

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 $[(\text{CH}_3)_3\text{P}-\text{H}]^+$ 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 hexamethylbenzene¹⁰ 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 homonuclear direct dipolar coupling between protons is typically very large ($>10\text{kHz}$ 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 ($\nu_r < (M_2)_{\text{H-P}}^{1/2}$).

For the $[(\text{CH}_3)_3\text{P}-\text{H}]^+$ complex, the ^1H - ^{31}P direct dipolar coupling may be estimated from a second moment calculation, yielding $(M_2)_{\text{H-P}}^{1/2} \sim 7.7\text{ kHz}$. This result is somewhat larger than the experimental result,¹² $(M_2)^{1/2} \sim 6.3\text{ kHz}$, but in either case shows that the direct dipolar coupling interaction is much larger than the measured isotropic J coupling, $\sim 550\text{ Hz}$. The estimated ^1H - ^1H homonuclear contribution to the dipolar Hamiltonian is $(M_2)_{\text{H-H}}^{1/2} < 2.1\text{ kHz}$. 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 Waugh¹¹ have shown from theoretical arguments that such an interaction can be removed by slow magic-angle spinning. The anticipated result of such slow spinning ($\nu_r < (M_2)_{\text{P-H}}^{1/2}$) 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.

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Total Synthesis of Vineomycin B₂ Aglycon

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The vineomycin A₁, A₂, B₁, and B₂ 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 B₂ (1) produces compound 3,¹ the methyl ester of vineomycin B₂ "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 B₂ aglycon 3 is described herein. Two all-carbon Diels-Alder reactions using siloxy dienes⁶ 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 4⁹ 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 13¹⁵ followed by methylation as shown gave rise to anthraquinone 14,^{12a,b} mp

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(7) This diene was prepared by silylation ($\text{LDA}/\text{Me}_3\text{SiCl}$) of methyl 2-ethynyl-4-pentenoate⁸ followed by distillation (bp 72-78 °C (0.8 mmHg)).

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(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.; Sekezi, 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 ($\text{LDA}/\text{Me}_3\text{SiCl}$) of methyl 2-ethynyl-4-methyl-4-pentenoate⁸ followed by distillation (bp 48-52 °C (0.8 mmHg)).

(8) Graham, J. D.; Darby, J. S. *J. Magn. Reson.* **1976**, *23*, 369.

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(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.

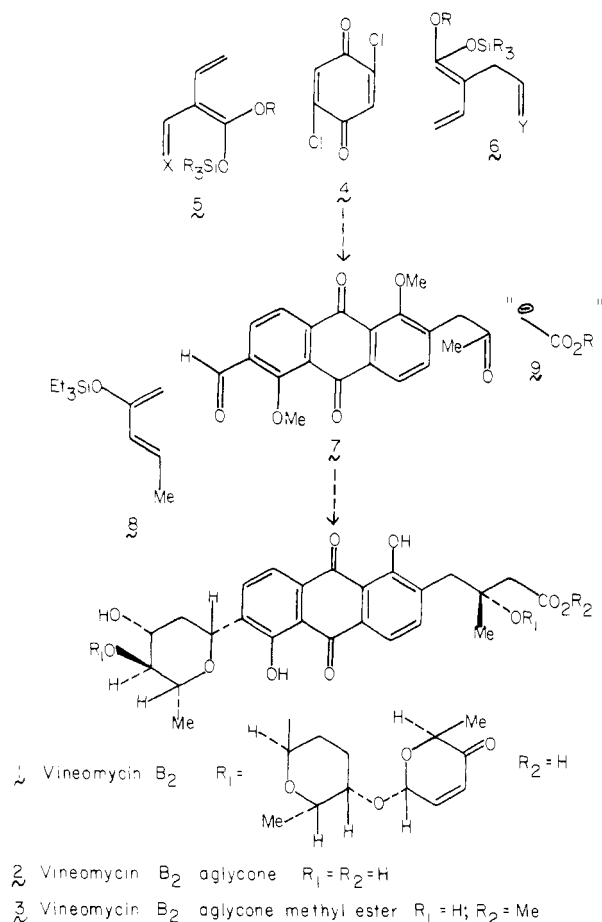
(13) Stevenson, R. L. *J. Catal.* **1971**, *21*, 113.

(14) The variation in the intensity of each doublet component in the individual sidebands may be explained¹⁵ 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

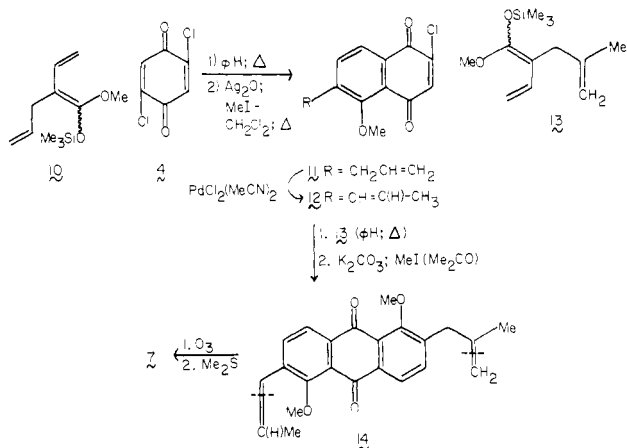
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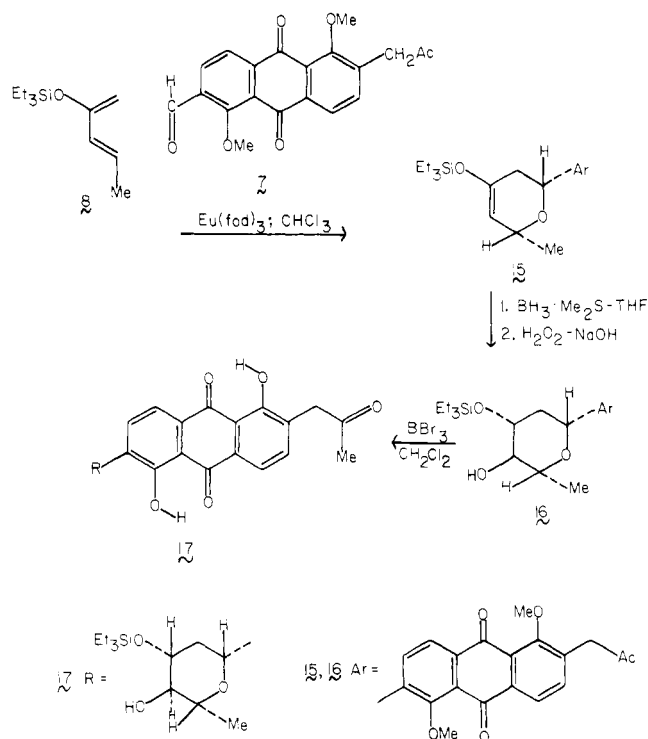


149–150 °C, in 80% yield. Ozonolysis followed by reduction provided keto aldehyde 7,^{12a} mp 187.5–188.5 °C, in 8% yield.



Reaction of 7 with diene 8 (0.05 equiv of Eu(fod)₃¹⁶ in CHCl₃ at 65 °C) gave a 92% yield of 15.^{12a} The advantages of the recently introduced¹⁷ lanthanide catalysis of the hetero Diels–Alder reaction are easily seen in this application. Thus, endo addition, which is the consequence of the pericyclic mode¹⁸ 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 with several acetic acid dianion equivalents were unsuccessful, possibly due to competing reactions from the quinone. Accordingly, 16 was converted to 17¹⁹ as shown. Analogy²⁰ 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 K₂CO₃ 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, [α]_D +109.1° (C 0.00066, CDCl₃) is in close accord with that of an authentic sample, [α]_D +109.2° (c 0.00065, CDCl₃). Similar treatment of 22 afforded optically pure 19 (absolute configurations arbitrarily drawn). The 500-MHz proton NMR spectrum of 19 differs very slightly²³ from that of 3. Therefore, it can be

(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.

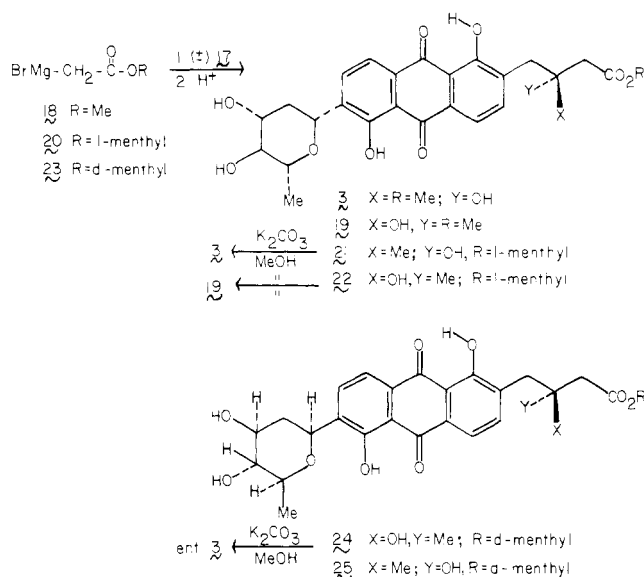
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(22) Cf.: Mitsui, S.; Kudo, Y. *Tetrahedron* **1967**, *23*, 4271.



claimed with surety that the total synthesis of the homogeneous vineomycin B₂ 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 (CDCl₃) 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 C₁₃ and the proton spectra of the derived tetraacetate of the secondary alcohols 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

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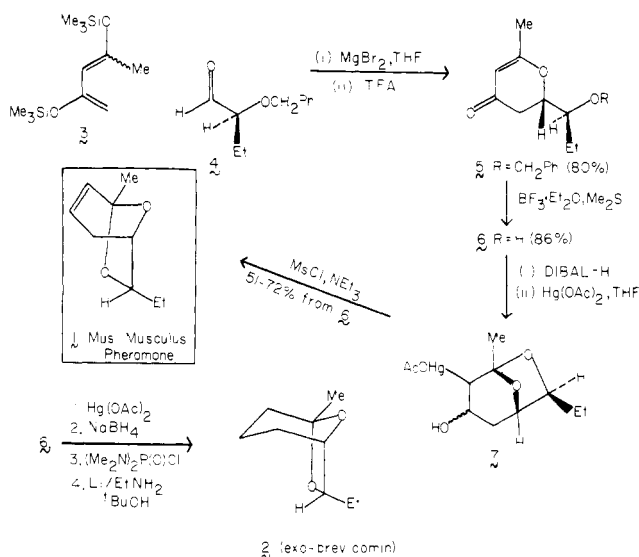
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Following painstaking research,¹ Novotny, Carmack, and associates detected a volatile substance in the urine of *Mus musculus*² that appears to be a crucial mouse pheromone or pheromone adjuvant. Small amounts of the pheromone were obtained through 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*-dehydrobrevicomine system 1.³ Recent data accu-

mulated 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 3⁴ 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 3⁴ with aldehyde 4⁵ 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*-brevicomine (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 Ireland⁹ afforded 2.¹⁰ More



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

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(5) Prepared from 4-benzoyloxy-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, ¹H NMR, and mass spectra. Full experimental details will be reported in due course.

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

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(2) The common house mouse.