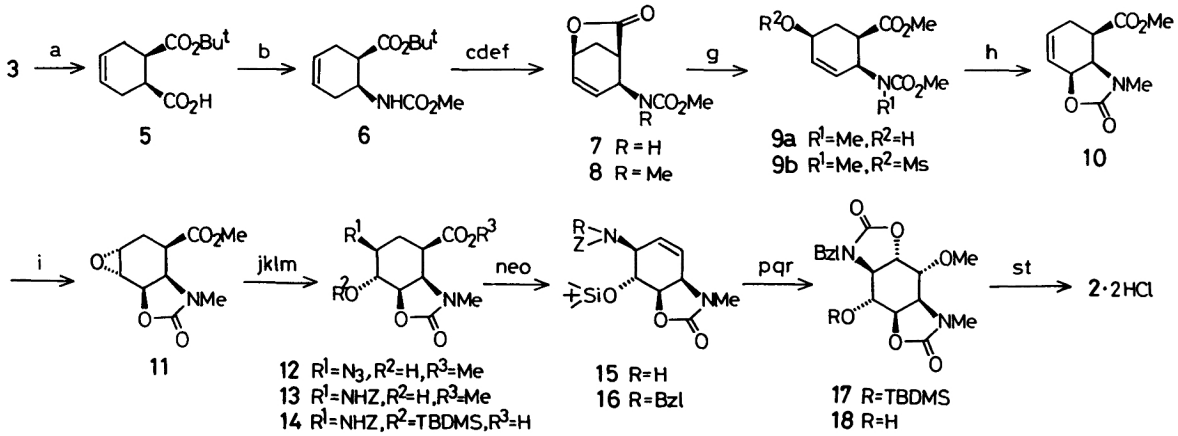
treatment to give the γ-lactone **7** in 92% yield. The N-methyl group, required for the biological activity[9] was introduced at this stage with methyl iodide and silver oxide in 95% yield. An allyl alcohol **9a** obtained by careful methanolysis with sodium methoxide[10] was mesylated with methanesulfonic anhydride[11] and triethylamine. Under reflux-temperature of 1,2-dichloroethane (one pot reaction) the mesylate **9b** cleanly underwent cyclocarbamation to afford the desired cyclic carbamate **10** in 95% yield. Epoxidation of **10** with MCPBA afforded a single epoxide **11** in 92% yield, the stereochemistry of which was assigned to α based on the steric hindrance and final proof by conversion to the natural product. The epoxide opening with $TMSN_3$ was best carried out in the presence of $ZnCl_2$[12] to afford **12** after work-up and the resulting azide **12** was converted into the amino derivative **13** by catalytic reduction followed by the protection in 87% yield from the epoxide **11**. The hydroxyl group at C-6 required for glycoside formation with 6-epipurpurosamine was protected with TBDMS ether (92% yield), and then the ester group was hydrolyzed to afford the acid **14** quantitatively. The most crucial step of the present approach was found to be the conversion of the acid **14** to the olefin **15**. This difficulty was overcome by applying Barton's radical-mediated reaction.[13] The acid **14** was treated with 1-oxa-2-oxo-3-thia-indolizinium chloride (Barton's reagent) and bromotrichloromethane in benzene under reflux to yield a single bromo derivative (71% yield) and DBU treatment afforded **15** in 72% yield. After further protection of the amino group at C-1 with benzyl group[14] (quantitative yield), **16** was oxidized with osmium tetraoxide-trimethylamine N-oxide to give α-cis-glycol quantitatively. After protection of the hydroxyl group at C-2 through cyclic 1,2-trans carbamation with NaH, O-methylation at C-3 was smoothly accomplished with $NaH\text{-}CH_3I$ (one pot reaction) to afford **17** in 95% yield. Fluoride anion treatment of **17** generated the free hydroxyl group at C-6 quantitatively. Since 1,4-diamino and 2,5-dihydroxyl groups are suitably protected as cyclic carbamates, the alcohol **18** is a proper intermediate for the total synthesis of fortimicin A.[4a] The deprotection of **18** completed the total synthesis of fortamine as the dihydrochloride in 98% yield. The key intermediate **18** and fortamine dihydrochloride were respectively confirmed to be identical in all respects with the corresponding authentic samples[15] prepared from natural fortimicin A. Since the dihydrochloride has already been converted to the free fortamine,[4b] the enantioselective synthesis of (-)-fortamine was completed in 22% overall yields from the chiral half ester **3**. Furthermore, the present approach provides useful intermediates for the synthesis of variously substituted 1,4-aminocyclitols useful for the study of the structure-activity relationships on modification at C-3.

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 59430024) from the Ministry of Education, Science, and Culture of Japan. We are also grateful to Kyowa Hakko Kogyo Co. for generous donation of fortimicin A.



1 R^1=6-epi-purpurosamine B
R^2=$COCH_2NH_2$
2 R^1=R^2=H

Scheme 1. Synthetic strategy for (-)-fortamine.



a =<, H^+; NaOH b $ClCO_2Et$, Et_3N; NaN_3; Δ ; MeOH, p-TsOH c TFA d I_2, KI, $NaHCO_3$ e DBU f MeI, Ag_2O g NaOMe
h Ms_2O, Et_3N i MCPBA j $TMSN_3$, $ZnCl_2$; HCl, MeOH k H_2, Pd/C; ZCl, $NaHCO_3$ l TBDMSCl, imidazole m NaOH
n  , DMAP, $CBrCl_3$ o NaH, BztBr p OsO_4, Me_3N+O q NaH, MeI r n-Bu_4NF s 6N HCl t H_2, Pd black

Scheme 2. Enantioselective synthesis of (-)-fortamine.

References

1) Creation of Novel Chiral Synthons with Enzymes and Applications to Natural Product Synthesis, Part 21. See for Part 20; M.Ohno, S.Kobayashi, and K.Adachi, CHIMIA, in press (1986).

2) Fortimicin A; a) T.Nara, M.Yamamoto, I.Kawamoto, K.Takayama, R.Okachi, S.Takasawa, T.Sato, and S.Sato, J. Antibiot., 30, 533 (1977); b) R.Okachi, S.Takasawa, T.Sato, S.Sato, M.Yamamoto, I.Kawamoto, and T.Nara, ibid., 30, 541 (1977); c) 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.Mitsher, ibid., 30, 552 (1977); d) R.L.Girolami and J.M.Stamm, ibid., 30, 564 (1977); Istamycin A; Y.Okami, K.Hotta, M.Yoshida, D.Ikeda, S.Kondo, and H.Umezawa, ibid., 32, 964 (1979); Sporaricin A; T.Deushi, M.Nakayama, I.Watanabe, T.Mori, H.Naganawa, and H.Umezawa, ibid., 32, 187 (1979).

3) J.F.Kennedy and C.A.White, "Bioactive Carbohydrates: In Chemistry, Biochemistry and Biology," John Willey & Sons, New York (1983).

4) a) Fortimicin B from myo-inositol; Y.Honda and T.Suami, Bull. Chem. Soc. Jpn., 55, 1156 (1982); b) (±)-Fortamine and (±)-2-deoxyfortamine from 1,3-cyclohexadiene; S.Knapp, M.J.Sebastian, and H.Ramanathan, J. Org. Chem., 48, 4786 (1983); c) Resolved (-)-fortamine from 1,3-cyclohexadiene; S.Knapp, M.J.Sebastian, H.Ramanathan, P.Bharadwaj, and J.A.Potenza, Tetrahedron, 42, 3405 (1986); d) Resolved (-)-3-de-O-methylfortamine from 1,2;4,5-dianhydro-

epi-inositol; J.Schubert, R.Schwesinger, and H.Prinzbach, Angew. Chem., Int. Ed. Engl., 23, 167 (1984); e) Resolved (-)-2-deoxyfortamine from dianhydro-deoxy-epi-inositol; R.Kühlmeyer, R.Schwesinger, and H.Prinzbach, Tetrahedron Lett., 25, 3429 (1984); f) (±)-Fortamine from trans-1,3-cyclohexadiene 5,6-diol diacetate; C.H.Kuo and N.L.Wendler, ibid., 25, 2291 (1984).

5) 2-Deoxyfortamine is an aminocyclitol moiety of istamycin A (sannamycin A) possessing potent antimicrobial activity, and 3-O-demethylfortimicin A is reported to have an improved activity against Pseudomonas. J.R.Martin, P.Johnson, J.Tadanier, and A.W.Goldstein, Antimicrob. Agents Chemother., 18, 766 (1980).

6) M.Kurihara, K.Kamiyama, S.Kobayashi, and M.Ohno, Tetrahedron Lett., 26, 5831 (1985).

7) S.Kobayashi, K.Kamiyama, T.Iimori, and M.Ohno, Tetrahedron Lett., 25, 2557 (1984).

8) Purified half ester **3** after recrystalization from ether-hexane was used; $[\alpha]_D^{20}$+17.7 (c 1.00, EtOH). Now, it is quite easy to prepare this chiral half ester in multi hundred gram scale in the laboratory.

9) D.Ikeda, Y.Horiuchi, S.Kondo, and H.Umezawa, J. Antibiot., 33, 1281 (1980).

10) It was required to keep the reaction condition strictly below 0 °C within 1 h in order to avoid the epimerization at the ester group.

11) Initially, we examined the mesylation with methanesulfonyl chloride and obtained the allylic chloride instead of the mesylate. Therefore, we expected the direct formation of the cyclic carbamate **10** (S_N2' type) with methanesulfonic anhydride, because the poor nucleophilicity of the mesylate anion would be favored by cyclocarbamation. Furthermore, the introduction of the methyl substituent on the carbamate nitrogen was found to enhance the nucleophilicity of the carbamate considerably. De-N-methyl derivative (**9**, R^1=H, R^2=Ms) underwent cyclocarbamation under the same reaction condition only in 41% yield. We also observed the similar substituent effect on the iodo cyclocarbamation. Y.-F.Wang, T.Izawa, S.Kobayashi, and M.Ohno, J. Am. Chem. Soc., 104, 6465 (1982).

12) L.Birkofer and W.Kaiser, Liebigs. Ann. Chem., 1975, 266.

13) D.H.R.Barton, D.Crich, and W.B.Motherwell, Tetrahedron, 41, 3901 (1985).

14) If Z-amino group of **15** was not further protected with benzyl group, undesirable N-methylation also took place very smoothly during the O-methylation (at C-3 hydroxyl) step.

15) 4-N-Benzyloxycarbonyl-1,2-N,O-carbonyl-5,6-O-cyclohexylidene fortamine prepared from fortimicin A by the literature procedures[2c,4a,16] was treated with (1) NaH, $PhCH_2Br$, (2) H^+, and (3) NaH to give the authentic sample of **18**. $[\alpha]_D^{20}$-69.6 (c 1.00, CH_3OH).

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

(Received August 23, 1986)