spectra were also successfully acquired, one must conclude that significant $^1H-^{31}P$ direct dipolar coupling exists for the −2 and −67 ppm species. This implies that any molecular rotational motion be either anisotropic or isotropic and in the slow correlation time limit if substantial translational diffusion is present. Since two well-resolved resonances are observed, any chemical exchange between these two sites is in the slow exchange limit.

A key feature in the NMR evidence for the $[(CH_3)_3P-H]^+$ complex is the observation of $^1H-^{31}P$ J coupling. Figure 1b represents one of the few reported heteronuclear proton J couplings observed in a solid. The only previous observation of ^1H J coupling in a solid is the $^1H-^{13}C$ coupling for pivalic acid,[8] a plastic crystal where molecular motional averaging is sufficient to give rise to a J-resolved spectrum, and for adamantane[9,10] and hexamethylbenzene[10] where multiple-pulse decoupling was used to remove the already motionally reduced $^1H-^1H$ homonuclear coupling. However, for the general case, ^1H-coupled, J-resolved solid-state spectra are *not* observed because (1) *direct* dipolar coupling between the ^1H spins and the observed nucleus is usually much larger than the *indirect* (J) coupling and (2) the *homo*nuclear direct dipolar coupling between protons is typically very large (>10kHz for most organic solids), rendering the overall spin Hamiltonian homogeneous. As a consequence of this latter condition, one must magic-angle spin at (unattainable) rates greater than the frequency width of the $^1H-^1H$ homonuclear coupling in order to eradicate the $^1H-^{31}P$ direct dipolar coupling and to obtain a high-resolution ^{31}P spectrum.[11] In the absence of a large $^1H-^1H$ homonuclear coupling, the $^1H-^{31}P$ direct dipolar interaction is inhomogeneous and removable by slow magic-angle spinning ($\nu_r < (M_2)_{H-P}^{1/2}$).

For the $[(CH_3)_3P-H]^+$ complex, the $^1H-^{31}P$ direct dipolar coupling may be estimated from a second moment calculation, yielding $(M_2)_{H-P}^{1/2} \sim 7.7$ kHz. This result is somewhat larger than the experimental result,[12] $(M_2)^{1/2} \sim 6.3$ kHz, but in either case shows that the *direct* dipolar coupling interaction is much larger than the measured isotropic J coupling, ~550 Hz. The estimated $^1H-^1H$ homonuclear contribution to the dipolar Hamiltonian is $(M_2)_{H-H}^{1/2} < 2.1$ kHz. This value includes both estimated contributions from methyl protons and adjacent zeolite framework protons.[13]

We conclude that the ^{31}P dipolar Hamiltonian is dominated by a reasonably large $^{31}P-^1H$ direct dipolar interaction. Thus, the $^1H-^1H$ coupling term serves as a minor perturbation so that the $^{31}P-^1H$ interaction is, to a good approximation, that of an isolated dipole pair, i.e., an inhomogeneous interaction. Maricq and Waugh[11] have shown from theoeretical arguments that such an interaction can be removed by slow magic-angle spinning. The anticipated result of such slow spinning ($\nu_r < (M_2)_{P-H}^{1/2}$) is the generation of intense dipolar-derived spinning sidebands and a J-resolved ^{31}P spectrum. This is clearly observed in the experimental spectrum (Figure 1b).[14]

Additional work is needed to develop an understanding of the factors influencing ^{31}P chemical shifts in acidic catalysts, but preliminary experiments show the ^{31}P chemical shift to appear in a distinctly different position as a consequence of interaction of the trimethylphosphine with Lewis sites.

Acknowledgment. We thank P. N. Tutunjian and L. L. Sterna for useful discussions and P. P. Gentempo for expert technical assistance. This research was funded, in part, by the Robert A. Welch Foundation under Grant A-257.

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(9) Terao, T.; Miura, H.; Saika, A. *J. Magn. Reson.* **1982**, *49*, 365.
(10) Zilm, K. W.; Grant, D. M. *J. Magn. Reson.* **1982**, *48*, 524.
(11) Maricq, M. M.; Waugh, J. S. *J. Chem. Phys.* **1979**, *70*, 7.
(12) The experimental value includes small contributions from the chemical shift and J-coupling anisotropies as well. The latter quantity is estimated to be less than 100 Hz on theoretical grounds (Tutunjian, P. N., private communication). The small reduction in the experimental value for $(M_2)^{1/2}$ may reflect some motional averaging of the P–H direct dipolar coupling and/or a correction in the P–H bond distance.
(13) Stevenson, R. L. *J. Catal.* **1971**, *21*, 113.
(14) The variation in the intensity of each doublet component in the individual sidebands may be explained[15] as arising from magic-angle spinning modulation of three anisotropic interactions, viz., the direct dipolar, the indirect dipolar,[16] and the chemical shift. This asymmetry has been discussed for the case of static samples by VanderHart and Gutowsky.[17]
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(16) Tutunjian, P. N.; Waugh, J. S. *J. Magn. Reson.* **1982**, *49*, 155.
(17) VanderHart, D. L.; Gutowsky, H. S. *J. Chem. Phys.* **1968**, *49*, 261.

Total Synthesis of Vineomycin B_2 Aglycon

Samuel J. Danishefsky,* Biing Jium Uang, and George Quallich

Department of Chemistry, Yale University
New Haven, Connecticut 06511

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The vineomycin A_1, A_2, B_1, and B_2 antibiotics, obtained from *Streptomyces matensis vineus*, have demonstrated activity against Gram-positive bacteria and against sarcoma 180 solid tumors in mice.[1-4] Methanolysis of vineomycin B_2 (**1**) produces compound **3**,[1] the methyl ester of vineomycin B_2 "aglycon" **2**. A notable feature of these antibiotics is the presence of a β-C-glycosidic bond joining an unsymmetrical anthraquinone to a 2,6-dideoxyglucose segment. The biological activities of the C-glycosidal vineomycins are similar, at least qualitatively, to those of the clinically important O-glycosidal adriamycin series.[5]

A total synthesis of vineomycin B_2 aglycon **3** is described herein. Two all-carbon Diels–Alder reactions using siloxy dienes[6] led to keto aldehyde **7**. A Lewis acid catalyzed hetero Diels–Alder reaction provided the C-glycoside. A Reformatsky equivalent process, using a chiral auxiliary in **9**, facilitated access to enantiomerically homogeneous aglycon **3**. The absence of a solution to the nettlesome problem of relating the remotely disposed dissymmetries of the tertiary alcohol and glycosidic segments necessitated recourse to HPLC to obtain diastereomerically homogeneous product.

Cycloaddition of the mixed ketene acetal **10**[7,8] and quinone **4**[9] followed by methylation afforded a 70% yield of **11**,[10,11,12a,b] mp 96.5–97 °C, whose conversion to the styrene-like system **12**,[12a,b] mp 139–140 °C, was smoothly accomplished (93%) through the action of $PdCl_2$–bis(acetonitrile)[13,14] in refluxing CH_2Cl_2 for 12 h. Cycloaddition of compound **12** and siloxy diene **13**[15] followed by methylation as shown gave rise to anthrquinone **14**,[12a,b] mp

(1) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Ōmura, S. *J. Antibiot.* **1981**, *34*, 1517.
(2) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Ōmura, S. *Chem. Pharm. Bull.* **1981**, *29*, 1788.
(3) Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171.
(4) Ohta, K.; Kamiya, K. *J. Chem. Soc., Chem. Commun.* **1981**, 154.
(5) Casady, J. M.; Douros, J. D. "Anticancer Agents Based On Natural Product Models", Academic Press: New York, 1980.
(6) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.
(7) This diene was prepared by silylation (LDA/Me_3SiCl) of methyl 2-ethylenyl-4-pentenoate[8] followed by distillation (bp 72–78 °C (0.8 mmHg)).
(8) Herrmann, T. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.
(9) Ling, A. R. *J. Chem. Soc.* **1892**, *61*, 558.
(10) For the first example of the annulation of a quinone by a siloxy diene, see: Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(11) Cf.: Brassard, P.; Roberge, G. *J. Org. Chem.* **1981**, *46*, 4161. For a conceptually related annulation, see: Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekezaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.
(12) (a) The IR, NMR, and mass spectra of this compound gave IR, NMR, and mass spectra consistent with the structures proposed. (b) Satisfactory combustion analytical data were obtained for this compound.
(13) Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973.
(14) Cf.: Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1966**, *88*, 3491.
(15) This diene was prepared by silylation (LDA/Me_3SiCl) of methyl 2-ethenyl-4-methyl-4-pentenoate[8] followed by distillation (bp 48–52 °C (0.8 mm Hg)).

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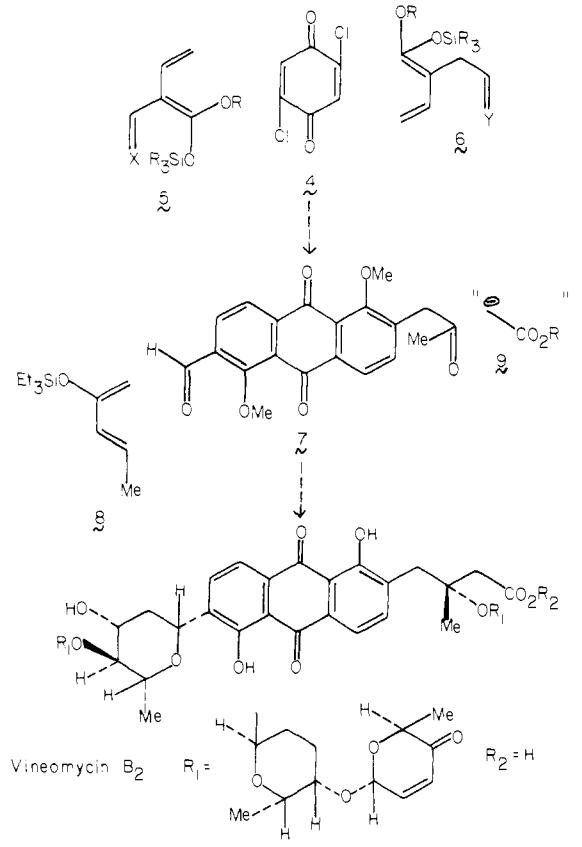
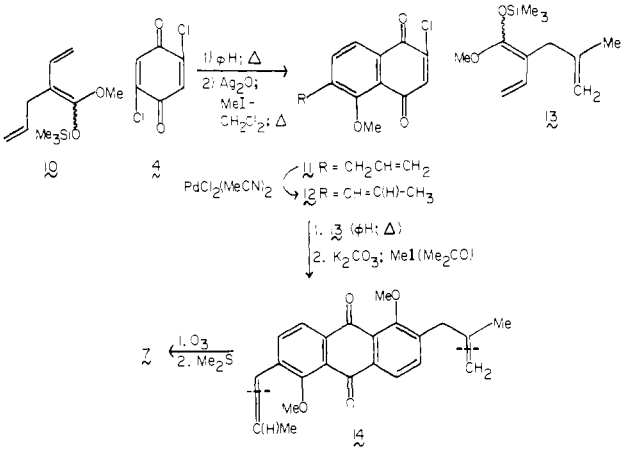


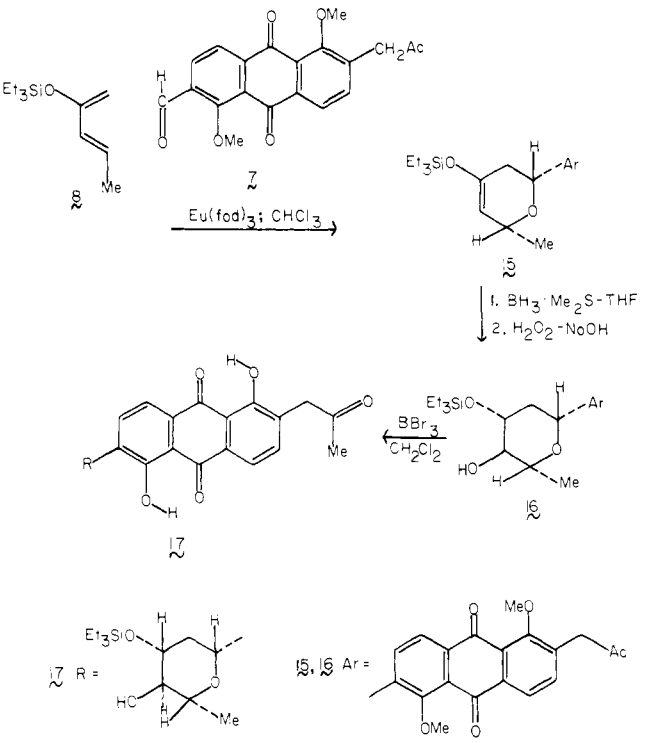
2 Vineomycin B_2 aglycone $R_1 = R_2 = H$

3 Vineomycin B_2 aglycone methyl ester $R_1 = H$; $R_2 = Me$

149–150 °C, in 80% yield. Ozonolysis followed by reduction provided keto aldehyde **7**,[12a] mp 187.5–188.5 °C, in 8% yield.



Reaction of **7** with diene **8** (0.05 equiv of $Eu(fod)_3$[16] in $CHCl_3$ at 65 °C) gave a 92% yield of **15**.[12a] The advantages of the recently introduced[17] lanthanide catalysis of the hetero Diels–Alder reaction are easily seen in this application. Thus, endo addition, which is the consequence of the pericyclic mode[18] fostered by lanthanides such as $Eu(fod)_3$, provides the stereochemistry required for the C-glycoside. Furthermore, the mildness of the catalysis is conducive to survival of the otherwise acid-vulnerable silyl enol ether functionality housed in **15**. This feature lent itself to exploitation. Hydroboration of the silyl enol ether occurred anti to the aryl and methyl groups. *In this fashion, the four chiral centers of the C-glycoside are established in two steps leading to compound* **16**[12a] *in 70% yield.*



Attempted reactions of **16** wiht several acetic acid dianon equivalents were unsuccessful, possibly due to competing reactions from the quinone. Accordingly, **16** was converted to **17**[19] as shown. Analogy[20] suggested that a metal phenoxide species (generated in situ) might be less vulnerable to nucleophilic attack by external enolates.

Reaction of **17** with the bromomagnesium salt **18**[21,22] in THF was diastereometrically random, giving a 40% yield of a mixture of *rac*-**3** and *rac*-**19**. Proton NMR spectroscopy at 500 MHz suggested the possibility of a mixture, but no chromatographic regimen that we could devise provided for either preparative or even analytical separation. Reaction of **17** with bromomagnesium derivative **20**, prepared via *l*-menthyl acetate,[21] afforded four products. Through repeated HPLC the mixture could be divided into compound **21** (which is the *l*-menthyl ester of **2**) and the *l*-menthyl ester of one of the two antipodes of *epi*-**2** (arbitrarily shown as **22**). The remaining two components were inseparable. Similarly, reaction of racemic **17** with bromomagnesium derivative **23**, derived from *d*-menthyl acetate, afforded a corresponding mixture. By repeated HPLC shaving and recycling this could be divided into **24** (i.e., the *d*-menthyl ester of *ent*-**2**) and the *d*-menthyl ester of *epi*-**2** (arbitrarily shown as **25**). Again, the remaining two components were inseparable.

Treatment of **21** with K_2CO_3 in methanol afforded fully synthetic optically pure vineomycin aglycon methyl ester **3**. The infrared, NMR (500 MHz), and mass spectra of fully synthetic **3**, mp 183–184 °C (lit.[3] 184–185 °C), were exactly the same as those obtained from an authentic sample. The optical rotation, $[\alpha]_D$ +109.1° (*C* 0.000 66, $CDCl_3$) is in close accord with that of an authentic sample, $[\alpha]_D$ +109.2° (*c* 0.000 65, $CDCl_3$). Similar trreatment of **22** afforded optically pure **19** (absolute configurations arbitrarily drawn). The 500-MHz proton NMR spectrum of **19** differs very slightly[23] from that of **3**. *Therefore, it can be*

(16) This is the trade name for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

(17) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716; (b) *Ibid.* **1983**, *105*, 6968.

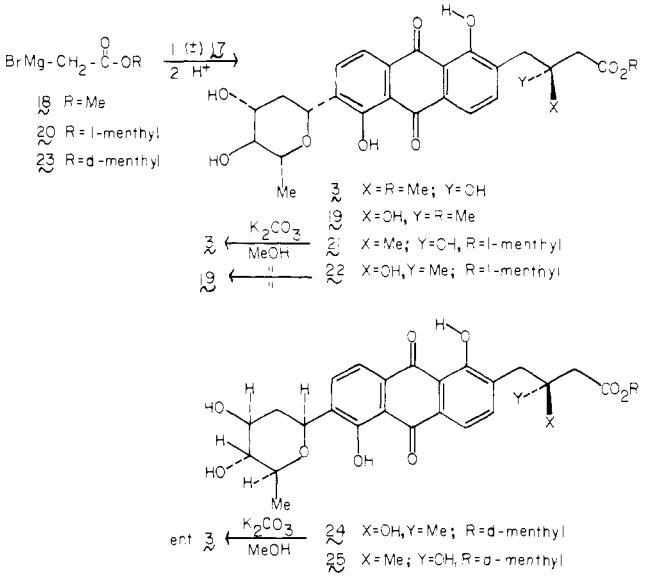
(18) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 6458.

(19) Compound **17** was not characterized but used directly in the next step. The presence of the triethylsilyl group is suggested by the NMR spectrum of the crude material.

(20) Kende, A. S.; Tsay, Y.-G. *J. Chem. Soc., Chem. Commun.* **1977**, 140.

(21) The organomagnesium salt was prepared by deprotonation (LDA) of the corresponding acetate followed by the addition of 1 equiv of $MgBr_2$ in THF.

(22) Cf.: Mitsui, S.; Kudo, Y. *Tetrahedron* **1967**, *23*, 4271.



claimed with surety that the total synthesis of the homogeneous vineomycin B_2 aglycon has been achieved.

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(23) In the 500-HMz NMR spectrum of **3**, the benzylic methylene protons (adjacent to the tertiary alcohol center) give rise to an AB quartet: δ ($CDCl_3$) 3.12 (d, J = 13, 5 Hz, 1 H) and 3.04 (d, J = 13.5 Hz, 1 H). In epimer **19** the corresponding resonances appear at δ 3.10 (d, J = 13.5 Hz, 1 H) and 3.06 (d, J = 13.5 Hz, 1 H). *The remainder of the spectra are totally superimposable. Both the C_{13} and the proton spectra of the derived tetraacetate of the secondary alchols give every appearance as representing a single compound. Conceivably, the very small difference in the epimeric "polyol" spectra reflects weak intramolecular associations due to hydrogen bonding.*

Diastereofacial Control in the Lewis Acid Catalyzed Cyclocondensation Reaction of Aldehydes with Activated Dienes: A Synthesis of the *Mus musculus* Pheromone

Samuel J. Danishefsky,* William H. Pearson, and Daniel F. Harvey

Department of Chemistry, Yale University
New Haven, Connecticut 06511

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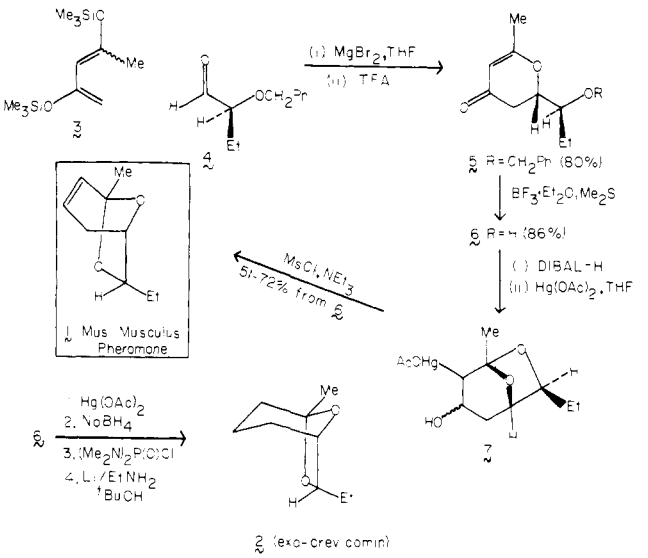
Following painstaking research,[1] Novotny, Carmack, and associates detected a volatile substance in the urine of *Mus musculus*[2] that appears to be a crucial mouse pheromone or pheromone adjuvant. Small amounts of the pheromone were obtained through glass capillary gas chromatography. In a notable demonstration of the power of Fourier transform infrared spectroscopy and mass spectroscopy in the structural elucidation of trace organic components, the structure of the active component was determined to be the *exo*-dehydrobrevicomin system **1**.[3] Recent data accumulated by the Indiana chemists indicate that pheromone **1**, whose concentration shows a clear dependency on mouse testosterone levels, plays a central role in promoting the libido and aggressive characteristics of the *Mus musculus*. Given its important biological role, its difficult accessibility from natural sources, and its compactly housed functionality, pheromone **1** is an attractive target for synthesis. Indeed, two syntheses of **1** have been realized by the Novotny–Carmack group.[1] Below we describe a concise synthesis of pheromone **1**, which serves to illustrate several thematic pursuits of our laboratory.

The first step underscores the utility of functionalized dienes of type **3**[4] in Lewis acid catalyzed cyclocondensation reactions with aldehydes. The extendability of the process to the 1-alkyl-1,3-dioxygenated dienes (cf. **3**) allows construction of the versatile and valuable 2,6-disubstituted-2,3-dihydropyran-4-ones in one step. This step also illustrates another important development. Magnesium bromide in THF is a very selective catalyst for promoting diastereofacial control in the cyclocondensation of α-oxygenated aldehydes with various silyloxy dienes. The relative configurations of up to four chiral centers are subject to specific control in one operation. The synthesis shown herein is only a modest exploitation of this capability in that it is used to control only two centers.

Reaction of diene **3**[4] with aldehyde **4**[5] in THF under the influence of anhydrous magnesium bromide affords a single dihydropyrone. The stereochemistry of compound **5**,[6] which is the only isolated product of the cyclocondensation reaction, could not be determined at this stage. However, the assignment follows from its conversion in the manner indicated to *exo*-brevicomin (**2**). Transformation of **6**, obtained from **5**,[7] to the bridged ketal series was smoothly accomplished by intramolecular oxymercuration followed by reduction of the α-mercurio ketone with sodium borohydride. Deoxygenation of the resultant epimeric alcohols according to the methodology of Ireland[9] afforded **2**.[10] More



(1) (a) Novotny, M.; Schwende, F. J.; Wiesler, D.; Jorgenson, J. W.; Carmack, M. *Experientia*, in press. (b) Wiesler, D.; Schwende, F. J.; Carmack, M.; Novotny, M. *J. Org. Chem.* **1984**, *49*, 882. We thank these authors for disclosure of their work prior to publication.

(2) The common house mouse.

(3) This compound has been previously mentioned as an intermediate in a synthesis of *exo*-brevicomin: Chauquin, P.; Morizur, J. P.; Kossanyi, J. *J. Am. Chem. Soc.* **1977**, *99*, 903.

(4) (a) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1. (b) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B.-J. *J. Org. Chem.* **1984**, *49*, 392.

(5) Prepared from 4-benzyloxy-2-hexene by ozonolysis (77%). See, for example: Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. Full details will be reported elsewhere. For the preparation of optically active **4**, see: Asami, M.; Mukaiyama, T. *Chem. Lett.* **1983**, 93. Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021.

(6) The structure assignment of this compound is consistent with its IR, ^{1}H NMR, and mass spectra. Full experimental details will be reported in due course.

(7) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.

(8) The lability of this diol precluded its purification and characterization.

0002-7863/84/1506-2455$01.50/0