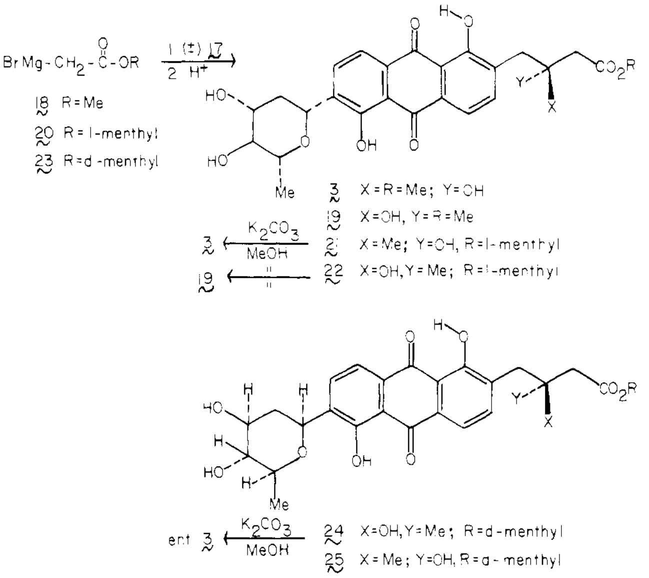

claimed with surety that the total synthesis of the homogeneous vineomycin B_2 aglycon has been achieved.

Acknowledgment. This work was supported by PHS Grant CA49902. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210. We also thank Professor N. Ikekawa and Professor M. Ohno for providing us with samples of vineomycin B_2 and aquayamycin for purposes of preparing aglycon **3**.

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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

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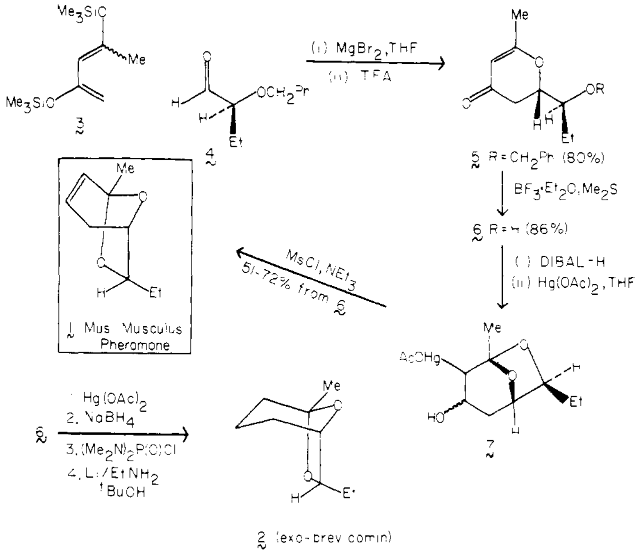
Following painstaking research,[1] Novotny, Carmack, and associates detected a volatile substance in the urine of *Mus musculus*[2] that appears to be a crucial mouse pheromone or pheromone adjuvant. Small amounts of the pheromone were obtained through glass capillary gas chromatography. In a notable 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



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[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.

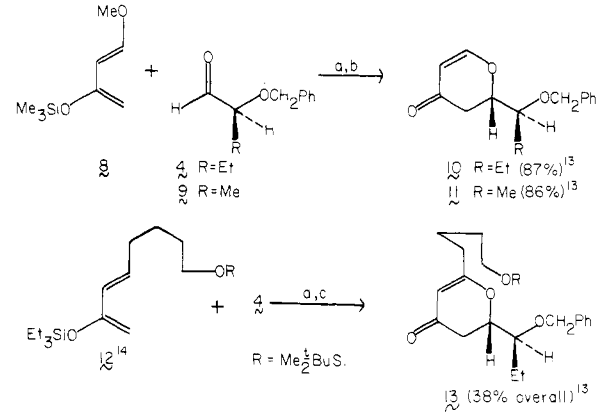
[6] The structure assignment of this compound is consistent with its IR, ^1H NMR, and mass spectra. Full experimental details will be reported in due course.

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

[8] The lability of this diol precluded its purification and characterization.

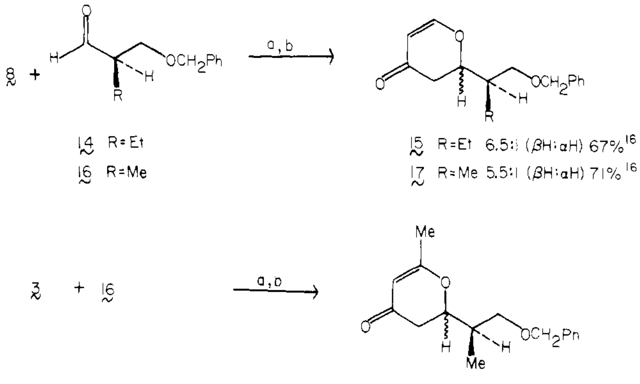
importantly, reduction of **6** to a "glycal"[8] followed by intramolecular oxymercuration gave **7**, which was treated with mesyl chloride and triethylamine to afford the desired **1**.[11a] The use of organomercurials for the installation of functionality at fixed cites is a continuing interest in our laboratory.[11]

The ability of the magnesium bromide-THF system to provide strong diasterofacial control in the cyclocondensation of α-oxygenated aldehydes with silyloxy dienes is quite general. Some additional cases are shown below. In these cases, as well as in the reaction of **3** and **4**, serious mixtures of facial isomers resulted when $BF_3{\cdot}OEt_2$, $ZnCl_2$, or Yb(fod)$_3$ were used in various solvents.[12] In each instance, the product of the $MgBr_2$–THF reaction is the one that is consistent with chelation control (see **10**,[6] **11**,[6] **13**[6]).



a) $MgBr_2$. THF b) HCAc, H_2O c) Pd(OAc)$_2$, CH_3CN

The possibilities of realizing facial control with β-alkoxyaldehydes were investigated. Toward this end, the reactions of dienes **3** and **8** with aldehydes **14** and **16**[15] were examined. In these more sensitive and less reactive cases, it was advantageous to employ 4:1 benzene–ether as the solvent system and magnesium bromide as the catalyst.



a) $MgBr_2$, benzene/ether
b) TFA, CH_2C_2

It will be recognized that, in each case, the major or virtually sole product[16] of the magnesium bromide induced cyclocondensation process is the one that is consistent with chelation control. Such chelation would find precedent in recent syntheses.[17,18] In the accompanying communication the hypothesis of chelation is probed in a critical way.

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[9] Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

[10] For two recent syntheses of *exo*-brevicomin, see: Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077. Cohen, T.; Bhupathy, M. *Tetrahedron Lett.* **1983**, *24*, 4163.

[11] (a) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (b) Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.* **1983**, *24*, 15.

[12] For previous work using these catalysts, see: Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457. Bednarski, M. D.; Danishefsky, S.; *Ibid.* **1983**, *105*, 3716.

[13] Ratios were determined by high-field ^{1}H NMR: **10**, >50:1; **11**, 40:1; **13**, >50:1.

[14] For the preparation and use of this diene in the synthesis of spiroketals, see ref 11a.

[15] Diethyl ethylmalonate was reduced ($LiAlH_4$) to the diol, monoprotected (NaH, $PhCH_2Br$, Bu_4NI) and oxidized (PCC) to give **14**. Methallyl alcohol was benzylated (NaH, $PhCH_2Br$, Bu_4NI), hydroborated ($BH_3{\cdot}THF$) and oxidized (PCC) to give **16**. (See: Paterson, I.; Patel, S. K.; Porter, J. R. *Tetrahedron Lett.* **1983**, *24*, 3395).

[16] The stereochemistry of these adducts was determined by chemical and spectroscopic methods. Details will be presented in the full account of this work.

[17] (a) Isolasalocid A: Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. (b) Monensin: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120.

[18] For incisive background studies, see: (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748. (b) Still, W. C.; McDonald, J. H., III; *Tetrahedron Lett.* **1980**, *21*, 1031. Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035.

On the Relationship of Topological and Diastereofacial Control in the Lewis Acid Catalyzed Cyclocondensation Reaction of Alkoxyaldehydes with Activated Dienes: Metal Tunable Asymmetric Induction

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In previous papers in this series,[1] a pericyclic mode has been identified in the title reaction. During these investigations, an interesting and important effect was noted. Where the pericyclic pathway was most obvious, the topology of the reaction was endo. Thus, diene **1** reacts with aldehydes (**2**) to afford cis 2,3-dihydropyran derivatives **3**.[1b,2] Since no obvious attractive forces between the simple alkyl (R) function of the aldehyde and the diene presented themselves, it was hypothesized[2] that the Lewis acid catalyst binds anti to the R group of the aldehyde. It was further hypothesized that the effective size of the catalyst–solvent array is more substantial than the R group of the aldehyde. Thus, the observed endo directivity of the R group is actually a consequence of exo directivity of the catalyst–solvent ensemble.

In the preceding communication[3] it was reported that α- and β-alkoxyaldehydes react with activated dienes under magnesium bromide catalysis to provide 2,3-dihydro-4-pyrones. In these reactions, a high order of diastereofacial control was exhibited. In the case of the α-substrates there was virtually total specificity while with the β-systems strong selectivity (~5–10:1) pertained. In all cases the sole or principal product was the one whose relative stereochemistry was consistent with chelation control.[4]

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[1] (a) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 6458. (b) Bednarski, M. D.; Danishefsky, S. *Ibid.* **1983**, *105*, 3716.

[2] Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457.

[3] See preceding communication.

[4] For a systematic study of the addition of organometallic reagents to α- and β-alkoxyaldehydes, see: Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035.

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