The First Enantioselective Synthesis of Fortamine, the 1,4-Diaminocyclitol Moiety of Fortimicin A, by Chemicoenzymatic Approach

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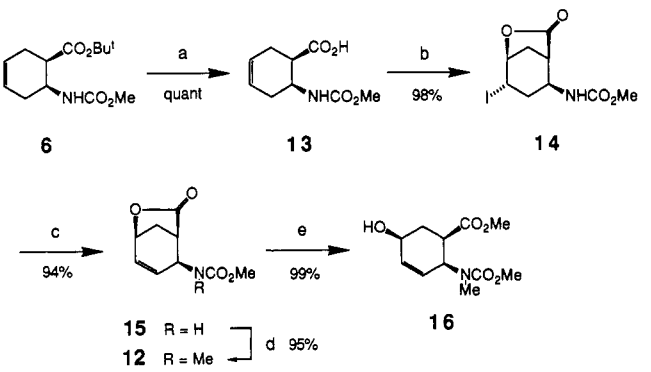
Fortamine, the 1,4-diaminocyclitol moiety of deoxyaminoglycoside antibiotic fortimicin A, has been synthesized enantioselectively for the first time from 1-methyl (1*S*,2*R*)-1,2-cyclohex-4-enedicarboxylate in 22% overall yield.

Introduction

Fortimicin A was isolated by Nara in 1977 from the culture broth of *Micromonospora olivoasterospora* as a new class of deoxyaminoglycoside antibiotics,[1] and the structure was established by Egan.[2] Since then, a number of related antibiotics have been isolated,[3] and some typical examples are shown in Figure 1. These substances are active against both Gram-positive and -negative bacteria including most aminoglycoside-resistant bacteria. In addition to their medicinal importance,[4] these antibiotics are of interest because they possess the unique 1,4-diaminocyclitol skeleton instead of the usual 1,3-diaminocyclitol skeleton seen in classical aminoglycoside antibiotics such as the streptomycins and kanamycins. Umezawa has made a number of significant contributions to the field of modified aminoglycoside antibiotics. Based on an investigation of the mechanism of kanamycin A by kanamycin-resistant bacteria, he rationally designed deoxykanamycins.[5] Among the synthesized derivatives, the 3′,4′-dideoxykanamycin B[6]) (dibekacin) has been found useful for resistant bacteria. These results also indicate that all of the hydroxyl groups are not necessary for antimicrobial activity. Therefore, we have been interested in establishing a general route to various deoxyaminoglycosides having 1,4-diaminocyclitol skeletons.

Among several natural members shown in Figure 1, we selected fortimicin A as a target compound because fortimicin A is representative of this family. Furthermore, in the aminocyclitol moiety of fortimicin A, which is called fortamine (1), all of the cyclohexane carbons are asymmetric and substituted with oxygen or nitrogen functional groups. From a synthetic point of view, construction of such a polyfunctional cyclohexane derivative under stereo- and regiochemical control would be challenging. Indeed,

Scheme I[a]



[a] CF_3CO_2H, 0 °C, quatitative. [b] I_2, KI, $NaHCO_3/H_2O$–CH_2Cl_2, room temperature, 98%. [c] (1) DBU/C_6H_6, reflux, 94%. [d] MeI, Ag_2O/DMF, room temperature, 95%. [e] NaOMe/MeOH, 0 °C, 99%.

the synthesis of fortamine has been reported by several groups,[7] but enantiomerically pure fortamine has been obtained only by classical resolution of racemic intermediates.[7c] These facts clearly show that the suitable chiral cyclohexanes are not easily available from natural sources. Therefore, we have employed a chemicoenzymatic approach[8] using pig liver esterase (PLE) to obtain an optically active cyclohexane intermediate. As reported in a previous paper, we have shown that the PLE-catalyzed hydrolysis of the meso diester **2** (Figure 2) furnishes quantitatively the monoester **3** with excellent enantioselection[9]) (>96% ee). The chiral monoester **3** was then converted to all of the stereoisomers of the β-amino esters, **4**–**7**, in a stereoselective manner.[9] We describe in this paper the first enantioselective synthesis of natural fortamine starting from the β-amino ester **6**.[10] It should be mentioned here that the β-amino ester **4** has been used to

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(3) Sporaricin A; (a) Deushi, T.; Iwasaki, A.; Kamiya, K.; Kunieda, T.; Mizoguchi, T.; Nakayama, M.; Itoh, H.; Mori, T.; Oda, T. *J. Antibiot.* **1979**, *32*, 173. (b) Iwasaki, A.; Itoh, H.; Mori, T. *Ibid.* **1979**, *32*, 180. (c) Deushi, T.; Nakayama, M.; Watanabe, I.; Mori, T.; Naganawa, H.; Umezawa, H. *Ibid.* **1979**, *32*, 187. Istamycin A and B: (d) Okami, Y.; Hotta, K.; Yoshida, M.; Ikeda, D.; Kondo, S.; Umezawa, H. *Ibid.* **1979**, *32*, 964. (e) Hotta, K.; Saito, N.; Okami, Y. *Ibid.* **1980**, *33*, 1502. Sannamycin A: (f) Deushi, T.; Iwasaki, J.; Kamiya, K.; Mizoguchi, T.; Nakayama, M.; Itoh, H.; Mori, T. *Ibid.* **1979**, *32*, 1061. (g) Watanabe, I.; Deushi, T.; Yamaguchi, T.; Kamiya, K.; Nakayama, M.; Mori, T. *Ibid.* **1979**, *32*, 1066. (h) Iwasaki, A.; Itoh, H.; Mori, T. *Int. J. Syst. Bacteriol.* **1981**, *31*, 280.

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(7) (a) Fortimicin B from *myo*-inositol; Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1156. (b) (±)-Fortamine and (±)-2-deoxyfortamine from 1,3-cyclohexadiene: Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.* **1983**, *48*, 4786. (c) Resolved (−)-fortamine from 1,3-cyclohexadiene: Knapp, S.; Sebastian, M. J.; Ramanathan, H.; Bharadwaj, P.; Potenza, J. A. *Tetrahedron* **1986**, *42*, 3405. (d) Resolved (−)-3-de-*O*-methylfortamine from 1,2:4,5-dianhydro-*epi*-inositol: Schubert, J.; Schwesinger, R.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 167; Schubert, J.; Schwesinger, R.; Knothe, L.; Prinzbach, H. *Liebigs Ann. Chem.* **1986**, 2009. (e) Resolved (−)-2-deoxyfortamine from dianhydrodeoxy-*epi*-inositol: Kühlmeyer, R.; Schwesinger, R.; Prinzbach, H. *Tetrahedron Lett.* **1984**, *25*, 3429. (f) (±)-Fortamine from *trans*-1,3-cyclohexadiene-5,6-diol diacetate: Kuo, C. H.; Wendler, N. L. *Ibid.* **1984**, *25*, 2291.

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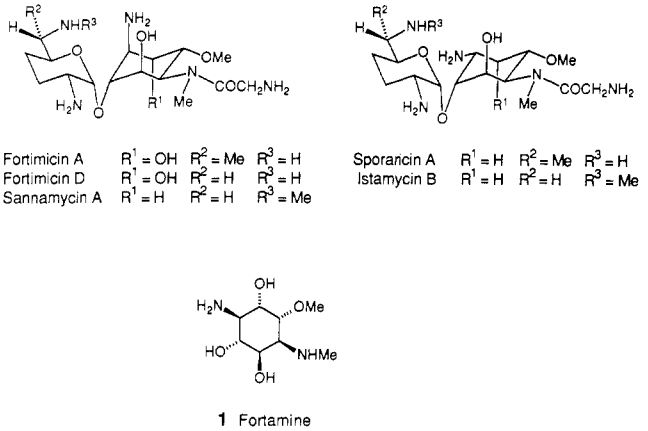

Figure 1.

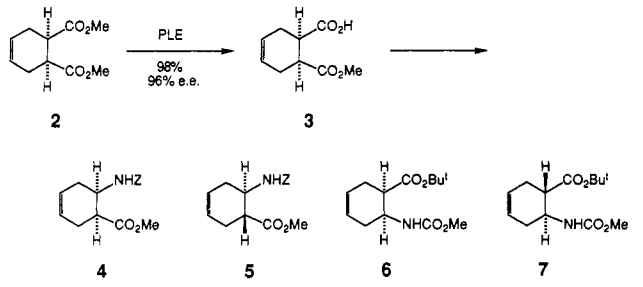

Figure 2.

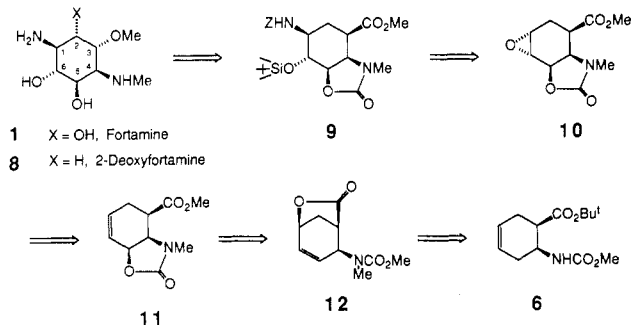

Figure 3.

synthesize carbapenems such as *cis*-carbapenem,[11] thienamycin,[12] and a 1β-methylthienamycin intermediate.[13]

Synthetic Strategy for Fortamine

β-Amino esters **4–7** are all considered to be useful starting materials for the synthesis of a variety of 1,4-diaminocyclitols. Furthermore, we envisaged appropriate synthetic routes to fortamine starting from any stereoisomer. Among several possibilities, we concentrated our synthetic efforts according to the strategy starting from the *cis*-β-amino ester **6** shown in Figure 3. Since we were also interested in the synthesis of 2-deoxyfortamine (**8**), the aminocyclitol moiety of another deoxyaminoglycoside antibiotic sannamycin A,[3] our strategy was designed in such a way to functionalize at C-2 and C-3 (carbon number is expressed according to the fortamine numbering) at a later stage of the synthesis. Thus, we set methyl ester **9**

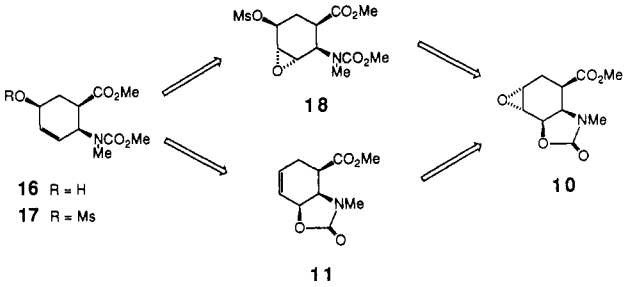

Figure 4.

as a subgoal. The methyl ester **9** has four of six functional groups of fortamine with the desired stereochemistry and could be transformed to both fortamine (**1**) and 2-deoxyfortamine (**8**) through the oxidative decarboxylation of the methoxycarbonyl group. A 1,2-amino alcohol functional group at C-1 and C-6 with anti stereochemistry in **9** might be constructed from the α-epoxide **10**. In the epoxide opening nitrogen nucleophile is expected to attack the less hindered C-1 preferentially affording the desired isomer. The other 1,2-amino alcohol group at C-4 and C-5 with syn stereochemistry might, in turn, be constructed in a protected form by intramolecular cyclocarbamation utilizing the nucleophilic character of the carbamate oxygen (vide infra).

Preparation of Subgoal 16

Conversion of **6** to the bicyclic lactone **12** was straightforward (Scheme I). Thus, *tert*-butyl ester **6** was hydrolyzed with trifluoroacetic acid (TFA, room temperature, quantitative yield), and the resulting carboxylic acid **13** was subjected to iodolactonization under two-phase conditions, furnishing the iodolactone **14** (I_2, KI, $NaHCO_3$/CH_2Cl_2–H_2O, room temperature, 98%). Treatment of **14** with DBU in refluxing benzene (DBU/benzene, 80 °C) furnished the bicyclic lactone **15** in 94% yield. *N*-Methylation of **15** to **12** was cleanly achieved through use of methyl iodide and silver oxide (MeI, Ag_2O/DMF, room temperature, 95%). Methanolysis of the lactone **12** with NaOMe in methanol at 0 °C afforded the allyl alcohol **16** in quantitative yield. The overall yield of **16** from the chiral monoester **3** was 74%. When the methanolysis was carried out at room temperature, epimerization of the methoxycarbonyl group occurred, furnishing an inseparable equilibrium mixture of **16** and its epimer.

The next objective was introduction of an oxygen functionality at C-5 (fortamine numbering). Two routes of the α-epoxide **10**, via the intermediary of either **18** or **11**, were envisioned, and this is shown in Figure 4. Peracid oxidation of olefinic mesylate **17** would occur from the less hindered α-face to afford the α-epoxide **18** preferentially. Subsequent nucleophilic attack of the carbamate oxygen at the adjacent epoxide carbon would result in formation of another epoxide between C-6 and C-1. Alternatively, the mesylate **17** would be expected to undergo direct cyclocarbamation in an S_N2' fashion. We have previously demonstrated the nucleophilic character of the carbamate oxygen in iodocyclocarbamation of olefinic carbamates. Stereoselective cyclization in acylic systems has successfully been applied to the synthesis of several biologically interesting compounds having 1,2- or 1,3-amino alcohol groups, such as negamycin,[14] bestatin,[15] and 6-*epi*-

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(12) Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 1057.

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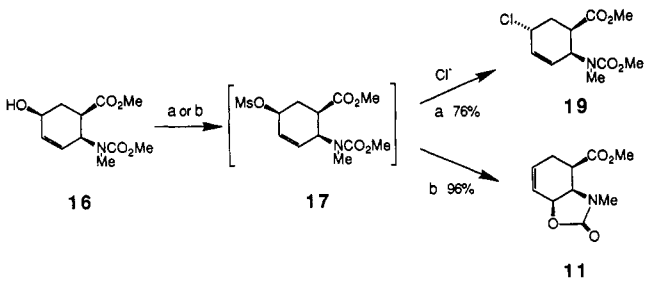
(14) (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (b) Ohno, M.; Kobayashi, S.; Izawa, T.; Wang, Y.-F. *J. Chem. Soc. Jpn. Chem. Ind. Chem.* **1983**, *12*, 99.

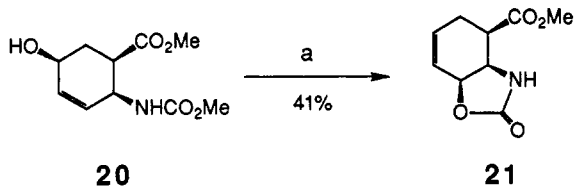
(15) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.

Scheme II[a]



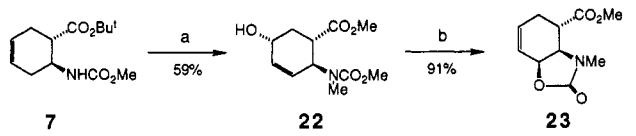
[a] MsCl, $Et_3N/ClCH_2CH_2Cl$, room temperature. [b] Ms_2O, $Et_3N/ClCH_2CH_2Cl$, 0 °C to reflux.

Scheme III[a]



[a] Ms_2O, $Et_3N/ClCH_2CH_2Cl$, 0 °C to reflux, 41%.

Scheme IV[a]



[a] (1) CF_3CO_2H, 0 °C to quantitative, (2) I_2, KI, $NaHCO_3/H_2O$–CH_2Cl_2, room temperature, 87%, (3) DBU/C_6H_6, reflux, 73%, (4) MeI, Ag_2O/DMF, room temperature, quantitative (5) NaOMe/MeOH, 0 °C, 93%. [b] Ms_2O, $Et_3N/ClCH_2CH_2Cl$, 0 °C, then reflux, 91%.

purpurosamine B,[16] the amino sugar moiety of fortimicin A and sannamycin A. Epoxidation of the resulting olefinic cyclocarbamate **11** would give the α-epoxide **10**.

As shown in Scheme II, attempted mesylation of the allylic alcohol **16** with methanesulfonyl chloride and triethylamine in 1,2-dichloroethane at room temperature yielded the chloride **19** (76%) instead of the expected mesylate **17**. This result led us to examine mesylation with methanesulfonic anhydride, since the mesylate anion is not a good nucleophile. Furthermore, cyclocarbamation by the adjacent carbamate oxygen might directly occur. As expected, the olefinic cyclocarbamate **11** was isolated in 96% yield by treatment with Ms_2O and triethylamine in 1,2-dichloroethane initially at 0 °C for 2 h and then at reflux for 1 h.

Corresponding treatment of the de-*N*-methyl derivative **20** gave the cyclization product **21** (Scheme III) in only 41% yield. Introduction of methyl group on the nitrogen atom enhances the nucleophilicity of carbamate oxygen in iodocyclocarbamation.[14] The syn-isomers **16** and **20** have the correct syn stereochemistry for S_N2' reaction.[17] We also examined the corresponding reaction of anti-isomer **22** under the same reaction conditions and obtained the cyclocarbamate **23** in 91% yield (Scheme IV). These results suggest the occurrence of a cationic intermediate in these cyclizations.

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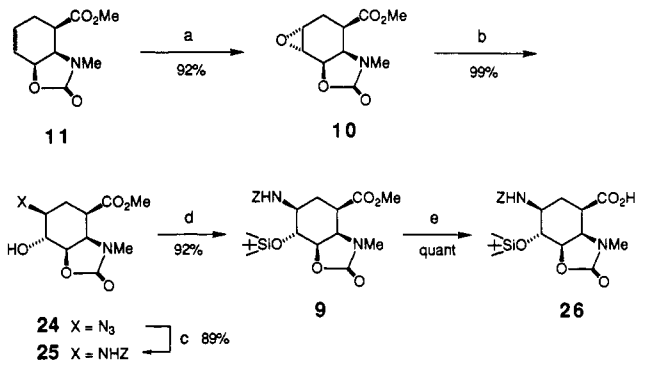
Scheme V[a]



[a] MCPBA/CH_2Cl_2, room temperature, 92%. [b] (1) $TMSN_3$, $ZnCl_2/ClCH_2CH_2Cl$, reflux, (2) catalyst, HCl/MeOH, room temperature, 99%. [c] (1) H_2, Pd/C/MeOH, room temperature, (2) CbzCl, $NaHCO_3$/dioxane–H_2O, room temperature, 89%. [d] TBDMSCl, imidazole/DMF, room temperature 92%. [e] NaOH/MeOH–H_2O, room temperature, quantitative.

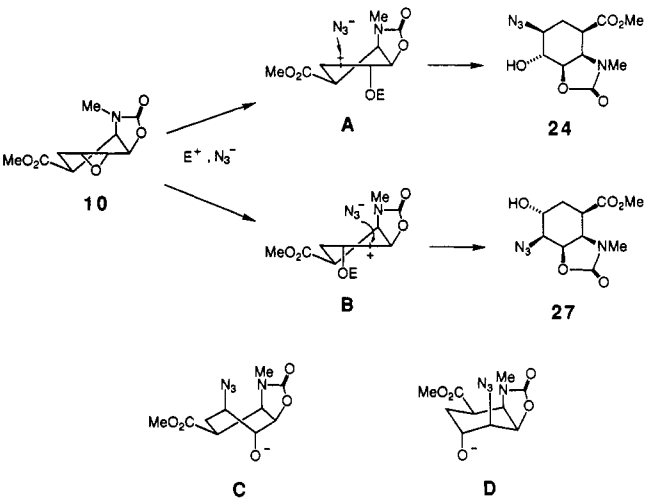


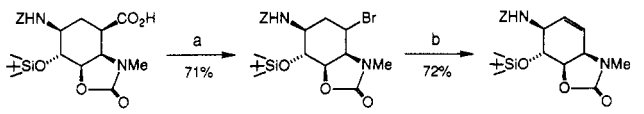
Figure 5.

As shown in Scheme V, epoxidation of **11** with *m*-chloroperbenzoic acid (MCPBA, CH_2Cl_2, room temperature) afforded the single epoxide **10** in 92% yield. The stereochemistry of **10** was tentatively assigned as α based on steric considerations.

Opening of the epoxide ring with nitrogen nucleophiles was examined next. Treatment of **10** with sodium or lithium azide in DMF or dioxane–H_2O at 100 °C gave the desired azido alcohol **24**, but the yield was very low. Another nitrogen nucleophile such as benzylamine was found not reactive. On the other hand, we found that Lewis acid promoted azidolysis proceeded very cleanly and with excellent regioselectivity. Thus, when **10** was reacted with trimethylsilyl azide and zinc chloride[18] in refluxing 1,2-dichloroethane, a mixture of azido alcohol **24** and its trimethylsilyl ether was obtained. Treatment of the crude mixture with a catalytic amount of 6 N HCl in MeOH gave the azido alcohol **24** in 99% yield. Exclusive formation of **24** might be due to both steric and electronic factors, and this is shown in Figure 5. From an electronic point of view, the cationic intermediate B might be less stable compared to A, since the carbocation in B is β to an electron-deficient carbamate oxygen Figure 5). Destabilization of carbocations by an oxygen atom at the β-position has been observed.[19] From a stereochemical point

(18) Birkofer, L.; Kaiser, W. *Liebigs Ann. Chem.* **1975**, 266.

Scheme VI[a]



26 28 29

[a]  , DMAP, $CBrCl_3/C_6H_6$–THF, reflux, 71%. [b] DBU/ toluene, reflux, 72%.

of view, there seems to be a severe 1,3-diaxial interaction between the approaching azide anion and the carbamate nitrogen in the transition state B. Therefore, the reaction might proceed through the more favored transition state A to afford **24** in a regioselective manner.

The unsuccessful epoxide ring opening with lithium or sodium azide described above might also be explained by considering intermediates C and D. The desired C-1 attack by the nitrogen nucleophile through diaxial epoxide opening requires the twist-boat transition state C, and the C-2 attack with the chairlike transition state D suffers from a 1,3-diaxial interaction.

The azido alcohol **24** was converted to the subgoal **9** in three conventional steps in 81% overall yields ((1) H_2, Pd-C/MeOH, room temperature, (2) $ClCO_2CH_2Ph$, $NaHCO_3$/dioxane–H_2O, 0 °C to room temperature, 89% for two steps, (3) TBDMSCl, imidazole/DMF, room temperature, 92%). The hydroxyl group at C-6, which is required for glycoside formation with 6-*epi*-purpurosamine B, was protected as the TBDMS ether. Saponification (NaOH/MeOH-H_2O, room temperature) of the methyl ester in **9** gave the carboxylic acid **26** in quantitative yield.

Synthesis of Fortamine

Oxidative Decarboxylation of the Carboxylic Acid 26. Four of six chiral centers in fortamine were successfully introduced in a stereoselective manner with suitable functional groups. To introduce the remaining oxygen functional groups at C-2 and C-3, it was necessary to convert **26** into the olefinic derivative **29**, and this proved to be experimentally challenging. Hunsdiecker-type reactions of **26** were uniformly unsuccessful, as was Bayer–Villiger oxidation of the corresponding methyl ketone or mixed anhydride derived from **26**. Ultimately, Barton's method[20] was found to be successful. Thus, treatment of the carboxylic acid **26** with Barton's reagent (1-oxa-2-oxo-3-thiaindolizinium chloride, prepared in situ from 2-mercaptopyridine *N*-oxide sodium salt and phosgene dimer), bromotrichloromethane, and (dimethylamino)-pyridine (DMAP) in refluxing benzene gave the single bromide **28** in 71% yield. Dehydrobromination of **28** with DBU afforded the olefinic derivative **29** (DBU, toluene, reflux, 72%; Scheme VI).

Synthesis of Fortamine. Our plan for final introduction of the functional groups at C-2 and C-3 was as follows: Osmylation of **29** from the less hindered side was expected to give the desired α-cis glycol, thereby setting all the chiral centers in fortamine. Selective O-methylation at C-3 would then be achieved by internal cyclocarbamation between the C-2 hydroxyl and the C-1 (benzyloxycarbonyl)amino group, followed by O-methylation of the remaining free hydroxyl group at C-3.

Hydroxylation and cyclocarbamation proceeded smoothly as expected. However, undesired N-methylation accompanied the O-methylation of the de-*N*-benzyl derivative of **32**. Therefore, the (benzyloxycarbonyl)amino group of **29** was first protected with a benzyl group (NaH, BzlBr/DMF, 0 °C, 96%).

Hydroxylation of **30** (Scheme VII) with 5 mol % of osmium tetroxide with trimethylamine *N*-oxide as the cooxidant proceeded rather slowly at 50 °C, but after 3 days glycol **31** was isolated in almost quantitative yield. The use of *N*-methylmorpholine *N*-oxide instead of trimethylamine *N*-oxide resulted in recovery of **30** even after heating for 1 week.

Treatment of the diol **31** with sodium hydride in DMF at 0 °C, followed by addition of methyl iodide (one-pot reaction), afforded the fully protected fortamine **33** in 95% yield (NaH, DMF, 0 °C, then MeI). Fluoride anion treatment (n-Bu_4NF, THF, room temperature, quantitative) of **33** generated the free hydroxyl group, which was necessary for glycoside formation. Other functional groups, 1,4-diamino and 2,5-dihydroxyl groups, are mutually protected in the two cyclic carbamates. Therefore, **34** is considered to be a key intermediate for the total synthesis of fortimicin A.[7]

The structure of each intermediate so far has been tentatively assigned, based on mechanistic and steric considerations. With methoxyl derivative **33** or **34** in hand, we could confirm the structure by comparison with the authentic sample derived from natural fortimicin A. The preparation of authentic **34** is shown in Scheme VIII. Synthetic **34** was found to be identical with the authentic sample in all respects (IR, ^1H NMR, MS, TLC, and optical rotation).

Acid hydrolysis of the carbamates and hydrogenolysis of the *N*-benzyl group of **34** completed the total synthesis of fortamine **1**, which was isolated as the dihydrochloride ((1) 6 N HCl, reflux, (2) H_2, Pd black, 98%). Synthetic fortamine dihydrochloride showed spectral data consistent with those of reported data.[21] Since fortamine dihydrochloride has already been converted to the free form,[22] the first enantioselective synthesis of (−)-fortamine was completed in 22% overall yields from the chiral monoester **3**.

It should be emphasized that all the functional groups could be introduced in complete stereo- and regioselective manners in the present synthesis. Furthermore, the present approach would provide potential intermediates for the synthesis of variously substituted 1,4-diaminocyclitols useful for the study of the structure–activity relationships by modification at C-2 and particularly at C-3.

Experimental Section

General Procedures. Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Silica gel (Wakogel C-200, C-300 or Fujigel BW 200) was used for column chromatography, and silica gel (Kiesel gel 60 F_{254}, Merck) for analytical thin-layer chromatography. Melting points were measured on a Yanagimoto micromelting apparatus and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX-100 (100 MHz) or JEOL GX-400 (400 MHz) spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal reference, unless stated otherwise. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were

(19) See, for example: (a) Ernst, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 207. (b) Niwayama, S.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 6313.

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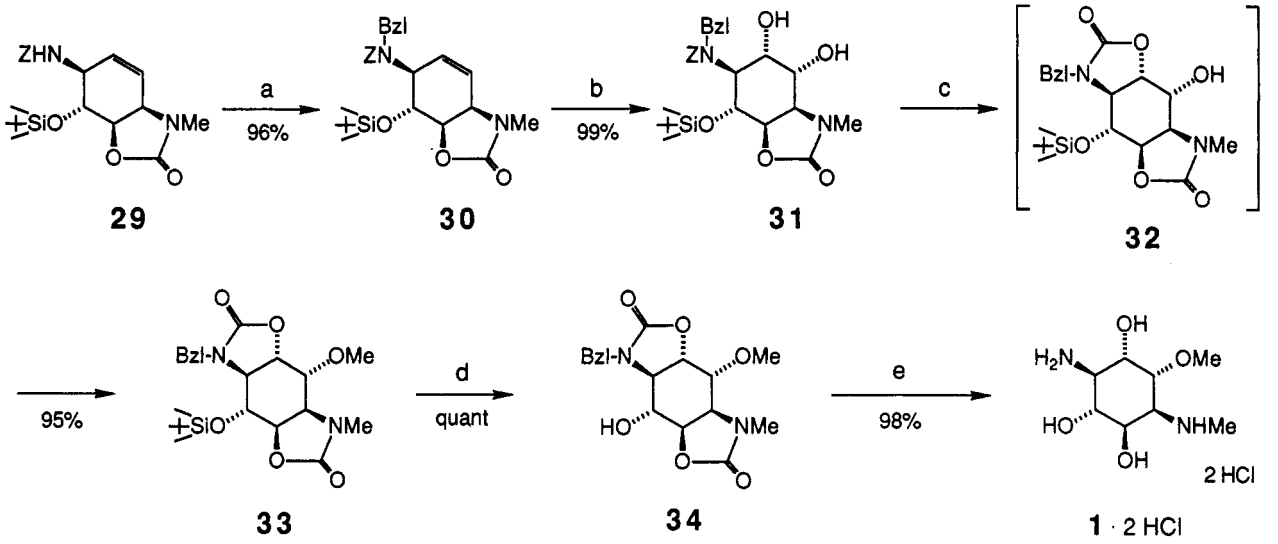
(21) Sano, H.; Sakaguchi, T.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2727.

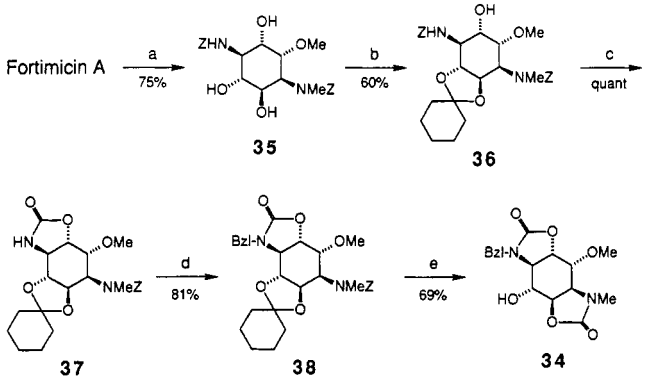
(22) Rosenbrook, Jr., W.; Fairgrieve, J. S. *J. Antibiot.* **1981**, *34*, 681.

Scheme VII[a]



[a] NaH, BzlBr/DMF, 0 °C, 96%. [b] Catalyst, OsO_4, Me_3N *N*-oxide/*t*-BuOH–H_2O, 50 °C, 99%. [c] NaH/DMF, 0 °C, then MeI/DMF, 0 °C, 95%. [d] *n*-Bu_4NF/THF, room temperature quantitative. [e] (1) 6 N HCl, reflux, (2) H_2, Pd black/MeOH, room temperature 98%.

Scheme VIII[a]



[a] (1) $Ba(OH)_2/H_2O$ reflux, (2) 6 N HCl, reflux, (3) $ClCO_2CH_2Ph$, $NaHCO_3$/dioxane–H_2O, room temperature, 75%. [b] 1,1-Dimethoxycyclohexane, *p*-TsOH/DMF, 50 °C, 30 mmHg, 60%. [c] NaH/DMF, 0 °C, quantitative. [d] NaH, BzlBr/DMF, 40 °C, 81%. [e] (1) AcOH/MeOH–H_2O, 60 °C, (2) NaH/DMF, 0 °C, 69%.

obtained on a JASCO A-102 spectrometer. Mass spectra were obtained on a JEOL JMS-01 SG-2 mass spectrometer. Optical rotations were measured with a JASCO DIP-140 digital polarimeter.

(1*R*,6*S*)-6-[(Methoxycarbonyl)amino]cyclohex-3-enecarboxylic Acid (13). A mixture of *tert*-butyl ester **6** (206.0 mg, 0.81 mmol) and trifluoroacetic acid (1 mL) was stirred at 0 °C for 20 min. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (2:1 hexane/Et_2O) to give the β-amino ester **13** (160.5 mg, quantitative yield) as a white crystalline solid. **13**: mp 116.0–117.0 °C (Et_2O). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.32; H, 6.74; H, 6.98. MS, *m/e* 199 (M^+), 181, 168; $[\alpha]^{20}_D$ −27.1° (*c* 1.00, $CHCl_3$); R_f 0.39 (AcOEt:hexane = 1:1); IR (KBr) 3420, 3300–2800, 1705, 1670, 1525 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.02–2.70 (m, 4 H), 2.86 (m, 1 H), 3.65 (s, 3 H), 4.20 (m, 1 H), 5.44 (br d, *J* = 9 Hz, 1 H, NH), 5.48–5.78 (m, 2 H), 9.68 (br s, 1 H, CO_2H).

(1*R*,2*S*,4*S*,5*S*)-2-[(Methoxycarbonyl)amino]-4-iodo-7-oxo-6-oxabicyclo[3.2.1]octane (14). To a solution of carboxylic acid **13** (11.41 g, 57.3 mmol) in CH_2Cl_2 (100 mL) was added 0.5 N $NaHCO_3$ solution (344 mL), KI (57.10 g, 344 mmol), and I_2 (29.09 g, 114.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 20 h and poured into aqueous $Na_2S_2O_3$ solution. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (3:1 CH_2Cl_2/Et_2O) to give the iodolactone **14** (18.19 g, 98%) as a white crystalline solid. **14**: mp 158.5–159.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_9H_{12}INO_4$: C, 33.25; H, 3.72; N, 4.31. Found: C, 33.39; H, 3.60; N, 4.01. MS, *m/e* 325 (M^+), 294, 251, 198; $[\alpha]^{20}_D$ −98.1° (*c* 1.00, $CHCl_3$); R_f 0.38 (AcOEt:hexane = 1:1); IR (KBr) 3350–3300, 1770, 1705, 1535 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.21 (ddd, $J_{3a,3b}$ = 16.0, $J_{2,3b}$ = 11.5, $J_{3b,4}$ = 6.0 Hz, 1 H), 2.37–2.62 (m, $J_{5,8b} = J_{1,8b}$ = 5.5, $J_{3a,4}$ = 2.0 Hz, 2 H), 2.84 (m, 1 H), 2.88 (d, $J_{8a,8b}$ = 12.5 Hz, 1 H), 3.69 (s, 3 H), 4.17 (m, $J_{1,2}$ = 2.0 Hz, 1 H), 4.49 (m, $J_{3a,4}$ = 2.0 Hz, 1 H), 4.81 (dd, $J_{5,8b}$ = 5.5, $J_{4,5}$ = 4.0 Hz, 1 H), 5.30 (br d, $J_{2,NH}$ = 8.5 Hz, 1 H).

(1*R*,2*S*,5*S*)-2-[(Methoxycarbonyl)amino]-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene (15). A mixture of iodolactone **14** (28.5 g, 87.7 mmol) and DBU (15.2 g, 100 mmol) in benzene (100 mL) was heated at refluxing temperature for 3 h. The precipitate was filtered off. The filtrate was diluted with AcOEt, washed (1 N, HCl, saturated $Na_2S_2O_3$, H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by recrystallization from CH_2Cl_2–hexane to give the olefinic lactone **15** (8.83 g) as white crystals. The mother liquor was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (5:1 CH_2Cl_2/AcOEt) to give **15** (7.47 g, total 16.3 g, 94%). **15**: mp 142.0–142.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.85; H, 5.57; N, 6.81. MS, *m/e* 197 (M^+), 152; $[\alpha]^{20}_D$ −51.0° (*c* 1.00, $CHCl_3$); R_f 0.24 (AcOEt:hexane = 1:1); IR (KBr) 3300, 1700, 1690, 1525 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.17 (d, $J_{8a,8b}$ = 11.5 Hz, 1 H), 2.57 (dddd, $J_{8a,8b}$ = 11.5, $J_{1,8b} = J_{5,8b}$ = 5.5, $J_{4,8b}$ = 1.0 Hz, 1 H), 3.02 (dddd, $J_{1,2} = J_{1,8b}$ = 5.5, $J_{1,3} = J_{1,5}$ = 1.5 Hz, 1 H), 3.70 (s, 3 H), 4.71 (m, 1 H), 4.81 (m, $J_{4,5} = J_{5,8b}$ = 5.5, $J_{1,5} = J_{3,5}$ = 1.5 Hz, 1 H), 5.10 (br d, $J_{2,NH}$ = 9 Hz, 1 H, NH), 5.74 (dddd, $J_{3,4}$ = 9.5, $J_{2,3}$ = 3.0, $J_{1,3} = J_{3,5}$ = 1.5 Hz, 1 H), 6.34 (dddd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.5, $J_{2,4}$ = 3.0, $J_{4,8b}$ = 1.0 Hz, 1 H).

(1*R*,2*S*,5*S*)-2-[*N*-Methyl(methoxycarbonyl)amino]-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene (12). A mixture of olefinic lactone **15** (7.46 g, 37.8 mmol), MeI (22.8 g, 161 mmol) and Ag_2O (8.80 g, 38.0 mmol) in DMF (20 mL) was stirred at room temperature for 2 days. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and the precipitate was filtered off on Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (2:1 hexane/AcOEt) to give **12** (7.63 g, 95%) as a colorless oil. **12**: MS, *m/e* 211 (M^+), 192, 167; $[\alpha]^{20}_D$ −88.4° (*c* 1.20, $CHCl_3$); R_f 0.26 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 1775, 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.18 (d, $J_{8a,8b}$ = 11.5 Hz, 1 H), 2.54 (dddd, $J_{8a,8b}$ = 11.5, $J_{1,8b} = J_{5,8b}$ = 5.5, $J_{4,8b}$ = 1.0 Hz, 1 H), 2.76 (s, 3 H), 3.10 (m, 1 H), 3.75 (s, 3 H), 4.77 (m, $J_{4,5} = J_{5,8b}$ = 5.5 Hz, 1 H), 5.12 (m, 1 H), 5.76

(m, $J_{3,4}$ = 9.5 Hz, 1 H), 6.46 (m, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.5, $J_{2,4}$ = 2.5 Hz, 1 H).

Methyl (1*R*,2*S*,5*S*)-5-Hydroxy-2-[*N*-methyl(methoxycarbonyl)amino]cyclohex-3-enecarboxylate (16). To a solution of olefinic lactone **12** (2.30 g, 10.9 mmol) in MeOH (20 mL) was added NaOMe (589 mg, 10.9 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized with 2 N HCl and poured into saturated NaCl solution. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **16** (2.63 g, 99%) as a colorless oil. **16**: MS, *m/e* 243 (M^+), 226, 225, 211; $[\alpha]^{20}_D$ +15.7° (*c* 1.58, $CHCl_3$); R_f 0.30 (AcOEt:hexane = 4:1); IR ($CHCl_3$) 3440, 1725, 1685, 1450 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.78–2.29 (m, 2 H), 2.82 (s, 3 H), 2.96 (m, 1 H), 3.50 (br s, 1 H, OH), 3.67 (s, 3 H), 3.72 (s, 3 H), 4.18 (m, 1 H), 4.98 (m, 1 H), 5.56 (ddd, $J_{3,4}$ = 10.5, J = 3.8, J = 1.8 Hz, 1 H), 6.06 (dt, $J_{3,4}$ = 10.5, J = 2.5 Hz, 1 H).

Methyl (1*R*,2*S*,5*R*)-5-Chloro-2-[*N*-methyl(methoxycarbonyl)amino]cyclohex-3-enecarboxylate (19). To a mixture of **16** (156 mg, 0.64 mmol) and Et_3N (152 mg, 1.5 mmol) in 1,2-dichloroethane (5 mL) was added methanesulfonyl chloride (114 mg, 0.99 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with CH_2Cl_2, washed (H_2O, saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane/AcOEt) to give **19** (128 mg, 76%) as a colorless oil. **19**: MS, *m/e* 263 (M^+ + 2), 261 (M^+), 229, 226; $[\alpha]^{20}_D$ +278° (*c* 1.15, $CHCl_3$); R_f 0.62 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 1735, 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.17 (m, $J_{6a,6b}$ = 15.0, $J_{1,6a}$ = 4.8 Hz, 1 H), 2.42 (ddd, $J_{6a,6b}$ = 15.0, $J_{1,6b}$ = 11.5, $J_{5,6b}$ = 4.2 Hz, 1 H), 2.76 (s, 3 H), 3.32 (ddd, $J_{1,6b}$ = 11.5, $J_{1,2}$ = 6.5, $J_{1,6a}$ = 4.8 Hz, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 4.74 (m, $J_{5,6b}$ = 4.2, $J_{5,6a}$ = 3.0 Hz, 1 H), 5.14 (m, 1 H), 5.68 (ddd, $J_{3,4}$ = 10.0, $J_{2,3}$ = 4.8, $J_{3,5}$ = 1.0 Hz, 1 H), 6.18 (dddd, $J_{3,4}$ = 10.0, $J_{4,5}$ = 5.0, $J_{2,4}$ = 2.0, $J_{4,6a}$ = 1.0 Hz, 1 H).

Methyl (1*R*,2*R*,6*S*)-9-Methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]non-4-enecarboxylate (11). To a mixture of **16** (2.54 g, 10.4 mmol) and Et_3N (3.16 g, 31.2 mmol) in 1,2-dichloroethane (20 mL) was added methanesulfonic anhydride (2.96 g, 16.8 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h and then at refluxing temperature for 1 h. The mixture was diluted with CH_2Cl_2, washed (saturated $NaHCO_3$, 1 N HCl, H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **11** (2.12 g, 96%) as a colorless oil. **11**: MS, *m/e* 211 (M^+), 179; $[\alpha]^{20}_D$ −20.5° (*c* 1.10, $CHCl_3$); R_f 0.23 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17–2.47 (m, $J_{2,3a}$ = 8.5, $J_{2,3b}$ = 7.2, $J_{3a,4}$ = 4.6, $J_{3b,4}$ = 3.2, $J_{3a,5}$ = $J_{3b,5}$ = 2.0 Hz, 2 H), 2.75 (s, 3 H), 2.85 (ddd, $J_{2,3a}$ = 8.5, $J_{2,3b}$ = 7.2, $J_{1,2}$ = 2.2 Hz, 1 H), 3.79 (s, 3 H), 4.46 (dd, $J_{1,6}$ = 7.7, $J_{1,2}$ = 2.2 Hz, 1 H), 5.00 (m, $J_{1,6}$ = 7.7, $J_{5,6}$ = 3.2, $J_{4,6}$ = 0.6 Hz, 1 H), 5.68 (m, $J_{4,5}$ = 10.0, $J_{5,6}$ = 3.2, $J_{3a,5}$ = $J_{3b,5}$ = 2.0 Hz, 1 H), 6.08 (m, $J_{4,5}$ = 10.0, $J_{3a,4}$ = 4.6, $J_{3b,4}$ = 3.2, $J_{4,6}$ = 0.6 Hz, 1 H).

Methyl (1*R*,2*S*,5*S*)-5-Hydroxy-2-[(methoxycarbonyl)amino]cyclohex-3-enecarboxylate (20). A mixture of lactone **15** (986 mg, 5.0 mmol) and NaOMe (267 mg, 4.9 mmol) in MeOH (20 mL) was stirred at −10 °C for 1 h. HCl (2 N, 3 mL) was added to the mixture, and the most of MeOH was removed in vacuo. The mixture was extracted with CH_2Cl_2, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **20** (1.06 g, 92%) as a colorless oil. **20**: MS, *m/e* 229 (M^+), 212, 211; $[\alpha]^{20}_D$ +56.6° (*c* 1.50, $CHCl_3$); R_f 0.29 (AcOEt:hexane = 4:1); IR ($CHCl_3$) 3440, 1725, 1510 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.90 (ddd, $J_{6a,6b}$ = 13.8, $J_{1,6b}$ = 10.0, $J_{5,6b}$ = 7.5 Hz, 1 H), 2.17 (ddd, $J_{6a,6b}$ = 13.8, $J_{5,6a}$ = 5.5, $J_{1,6a}$ = 4.0 Hz, 1 H), 2.54 (br s, 1 H, OH), 2.85 (m, $J_{1,6b}$ = 10.0, $J_{1,2}$ = 4.2, $J_{1,6a}$ = 4.0 Hz, 1 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 4.20 (m, 1 H), 4.52 (m, 1 H), 5.52 (br d, $J_{2,NH}$ = 10 Hz, 1 H, NH), 5.70 (m, $J_{3,4}$ = 10.0, $J_{2,3}$ = 3.5, J = 1.0 Hz, 1 H), 5.88 (m, $J_{3,4}$ = 10.0 Hz, 1 H).

Methyl (1*R*,2*R*,6*S*)-8-Oxo-9-aza-7-oxabicyclo[4.3.0]non-4-enecarboxylate (21). To a mixture of **20** (200 mg, 0.87 mmol) and Et_3N (305 mg, 3.0 mmol) in 1,2-dichloroethane (12 mL) was added methanesulfonic anhydride (379 mg, 2.18 mmol) at 0 °C, and the mixture was stirred at 0 °C for 45 min and then at refluxing temperature for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **21** (70 mg, 41%) as a colorless oil. **21**: MS, *m/e* 197 (M^+), 166; $[\alpha]^{20}_D$ −12.3° (*c* 1.10, $CHCl_3$); R_f 0.12 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 3440, 1760, 1730 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.32–2.52 (m, 2 H), 2.83 (ddd, $J_{2,3a}$ = $J_{2,3b}$ = 8.0, $J_{1,2}$ = 2.3 Hz, 1 H), 3.76 (s, 3 H), 4.50 (m, $J_{1,6}$ = 8.0 Hz, 1 H), 5.08 (m, $J_{1,6}$ = 8.0 Hz, 1 H), 5.62–5.94 (m, 2 H), 6.10 (m, $J_{4,5}$ = 10.0, $J_{3b,4}$ = 3.5 Hz, 1 H).

Methyl (1*S*,2*S*,5*R*)-5-Hydroxy-2-[*N*-methyl(methoxycarbonyl)amino]cyclohex-3-enecarboxylate (22). **22** was prepared from **7** in a manner similar to the preparation of **16** from **6**. Reaction conditions and yields of each steps are shown in Scheme IV. Typical data are as follows:

(1*S*,6*S*)-6-[(Methoxycarbonyl)amino]cyclohex-3-enecarboxylic acid: mp 104.5–105.0 °C (Et_2O–hexane). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.21; H, 6.54; N, 7.19. MS, *m/e* 199 (M^+), 182, 181, 168; $[\alpha]^{20}_D$ +51.5° (*c* 1.00, $CHCl_3$); IR (KBr) 3320, 3300–2800, 1700, 1540 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.80–2.92 (m, 5 H), 3.68 (s, 3 H), 4.04 (m, 1 H), 5.04 (br s, 1 H, NH), 5.48–5.81 (m, 2 H), 8.62 (br s, 1 H, CO_2H).

(1*S*,2*S*,4*R*,5*R*)-2-[(Methoxycarbonyl)amino]-4-iodo-7-oxo-6-oxabicyclo[3.2.1]octane: mp 162.5–164.0 °C (dec, CH_2Cl_2–hexane). Anal. Calcd for $C_9H_{12}INO_4$: C, 33.25; H, 3.72; N, 4.31. Found: C, 33.40; H, 3.72; N, 4.59; MS, *m/e* 325 (M^+), 294, 198; $[\alpha]^{20}_D$ +22.5° (*c* 1.00, $CHCl_3$); IR (KBr) 3420, 1780, 1710, 1510 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.12–2.52 (m, 2 H), 2.73–3.20 (m, 3 H), 3.72 (s, 3 H), 4.14–4.46 (m, 2 H), 4.89 (dd, J = 5.5, J = 4.0 Hz, 1 H), 5.56 (br d, 1 H, NH).

(1*S*,2*S*,5*R*)-2-[(Methoxycarbonyl)amino]-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene: mp 147.0–148.0 °C (AcOEt–hexane). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.53; H, 5.58; N, 7.09. MS, *m/e* 197 (M^+), 153, 152; $[\alpha]^{20}_D$ +259° (*c* 1.00, $CHCl_3$); IR (KBr) 3280, 1770, 1680, 1540 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.20 (d, $J_{8a,8b}$ = 11.5 Hz, 1 H), 2.44 (ddd, $J_{8a,8b}$ = 11.5, $J_{1,8a}$ = $J_{5,8a}$ = 5.5 Hz, 1 H), 3.06 (m, 1 H), 3.72 (s, 3 H), 4.48 (m, 1 H), 4.83 (m, $J_{4,5}$ = $J_{5,8a}$ = 5.5 Hz, 1 H), 5.16 (br d, $J_{2,NH}$ = 7.5 Hz, 1 H, NH), 5.74 (m, $J_{3,4}$ = 9.5, $J_{2,3}$ = 4.0, $J_{1,3}$ = $J_{3,5}$ = 1.2 Hz, 1 H), 6.40 (m, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.5 Hz, 1 H).

(1*S*,2*S*,5*R*)-2-[*N*-Methyl(methoxycarbonyl)amino]-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene: mp 70.5–72.5 °C (Et_2O–hexane). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.87; H, 6.16; N, 6.48. MS, *m/e* 211 (M^+), 192, 167; $[\alpha]^{20}_D$ +222° (*c* 1.00, $CHCl_3$); IR (KBr) 1775, 1685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.29 (m, $J_{8a,8b}$ = 11.5 Hz, 1 H), 2.47 (m, $J_{8a,8b}$ = 11.5, $J_{1,8a}$ = $J_{5,8a}$ = 4.2, J = 0.8 Hz, 1 H), 2.92 (s, 3 H), 2.92–3.04 (m, 1 H), 3.76 (s, 3 H), 4.80–4.94 (m, 2 H), 5.74 (m, $J_{3,4}$ = 9.5, $J_{2,3}$ = 3.8, J = 1.8, J = 1.0 Hz, 1 H), 6.50 (m, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.5, J = 2.1, J = 0.6 Hz, 1 H).

22: colorless oil; MS, *m/e* 243 (M^+), 236, 235, 199; $[\alpha]^{20}_D$ +106° (*c* 1.18, $CHCl_3$); R_f 0.33 (AcOEt:hexane = 4:1); IR ($CHCl_3$) 3420, 1735, 1690, 1455 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.60–2.46 (m, 3 H), 2.63–2.90 (m, 1 H), 2.76 (s, 3 H), 3.67 (s, 3 H), 3.68 (s, 3 H), 4.33 (m, 1 H), 4.92 (m, 1 H), 5.46 (m, $J_{3,4}$ = 9.8, J = 2.0, J = 2.0 Hz, 1 H), 5.89 (m, $J_{3,4}$ = 9.8 Hz, 1 H).

Methyl (1*R*,2*S*,6*S*)-9-Methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]non-4-enecarboxylate (23). To a mixture of **22** (155 mg, 0.64 mmol) and Et_3N (312 mg, 3.08 mmol) in 1,2-dichloroethane (5 mL) was added methanesulfonic anhydride (167 mg, 0.96 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h and then at refluxing temperature for 1 h. The mixture was diluted with CH_2Cl_2, washed (H_2O, saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **23** (122 mg, 91%) as a white crystalline solid. **23**: mp 73.0–74.5 °C (AcOEt–hexane). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.18; N, 6.36. MS, *m/e* 211 (M^+), 196, 180, 179; $[\alpha]^{20}_D$ +49.2° (*c* 1.00, $CHCl_3$); R_f 0.23 (AcOEt:hexane = 1:1); IR (KBr) 1760, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (m, $J_{3a,3b}$ = 17.4, $J_{2,3a}$ = 7.3, $J_{3a,4}$ = 4.0, $J_{3a,5}$ = 1.6 Hz, 1 H), 2.41 (m, $J_{3a,3b}$ = 17.4, $J_{2,3b}$ = 4.9, $J_{3b,4}$ = 4.0 Hz, 1 H), 2.77 (m, $J_{1,2}$ = $J_{2,3a}$ = 7.3, $J_{2,3b}$ = 4.9 Hz, 1 H), 2.84 (s, 3 H), 3.75 (s, 3 H), 4.16 (t, $J_{1,2}$ = $J_{1,6}$ = 7.3 Hz, 1 H), 4.93 (m, $J_{1,6}$ = 7.3, $J_{5,6}$ = 3.3

Hz, 1 H), 5.87 (m, $J_{4,5}$ = 10.1, $J_{5,6}$ = 3.3, $J_{3a,5}$ = $J_{3b,5}$ = 1.6 Hz, 1 H), 6.06 (m, $J_{4,5}$ = 10.1, $J_{3a,4}$ = $J_{3b,4}$ = 4.0, $J_{4,6}$ = 1.0 Hz, 1 H).

Methyl (1*R*,2*R*,4*R*,5*R*,6*S*)-4,5-Epoxy-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonanecarboxylate (10). To a solution of **11** (211.2 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added *m*-chloroperbenzoic acid (ca. 80% purity, 212 mg, ca. 1.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 days. The mixture was diluted with CH_2Cl_2, washed (aqueous $Na_2S_2O_3$, saturated $NaHCO_3$, H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane/AcOEt) to give **10** (208 mg, 92%) as a white crystalline solid. **10**: mp 84.0–85.0 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.76; H, 5.81; N, 6.01. MS, *m/e* 227 (M^+), 219, 196, 183; $[\alpha]^{20}_D$ −1.38° (*c* 1.01, $CHCl_3$); R_f 0.44 (AcOEt:hexane = 2:1); IR (KBr) 1765, 1730, 1435 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.03 (ddd, $J_{3a,3b}$ = 15.2, $J_{2,3b}$ = 12.3, $J_{3b,4}$ = 1.3 Hz, 1 H), 2.49 (ddd, $J_{3a,3b}$ = 15.2, $J_{2,3a}$ = 4.0, $J_{3a,4}$ = 3.2 Hz, 1 H), 2.71 (s, 3 H), 2.91 (ddd, $J_{2,3b}$ = 12.3, $J_{2,3a}$ = 4.0, $J_{1,2}$ = 2.0 Hz, 1 H), 3.15 (m, $J_{4,5}$ = 3.7 Hz, 1 H), 3.37 (m, 1 H), 3.77 (s, 3 H), 4.28 (m, $J_{1,6}$ = 8.0, $J_{1,2}$ = 2.0 Hz, 1 H), 4.82 (m, $J_{1,6}$ = 8.0, $J_{5,6}$ = 1.0 Hz, 1 H).

Methyl (1*R*,2*R*,4*S*,5*R*,6*R*)-4-Azido-5-hydroxy-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonanecarboxylate (24). To a solution of **10** (795.3 mg, 3.50 mmol) in 1,2-dichloroethane (10 mL) was added trimethylsilyl azide (485 mg, 4.21 mmol) and $ZnCl_2$ (200 mg, 1.47 mmol) at room temperature, and the mixture was heated at refluxing temperature for 1.5 h and poured into saturated NaCl solution. The mixture was extracted with CH_2Cl_2, and the organic phase was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in MeOH (10 mL), and 1 drop of 6 N HCl was added to the above MeOH solution. The mixture was stirred at room temperature for 10 min and concentrated in vacuo to give **24** (941 mg, 99%) as a white crystalline solid. **24**: mp 127.0–128.0 °C (CH_2Cl_2–hexane); MS, *m/e* 270 (M^+), 227, 210; $[\alpha]^{20}_D$ −73.3° (*c* 1.00, $CHCl_3$); R_f 0.30 (AcOEt:hexane = 2:1); IR (KBr) 3360, 2100, 1740–1720 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.72 (ddd, $J_{3a,3b}$ = 14.0, $J_{2,3b}$ = 9.2, $J_{3b,4}$ = 5.0 Hz, 1 H), 2.17 (ddd, $J_{3a,3b}$ = 14.0, $J_{2,3a}$ = 6.0, $J_{3a,4}$ = 4.0 Hz, 1 H), 2.78 (s, 3 H), 3.03 (m, 1 H), 3.31–3.78 (m, $J_{4,5}$ = 9.0 Hz, 3 H), 3.80 (s, 3 H), 4.14 (dd, $J_{1,6}$ = 7.2, $J_{1,2}$ = 4.1 Hz), 4.52 (t, $J_{1,6}$ = $J_{5,6}$ = 7.2 Hz, 1 H).

Methyl (1*R*,2*R*,4*S*,5*R*,6*R*)-4-[(Benzyloxycarbonyl)amino]-5-hydroxy-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonanecarboxylate (25). A mixture of **24** (270 mg, 1.00 mmol) and a catalytic amount of 10% Pd/C in MeOH (10 mL), was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give the crude amine. To a solution of the crude amino in dioxane (8 mL) was added benzyl chloroformate (240 mg, 1.4 mmol) and 0.5 N $NaHCO_3$ (6 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h and poured into H_2O. The reaction mixture was extracted with AcOEt, and the extract was washed (H_2O, saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **25** (335 mg, 89%) as a white crystalline solid. **25**: mp 146.5–147.0 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.14; H, 5.86; N, 7.40. Found: C, 57.34; H, 5.93; N, 7.20. MS, *m/e* 378 (M^+), 346, 271, 239; $[\alpha]^{20}_D$ −24.8° (*c* 1.00, $CHCl_3$); R_f 0.30 (CH_3OH:CH_2Cl_2 = 1:20); IR (KBr) 3300, 1750–1670 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.61 (m, 1 H), 2.24 (m, 1 H), 2.63 (s, 3 H), 3.01 (m, 1 H), 3.40–3.68 (m, 3 H), 3.73 (s, 3 H), 4.22 (m, 1 H), 4.46 (m, 1 H), 4.90 (d, *J* = 12.2 Hz, 1 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.86 (br d, *J* = 7 Hz, 1 H, NH), 7.25 (s, 5 H).

Methyl (1*R*,2*R*,4*S*,5*R*,6*R*)-4-[(Benzyloxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonanecarboxylate (9). To a solution of **25** (1.58 g, 4.18 mmol) in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (1.35 g, 8.96 mmol) and imidazole (680 mg, 10.0 mmol) at room temperature, and the mixture was stirred at room temperature for 12 h and poured into H_2O. The reaction mixture was extracted with AcOEt, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/Et_2O) to give **9** (1.89 g, 92%) as a white crystalline solid. **9**: mp 131.0–132.0 °C (Et_2O). Anal. Calcd for $C_{24}H_{36}N_2O_7Si$: C, 58.51; H, 7.37; N, 5.69. Found: C, 58.54; H, 7.46; N, 5.58. MS, *m/e* 435 ($M^+ - C_4H_9$); $[\alpha]^{20}_D$ +2.22° (*c* 1.00, $CHCl_3$); R_f 0.40 (AcOEt:hexane = 1:1); IR (KBr) 3320, 1760–1685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.88 (s, 9 H), 1.54 (td, $J_{2,3b}$ = $J_{3a,3b}$ = 13.5, $J_{3b,4}$ = 10.5 Hz, 1 H), 2.40 (m, 1 H), 2.73 (s, 3 H), 3.02 (dt, $J_{2,3b}$ = 13.5, $J_{1,2}$ = $J_{2,3a}$ = 3.5 Hz, 1 H), 3.60–3.96 (m, 2 H), 3.75 (s, 3 H), 4.26 (ddd, $J_{1,6}$ = 7.5, $J_{1,2}$ = 3.5, $J_{1,3a}$ = 1.5 Hz, 1 H), 4.45 (m, $J_{1,6}$ = 7.5, $J_{5,6}$ = 4.5 Hz, 1 H), 4.86 (br d, $J_{4,NH}$ = 8 Hz, 1 H, NH), 5.08 (s, 2 H), 7.33 (s, 5 H).

(1*R*,2*R*,4*S*,5*R*,6*R*)-4-[(Benzyloxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonanecarboxylic Acid (26). A solution of methyl ester **9** (1.85 g, 3.76 mmol) in MeOH (30 mL) and 1 N NaOH (10 mL, 10 mmol) was stirred at room temperature for 12 h and was acidified with dilute HCl solution. The reaction mixture was extracted with AcOEt, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **26** (1.80 g, quantitative yield) as an amorphous solid. **26**: MS, *m/e* 421 ($M^+ - C_4H_9$), 377; $[\alpha]^{20}_D$ −10.3° (*c* 1.00, $CHCl_3$); R_f 0.45 (CH_2Cl_2:CH_3OH:AcOH = 200:10:1); IR ($CHCl_3$) 3440, 1750, 1720 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.12 (s, 3 H), 0.87 (s, 9 H), 1.70–2.40 (m, 2 H), 2.70–2.84 (m, 1 H), 2.82 (s, 3 H), 3.68–4.10 (m, 2 H), 4.12 (t, $J_{1,2}$ = $J_{1,6}$ = 6.0 Hz, 1 H), 4.39 (m, $J_{1,6}$ = 6.0, $J_{5,6}$ = 4.0 Hz, 1 H), 5.08 (s, 2 H), 5.20 (br s, 1 H, NH), 6.38 (br s, 1 H, CO_2H), 7.32 (s, 5 H).

(1*R*,4*S*,5*R*,6*R*)-4-[(Benzyloxycarbonyl)amino]-2-bromo-5-[(*tert*-butyldimethylsilyl)oxy]-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonane (28). To a mixture of 2-mercaptopyridine *N*-oxide sodium salt (1.19 g, 8.0 mmol) and (dimethylamino)-pyridine (244 mg, 2.0 mmol) in benzene (20 mL) was added phosgene dimer (890 mg, 4.5 mmol) at 0 °C, and the mixture was stirred at room temperature overnight. Bromotrichloromethane (5.0 mL, 51 mmol) and **26** (1.45 g, 3.03 mmol) in THF (30 mL) were added to the above mixture, and the mixture was heated under refluxing for 10 h. Insoluble material was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/Et_2O) to give **28** (1.11 g, 71%) as an amorphous solid. **28**: MS, *m/e* 458 ($M^+ + 2 - C_4H_9$), 456, 433; $[\alpha]^{20}_D$ −8.78° (*c* 1.10, $CHCl_3$); R_f 0.42 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 3420, 1760, 1720 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 2.18–2.38 (m, 2 H), 3.00 (s, 3 H), 3.75–4.02 (m, 3 H), 4.10–4.44 (m, 2 H), 5.07 (s, 2 H), 5.12 (br s, 1 H, NH), 7.32 (s, 5 H).

(1*R*,4*S*,5*R*,6*R*)-4-[(Benzyloxycarbonyl)amino]-2-bromo-5-[(*tert*-butyldimethylsilyl)oxy]-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]nonane (29). A mixture of **28** (340 mg, 0.66 mmol) and DBU (764 mg, 5.0 mmol) in toluene (25 mL) was heated at refluxing temperature for 12 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **29** (207 mg, 72%) as a white crystalline solid. **29**: mp 166.5–167.0 °C (Et_2O–hexane). Anal. Calcd for $C_{22}H_{32}N_2O_5Si$: C, 61.08; H, 7.46; N, 6.48. Found: C, 60.98; H, 7.47; N, 6.22; MS, *m/e* 375 ($M^+ - C_4H_9$); $[\alpha]^{20}_D$ +7.51° (*c* 1.00, $CHCl_3$); R_f 0.18 (AcOEt:hexane = 1:1); IR (KBr) 3300, 1745, 1685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.10 (s, 6 H), 0.15 (s, 3 H), 0.88 (s, 9 H), 2.87 (s, 3 H), 3.90 (t, $J_{4,5}$ = $J_{5,6}$ = 6.0 Hz, 1 H), 4.00–4.30 (m, 2 H), 4.44 (dd, $J_{1,6}$ = 7.5, $J_{5,6}$ = 6.0 Hz, 1 H), 4.90 (br d, $J_{4,NH}$ = 8 Hz, 1 H, NH), 5.02 (d, *J* = 12.0 Hz, 1 H), 5.14 (d, *J* = 12.0 Hz, 1 H), 5.68–5.98 (m, $J_{2,3}$ = 10.0 Hz, 2 H), 7.32 (s, 5 H).

(1*R*,4*S*,5*R*,6*R*)-4-(*N*-Benzyl-*N*-(benzyloxycarbonyl)amino)-5-[(*tert*-butyldimethylsilyl)oxy]-9-methyl-8-oxo-9-aza-7-oxabicyclo[4.3.0]non-2-ene (30). To a solution of **29** (70 mg, 0.16 mmol) in DMF (4 mL) was added NaH (ca. 60% dispersion in mineral oil, 15 mg, ca. 0.38 mmol) at 0 °C. After this was stirred for 40 min at 0 °C, benzyl bromide (432 mg, 2.53 mmol) was added, and the mixture was stirred at 0 °C for 1 h and poured into dilute HCl solution. The reaction mixture was extracted with ether, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/Et_2O) to give **30** (81 mg, 96%) as an amorphous solid. **30**: MS, *m/e* 465 ($M^+ - C_4H_9$); $[\alpha]^{20}_D$ +18.2° (*c* 1.00, $CHCl_3$); R_f 0.43 (AcOEt:hexane = 1:1); IR (KBr) 1750, 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.04, 0.16, 0.20 (each s, total 6 H), 0.92 (s, 9 H), 2.68, 2.81 (each s, total

3 H), 3.76–4.48 (m, 5 H), 4.74–5.28 (m, 3 H), 5.44–5.80 (m, 2 H), 7.27 (m, 10 H).

1-*N*-Benzyl-1-*N*-(benzyloxycarbonyl)-6-*O*-(*tert*-butyldimethylsilyl)-4,5-*N*,*O*-carbonyl-3-de-*O*-methylfortamine (31). To a solution of **30** (220 mg, 0.42 mmol) in *t*-BuOH (2 mL) and H_2O (0.5 mL) was added trimethylamine *N*-oxide dihydrate (94 mg, 0.85 mmol) and OsO_4 (0.04 M solution in *t*-BuOH, 0.2 mL, ca. 2 mol %), and the mixture was stirred at 50 °C for 3 days. Activated charcoal was added, and the mixture was stirred at room temperature for 1 h. Charcoal was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **31** (232 mg, 99%) as an amorphous solid. **31**: MS, *m/e* 499 ($M^+ - C_4H_9$); $[\alpha]^{20}_D$ +13.0° (*c* 1.00, $CHCl_3$); R_f 0.33 (CH_3OH:CH_2Cl_2 = 1:20); IR ($CHCl_3$) 3400, 1750, 1680 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 0.91 (s, 9 H), 2.04 (br s, 2 H, OH), 2.88 (s, 3 H), 3.16–4.60 (m, 8 H), 5.14 (s, 2 H), 7.30–7.36 (m, 10 H).

1-*N*-Benzyl-6-*O*-(*tert*-butyldimethylsilyl)-1,2:4,5-di-*N*,*O*-carbonylfortamine (33). To a solution of **31** (70 mg, 0.13 mmol) in DMF (2 mL) was added NaH (ca. 60% dispersion in mineral oil, 12 mg, ca. 0.3 mmol) at 0 °C. After this was stirred at 0 °C for 30 min, methyl iodide (0.1 mL, ca. 0.23 g, ca. 1.6 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched by adding acetic acid and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **33** (55 mg, 95%) as an amorphous solid. **33**: MS, *m/e* 462 (M^+), 405; $[\alpha]^{20}_D$ −61.2° (*c* 1.00, $CHCl_3$); R_f 0.28 (AcOEt:hexane = 1:1); IR ($CHCl_3$) 1755 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.24 (s, 3 H), 0.92 (s, 9 H), 2.87 (s, 3 H), 3.44 (s, 3 H), 3.70–4.14 (m, 5 H), 4.39 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 6.0 Hz, 1 H), 4.43 (d, J = 14.0 Hz, 1 H), 4.74 (d, J =14.0 Hz, 1 H), 7.25–7.38 (m, 5 H).

1-*N*-Benzyl-1,2:4,5-di-*N*,*O*-carbonylfortamine (34). A mixture of **33** (276 mg, 0.60 mmol) and *n*-Bu_4NF (1.0 M solution in THF, 0.6 mL, 0.6 mmol) in THF (20 mL) was stirred at room temperature for 1 day and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **34** (207 mg, quantitative yield) as an amorphous solid. **34**: MS, *m/e* 348 (M^+), 330, 256; $[\alpha]^{20}_D$ −70.0° (*c* 1.00, CH_3OH); R_f 0.32 (CH_3OH:CH_2Cl_2 = 1:25); IR ($CHCl_3$) 3360, 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 3 H), 3.51 (s, 3 H), 3.75 (dd, $J_{1,2}$ = 11.0, $J_{1,6}$ = 10.7 Hz, 1 H), 3.81 (dd, $J_{1,6}$ = 10.7, $J_{5,6}$ = 6.1 Hz, 1 H), 3.85 (dd, $J_{4,5}$ = 7.6, $J_{3,4}$ = 1.8 Hz, 1 H), 4.00–4.04 (m, $J_{2,3}$ = 2.1 Hz, 2 H), 4.40 (dd, $J_{4,5}$ = 7.6, $J_{5,6}$ = 6.1 Hz, 1 H), 4.48 (d, J = 15.0 Hz, 1 H), 4.69 (d, J = 15.0 Hz, 1 H), 7.27–7.40 (m, 5 H).

Fortamine Dihydrochloride (1·2HCl). A solution of **34** (97 mg, 0.28 mmol) in 6 N HCl was heated at refluxing temperature for 1 day and concentrated in vacuo. The resdue was dissolved in MeOH (10 mL), and Pd black (20 mg) was added to the mixture. The mixture was stirred under a hydrogen atmosphere at room temperature for 2 days. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was passed through a column of IR-120B (H^+) resin (eluted with H_2O, then aqueous NH_3). The eluent was concentrated in vacuo, and the residue was treated with 1 N HCl solution. The solution was concentrated in vacuo to give fortamine dihydrochloride (1·2HCl, 76 mg, 98%) as an amorphous solid. 1·2HCl: $[\alpha]^{20}_D$ +4.1° (*c* 0.80, H_2O); R_f 0.27 (*n*-BuOH:pyridine:H_2O:AcOH = 6:4:3:1); ^1H NMR (100 MHz, D_2O, DSS as internal standard) δ 2.86 (s, 3 H), 3.52 (s, 3 H), 3.53 (t, $J_{1,6}$ = $J_{1,2}$ = 8.0 Hz, 1 H), 3.74 (dd, $J_{3,4}$ = 6.0, $J_{4,5}$ = 4.5 Hz, 1 H), 3.87 (t, $J_{1,6}$ = $J_{5,6}$ = 8.0 Hz, 1 H), 4.01 (dd, $J_{3,4}$ = 6.0, $J_{2,3}$ = 3.0 Hz, 1 H), 4.21 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1 H), 4.22 (dd, $J_{1,2}$ = 8.0, $J_{2,3}$ = 3.0 Hz, 1 H).

1,4-Bis-*N*-(benzyloxycarbonyl)fortamine (35) from Fortimicin A. A mixture of fortimicin A disulfate (18.05 g, 30.0 mmol) and $Ba(OH)_2·8H_2O$ (37.86 g, 120 mmol) in H_2O was heated at refluxing temperature for 1 day. The insoluble material was filtered off, CO_2 gas was passed into the filtrate, and the precipitate was filtered off again. The filtrate was concentrated in vacuo, and the residue was passed through the column of AG2-X8 (OH^-) resin (eluted with H_2O). The eluent was concentrated in vacuo, and the residue was dissolved in 6 N HCl solution (100 mL). The mixture was heated at refluxing temperature for 10 h and concentrated in vacuo, and the residue was dissolved in H_2O (150 mL) and dioxane (150 mL). To the solution was added $NaHCO_3$ (21.0 g, 250 mmol) and benzyl chloroformate (22.7 g, 133 mmol), and the mixture was stirred at room temperature for 3 days and poured into H_2O. The reaction mixture was extracted with AcOEt, and the extract was washed (H_2O, saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5:1–1:1 hexane/AcOEt) to give **35** (10.73 g, 75%) and 2,6-bis(*N*-benzyloxycarbonyl)-6-*epi*-purpurosamine B (5.20 g, 41%). **35**: mp 166.0–166.5 °C (Et_2O). Anal. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.93; H, 6.39; N, 5.93. MS, *m/e* 474 (M^+), 382; $[\alpha]^{20}_D$ +52.1° (*c* 1.00, CH_3OH); R_f 0.54 (AcOEt); IR (KBr) 3360–3200, 1660 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.05 (s, 3 H), 3.28 (s, 3 H), 3.42–4.40 (m, 9 H), 5.08 (s, 2 H), 5.09 (d, J = 12.0 Hz, 1 H), 5.22 (d, J =12.0 Hz, 1 H), 6.45 (br d, J = 8 Hz, 1 H, NH), 7.34 (s, 10 H).

1,4-Bis-*N*-(benzyloxycarbonyl)-5,6-*O*-cyclohexylidenefortamine (36). A mixture of **35** (132 mg, 0.28 mmol), 1,1-dimethoxycyclohexane (1 mL), and *p*-TsOH (catalytic amount) in DMF (10 mL) was heated at 50 °C under 30 mmHg for 4 h. Et_3N was added, and the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **36** (92 mg, 60%) as an amorphous solid. **36**: MS, *m/e* 554 (M^+); $[\alpha]^{20}_D$ +24.5° (*c* 1.02, CH_3OH); R_f 0.45 (AcOEt:benzene = 1:1); IR ($CHCl_3$) 1765, 1685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.72–2.44 (m, 10 H), 3.07 (s, 3 H), 3.38 (s, 3 H), 3.48–4.22 (m, 5 H), 4.54 (dd, $J_{3,4}$ = 6.0, $J_{4,5}$ = 3.8 Hz, 1 H), 5.09 (s, 2 H), 5.12 (s, 2 H), 5.34 (d, $J_{1,NH}$ = 7.2 Hz, 1 H, NH), 7.36 (s, 5 H), 7.38 (s, 5 H).

4-*N*-(Benzyloxycarbonyl)-1,2-*N*,*O*-carbonyl-5,6-*O*-cyclohexylidenefortamine (37). To a solution of **36** (153 mg, 0.28 mmol) in DMF (8 mL) was added NaH (ca. 60% dispersion in mineral oil, 80 mg, ca. 2.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 h and poured into H_2O. The reaction mixture was extracted with $CHCl_3$, and the extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/Et_2O) to give **37** (123 mg, quantitative yield) as an amorphous solid. **37**: mp 79–88 °C ($CHCl_3$–petroleum ether). Anal. Calcd for $C_{23}H_{30}N_2O_7$: C, 61.87; H, 6.77; N, 6.27. Found: C, 61.59; H, 7.05; N, 6.00. MS, *m/e* 446 (M^+), 402, 348; $[\alpha]^{20}_D$ −8.48° (*c* 1.00, CH_3OH); R_f 0.44 (AcOEt:hexane = 1:1); IR (KBr) 3250, 1760, 1680 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.78–2.46 (m, 10 H), 3.14 (s, 3 H), 3.43 (s, 3 H), 3.75–4.16 (m, 5 H), 4.74 (dd, $J_{1,2}$ = 5.5, $J_{2,3}$ = 2.5 Hz, 1 H), 5.10 (d, J = 12.0 Hz, 1 H), 5.20 (d, J = 12.0 Hz, 1 H), 5.70 (s, 1 H, NH), 7.36 (s, 5 H).

1-*N*-Benzyl-4-*N*-(benzyloxycarbonyl)-1,2-*N*,*O*-carbonyl-5,6-cyclohexylidenefortamine (38). To a solution of **37** (189 mg, 0.42 mmol) in DMF (10 mL) was added NaH (ca. 60% dispersion in mineral oil, 25 mg, ca. 0.63 mmol). After this was stirred at 40 °C for 20 min, benzyl bromide (432 mg, 2.5 mmol) was added, and the mixture was stirred at 40 °C for 2 h and poured into H_2O. The reaction mixture was extracted with Et_2O, and the extract was washed (H_2O, saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/Et_2O) to give **38** (184 mg, 81%) as am amorphous solid. **38**: MS, *m/e* 536 (M^+), 492; $[\alpha]^{20}_D$ −20.7° (*c* 1.05, $CHCl_3$); R_f 0.20 (Et_2O:hexane = 1:1); IR ($CHCl_3$) 1755, 1685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.80–1.80 (m, 10 H), 3.10 (s, 3 H), 3.36 (s, 3 H), 3.40–4.06 (m, 5 H) 4.38 (d, J = 15.0 Hz, 1 H), 4.58 (d, J = 15.0 Hz, 1 H), 4.67 (dd, $J_{3,4}$ = 5.2, $J_{4,5}$ = 2.5 Hz, 1 H), 5.06 (d, J = 12.0 Hz, 1 H), 5.22 (d, J = 12.0 Hz, 1 H), 7.22–7.52 (m, 10 H).

1-*N*-Benzyl-1,2:4,5-di-*N*,*O*-carbonylfortamine (34) from 38. To a solution of **38** (130 mg, 0.24 mmol) in MeOH (3 mL) was added 50% aqueous AcOH (12 mL), and the mixture was heated at 60 °C for 4 h. The mixture was concentrated in vacuo, and the residue was dissolved in DMF (5 mL). To the solution was added NaH (ca. 60% dispersion in mineral oil, 19 mg, ca. 0.48 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 h. AcOH was added, and the mixture was concentrated in vacuo. MeOH was added to the residue, and insoluble material was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give **34** (58 mg, 69%) as an amorphous solid. **34**: MS, *m/e* 348 (M^+), 330, 256; $[\alpha]^{20}_D$ −69.6° (*c* 1.00, CH_3OH); IR ($CHCl_3$) 3360, 1755 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.84 (s, 3 H), 3.50 (s, 3 H), 3.68–4.07 (m, 5 H), 4.38 (dd, $J_{4,5}$ = 7.5, $J_{5,6}$ = 6.0 Hz, 1

H), 4.49 (d, J = 15.0 Hz, 1 H), 4.67 (d, J = 15.0 Hz, 1 H), 7.26–7.40 (m, 5 H).

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Registry No. 1·2HCl, 72351-21-4; **6**, 91259-93-7; **7**, 91280-46-5; **9**, 124287-83-8; **10**, 111535-89-8; **11**, 111515-79-8; **12**, 111515-76-5; (1*S*,5*R*)-**12**, 124375-96-8; **13**, 124287-84-9; (1*S*)-**13**, 124375-93-5; **14**, 124287-85-0; (1*S*,4*R*,5*R*)-**14**, 124375-94-6; **15**, 111515-77-6; (1*S*,5*R*)-**15**, 124375-95-7; **16**, 111515-78-7; **19**, 124287-86-1; **20**, 111515-87-8; **21**, 111515-88-9; **22**, 111515-89-0; **23**, 111515-90-3; **24**, 111515-80-1; **25**, 111515-81-2; **25** amine, 124287-89-4; **26**, 111515-82-3; **28**, 124287-87-2; **29**, 111515-83-4; **30**, 111515-84-5; **31**, 124287-88-3; **33**, 111515-85-6; **34**, 111515-86-7; **35**, 72351-18-9; **36**, 74615-83-1; **37**, 74615-84-2; **38**, 124375-92-4; fortimicin A disulfate, 72275-67-3.

Supplementary Material Available: ^{1}H NMR spectra of compounds **11**, **12**, **16**, **19**, **20**, **21**, **24**, **26**, **28**, **30**, **31**, **33**, **34**, **36**, and **38** (15 pages). Ordering information is given on any current masthead page.

Synthesis of Hydroxyquinones and Related Compounds: Semisquaric Acids, (±)-Terreic Acid, (±)-Perezone, and (±)-Isoperezone

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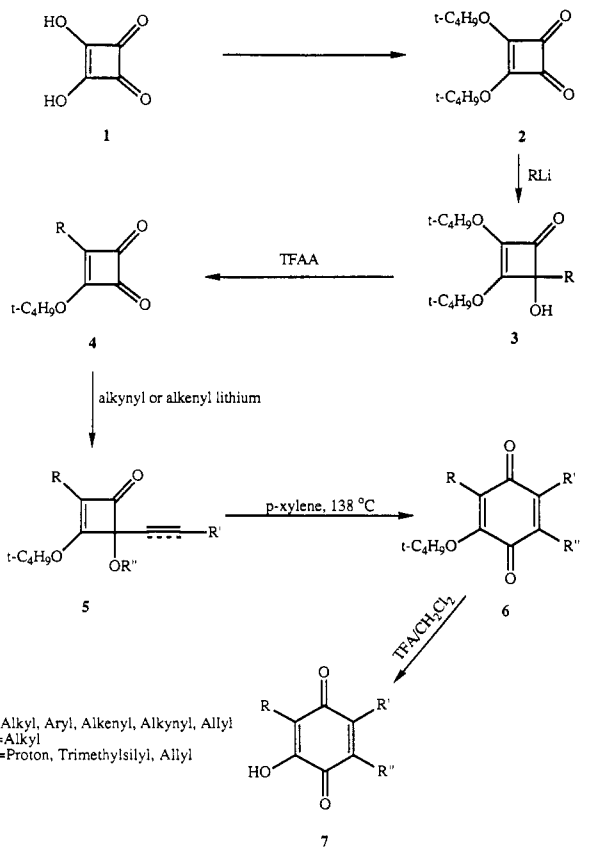
tert-Butoxyquinones were prepared from the thermal ring expansion of 4-alkynyl-, 4-alkenyl-, and 4-aryl-*tert*-butoxycyclobutenones and shown to be readily converted to hydroxyquinones upon treatment with trifluoroacetic acid at low temperature. This is a useful transformation since no reliable general route to hydroxyquinones has previously been available. The synthetic scope of this methodology as well as its specific utilization in the synthesis of a semisquaric acid, and the natural products, (±)-terreic acid, (±)-perezone, and (±)-isoperezone, are described.

Introduction

Although hydroxyquinones are among the most abundant of the naturally occurring quinones, no methodology has previously been confirmed to be generally applicable for their synthesis.[1] Indeed, in view of the ubiquity of these compounds, it is surprising that so few examples have been synthesized in the laboratory. A viable solution to this problem is now presented. Specifically, 2,3-di-*tert*-butoxycyclobutenedione **2**,[2] in conjunction with the recently reported ring expansions of 4-alkynyl-, 4-alkenyl-, and 4-arylcyclobutenones to quinones and related compounds, is reported here to be a useful synthon for hydroxyquinones. In this regard, cyclobutenedione **2**, readily available from squaric acid **1**, was converted to a variety of hydroxyquinones **7** as outlined in Scheme I. This was accomplished by its initial treatment with an organolithium reagent (alkyl, aryl, alkenyl, or alkynyl) to give the cyclobutenones **3**, which are readily hydrolyzed to the cyclobutenediones **4** upon treatment with trifluoroacetic anhydride (TFAA).[3] These were then converted to the cyclobutenones **5** by the regiospecific addition of an alkynyl-, alkenyl-, or aryllithium reagent to the more electrophilic (nonvinylogous ester) carbonyl group. Thermolysis of **5** gave the *tert*-butoxyquinones **6**, members of a rare class of quinones.[4-6] These were then converted to the hydroxyquinones **7** upon treatment with trifluoroacetic acid at 0 °C.[7]

Scheme I



(1) An outstanding source listing for the structures of naturally occurring quinones is Thompson, R. H. *Naturally Occurring Quinones*; Chapman and Hall: London, 1987; Vols. I, II, III.

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