bromide (LiBr, THF; >95%). A number of potential macrocyclizations based on known homoallylic alcohol preparations[9] were examined. While cyclizations using related allylsilanes and stannanes with Lewis acids or using relatively reactive allyl organometallics failed, the threo-selective Hiyama/Heathcock[10] reaction using $CrCl_2$ (5 equiv, THF) was effective at cyclizing **2** (4 mM concentration, 25 °C, 6 h) and gave a 4:1 mixture of the desired isomer **8** and its diastereomer **9** in 64% combined yield. The product appeared as a single spot on TLC but was readily separated on a 50-mg scale by MPLC. The 4:1 mixture was formed only from **7** since the same distribution was obtained on cyclizing either pure **7** or the mixture of olefinic isomers produced by the deselenation described above. Deprotection of **8** (Na/NH_3, −78 °C, <1 min; 51%) gave racemic asperdiol (**1**). An authentic sample of **1** was not available, and the assignment was made by comparison with published spectral data including ^1H and ^{13}C NMR. The identity of the minor product **9** as the other threo diastereomer was shown by separate epoxide deoxygenations of the acetates of **8** and **9** (3-methyl-2-(selenoxo)-benzothiazole, CH_2Cl_2, 25 °C, 5 h; 35–50%)[11] to yield a single deoxy derivative.

To analyze the remote stereoselection of the cyclization, we adopted a simplified molecular mechanics model of the cyclization transition state based on the premises that threo selection is an inherent property of the Cr(II) reaction[10b] and that stereoselection for a particular threo diastereomer depends on the relative strain of the conformations of the ring being formed. The model was constructed by starting with a gauche C2–C1–C14–C13 dihedral array (the putative threo-transition-state geometry) and generating (30° dihedral angle resolution) and energy minimizing all ring conformations of **8** and **9**. Depending on the particular C1,C14 substitution and length of the forming C1–C14 bond, two to five conformations each of **8** and **9** were found within 1 kcal of the ground-state structure. Our simple model thus shows no great preference for either **8** or **9**, and the observed 4:1 product distribution may well reflect transition-state contributions from several macrocycle conformations. Interestingly, the epoxide oxygen is calculated to prefer the less-hindered faces of the various conformations of **8** and **9** by an average of 5 kcal/mol.

In conclusion, diastereoselective macrocyclization provides an efficient approach to stereochemically complex macrocycles since it simultaneously creates a large ring and new asymmetric centers. As demonstrated, the chemical yields of such processes can be quite acceptable. Although complete stereocontrol by our remote epoxide was not found, a substantial and synthetically useful remote bias was observed.[12]

Supplementary Material Available: Complete experimental and spectral data of compounds **1–9** (9 pages). Ordering information is given on any current masthead page.

(9) Reviews: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357.

(10) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. For a related seven-membered cyclization, see: Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565.

(11) Calo, V.; Lopez, L.; Mincuzzi, A.; Pesce, G. *Synthesis* **1976**, 200.

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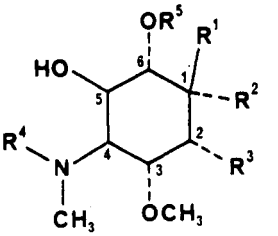
Total Synthesis of (±)-Fortamine and (±)-2-Deoxyfortamine

Summary: The efficient conversion of 1,3-cyclohexadiene (**7**) to the aminocyclitols (±)-fortamine (**4**, 13 steps, 30% overall yield) and (±)-2-deoxyfortamine (**5**, 10 steps, 54% overall yield) features four regiospecific epoxide-opening reactions.

Sir: In 1977 researchers at Kyowa Hakko Kogyo Co. and Abbott Laboratories reported[1] the discovery of a new group of broad spectrum antibiotics of the aminocyclitol class,[2] the fortimicins, which feature a 1,4-diaminocyclitol bearing a diamino sugar on the C-6 oxygen and an aminoacyl group on the C-4 nitrogen. Three important and representative fortimicins are fortimicin A (**1**),[1c] istamycin A (**2**),[3] and sporaricin A (**3**),[4] which differ in stereochemistry at C-1 and in substitution at C-2 and in the diamino sugar. The



1, $R^1 = NH_2$; $R^2 = H$; $R^3 = OH$; $R^4 = H_2NCH_2CO$, R^5 = 6-epipurpurosamine B
2, $R^1 = NH_2$; $R^2 = R^3 = H$; $R^4 = H_2NCH_2CO$, R^5 = purpurosamine C
3, $R^1 = R^3 = H$; $R^2 = NH_2$; $R^4 = H_2NCH_2CO$, R^5 = 6-epipurpurosamine B
4, $R^1 = NH_2$; $R^2 = R^4 = R^5 = H$; $R^3 = OH$
5, $R^1 = NH_2$; $R^2 = R^3 = R^4 = R^5 = H$
6, $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = NH_2$

respective aminocyclitols are fortamine (**4**), 2-deoxyfortamine (**5**), and sporamine (**6**, 2-deoxy-1-epi-**4**).[5] While previous fortimicin synthetic work has concentrated on modification of the natural antibiotics and the use of aminoglycosides and cyclitols as starting materials[6-11] we have embarked on a program of synthesis of aminocyclitol an-

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(2) Rinehart, K. L.; Suami, T. "Aminocyclitol Antibiotics"; American Chemical Society: Washington, DC, 1980.

(3) Okami, Y.; Hotta, K.; Yoshida, M.; Ikeda, D.; Kondo, S.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 964.

(4) Deushi, T.; Nakayama, M.; Watanabe, I.; Mori, T.; Naganawa, H.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 187.

(5) There are a variety of additional antibiotics containing **4**, **5**, and **6**. For some examples, see ref 2, pp 295–320, and: (a) (dactimicin) Shomura, T.; Kojima, M.; Yoshida, J.; Ito, M.; Amano, S.; Totsugawa, K.; Niwa, T.; Inouye, S.; Ito, T.; Niida, T. *J. Antibiot.* **1980**, *33*, 924. (b) (sporaricin C and D) Deushi, T.; Watanabe, I.; Iwasaki, A.; Kamiya, K.; Mizoguchi, T.; Nakayama, M.; Okuchi, M.; Itoh, H.; Mori, T. *Ibid.* **1982**, *34*, 811.

(6) Synthesis of fortimicin B from *myo*-inositol: Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1156.

(7) Synthesis of fortimicin A from fortimicin B: Tadanier, J.; Martin, J. R.; Kurath, P.; Goldstein, A. W.; Johnson, P. *Carbohydr. Res.* **1980**, *79*, 91.

(8) Synthesis of 6-epipurpurosamine derivatives from glucosamine: Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2825.

(9) Synthesis of istamycin A from 3′,4′-dideoxyneamine: Ikeda, D.; Miyasaka, T.; Yoshida, M.; Horiuchi, Y.; Kondo, S.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1365.

(10) Synthesis of dactimicin from fortimicin B: Atsumi, K.; Akita, E.; Niida, T. *J. Antibiot.* **1982**, *35*, 90.

(11) Synthesis of sporaricin A from fortimicin A: Carney, R. E.; McAlpine, J. B. *Curr. Chemother. Infect. Dis., Proc. Int. Congr. Chemother., 11th, 1979*, **1980**, *1*, 397.

0022-3263/83/1948-4786$01.50/0

tibiotics from noncarbohydrate precursors.[12] We report the synthesis of racemic **4** and **5** from 1,3-cyclohexadiene (**7**).

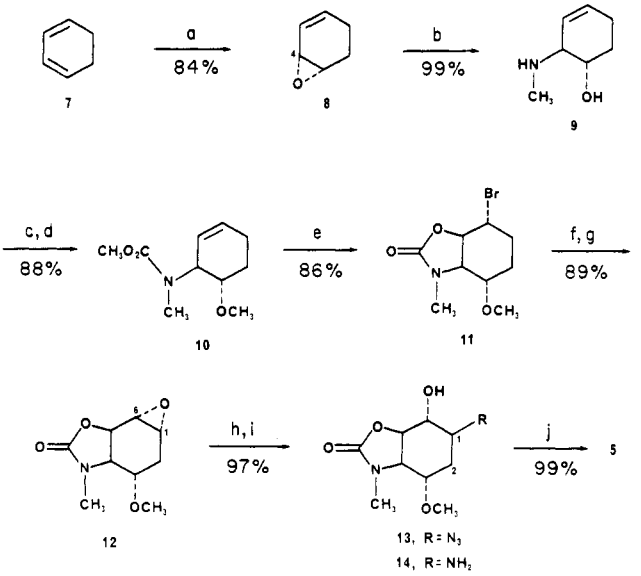
Monoepoxidation of **7** (Scheme I) using a modification of the literature procedure[13] gave reproduceably high distilled yields of epoxide **8**, which reacted with methylamine exclusively at C-4 (fortimicin numbering) to give the amino alcohol **9**. N-Acylation and O-methylation led to **10**, which was bromocyclized to **11** to establish the protected *cis*-4,5-methylamino alcohol.[12a] E2 elimination with DBU gave the C-6 alkene, and its reaction with CF_3CO_3H[14] gave a mixture of epoxides in which the exo–endo ratio varied between 9:1 and 23:1. The major product **12** was purified and subjected to methanolic sodium azide, resulting in a single azido alcohol, **13**.[15] Catalytic hydrogenation gave the amine **14**, which was converted to 2-deoxyfortamine (**5**) by acidic hydrolysis followed by neutralization or by direct basic hydrolysis using aqueous NaOH.[16]

The synthesis of fortamine (**4**, Scheme II) began with the epoxy carbamate **12**. Conversion of **12** to the allylic alcohol **15** was accomplished by the dependable selenophenolate addition/selenoxide elimination process.[17] Epoxidation of **15** was expected to give **16** as the result of exo attack and hydroxyl assistance.[18] Although the reaction proceeded in only 62% yield, only one epoxide was detected by TLC. Compound **16** was readily converted to a single, crystalline, azido diol (**17**) upon sodium azide treatment. Reduction to **18**[19] was followed by acidic hydrolysis, giving fortamine (**4**) as its dihydrochloride, and after neutralization as the free base.[20]

The regiospecificity of epoxide opening for **12** and **16** may be rationalized by assuming reactive conformations **19** and **20**, respectively. Each is a half-chair with pseudoequatoral methoxy and methylamino groups. The position of trans-diaxial ring opening[21] by NaN_3 or NaSePh is C-1 for both **19** and **20**. In contrast, the protected fortimicin 1,2-epoxide **21** was reported to undergo epoxide ring opening with NaN_3 at both C-1 and C-2 to give a 1:1.5 ratio of the respective azido alcohols.[22] It was reasonable to expect that the free hydroxyl of **20** would assume the pseudoaxial position more readily than the glycosylated oxygen at C-6 of **21** and hence give more product from attack at C-1.

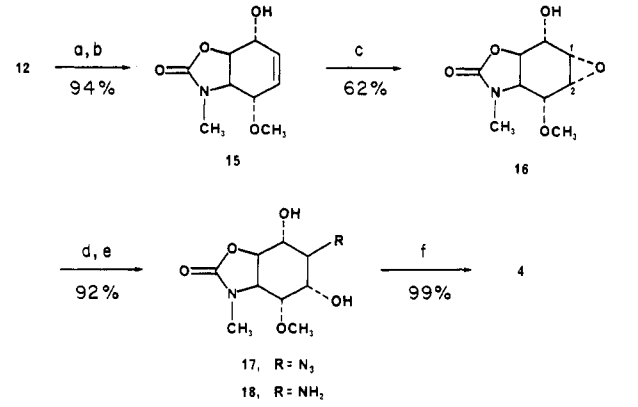
Because of the efficiency of the transformations in Schemes I and II, synthetic aminocyclitols **4** and **5** and the potential glycosylation substrates **13**, **15**, and **16** are now

Scheme I. Synthesis of 2-Deoxyfortamine

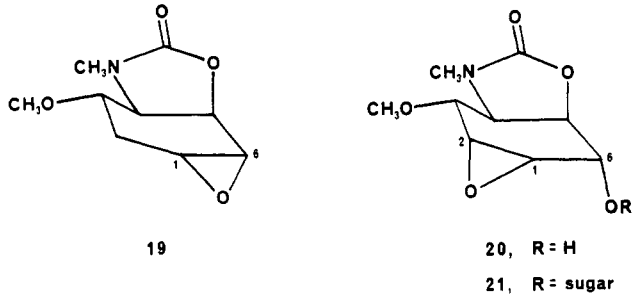


[a] CH_3CO_3H, Na_2CO_3. [b] CH_3NH_2, methanol, 70 °C. [c] $ClCO_2CH_3$, methanol, Na_2CO_3. [d] CH_3I, NaH, THF. [e] $BrClO_4$·2collidine, CH_2Cl_2, −78 °C; aqueous Na_2CO_3. [f] DBU, toluene, 85 °C. [g] $(CF_3CO)_2O$, 90% H_2O_2, CH_2Cl_2, 0 °C. [h] NaN_3, methanol, NH_4Cl, 65 °C. [i] H_2, Pd-C, methanol. [j] 4 N HCl, 100 °C; NaOH.

Scheme II. Synthesis of Fortamine



[a] PhSeNa, ethanol. [b] *m*-CPBA; *i*-Pr_2NH. [c] $(CF_3CO)_2O$, 90% H_2O_2, CH_2Cl_2, 0 °C. [d] NaN_3, methanol, NH_4Cl, 65 °C. [e] H_2, Pd-C, methanol. [f] 4 N HCl, 100 °C; NaOH.



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(13) A mixture of 5 g of **7**, 60 g of Na_2CO_3, and 100 mL of CH_2Cl_2 was treated dropwise with a mixture of 12 g of 40% aqueous CH_3CO_3H and 15 mL of CH_2Cl_2. The addition, which took 1 h, was controlled by monitoring gas evolution through a bubbler. Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423.

(14) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 89.

(15) The structures of both **12** and **13** are supported by their decoupled ^1H NMR spectra. For **12**, J[CH(5)–CH(6)] = 1 Hz. For **13**, J[CH-(1)–CH(2β)] = 9 Hz.

(16) The ^{13}C and ^1H NMR spectra of synthetic **5** matched the published spectra. Watanabe, I.; Deushi, T.; Yamaguchi, T.; Kamiya, K.; Nakayama, M.; Mori, T. *J. Antibiot.* **1979**, *32*, 1066.

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(19) The TLC characteristics and ^1H NMR spectrum of synthetic **18** matched those of **18** prepared from natural fortimicin B as follows: (1) $PhCH_2OCOCl$; (2) aqueous HCl, reflux; (3) NaH, THF; (4) H_2, Pd–C. Sano, H.; Sakaguchi, T.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2727.

(20) Synthetic **4**·2HCl had ^{13}C and ^1H NMR spectra matching those of authentic **4**·2HCl prepared from natural fortimicin B.

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(22) Martin, J. R.; Johnson, P.; Tadanier, J.; Cirovic, M.; Stanascek, R. S. *J. Antibiot.* **1982**, *35*, 46.

available in gram quantities. The synthesis and linking of the diamo sugar component and the optical resolution of **9** are subjects of current investigation.

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Supplementary Material Available: Complete experimental procedures, spectroscopic data, and melting points for compounds **9**–**17** (3 pages). Ordering information is given on any current masthead page.

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