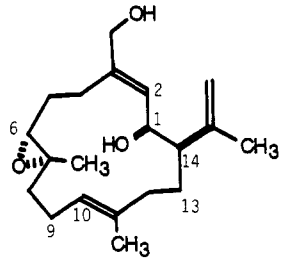
Synthesis of Asperdiol

Summary: A diastereoselective macrocyclization of an aldehydoallylic bromide using Cr(II) is described which allows a convenient synthesis of the 14-membered cembranoid asperdiol.

Sir: Asperdiol is a cembranoid antitumor agent that was isolated from a gorgonian and identified as **1** by Weinheimer and van der Helm in 1977.[1] Its structure poses



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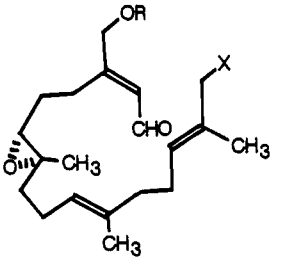

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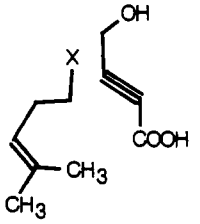
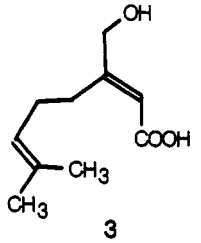
an interesting problem for the developing methodology of remote asymmetric induction and suggested to us an attractive approach based on a diastereoselective macrocyclization. The key step of this approach is a threo-selective cyclization that is directed by a conformational bias originating from the remote epoxide function in **2**. In this paper, we describe a simple preparation of **2** and its diastereoselective conversion to asperdiol.[2]

Preparation of the two segments necessary for assembly of **2** started from hydroxytetrolic acid and geraniol. Pure *E* hydroxy acid **3** was prepared by adding excess iso-





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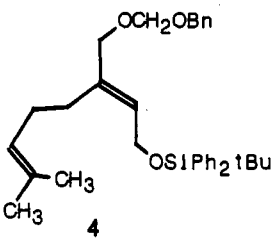

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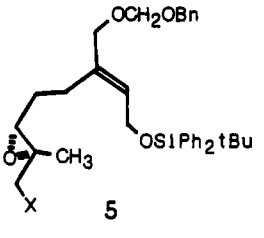

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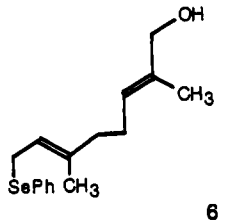
hexenylmagnesium bromide to hydroxytetrolic acid in the presence of Li_2CuCl_4 (THF, −78° → 25°; 75%). This reaction is related to previous additions of organocopper reagents to acetylenic acids and alcohols,[3] but its high stereoselectivity may simply reflect a fortuitous loss of the *Z* isomer as the butenolide.[4] Conversion to the bis-[(benzyloxy)methyl] derivative ($BnOCH_2Cl$, *i*-Pr_2NEt) and reduction ($LiAlH_4$, Et_2O) gave an alcohol, that which was protected (*t*-$BuPh_2SiCl$, imidazole, DMF) to give **4** (60% overall). Allylic oxidation (catalytic SeO_2, *t*-BuOOH) and epoxidation ($VO(acac)_2$, *t*-BuOOH)[5] gave an epoxy alcohol,[6] which was mesylated (MsCl, Et_3N) and displaced with LiBr/acetone to provide the first segment (**5**, X = Br; 60% overall). The second segment, **6**, was prepared from geranyl acetate by allylic oxidation as above and direct phenylselenation (PhSeSePh, $NaBH_4$, EtOH; 64%).[7]



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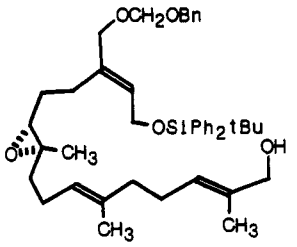
Alkylation of the dianion of **6** (2 equiv of $LiNiPr_2$, THF, −55 °C) with bromide **5** at low temperature (−70 °C, 5 min) gave the coupled product in 82% yield. The phenylseleno group was then removed with W-2 Raney nickel in acetone (>95%); however, substantial positional isomerization of the associated C10–C11 olefin occurred during the reduction (ratio of trisubstituted:disubstituted olefin 2:1). Other reductants (Bu_3SnH, Na[Hg]) gave similar results as did other methods[8] using phenylthio or phenyl sulfone analogues. Although pure **7** could be isolated on a gram scale by using $AgNO_3$-impregnated gel, the mixture of olefins served as well for the preparation of **1**.



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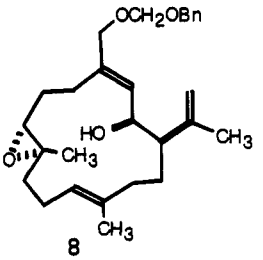

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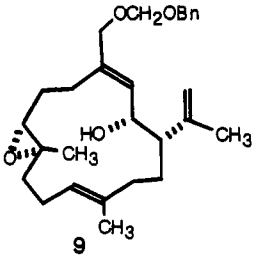

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Final refunctionalization of **2** (X = Br, R = CH_2OCH_2Ph) in preparation for macrocyclization consisted of conversion to the allylic chloride ($(Me_2N)_3P$, CCl_4, THF; 87%), desilylation (1 M Bu_4NF, THF; 94%), oxidation (MnO_2, CH_2Cl_2; 75%), and conversion to the

(1) Weinheimer, A. J.; Mateson, J. A.; van der Helm, D.; Poling, M. *Tetrahedron Lett.* **1977**, 1295. Martin, G. E.; Matson, J. A.; Weinheimer, A. J. *Ibid.* **1979**, 2195.

(2) Previous synthesis: Aoki, M.; Tooyama, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1983**, *24*, 2267.

(3) Jousseaume, B.; Duboudin, J.-G. *J. Organomet. Chem.* **1975**, *91*, C1. Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, 2583. Klein, J.; Turkel, R. M. *J. Am. Chem. Soc.* **1969**, *91*, 6186.

(4) In the case of the analogous methylmagnesium bromide addition, the crude product consisted of a 2:3 ratio of hydroxy acid to methylbutenolide.

(5) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(6) Since this approach derives all stereochemistry from that of the epoxide, chiral epoxidation (Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974) could be used to produce enantiomerically pure asperdiol.

(7) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9.

(8) [$(Ph_3P)_4Pd$, $NaBH_4$]: Kotake, H.; Yamamoto, T.; Kinoshita, H. *Chem. Lett.* **1982**, 1331. [Na, *t*-BuOH]: Kodama, M.; Takahashi, T.; Kojima, T.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 3397. [Bu_3SnH]: Corey, E. J.; Pearce, H. L.; Szekely, I.; Ishiguro, M. *Ibid.* **1978**, 1023. [Li/$EtNH_2$]: Grieco, P. A.; Masaki, Y. *J. Org. Chem.* **1974**, *39*, 2135. Kodama, M.; Matsuki, Y.; Ito, S. *Tetrahedron Lett.* **1976**, 1121. [Raney Ni]: Sevrin, M.; van Ende, D.; Krief, A. *Ibid.* **1976**, 2643. [Na/Hg]: Dabby, R. E.; Kenyon, J.; Mason, R. F. *J. Chem. Soc.* **1952**, 4881; Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

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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.

(12) This work was supported by grants from the National Science Foundation and the National Institutes of Health.

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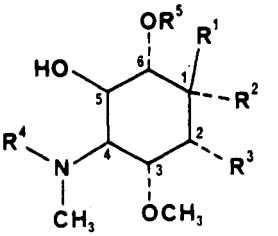
Received July 26, 1983

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-

(1) (a) Nara, T.; Yamamoto, M.; Kawamoto, I.; Takayama, K.; Okachi, R.; Takasawa, S.; Sato, T.; Sato, S. *J. Antibiot.* **1977**, *30*, 533. (b) Okachi, R.; Takasawa, S., Sato, T.; Sato, S.; Yamamoto, M.; Kawamoto, I.; Nara, T. *Ibid.* **1977**, *30*, 541. (c) Egan, R. S.; Stanaszek, R. S.; Cirovic, M.; Mueller, S. L.; Tadanier, J.; Martin, J. R.; Collum, P.; Goldstein, A. W.; DeVault, R. L.; Sinclair, A. C.; Fager, E. E.; Mitscher, L. A. *Ibid.* **1977**, *30*, 552.

(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.

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