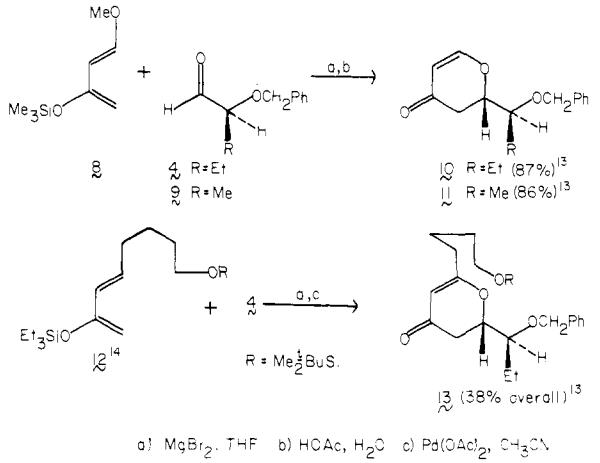
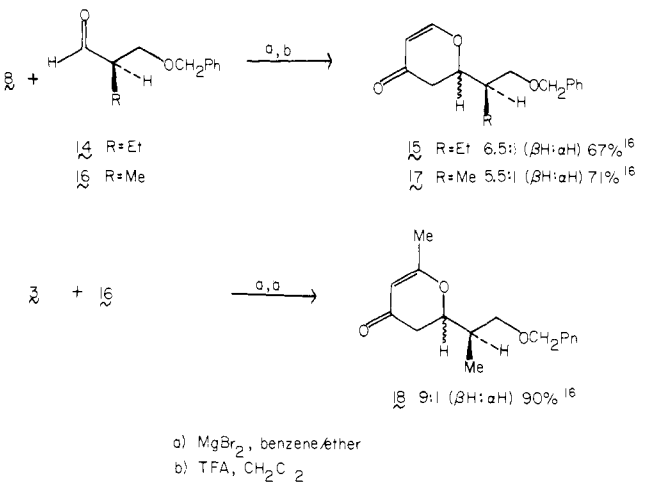
importantly, reduction of **6** to a "glycal"[8] followed by intramolecular oxymercuration gave **7**, which was treated with mesyl chloride and triethylamine to afford the desired **1**.[11a] The use of organomercurials for the installation of functionality at fixed cites is a continuing interest in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

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.

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.

Acknowledgment. This work was supported by PHS Grant AI 16943. A PHS Postdoctoral Fellowship (Grant 1 F32 CA07251) to W.H.P. is gratefully acknowledged. A Kent Fellowship to D.F.H. is also gratefully acknowledged. 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 are very grateful to Professors Novotny and Carmack for furnishing preprints of their isolation–synthesis papers.

(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 ^1H 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-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]

(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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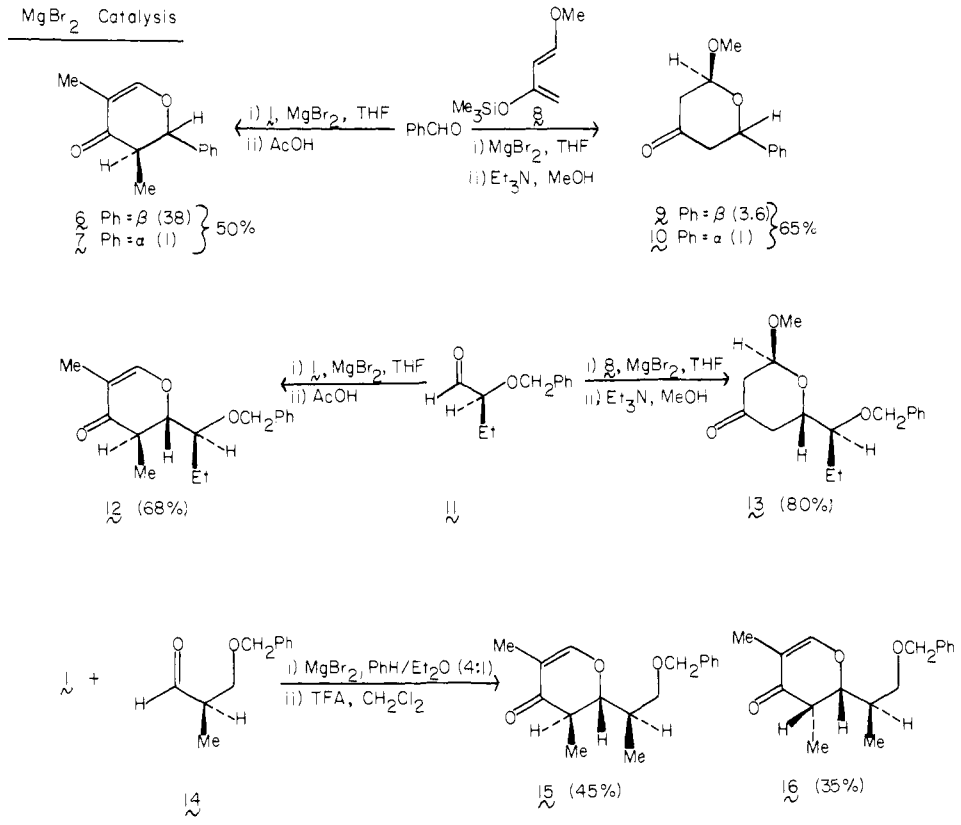
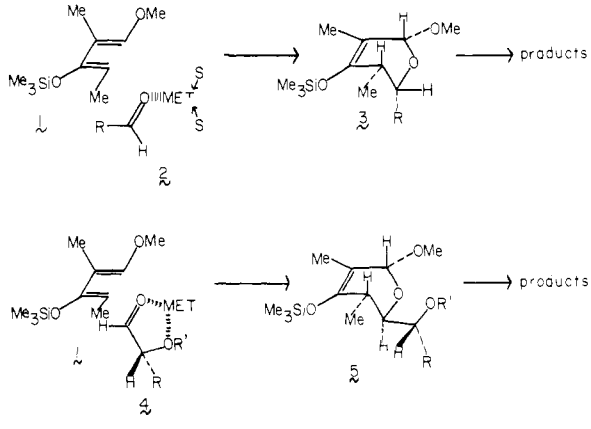
Scheme I



In analyses of this sort it is well to distinguish between plausible conjectures and experimentally supported arguments. Fortunately, in the case at hand, the proposals formulated above could be subjected to critical examination. If chelation in the Cram/Still sense[4,5] in fact pertains, the catalyst (MET) *must* be arrayed syn to the R group. Therefore, the topology of the process should be governed by the expression **1** + **4** → **5** wherein the R group of



the aldehyde (which now includes the α-alkoxy function) and the catalyst can both be oriented exo with respect to the diene. This connectivity between chelation moderated facial control and exo topology was tested experimentally.

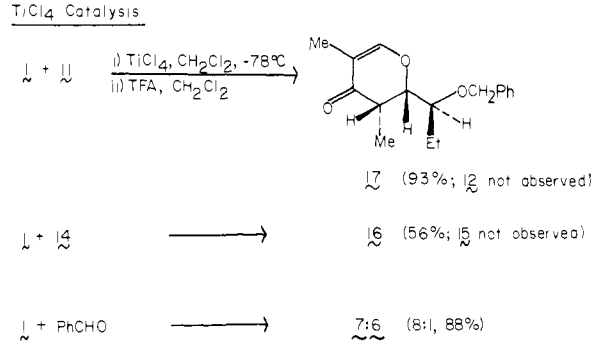
Important control experiments were performed. Magnesium bromide catalysis of the reaction of the nonchelatable benzaldehyde with diene **1** affords a 38:1 ratio[6] of the previously known[2] 2,3-dihydropyrones **6** and **7**. With the unsubstituted diene **8**, compounds **9** and **10**[1b] were produced in a 3.6:1 ratio. *By contrast, these same dienes reacted with aldehyde* ***11****, under the same conditions, to afford trans dihydropyrones* ***12*** *and* ***13****, with virtually complete specificity.*[8,9] *Having shown that the Mg-Br*$_2$*–THF catalyst–solvent system appears to be quite standard in favoring an endo topology with ordinary aldehydes, it seems reasonable to ascribe the change in topology to chelation control as proposed above.*

As described in the previous publication,[3] the magnesium bromide catalyzed reactions of the β-alkoxyaldehyde **14** with activated dienes had to be conducted in a benzene–ether mixture to avoid decomposition of the aldehyde. In this less complexing solvent system, reactions are more rapid but aldol products are seen in addition to the normal cyclocondensation adducts. The intermediate aldol products undergo cyclization (TFA) to complete the cyclocondensation process. Topological specificity is undermined as the pericyclic pathway gives way to a competitive Mukaiyama-like mechanism.[1] Of course, chelation by the magnesium bromide controls the diastereofacial outcome. Not surprisingly, reaction of **14** with diene **1** affords a 1.3:1 mixture of topological isomers **15** and **16**,[9] both of which are in the Cram/Still diastereofacial sense.[4,5]

Recently, Reetz and Jung[10] described the use of titanium tetrachloride to promote chelation control in the aldol condensation of β-alkoxyaldehydes with simple silyl enol ethers. Kuwajima and Nakamura[11] described the use of enoxytitanium species to promote stereoselective aldol condensations. These observations prompted us to explore the $TiCl_4$ catalyzed reaction of diene **1** with aldehydes **11** and **14**. The aldehydes were first combined with 1 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 5 min. To this was added 1.5 equiv of diene **1**. Treatment of the resultant aldols with 10% TFA in CH_2Cl_2 at room temperature for ca. 30 min cleanly affords the cis disubstituted pyrones **17** and **16** in yields of 93% and 56%,

(5) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram. D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.
(6) Ratio based on isolated yields of **6** and **7**.
(7) The relative amounts of endo directivity of dienes **1** and **8** parallels that seen with Eu(fod)$_3$ catalysis. See ref 1b.
(8) Compound **12** was the only isomer observed by 500-MHz ^{1}H NMR of the crude reaction mixture. Compound **13** and its α-anomer were formed in an 18:1 ratio by 500-MHz ^{1}H NMR.
(9) The stereochemistry of these adducts was determined by chemical and spectroscopic methods. Details will be presented in a full account of this work.
(10) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.
(11) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343, 3347.

respectively. It is interesting to note that with the nonchelatable benzaldehyde, under these same conditions, the topology of the process is changed, affording an 8:1 ratio of the trans and cis pyrones **7** and **6**, respectively.



In summary, the following stereochemical relationships can now be built into the cyclocondensation reaction with alkoxyaldehydes With magnesium bromide, strict chelation control is coupled to the exo pericyclic mode, leading to trans dihydropyrones. With titanium tetrachloride, strict chelation control is coupled to erythro stereochemistry in a Mukaiyama[1] aldol process, leading to cis dihydropyrones. Since the dihydropyrones are themselves amenable to the installation of additional chirality in a systematic fashion, a new strategy for asymmetric synthesis is at hand.

Acknowledgment. This work was supported by PHS Grant AI 16943. A PHS Postdoctoral Fellowship (Grant 1 F32 CA07251) to W.H.P. is gratefully acknowledged. A Kent Fellowship to D.F.H. is also gratefully acknowledged. 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.

Sulfoxide-Mediated Intramolecular Hydroxylation of a Remote Olefin in an Acyclic System

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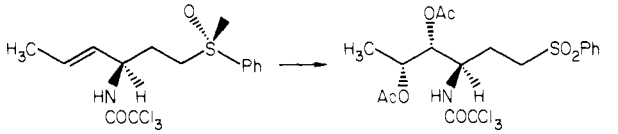
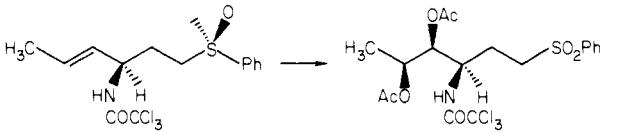
The development of procedures for diastereo- and enantioselective functionalization of acyclic olefinic systems has greatly facilitated the synthesis of complex natural products.[1-7] A criterion for successful use of this methodology is that participating functionality be proximate, i.e., allylic or homoallylic to the olefinic center.

In conjunction with our program to develop methods for stereoselective synthesis of biologically important amino hexoses from noncarbohydrate precursors,[7] we have found an example of stereospecific hydroxylation of an olefinic center in an acyclic system that is guided by a sulfoxide functionality more remote than homoallylic.[8]

Treatment of separate diastereoisomeric sulfoxides **1** and **3** with a catalytic amount of osmium tetroxide (3-5 mol %) and trimethylamine *N*-oxide[9] (3 equiv) furnished, after acetylation, the diastereoisomeric diacetate sulfones **2** (96%, mp 134-136 °C) and **4** (93%, mp 149-150 °C), respectively, as the sole products of



1 **2**

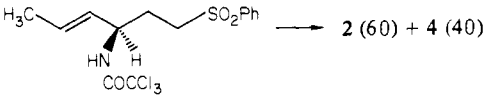


3 **4**

the individual reactions. The stereochemistry in **2** and **4** was tentatively assigned by observation of the acetate methyl absorptions in the ^{1}H NMR spectra. The acetate methyls in **2** were closely-spaced singlets (δ 1.74 and 1.71) whereas in **4** they were well-separated singlets (δ 1.87 and 1.74).[10] This difference was attributed to the fact that in the chain-extended configuration of **4**, hydrogen bonding between the amide proton and the carbonyl oxygen of the neighboring acetate generates a seven-membered ring in which the alkyl substituents are equatorial.

Initially, the stereochemistry of the individual sulfoxides **1** and **3** was assigned by assuming that a complexation between the oxygen of the sulfoxide and the osmium had occurred prior to hydroxylation of the olefin.[11] This supposition was subsequently confirmed by hydroxylation of the olefinic sulfone **5** and by X-ray analysis of the sulfoxide **1**.

In order to establish if the olefinic sulfone **5** was an intermediate and to assess the role of the amide functionality in determining the stereochemical outcome, **5** was independently prepared and hydroxylated under the same conditions. After acetylation, a 60:40 ratio of diacetate sulfones **2** and **4** was obtained in a 94% yield.



5

This result demonstrates that while the amide exerts a modest steric effect favoring formation of the anti (relative to the amide) hydroxylation product, complexation of the amide with the osmium is not occurring.[12] Furthermore, the fact that hydroxylation of

† Recipient of a Career Development Award, 1978-1983, from the National Cancer Institute (CA 00486).

(1) For a recent review, see: Bartlett, P. A. *Tetrahedron* **1980**, 2, and references therein.

(2) For the (a) diastereo- and (b) enantiospecific epoxidation of allyl alcohols, see: (a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958. Pierre, J.-L.; Chautempts, P.; Arnaud P. *Bull. Soc. Chim. Fr.* **1969**, 1317. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *Ibid.* **1974**, *96*, 5254. Chautemps, T.; Pierre, J.-L. *Tetrahedron* **1976**, 549. Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Chem. Soc.* **1979**, *101*, 159. (b) Yamada, S.; Mashiko, T.; Terashima, S. J. *Ibid.* **1977**, *99*, 1988. Michaeslon, R. C.; Palermo, R. E.; Sharpless, K. B. *Ibid.* **1977**, *99*, 1980. Katsuki, T.; Sharpless, K. B. *Ibid.* **1980**, *102*, 5974.

(3) For the diastereoselective epoxidation of homoallylic alcohols, see: Barlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4828.

(4) For the diastereoselective halo-hydroxylation of allyl and homoallyl amides, see: Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. Parker, K. A.; O'Fee, R. *Ibid.* **1983**, *105*, 654.

(5) For the enantioselective hydroxylation of olefins with osmium tetroxide, see: Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

(6) For the diastereoselective hydroxylation of allyl alcohols with osmium tetroxide, see: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943; **1983**, 3947. Stork, G.; Kahn, M. *Ibid.* **1983**, *24*, 3951.

(7) For the diastereoselective hydroxylation of an allyl amide with osmium tetroxide, see: Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

(8) Johnson and co-workers have found that a sulfoximine group will guide the stereospecific hydroxylation of an adjacent olefinic center. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.*, following paper in this issue.

(9) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.

(10) Spectra were determined in benzene-d_6.

(11) This assumption was based on the fact that both Os^{8+} and the sulfoxide oxygen are hard species.

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