standard deviations calculated by using methods similar to those described previously.[17] Absorption corrections were applied (empirical ψ-scan method, $\mu_{Mo} = 46.6$ cm^{-1}). The minimum and maximum multipliers were 1.00 and 1.46, respectively.

The structure was solved by direct methods with use of the MULTAN[18] package and the 300 reflections with the highest values of $|E|$. An E map based upon these reflections revealed positions for the rhenium atom and 8 of the other non-hydrogen atoms. Difference electron density maps revealed positions for the rest of the 25 non-hydrogen atoms. The model was refined by a full-matrix least-squares technique with use of the 4656 reflections with $F_o > 3\sigma(F_o)$ and standard atomic form factors.[19] The effects of anomalous scattering for the rhenium and phosphorus atoms were included in the calculated structure amplitudes.[20] A difference electron density map calculated after refinement on the isotropic model had converged ($R_1 = \sum||F_o| - |F_c||/\sum|F_o| = 0.108$; $R_2 = [\sum w(F_o - F_c)^2/\sum w(F_o)^2]^{1/2} = 0.122$) demonstrated (nonstatistical) disorder of the nitrosyl and Re-bonded methyl group (the occupancies of 0.6 and 0.4 were estimated from the electron density difference map peaks from a map calculated with the disordered atoms removed) and gave positions for the disordered atoms and for all the hydrogen atoms except those on the Re-bonded methyl group. The hydrogen atoms position and isotropic thermal parameters were included in the parameters being refined. All non-hydrogen atoms except the disordered nitrogen and carbon atoms were assumed to vibrate anisotropically. This final model converged with $R_1 = 0.025$ and $R_2 = 0.032$. The highest peak on the final difference electron density map was near the rhenium atom and was about 22% of the height of a typical carbon atom. The estimated error in an observation of unit weight was 1.15 and the final data to variable ratio was 11.7.

Acknowledgment. Support from the Department of Energy, Division of Basic Energy Sciences, is gratefully acknowledged. We thank Dr. Nicholas Vollendorf for first suggesting the structural assignments of **11** and **12**.

Registry No. 3, 38814-45-8; **6**, 80668-22-0; **8**, 94729-27-8; **9**, 94619-90-6; **9**-d_5, 94619-92-8; **10**, 94619-86-0; **11**, 94619-87-1; **12**, 94619-88-2; PMe_3, 594-09-2.

Supplementary Material Available: Listings of the final observed and calculated structure amplitudes (×10), atomic coordinates, and associated thermal parameters (24 pages). Ordering information is given on any current masthead page.

(17) Haller, K. J.; Enemark, J. H. *Inorg. Chem.* **1978**, *17*, 3552-3558.
(18) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A*, **1971**, *A27*, 368-376.
(19) Atomic form factors were from the following: Cromer, D. T.; Mann, J. B. "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. pp 9-101, Table 2.2B. The form factor for hydrogen was from the following: Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175-3187.
(20) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970**, *53*, 1891-1898.

On the Scope, Mechanism, and Stereochemistry of the Lewis Acid Catalyzed Cyclocondensation of Activated Dienes with Aldehydes: An Application to the Erythronolide Problem

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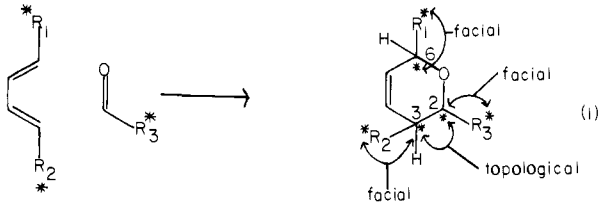
Abstract: The scope of the titled reaction is described. Pericyclic and aldol-like pathways have been identified. To a great extent these are a function of the catalyst/solvent system and of structural features in the aldehyde. The pericyclic pathway tends to favor a topology leading to *cis*-2,3-dihydropyran. A complementary threo-selective siloxonium (aldol-like) pathway is favored by borontrifluoride catalysis. These capabilities are coordinated in a synthesis of the C_1-C_9 fragment of 6a-deoxyerythronolide.

The ability of selected aldehydes bearing strongly electrophilic α-substituents to function as heterodienophiles (eq 1) has been



(1)

known for some time.[1-3] Even in these cases the substitution patterns of the diene participants have been quite simple. Therefore, extensive functional group manipulations would be required to convert the primary cycloadducts to more complex structures.

In such cycloaddition reactions, the issue of the relative configurations at positions 2 and 3 is one of topology. The emerging relationship of both centers relative to preexisting dissymmetric elements in either the aldehyde (cf. R^*_3) or in the diene (cf. R^*_1 or R^*_2) falls under the category of diastereofacial selectivity.[4]

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(1) For a recent comprehensive review of Diels-Alder cycloadditions with heterodienophiles, see: Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(2) For a very early foray into this area, see: Paul, R.; Ischelitcheff, S. *C. R. Hebd. Seances Acad. Sci.* **1947**, *224*, 1722. Recently, the use of ultrahigh pressure (~20 kbar) has extended the scope of reactivity of nonactivated carbonyl participants. See: Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41.
(3) The possibility of employing Lewis acid catalysis in this type of cycloaddition was noted by J. W. Scheeren and associates in two publications which preceded our own.[12a] However, these workers confined their reports to the case of activated aldehydes (cf. glyoxylate) which in fact do not require catalysis. Mention was made that Lewis acid catalysis could allow for the process to be extended to simple aldehydes but no examples were given. In a paper that appeared after our work,[12a] the extension to unactivated aldehydes was described. Cf., inter alia: van Balen, H. C. J. G.; Broekhuis, A. A.; Scheeren, J. W.; Nivard, R. J. F., *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 36. Aben, R. W.; Scheeren, J. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3132. Aben, R. W.; Scheeren, J. W. *Synthesis* **1982**, 779.

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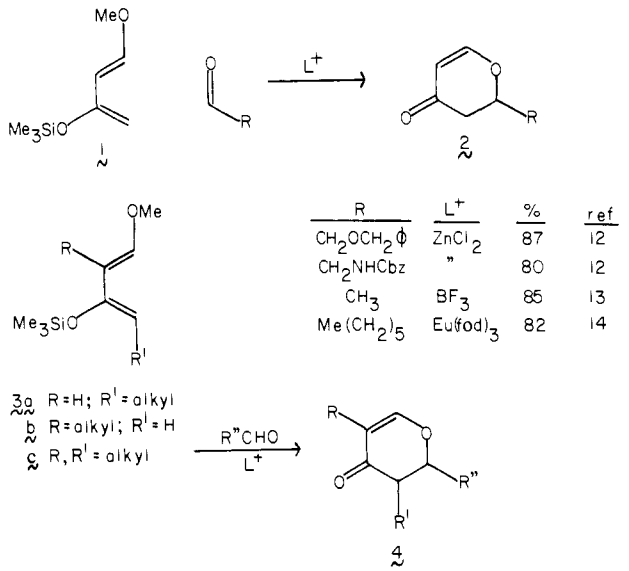
Scheme I



R	L^+	%	ref
$CH_2OCH_2\phi$	$ZnCl_2$	87	12
CH_2NHCbz	"	80	12
CH_3	BF_3	85	13
$Me(CH_2)_5$	$Eu(fod)_3$	82	14

Though neither the topological nor the diastereofacial aspects of these processes had been brought under control, heterocycloadditions were used by the Polish school in the synthesis of simple hexoses.[5] Furthermore, a fascinating extension of hetero [2 + 4] cycloadditions is the basis for the David synthesis of di- and trisaccharides.[6]

Enol silylation provides convenient access to extensively functionalized 1,3-butadienes.[7-9] Previously siloxy dienes had found application in [2 + 4] cycloadditions with C=C dienophiles.[10,11] In analogy with the all-carbon process, it was proposed that Lewis acids might broaden the range of usable dienophilic aldehydes with such dienes.

It was found[12,13] that under appropriate Lewis acid catalysis the parent diene **1** reacts with virtually any aldehyde to provide products of the type **2** (Scheme I). In the initial experiments, zinc chloride in benzene or borontrifluoride etherate in methylene chloride were used to provide pyrones **2**. The presumed primary product of cycloaddition (vide infra) was neither isolated nor detected.

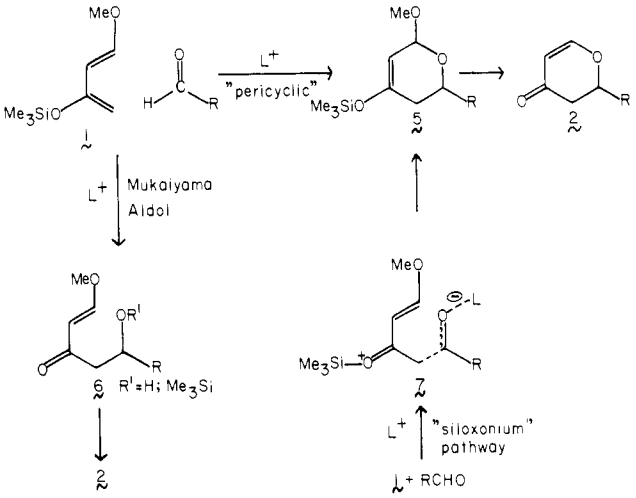
Subsequently, all of diene types **3** were shown to function in the process. New catalytic systems including $Eu(fod)_3$,[14] $TiCl_4$,[15] and $MgBr_2$[15] were introduced. The use of the chiral catalyst $Eu(hfc)_3$ and its interactions with chiral auxiliaries provided some enantioselectivity in the cycloadditions.[16,17]

This paper describes experiments addressed to the related issues of stereochemistry[18] and mechanism.[19] Variations in the nature of the catalyst allowed for the attainment of considerable latitude in the control of the topological outcome.[20a] A new route to polypropionate-derived chiral arrays was developed and was demonstrated in a synthesis of the "eastern zone" (carbons 1–9) of 6a-deoxyerythronolide B (see **37**).

Discussion of Results

The pericyclic mechanistic model contemplates a cycloaddition between the reactants by analogy with the catalyzed all-carbon Diels–Alder reaction. Though this "parent" process is not without its own difficult questions of detail and nuance,[21] it nevertheless provides a convenient framework for perception and experimentation.

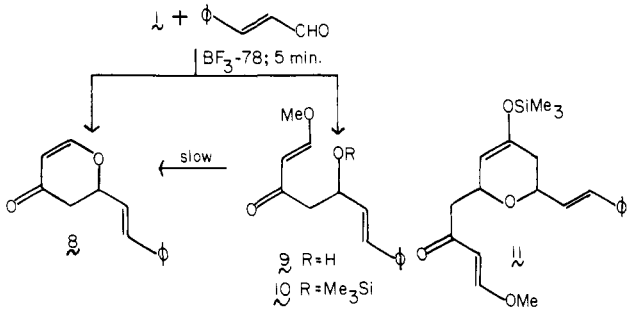
At the other extreme, a Mukaiyama variant of the aldol condensation[22a] might serve to join the reactants. Ring closures by the alcohol on the β-carbon of the β-alkoxy enone **6** would complete the cyclocondensation. An intermediary "siloxonium" variant presupposes initial carbon–carbon bond formation in the Mukaiyama aldol manner. If siloxonium species **7** undergoes cyclization before desilylation, compound **5** is produced. Experimental differentition between the pericyclic and the siloxonium models would be difficult by kinetic means. However, in its stereochemical outcome, the siloxonium pathway might resemble a Mukaiyama process.



The cycloaddition of parent diene **1** with cinnamaldehyde had been described by Kerwin.[23] Only the heterocycloaddition leading to the styryldihydropyrone **8** was observed. Closer examination of the product mixture from this reaction under boron trifluoride etherate catalysis (−78 °C, 4 h, to 0 °C) led to the isolation of the hydroxy enone **9** (6%) along with styrylpyrone **8** (72%). Upon rapid quenching after addition of the catalyst at −78 °C (5 min), the yield of **8** fell to 38%. The aldol-like products **9** and **10** constituted a major fraction of the product mixture (40% com-

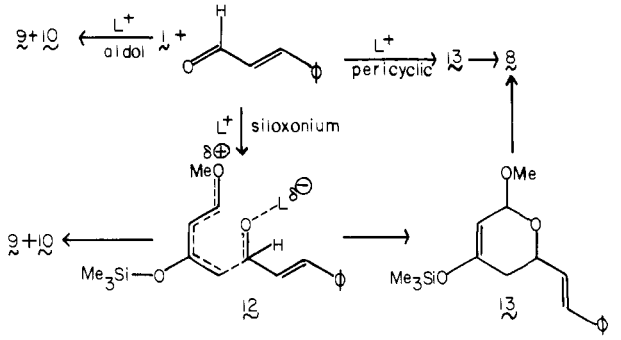
(4) Izumi, Y.; Tai, A. "Stereodifferentiating Reactions"; Kodanshar Ltd.: Tokyo; Academic Press: New York, 1977.
(5) Konowal, A.; Jurczak, J.; Zamojski, A. *Tetrahedron* **1976**, *32*, 2976 and references cited therein; Zamojski, A.; Banaszek, A.; Gyrienkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.
(6) David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Chem. Commun.* **1978**, 535. David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. David, S.; Lubineau, A. *Nouv. J. Chim.* **1977**, *1*, 375.
(7) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464.
(8) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3329.
(9) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(10) Danishevsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.
(11) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.
(12) (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) The yields reported in ref 12a are unoptimized and can generally be improved by use of the homogeneous $ZnCl_2$/THF catalyst/solvent system described in this work.
(13) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981.
(14) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(15) Danishefsky, S.; Pearson, W.; Harvey, D., unpublished results.
(16) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451.
(17) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968.
(18) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.
(19) Larson, E. R.; Danishefsky, S. J. *Tetrahedron Lett.* **1982**, *23*, 1975.
(20) (a) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457. (b) Larson, E. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 6458.
(21) (a) For recent reviews of the theory and mechanism of the carbocyclic Diels–Alder reaction, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. Gleiter, R.; Böhm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237. (b) For evidence of an analogous ionic intermediate involved in a Lewis acid catalyzed carbocyclic Diels–Alder reaction, see: Thompson, H. W.; Melillo, D. G. *J. Am. Chem. Soc.* **1970**, *92*, 3218. A similar two-step ionic pathway for the protic acid catalyzed formation of dihydropyrans from aldehydes and dienes has been proposed without experimental backing: Ansell, M. F.; Charalambides, A. A. *J. Chem. Soc., Chem. Commun.* **1972**, 739. (c) Eisler, B.; Wasserman, A. *J. Chem. Soc.* **1953**, 979. Bock, C. W.; George, P.; Trachtman, M.; Zanger, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 26.
(22) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Cf. an analogous two-step procedure for the synthesis of γ-pyrones: Koreeda, M.; Akagi, H. *Tetrahedron Lett.* **1980**, 1197. Morgan, T. A.; Ganem, B. *Tetrahedron Lett.* **1980**, 2773.
(23) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3183.

bined), along with unreacted aldehyde and the bis adduct **11**[24]



(3%). The yield of pyrone **8** remained at ca. 40% despite several attempts at early quenching, indicating a rapid, initial formation of pyrone. The aldol products **9** and **10** were independently resubjected to the reaction conditions employed above. Each underwent only slow conversion to **8**: after 4 h, the conversion of the silyloxy dienone **10** to **8** is 75%. The hydroxy derivative **9** underwent conversion somewhat more rapidly (70% after 1.5 h). *However, neither compound cyclizes with sufficient rapidity to account for the bulk of pyrone which is obtained within a few minutes at −78 °C.*

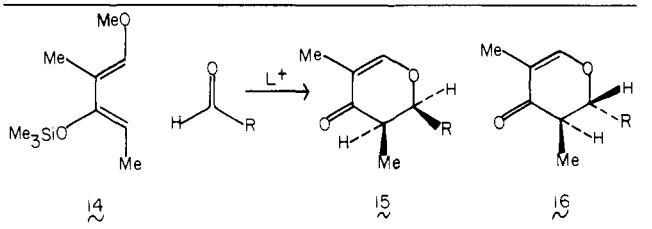
An aldol pathway has been demonstrated, as has a pathway to pyrone **8** that is independent of the obvious aldol type of intermediates. Compound **8** might be arising from a pericyclic pathway, via an undetected intermediate, **13**, while a concurrent Mukaiyama process leads to **9** and **10**. Alternatively, a single siloxonium entity, **12**, might account for all the products as shown.



Stereochemical markers present in the diene **14**[25] would address the question of topology. Therefore, a survey of reaction conditions and substrates for the cyclocondensation of the dimethyl diene **14** with a broad range of aldehydes was undertaken. *A remarkable reversal of product stereochemistry could be achieved by changing the catalyst/solvent system.* For instance, boron trifluoride etherate in dichloromethane is a trans-selective system, while the zinc chloride in tetrahydrofuran conditions promotes cis selectivity. The data are summarized in Table I. The NMR coupling constants of the protons at C_2 and C_3 (1–5 Hz for the cis series vs. 8–12 Hz for the trans series) provide a very reliable means for establishing their relative configurations.

When the reaction of diene **14** with benzaldehyde, under catalysis by zinc chloride in tetrahydrofuran, was quenched, without aqueous workup conditions, and the mixture purified by rapid chromatography, the enol ether **17** was isolated in 41% yield, in addition to **15b** (26%). Brief treatment of **17** with trifluoroacetic acid effected its smooth conversion to **15b** thus confirming the cis stereochemistry at the enol ether stage. This is the fact example of the isolation of a type **5** intermediate from the cyclocondensation process.[26] In all of the zinc chloride cases studied, save for one

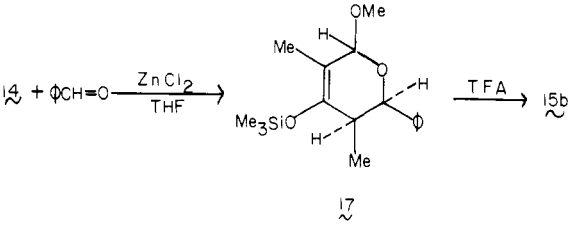
Table I



	R	method	15 (yield)	16 (yield)
a	ηC_5H_{11}	A (i BF_3-CH_2Cl_2-78°; ii TFA)	2i	69
		B (i $ZnCl_2$-THF; ii $NaHCO_3$; iii TFA)	9i	2
b	Φ	A	23	68
		B	78	<2
c	$\Phi(CH_2)_3$	A	17	64
		B	83	<2
d	ΦCH_2OCH_2	A	17	68
		B	66	24

significant deviation (entry d, Table I), virtually exclusive cis selectivity is observed. No acyclic intermediates such as **9** or **10** were detected.

The other configurational relationship in compound **17**, i.e., the relationship of the "anomeric" center relative to chiral centers C_2 and C_3, was not readily settled with certainty.[27] The stereospecificity of its formation suggests that it arose from a suprafacial cycloaddition of diene **14**.



Siloxy diene **14** is the sole product of the enol silylation of (*E*)-1-methoxy-2-methylpent-1-en-3-one. By contrast, a 4:1 mixture of siloxy dienes **19** and **20**, respectively, is obtained by the enol silylation of **18**.[28]

The 4:1 mixture of dienes was treated with benzaldehyde under zinc chloride catalysis in tetrahydrofuran. After 36 h, only the *E,Z* isomer **19** was consumed. The enol ether **21** (53% based on the amount of **19** initially present) and the *cis*-pyrone **22** (31% based on **19** initially present) were isolated upon disappearance of the *E,Z* isomer (ca. 36 h). The (*E,E*)-diene **20** was recovered in a homogeneous state and then resubjected to the above reaction conditions. Very modest yields (11%) of the *trans*-pyrone **23** and even less of the cis isomer **22** (3%) were obtained (86 h). No intermediates of the type **5** could be isolated after the prolonged period required for reaction of this much slower diene.

The enoxy silane **21**, obtained from diene **19**, reacted with *m*-chloroperbenzoic acid to give a mixture of the siloxy ketone **24** (40%) and the hydroxy ketone **25** (39%).[29] The formation of these products served to support the stereochemical assignment at the anomeric center in **21**. The lack of detectable acyclic intermediates, the strict stereochemical suprafaciality in the mode of diene addition, and the massive difference in the rate of reactions of the dienes **19** and **20** (vide supra) are all consistent with

(24) The bis adduct **11** was independently synthesized from **8** and **1** by reaction with BF_3·Et_2O.

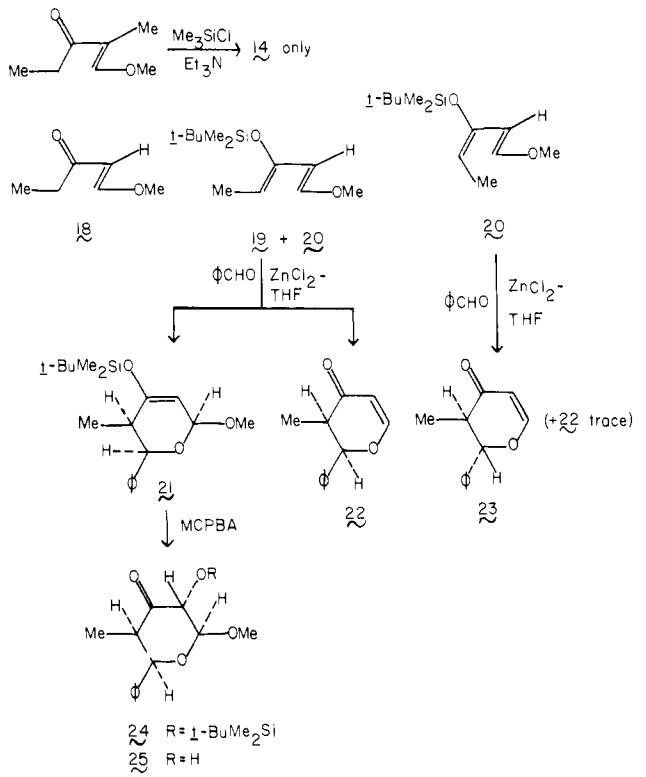
(25) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(26) The silyl enol ethers **5** are frequently unstable to prolonged exposure to the $ZnCl_2$ catalyst and may often be more efficiently prepared by use of the milder Eu(III) catalysts. See ref 17 and references therein.

(27) Rigorous ^1H NMR stereochemical characterization of **17**, with regard to anomeric configuration, was complicated by the paucity of vicinal coupling and, more importantly, by the lack of C_1 epimeric material for side-by-side comparison.

(28) We have found that formation of trisubstituted dienes of this type generally leads to mixtures of isomeric products.

(29) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

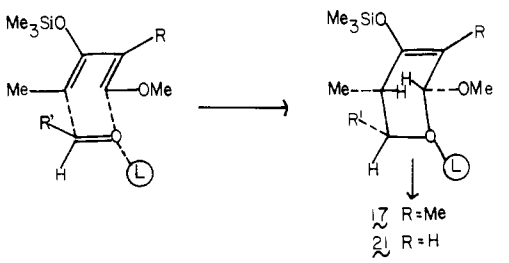


well-known patterns in the all-carbon pericyclic cycloaddition reaction.[21c,30]

The formation of the cis adducts of the type **17** and **21** by the cycloaddition pathway correlates with an endo alignment of the aldehyde R residue and the diene. The usual[31] explanations advanced for endo topology in the all-carbon reaction lack cogency for the heterocyclic variation discovered herein, since the specificity pertains even when the R group of the aldehyde is strictly aliphatic (e.g., C_5H_{11}). An alternative interpretation may be advanced based on the reasonable assumption of anti orientation of the Lewis acid catalyst/solvent array,[32a] relative to the R group of the aldehyde, on complexation of the carbonyl group. If the effective steric demand of the catalyst/solvent ensemble is greater than that of the R group, the apparent endo specificity observed for the R function could be the consequence of an exo specificity for the catalyst/solvent array. The absence of endo specificity in the purely thermal variation of the hetero Diels–Alder reaction with aldehyde dienophiles[33] would be accommodated in this explanation.

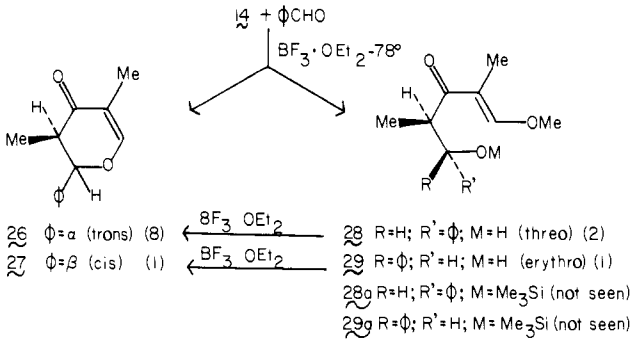
The deviation of the α-hetero-substituted aldehyde (Table I, entry d, R = CH_2OCH_2Ph) from the trend of virtually exclusive cis-product delivery would arise from chelation of the Lewis acid between the α-oxygen and the aldehyde carbonyl group. This chelation would locate the catalyst syn to the R group of the aldehyde and would then serve to direct the diene approach exo to the R group. Exploitation of chelation for diastereofacial selectivity is the subject of the succeeding paper.

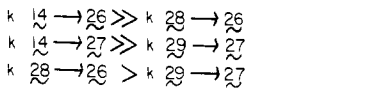
Turning to the boron trifluoride mediated variation, the reaction of homogeneous **14** and benzaldehyde under the standard conditions (methylene chloride, −78 °C) afforded, on quenching 5 min after catalyst addition, an 8:1 mixture of *trans*- and *cis*-pyrones **26** and **27** in 48% yield and a 2:1 mixture of threo and erythro aldol-like products **28** and **29** in 46% yield. Compounds **28** and **29** suffered clean conversion under trifluoroacetic acid catalysis to the corresponding pyrones thus vouchsafing the stereochemical assignments. Postponement of the workup until 45 min after charge resulted in only marginal alterations in the yields and ratios of products (**26**:**27** = 9:1, 46% combined; **28**:**29** = 1.5:1, 44% combined). Initial pyrone formation (within 5 min), as in the cinnamaldehyde case, is much more rapid than the conversion of any acyclic products present in the reaction medium. Again it is demonstrated that dihydropyrones **26** and **27** are not arising from acyclic products **28** and **29**. While silyl ethers **28a** and **29a** were not detected, it would seem most unlikely that their rates of the cyclization would surpass those of the hydroxy compounds.

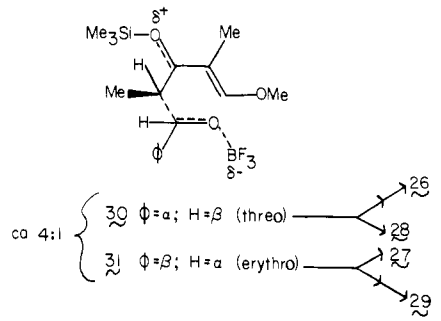


Further insights were gained by resubjecting a 1.5:1 mixture of the alcohols **28** and **29** to the reaction conditions. On quenching at partial conversion (30 min), the pyrones **26** and **27** were isolated in a 4:1 ratio and in 28% yields. A 67% recovery of erythro-enriched (**29**:**28** = 1.2:1) carbinols was realized. *Thus, alcohols **29** and **29** do undergo cyclization, but at a rate that is too slow to account for the significant amount of dihydropyrone isolated after early quenching. Of the two alcohols, the cyclization rate of the threo compound **28** (leading to trans-**26**) is significantly greater than that for the corresponding reaction of erythro isomer **29** (leading to cis-**27**).*

Again, it might be supposed that pyrones **26** and **27** arise from a pericyclic pathway, whereas alcohols **28** and **29** reflect a Mukaiyama reaction. Since the zinc chloride mediated process, which







has been shown to be an authentic cyloaddition, leads to largely

(30) See ref 21a.

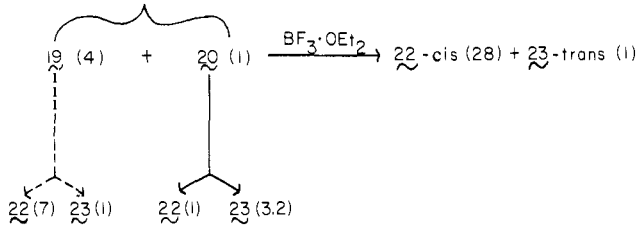
(31) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388. Salem, L. *Ibid.* **1968**, *90*, 553. Herndon, W. C.; Hall, L. H. *Theor. Chim. Acta* **1967**, *7*, 4. Houk K. N. *Tetrahedron Lett.* **1970**, 2621.

(32) (a) Cf. protonation of aldehyde carbonyls in superacid media (Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735. Olah, G. A.; O'Brien, D. H.; Calin, M. *Ibid.* **1967**, *89*, 3582) wherein the carbonyl-associated proton and alkyl residue adopt an anti disposition. (b) Protonation of α-chloro-substituted aldehydes in superacid media shows a divergence from the preferred anti orientation.[12a] The syn-protonated aldehyde is presumably stabilized by intramolecular hydrogen bonding involving the α-chloro substituent and the carbonyl associated photon. (Thil, L.; Riehl, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 591).

(33) For example, see ref 3 and also: Konowal, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1968**, *42*, 2045. Zamojski, A.; Konowal, A.; Jurczak, J. *Ibid.* **1970**, *44*, 1981.

cis product (see Table I), it seems unlikely that another pericyclic process, catalyzed by boron trifluoride, would be virtually exo specific (cf. 9:1 ratio of pyrones **26** and **27**). A more concise explanation involves the siloxonium arrays **30** and **31**. Consistent with the observed relative rates of cyclization for the *threo*- vs. *erythro*-alcohols (see above), the *threo* siloxonium array **30** cyclizes more efficiently than its erythro counterpart **31**. The latter exhibits a greater preference for formation of silyl-transfer acyclic product **29**. From this view, the 4:1 overall observed ratio of *trans*-**26** to *cis*-**27** dihydropyrone (see Scheme I) reflects the ratio of *threo*-*erythro*-siloxonium species, each of which exhibits different relative rates of cyclization/aldolization. The preference for threo stereochemistry in the authentic Mukaiyama aldol reaction of (*Z*)-enoxy silanes has been demonstrated by Chan.[34]

By contrast, reaction of a 4:1 mixture of **19** and **20** with benzaldehyde, under boron trifluoride etherate catalysis, afforded a 2.8:1 ratio of cis (**22**)/trans (**23**) in 73% yield. When the minor (*E*,*E*)-monomethyl diene **20**, isolated as described above, was subjected to these conditions, the *trans*-pyrone dominated (**23**:**22** = 3.2:1; 88:). Given this information, a crude estimate of the selectivity exhibited by the *E*,*Z* isomer **19** under boron trifluoride catalysis is ca. 8.5:1 in favor of formation of the *cis*-pyrone **22**.

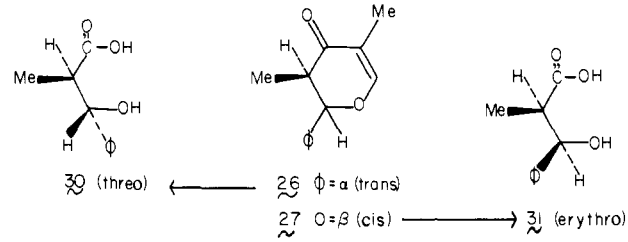


This result stands in sharp contrast to the strong trans preference of the dimethyldiene **14** under the same conditions. This difference might reflect a greater tendency for a pericyclic mechanism in the trisubstituted diene. Conceivably, the s-cis coplanar conformation, which is required for the pericyclic process, is more kinetically accessible in **14**, relative to **20**. Apparently cyclocondensations with boron trifluoride etherate are delicately balanced between several mechanistic variations which have very different stereochemical consequences. Small changes in the diene tilt the mechanism and stereochemistry sharply. Such effects can be exploited at the synthetic level.

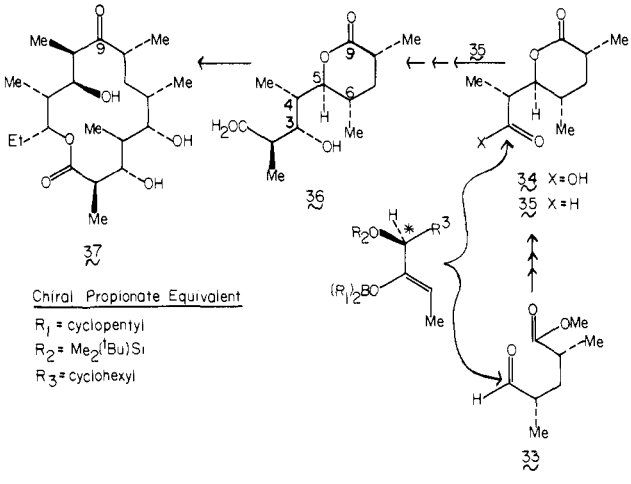
Control of the stereochemistry of the cyclocondensation reaction has implications for synthesis. Of course, many natural products such as carbohydrates,[35] spiro ketals,[36] and thromboxanes[37] contain pyranoid substructures.

Furthermore, a variety of options for opening of the pyran ring can be envisioned. In this way the cyclocondensation method can be applied to a whole range of acyclic targets bearing linear networks of chirality. In essence, the pyran ring is used as a matrix in which stereochemical control can be exercised.[38] This stereochemistry is transferred to an acyclic product.

For example, dihydropyrans **26** and **27** suffer oxidative cleavage upon treatment with ozone followed by hydrogen peroxide, giving rise to the β-hydroxy esters **30** and **31**, respectively.[18] The topological control in the synthesis of the dihydropyrans emerges as erythro–threo control in the aldol-like products.[39,40]



A synthesis of the eastern zone (carbons 1–9) of 6a-deoxyerythronolide B algycone (**37**) offered the opportunity to test the applicability of our stereochemical findings in a more complex setting. The total synthesis of **37** had been achieved in a brilliant tour de force by the Masamune group using stereocontrolled erythro aldol condensations.[41,42] The subunit **36** had served to



house the chirality of carbons 1–9 in the Masamune synthesis. This system had been constructed via the well-known Prelog–Djerassi lactone **34**.[43,44] The aldehyde **35**, derived from **34**, had been subjected to aldol condensation with a suitable propionate equivalent.[42] Aldol condensation proceeded in the erythro sense. The facial control in this process (in the Cram sense)[45,46] is furnished via the chiral auxiliary in the propionate, rather than through any biasing effects inherent in the aldehyde itself.[47a] The Masamune synthesis of **34** also had involved an aldol condensation in the erythro topological sense. As in the case of **35**, the diastereofacial control in the aldol condensation of **33** arises from a chiral auxiliary in the propionate, rather than from any special features in the aldehyde moiety.[47b]

The route followed herein involved two cyclocondensation reactions. As in the Masamune synthesis, the aldehyde **35** was to be employed, and an *erythro* topology in an overall aldol process is required to reach **36**. Thus, in both syntheses, the C_3–C_4 stereochemistry is established through an erythro, aldol-equivalent condensation. However, in the siloxy diene synthesis described here, the C_5–C_6 (rather than C_4–C_5) bond is established through the aldol-equivalent pathway. In such a construction, *threo* to-

(34) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029.

(35) For examples of carbohydrate targets, see: "Natural Products Chemistry"; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Kodanshu: Tokyo; Academic Press: New York, 1975; Vol. 2, Chapter 8.

(36) For examples, see: Wierenga, W. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, pp 299–338.

(37) E.g., thromboxane B_2. See: Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562. Schneider, W. P.; Morge, R. A. *Tetrahedron Lett.* **1976**, 3283.

(38) The 2,3-dihydro-γ-pyrone system allows utilization of the large body of carbohydrate synthetic techniques, even though a great number of the pyrans readily available by the cyclocondensation methodology would be very difficult to obtain from carbohydrate precursors.

(39) For a recent review of the stereoselective aldol condensation, see: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics Stereochem.* **1982**, *13*, 1.

(40) For a recent review of the aldol condensation as a tool for stereoselective organic synthesis, see: Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1983; Vol. II.

(41) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, D. R., Eds.; Pergamon: Oxford, 1980; pp 197–215.

(42) Masamune, S.; Hirama, M.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(43) Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785. Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2907, 6390.

(44) For recent syntheses of (±)-**34**, see: Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357 and references therein.

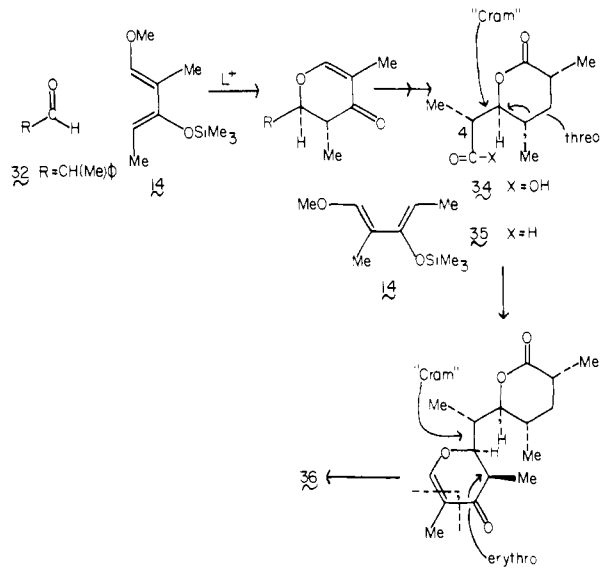
(45) Cram, D. J., Abd. Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.

(46) For a more recent review of the theory of stereochemical factors in nucleophilic additions to carbonyl derivatives, see: Anh, N. T. *Topics Curr. Chem.* **1980**, *88*, 146.

(47) (a) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Tetrahedron Lett.* **1979**, 3937.

pology is required in the first aldol step between diene **14** and the unspecified aldehyde **2**. The attractiveness of this construction in testing the methodology was obvious since, in principle, both erythro (zinc chloride catalysis) and threo (boron trifluoride etherate) capabilities had apparently been built into the cyclocondensation reaction.

While precedents were now available for guidance on the erythro–threo problem, no background information pertaining to the facial question was available. It is seen that in the construction proposed below, a Cram[45] type of facial control was required in



both aldol steps. This stands in contrast to the Masamune synthesis wherein "Cram" control was required in the construction of the C_3–C_4 bond, but "anti-Cram" specificity[45,46] was needed as the C_5–C_6 bond is fashioned. Thus, the synthesis described below provided an attractive setting for probing the matter of facial control in the cyclocondensation reaction.

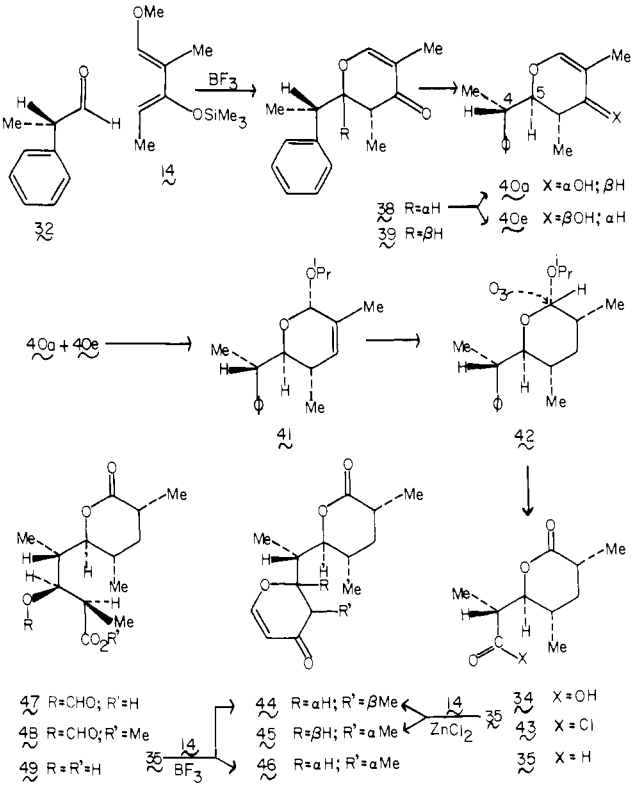
Aldehyde **32** should be readily available, ideally in resolved form.[48] It should in fact provide strong facial selectivity in the Cram sense. Its R function should be convertable to a carboxylic acid without eroding the stereointegrity of the α-chiral center at C_4. The usefulness of 2-phenylpropanal in these contexts was examined.

Reaction of **32** with diene **14** in methylene chloride at −78 °C under the influence of boron trifluoride etherate gave a mixture which was treated with trifluoroacetic acid in tetrahydrofuran. After 2.5 h at room temperature, a 95% yield of two products in a 4.3:1 ratio was obtained. An 80% yield of the major component, clearly a trans isomer, at a purity level of 94% was realized. The minor component was a cis isomer. At this stage, the configurational relationship of carbons **4** and **5** was unknown. Since the two compounds could be partially equilibrated on treatment with alumina–chloroform, it seemed that they belonged to a common C_4–C_5 series.[49] At this stage, it was presumed that the stereochemistry at C_4–C_5 is as shown in structures **38** and **39**, respectively. Subsequent events served to validate this presumption.

Treatment of **38** with diisobutylaluminum hydride in toluene afforded a mixture of epimers **40a** and **40e**. These compounds are readily separated by silica chromatography and were each, in fact, characterized (see Experimental Section). However, for purposes of the synthesis, the mixture was taken onward. Reaction of the **40a–40e** mixture with isopropyl alcohol and *p*-toluenesulfonic acid produced a 95% yield of the isopropyl glycoside formulated[50] as **41**.

Reduction of **41** in ethyl acetate solution was effected through the action of hydrogen over a palladium–aluminum catalyst. The resultant dihydro product, formulated as **42**, was subjected to the action of ozone in aqueous acetic acid containing a trace of trifluoroacetic acid. Oxidative workup was accomplished with hydrogen peroxide in aqueous acetic acid.[51] A Deslongchamps-like oxidation[52] had indeed accompanied the oxidative dismemberment of the phenyl substituent. The Prelog–Djerassi lactone **34**, mp 116–117 °C, was isolated in 56% yield, thereby confirming the stereochemical assignments of **38** and **42**.

The lactone acid **34** was converted to its acid chloride **43**, which underwent smooth Rosenmund reduction to afford **35** in high yield. As discussed above, erythro specificity was to be sought in the next aldol-equivalent process. Translated to the realm of the dihydropyrone, a cis condensation reaction would be necessary. Accordingly, aldehyde **35** was again subjected to the action of diene **14** but this time under the influence of zinc chloride in tetrahydrofuran. A major product, mp 188–189 °C, was obtained in 43% yield. Examination of its high-field NMR spectrum clearly indicated it to be one of the cis 2,3-dihydro-4-pyrone isomers. Unfortunately, the reaction also gave rise to a 27% yield of a stereoisomeric cis-fused 2,3-dihydropyran. It seemed very likely that these two compounds corresponded to facial isomers in the pericyclic cycloaddition reaction of **35** under zinc chloride catalysis. The alternative possibility of partial racemization at C_4 seemed unlikely. Thus, when the reaction between **35** and **14** was run to only partial completion, the recovered aldehyde was free of any detectable epimer. *That the major product mp 188–189 °C is in fact **44** was rigorously demonstrated by a single-crystal X-ray crystallographic determination.*[53] The minor compound obtained as an oil is therefore formulated as **45** as discussed above.



In keeping with previous trends, reaction of **35** with **14** under boron trifluoride catalysis gave a 1:2 mixture of the previously encountered **44** and a *trans*-dihydropyran formulated as **46**. The assignment of the major product to the Cram-like diastereofacial series[45,46] is not rigorous, and is based solely on analogy with cis isomer **44**, which belongs to this series. Interestingly, in the boron trifluoride mediated reaction, both the cis and trans topological isomers emerge as a single facial isomer.

(48) Consiglio, G.; Peno, P.; Flowers, L. I.; Pittmann, C. U. *J. Chem. Soc., Chem. Commun.* **1983**, 612.
(49) N. Kato, of these labs, unpublished results.
(50) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.
(51) Criegee, R.; Höver, H. *Chem. Ber.* **1960**, *93*, 2521.
(52) Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465.
(53) Adams, R. D.; Segmuller, B. E. *Acta Crystallogr., Sect. C* **1983**, *C39*, 780.

In the final step in the synthesis, **44** was subjected to ozonolysis followed by oxidation with hydrogen peroxide to afford the formate acid **47** in high yield. With a view toward ease of characterization, this compound was converted to the formate methyl ester **48**. Compounds **47** and **48** correspond to the C_1–C_9 fragment of the Masamune synthesis. The hydroxy acid **49** had been reported[52] but, in our hands, proved to be an unstable entity. Its instability toward acidic and basic reagents was described to us by Professor Masamune.[54] Our stereochemical assignments rest securely on the crystallographic determination of **44** and on the fully characterized **47** and **48**.

In summary, the synthetic exercise was a limited success. Good topological selectivity in opposite directions was realized with boron trifluoride etherate and with zinc chloride in tetrahydrofuran. The former regimen also resulted in excellent facial control in the Cram sense with 2-phenylpropanal.[55] However, strong facial control was decidedly lacking in the reaction of lactonic aldehyde **35** with diene **14** under zinc chloride catalysis.

In contemplating the extension of the cyclocondensation method to the construction of multiply chiral ensembles, a variety of options for facial selectivity will be necessary. Major progress in this regard was realized by methodology described in the following paper.

Experimental Section

All commercial chemicals were used as obtained without further purification, except for solvents which were purified and dried, where appropriate, before use by standard methods.[56] Preparative column chromatography was carried out on silica gel 60 (E. Merck, 9285, 230–400 mesh) using the flash technique.[57] Thin-layer chromatography was carried out on silica gel 60 GF 254 (E. Merck). Melting points were determined by using a Thomas-Hoover apparatus and are uncorrected. Routine ^{1}H NMR spectra were determined on a Varian EM-390 90-MHz instrument. Fourier transform NMR spectra were determined in $CDCl_3$ on a Jeol FX90Q 90 MHz (^{1}H)/22.5 MHz (^{13}C) instrument, a Varian FT 270 270-MHz instrument, or a Bruker WH500 500-MHz instrument, and all shifts are reported relative to internal $(CH_3)_4Si$. IR spectra were measured in solution ($CHCl_3$) on a Perkin-Elmer 710B spectrophotometer using NaCl cells. Mass spectra were determined on an Hewlett-Packard 5985 GC/MS system. Elemental analyses were performed by Dr. R. Rittner, Olin Research, New Haven, CT, or Galbraith Laboratories, Inc., Knoxville, TN.

Mechanistic and Stereochemical Studies. Reaction of 1-Methoxy-3-((Trimethylsilyl)oxy)-1,3-butadiene (1) with Cinnamaldehyde. To a cold (−78 °C) solution of 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (340 mg, 2.0 mmol) and cinnamaldehyde (265 mg, 2.0 mmol) in dry Et_2O (20 mL) was added $BF_3{\cdot}Et_2O$ (250 μL, 2.0 mmol) dropwise. After 4 h, the canary-yellow mixture was warmed to 0 °C, and saturated $NaHCO_3$ solution (2.5 mL) was added followed by brine (5 mL). The mixture was separated and the aqueous layer extracted with Et_2O (3 × 20 mL); then the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (60% Et_2O/hexane) gave in order of elution the styrylpyrone **8** (290 mg, 72%) and the hydroxy dienone **9** (24 mg, 6%).

Styrylpyrone **8**: ^{1}H NMR (90 MHz) δ 7.38 (m, 6 H), 6.78 (d, J = 16 Hz, 1 H), 6.32 (dd, J = 16, 6 Hz, 1 H), 5.45 (d, J = 6 Hz, 1 H), 5.02 (m, 1 H), 2.55 (m, 2 H); ^{13}C NMR (22.5 MHz) δ 191.9, 163.1, 135.8, 133.8, 128.9, 128.7, 127.0, 125.4, 107.4, 79.8, 42.1; IR ($CHCl_3$) 1680, 1600 cm^{-1}; MS, m/e 200 (M^+). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.76; H, 6.14.

Hydroxy dienone **9**: ^{1}H NMR (90 MHz) δ 7.67 (d, J = 13 Hz, 1 H), 7.34 (5 H, m), 6.70 (d, J = 16 Hz, 1 H), 6.36 (dd, J = 16, 6 Hz, 1 H), 5.61 (d, J = 13 Hz, 1 H), 4.76 (m, 1 H), 3.73 (s, 3 H), 3.56 (br s, 1 H, D_2O exch), 2.77 (d, J = 6 Hz, 2 H); ^{13}C NMR (22.5 MHz) δ 199.0, 163.6, 136.6, 130.6, 130.0, 128.4, 127.5, 126.4, 105.9, 68.7, 57.5, 47.0; IR ($CHCl_3$) 3500 (br), 1680, 1650, 1620, 1600 cm^{-1}; MS, m/e 232 (M^+). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.18; H, 7.11.

Reaction of 1 and Cinnamaldehyde with Early Quenching. The reaction was repeated exactly as above, except the mixture was quenched with saturated $NaHCO_3$ solution (2.5 mL) 5 min after addition of the $BF_3{\cdot}Et_2O$ was complete. Workup as above yielded a complex product mixture, which was separated by careful flash chromatography (65% Et_2O/hexane) to give, in order of elution, cinnamaldehyde (32 mg, 12%), the siloxy dienone **10** (170 mg, 28%), the bis adduct **11** (44 mg, 3%), the styrylpyrone **8** (152 mg, 38%), and the hydroxy dienone **9** (44 mg, 11%).

Siloxydienone **10**: ^{1}H NMR (90 MHz) δ 7.51 (d, J = 13 Hz, 1 H), 7.32 (m, 5 H), 6.59 (d, J = 16 Hz, 1 H), 6.22 (dd, J = 16, 6 Hz, 1 H), 5.60 (d, J = 13 Hz, 1 H), 4.81 (m, 1 H), 3.68 (s, 3 H), 2.83 (dd, J = 15, 8 Hz, 1 H), 2.55 (dd, J = 15, 5 Hz, 1 H), 0.09 (s, 9 H); ^{13}C NMR (22.5 MHz) δ 197.0, 163.2, 136.7, 132.0, 129.3, 128.4, 127.4, 126.3, 102.4, 70.3, 57.3, 49.5, 0.1; IR ($CHCl_3$) 1695, 1670, 1630, 1600, 1250, 840 cm^{-1}; MS, m/e 304 (M^+).

Bis Adduct **11**: ^{1}H NMR (90 mHz) δ 7.61 (d, J = 13 Hz, 1 H), 7.33 (m, 5 H), 6.63 (d, J = 16 Hz, 1 H), 6.23 (dd, J = 16, 5 Hz, 1 H), 5.57 (d, J = 13 Hz, 1 H), 4.83 (br s, 1 H), 4.77 (m, 1 H), 4.41 ("q", J = 6 Hz, 1 H), 3.60 (s, 3 H), 2.81 (dd, J = 14, 7 Hz, 1 H), 2.50 (dd, J = 14, 6 Hz), 2.12 (d, J = 6 Hz, 2 H), 0.17 (s, 9 H); ^{13}C NMR (22.5 MHz) δ 197.1, 163.1, 147.9, 136.7, 131.3, 128.9, 128.6, 127.7, 126.5, 106.2, 105.3, 69.9, 69.1, 57.5, 47.1, 35.3, 0.03; IR ($CHCl_3$) 1685, 1670, 1620, 1600, 1250, 840 cm^{-1}; MS, m/e 372 (M^+).

Cyclization of Acyclic Adducts 9 and 10. To a solution of the hydroxy dienone **9** (46 mg, 0.2 mmol) in dry Et_2O (1 mL) at −78 °C was added 0.2 M $BF_3{\cdot}Et_2O$ in Et_2O (1 mL) and the mixture stirred at −78 °C. Frequent TLC analysis (65% Et_2O/hexane) showed slow conversion of **9** to the dihydropyrone **8**. After 1.5 h, the mixture was quenched with saturated $NaHCO_3$ solution (0.5 mL), diluted with Et_2O (10 mL) and brine (5 mL), and separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (65% Et_2O/hexane) gave the dihydropyrone **8** (28 mg, 70%).

Treatment of the silyloxy dienone **10** (60 mg, 0.20 mmol) as above gave, after 4 h, pyrone **8** (30 mg, 75%) and hydroxy dienone **9** (4 mg, 10%).

Preparation of 2,3-Dihydro-3,5-dimethylpyrones 15 and 16. Typical $BF_3{\cdot}Et_2O$ Procedure (Method A). To a cold (−78 °C) solution of benzaldehyde (106 mg, 1.0 mmol) and the dimethyl diene **14** (220 mg, 1.1 mmol) in dry CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (125 μL, 1.0 mmol) dropwise. After 1.5 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution (1 mL), allowed to warm to 25 °C, then diluted with brine (5 mL), and separated and the aqueous layer extracted with CH_2Cl_2 (2 × 15 μL). The combined organic layers were washed with brine, dried, filtered, and evaporated. The residue was dissolved in CCl_4 (5 mL) and treated with trifluoroacetic acid (100 μL). When conversion of acyclic products to pyrone was complete (NMR or TLC analysis), the mixture was quenched with saturated $NaHCO_3$ solution (1 mL) and worked up as above. Flash chromatography of the residue gave, in order of elution, the *trans*-pyrone **16b** (137 mg, 68%) and the *cis*-pyrone **15b** (46 mg, 23%).

trans-Pyrone **16b**: mp 87–88 °C (hexane); ^{1}H NMR (90 MHz) δ 7.37 (s, 5 H), 7.30 (br s, 1 H), 4.89 (d, J = 12 Hz, 1 H), 2.77 (dq, J = 12, 7 Hz, 1 H), 1.72 (br s, 3 H), 0.92 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 194.7, 158.6, 137.6, 129.0, 128.7, 127.4, 113.1, 86.9, 44.7, 10.7, 10.3; IR (CCl_4) 1670, 1625 cm^{-1}; MS, m/e 202 (M^+). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.34; H, 7.05.

cis-Pyrone **15b**: mp 70–71 °C (hexane); ^{1}H NMR (90 MHz) δ 7.38 (br s, 6 H), 5.45 (d, J = 3 Hz, 1 H), 2.58 (qd, J = 7, 3 Hz), 1.73 (d, J = 1 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 197.2, 158.5, 136.7, 128.3, 127.8, 125.3, 112.3, 82.7, 45.5, 10.5, 9.8; IR (CCl_4) 1675, 1625 cm^{-1}; MS, m/e 202 (M^+). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.16; H, 6.80.

In a similar manner, the following were prepared (% yield).

From Hexanal, 16a (69%): ^{1}H NMR (90 MHz) δ 7.19 (br s, 1 H), 3.98 (dt, J = 11, 6 Hz, 1 H), 2.38 (dq, J = 11, 7 Hz, 1 H), 1.63 (d, J = 1 Hz, 3 H), 1.8–1.1 (m, 8 H), 1.11 (d, J = 7 Hz, 3 H), 0.89 (t, J = 6 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 195.5, 158.6, 112.4, 83.9, 43.5, 32.4, 31.6, 24.1, 22.5, 13.9, 10.7, 10.6; IR (CCl_4) 1675, 1630 cm^{-1}; MS, m/e 196 (M^+).

15a (21%): ^{1}H NMR (90 MHz) δ 7.20 (br s, 1 H), 4.28 (td, J = 7, 3 Hz, 1 H), 2.33 (qd, J = 8, 3 Hz, 1 H), 1.63 (br s, 3 H), 1.7–1.0 (m, 8 H), 1.02 (d, J = 8 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 197.7, 159.0, 111.9, 81.8, 43.2, 31.4, 30.2, 24.8, 22.4, 13.8, 10.4, 9.4; IR (CCl_4) 1675, 1625, cm^{-1}; MS, m/e 196 (M^+).

From (Benzyloxy)acetaldehyde, 16d (68%): ^{1}H NMR (90 MHz) δ 7.23 (s, 5 H), 7.11 (br s, 1 H), 4.59 (d, J = 12 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 3.98 (dt, J = 12, 3 Hz, 1 H), 3.73 (dd, J = 12, 3 Hz, 1 H), 3.60 (dd, J = 12, 3 Hz, 1 H), 2.66 (dq, J = 12, 7 Hz, 1 H), 1.65 (br s, 3 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 194.7, 158.2,

(54) Several attempts on our part to retrieve the hydroxy acid **49** from the formate acid **47** led to a mixture of products, each of which underwent facile interconversion on exposure to mild acid or mild base.

(55) For a discussion of diastereofacial selectivity in the Lewis acid mediated addition of silyl enol ethers to chiral aldehydes, see: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

(56) Perrin, D. D.; Amarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: Oxford, 1966.

(57) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

137.5, 128.2, 127.6, 127.5, 112.4, 83.0, 73.4, 69.2, 40.0, 10.5, 10.0; IR (CCl_4) 1675, 1630 cm^{-1}; MS, *m/e* 246 (M^+).

15d (17%): ^1H NMR (90 MHz) δ 7.23 (s, 5 H), 7.07 (br s, 1 H), 4.47 (br s, 2 H), 4.42 (td, J = 6, 3 Hz, 1 H), 3.63 (dd, J = 11, 6 Hz, 1 H), 3.48 (dd, J = 11, 6 Hz, 1 H), 2.42 (qd, J = 7, 3 Hz, 1 H), 1.60 (s, 3 H), 0.97 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 196.3, 158.2, 137.5, 128.3, 127.7, 127.5, 112.3, 80.2, 73.4, 68.6, 41.4, 10.4, 9.0; IR (CCl_4) 1675, 1625 cm^{-1}; MS, *m/e* 246 (M^+).

From 4-Phenylbutanal, 16c (64%): ^1H NMR (90 MHz) δ 7.18 (m, 6 H), 3.97 (dt, J = 11, 6 Hz, 1 H), 2.67 (t, J = 7 Hz, 3 H), 2.37 (dq, J = 11, 7 Hz, 1 H), 2.1–1.6 (m, 4 H), 1.63 (d, J = 1 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 195.3, 158.5, 141.8, 128.3, 125.8, 112.4, 83.5, 43.4, 35.5, 31.9, 26.1, 10.6; IR (CCl_4) 1670, 1625 cm^{-1}; MS, *m/e* 244 (M^+).

15c (17%): ^1H NMR (90 MHz) δ 7.20 (m, 6 H), 4.30 (td, J = 7, 3 Hz, 1 H), 2.67 (t, J = 7 Hz, 2 H), 2.35 (qd, J = 7, 3 Hz, 1 H), 2.0–1.5 (m, 4 H), 1.65 (br s, 3 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 197.3, 158.6, 141.5, 128.9, 128.2, 125.8, 111.9, 81.5, 43.2, 35.3, 29.6, 26.8, 10.4, 9.4; IR (CCl_4) 1675, 1620 cm^{-1}; MS, *m/e* 244 (M^+).

From 2-Phenylpropanol, *trans*-Cram 38 (73%): ^1H NMR (270 MHz) δ 7.34–7.14 (m, 6 H), 4.10 (dd, J = 9, 4.5 Hz, 1 H), 3.09 (qd, J = 7, 4.5 Hz, 1 H), 2.48 (dq, J = 9, 7 Hz, 1 H), 1.63 (s, 3 H), 1.38 (d, J = 7 Hz, 3 H), 1.17 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 1660, 1620 cm^{-1}; MS, *m/e* 230 (M^+).

***cis*-Cram 39 (17%)**: ^1H NMR (90 MHz) δ 7.5–7.0 (m, 6 H), 4.25 (dd, J = 11, 3 Hz, 1 H), 3.10 (dq, J = 11, 7 Hz, 1 H), 2.01 (1 H, qd, J = 7, 3 Hz), 1.67 (d, J = 1 Hz, 3 H), 1.41 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 198.1, 159.2, 141.9, 128.9, 127.3, 217.1, 112.4, 85.8, 41.3, 40.6, 19.3, 10.5, 9.5; IR ($CHCl_3$) 1665, 1625 cm^{-1}; MS, *m/e* 230 (M^+).

Typical $ZnCl_2$-Catalyzed Procedure (Method B): To a solution of anhydrous $ZnCl_2$ (136 mg, 1.0 mmol) in anhydrous THF at 25 °C was added benzaldehyde (106 mg, 1.0 mmol) followed by dimethyl diene **14** (400 mg, 2.0 mmol). After 26 h, the mixture was quenched with saturated $NaHCO_3$ solution (1 mL), the supernatent decanted, and the residue triturated with Et_2O (3 × 15 mL). The combined supernatants were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue (ca. 2:1 mixture of cycloadduct **17** and dihydropyrone **15b**) was dissolved in CCl_4 (5 mL) and treated with trifluoroacetic acid (50 μL). After 5 min, the mixture was evaporated and the residue purified by flash chromatography (40% Et_2O/hexane) to give the *cis*-dihydropyrone **15b** (158 mg, 78%).

The Following Were Similarly Obtained from Dimethyl Diene 14 (400 mg, 2.0 mmol) and RCHO (1.0 mmol): R = $CH_2(CH_2)_4$, *cis*-**15a** (178 mg, 91%), *trans*-**16a** (4 mg, 2%); R = $Ph(CH_3)CH$, *cis*-Cram **39** (184 mg, 80%), *cis-anti*-Cram **39** (26 mg, 11%), *trans*-**38** (0 mg, 0%); R = $PhCH_2OCH_2$, *cis*-**15d** (164 mg, 66%), *trans*-**16d** (57 mg, 24%); R = $Ph(CH_2)_3$, *cis*-**15c** (203 mg, 83%), *trans*-**16c** (0 mg, 0%).

cis-anti-Cram **39**: ^1H NMR (90 MHz) δ 7.27 (br s, 5 H), 7.08 (br s, 1 H), 4.31 (dd, J = 10, 3 Hz, 1 H), 3.11 (dq, J = 10, 7 Hz, 1 H), 2.61 (qd, J = 8, 3 Hz, 1 H), 1.63 (br s, 3 H), 1.21 (d, J = 7 Hz, 3 H), 1.13 (d, J = 8 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 197.8, 159.5, 143.4, 128.5, 127.6, 126.8, 112.0, 85.4, 41.7, 40.5, 17.6, 10.5, 9.4; IR ($CHCl_3$) 1665, 1620 cm^{-1}; MS, *m/e* 230 (M^+).

Isolation of Cycloadduct 17. To a solution of anhydrous $ZnCl_2$ (136 mg, 1.0 mmol) in dry THF (10 mL) at 25 °C were added benzaldehyde (106 mg, 1.0 mmol) and dimethyl diene **14** (200 mg, 1.0 mmol). After 36 h, Et_3N (0.3 mL) was added, the mixture passed through a short silica bed (230–400 mesh, 2 in. × 10 mm, prewashed with 1% Et_3N in Et_2O) under pressure, the silica washed with 1% Et_3N in Et_2O (25 mL), and the combined filtrates evaporated. Flash chromatography (30% Et_3O/hexane) gave, in order of elution, the silyl enol ether **17** (125 mg, 41%) and the *cis*-pyrone **15b** (53 mg, 26%).

Silyl enol ether **17**: ^1H NMR (90 MHz) δ 7.30 (s, 5 H), 5.21 (br s, 1 H), 4.73 (d, J = 3 Hz, 1 H), 3.43 (s, 3 H), 2.17 (qd, J = 7, 3 Hz, 1 H), 1.57 (br s, 3 H), 0.80 (d, J = 7 Hz, 3 H), 0.23 (s, 9 H); ^{13}C NMR (22.5 MHz) δ 151.9, 140.1, 128.1, 126.9, 125.5, 110.3, 101.6, 75.4, 53.1, 40.0, 12.4, 10.7, 1.0; IR (CCl_4) 1685, 1255, 835 cm^{-1}; MS, *m/e* 306 (M^+).

Treatment of a $CDCl_3$ solution of **17** with trace trifluoroacetic acid cleanly gave pure *cis*-**15b**.

Preparation of Monomethyl Dienes 19 and 20. To a cold (−5 °C) solution of 1-methoxypent-1-en-3-one (230 mg, 2.0 mmol) in Et_2O (10 mL) was added Et_3N (0.32 mL, 2.4 mmol) followed by dropwise addition of *tert*-butyldimethylsilyl triflate (0.48 mL, 2.1 mmol). After 1 h, the mixture was diluted with pentane (15 mL), the precipitated triethylammonium triflate removed by pipette, and the supernatent washed with ice cold saturated $NaHCO_3$ solution (2 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (4% Et_2O/hexane) gave a mixture of the monomethyl dienes **19** and **20** (4:1, 265 mg, 57%).

(*E,Z*)-diene **19**: ^1H NMR (90 MHz) δ 6.50 (d, J = 13 Hz, 1 H), 5.12 (d, J = 13 Hz, 1 H), 4.43 (q, J = 7 Hz, 1 H), 3.45 (s, 3 H), 1.54 (d, J = 7 Hz, 3 H), 0.97 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (22.5 MHz) δ 148.2, 147.2, 104.5, 103.9, 56.2, 26.0, 18.4, 11.5, −3.6; IR (CCl_4) 1665, 1630 cm^{-1}; MS, *m/e* 228 (M^+).

(*E,E*)-Diene **20**: ^1H NMR (90 MHz) δ 6.70 (d, J = 12 Hz, 1 H), 5.41 (d, J = 12 Hz, 1 H), 4.43 (q, J = 7 Hz, 1 H), 3.52 (s, 3 H), 1.57 (d, J = 7 Hz, 3 H), 0.95 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (22.5 MHz) δ 150.0, 146.9, 101.3, 99.1, 56.6, 25.8, 18.3, 11.5, −2.9; IR (CCl_4) 1665, 1630 cm^{-1}; MS, *m/e* 228 (M^+).

The above stereochemical assignments are based on the ^{13}C NMR chemical shifts of the C_2 resonances[58] (104.5 and 99.1 ppm, respectively, for the (*Z*)- and (*E*)-enol silane) which were determined by ^{13}C NMR–^1H NMR correlation via single-proton off-resonance decoupling experiments on isolated **20** and a 4:1 mixture of **19** and **20**.

Reactions of Diene 19 and 20 with Benzaldehyde under Zinc Chloride Catalysis. To a solution of anhydrous $ZnCl_2$ (136 mg, 1.0 mmol) in dry THF (10 mL) at 25 °C were added benzaldehyde (117 mg, 1.0 mmol) and the monomethyl diene mixture **19** and **20** (4:1, 228 mg, 1.0 mmol). After 36 h, dry Et_3N (0.3 mL) was added and the mixture filtered rapidly through a short bed of SiO_2 (230–400 mesh, 2 in. × 15 mm, prewashed with 1% Et_3N in Et_2O) under pressure. The bed was washed with 1% Et_3N/Et_2O (20 mL), and the combined filtrates were evaporated. Flash chromatography (6% Et_2O/hexane, then 33% Et_2O/hexane) gave, in order of elution, the unreacted (*E,E*)-diene **20** (28 mg, 60% recovery), the cycloadduct **21** (141 mg, 42%), and the *cis*-pyrone **22** (46 mg, 24%).

Cycloadduct **21**: ^1H NMR (500 MHz) δ 7.3 (m, 5 H), 5.35 ("t", J = 1.3 Hz, 1 H), 4.90 (d, J = 3.0 Hz, 1 H), 4.74 (d, J = 14 Hz, 1 H), 3.57 (s, 3 H), 2.24 (qd, J = 7.1, 3.0 Hz, 1 H), 0.97 (s, 9 H), 0.81 (d, J = 7.1 Hz, 3 H), 0.27 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (22.5 MHz) δ 158.7, 140.1, 128.1, 126.9, 125.5, 101.4, 99.6, 54.2, 39.8, 25.7, 18.1, 12.6, −4.1, −4.8; IR (CCl_4) 1665 cm^{-1}; MS, *m/e* 334 (M^+). Anal. Calcd for $C_{19}H_{30}SiO_3$: C, 68.22; H, 9.04. Found: C, 67.94; H, 9.04.

cis-Pyrone **22**: ^1H NMR (90 MHz) δ 7.45 (d, J = 6 Hz, 1 H), 7.35 (s, 5 H), 5.50 (d, J = 3 Hz, 1 H), 5.43 (d, J = 6 Hz, 1 H), 2.59 (qd, J = 7, 3 Hz, 1 H), 0.93 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 196.8, 162.3, 136.2, 128.4, 127.9, 125.3, 105.6, 82.8, 45.8, 9.7; IR (CCl_4) 1685, 1605 cm^{-1}; MS, *m/e* 188 (M^+). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.41; H, 6.59.

Reaction of the isolated (*E,E*)-diene **20**: To a solution of anhydrous $ZnCl_2$ (16 mg, 0.12 mmol) in dry THF (0.5 mL) at 25 °C was added benzaldehyde (22 mg, 0.2 mmol) then the (*E,E*)-diene **20** (28 mg, 1.2 mmol) in dry THF (0.5 mL). After 86 h, the mixture was quenched with dry Et_3N (0.1 mL) and filtered through a short bed of silica (230–400 mesh, 5 mm × 0.5 in., prewashed with 1% Et_3N/Et_2O). The bed was washed with 1% Et_3N/Et_2O (10 mL) and the combined filtrates evaporated. Flash chromatography (30% Et_2O/hexane) gave a mixture of *trans*-pyrone **23** and *cis*-**22** (3 mg, 14%, 4:1 trans/cis by ^1H NMR (500 MHz) and HPLC (25% Et_2O/hexane, SiO_2)).

trans-Pyrone **23**: ^1H NMR (90 MHz) δ 7.37 (d, J = 6 Hz, 1 H), 7.35 (s, 5 H), 5.45 (d, J = 6 Hz, 1 H), 4.92 (d, J = 13 Hz, 1 H), 2.81 (dq, J = 13, 7 Hz, 1 H), 0.90 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 194.5, 162.4, 137.1, 129.2, 128.7, 127.4, 106.5, 87.0, 45.0, 10.2; IR (CCl_4) 1680, 1605 cm^{-1}; MS, *m/e* 188 (M^+). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.53; H, 6.64.

Peracid oxidation of **21**: To a suspension of *m*-chloroperbenzoic acid (85%, 105 mg, 0.75 mmol) in dry hexane at −5 °C was added the silyl enol ether **21** (250 mg, 0.75 mmol). After 2 h, the mixture was warmed to 25 °C; then, after an additional 0.5 h, it was filtered through Celite and the filtrate evaporated. The residue was dissolved in acetonitrile (5 mL) and 48% aqueous HF (3 drops) added. After 5 min, saturated $NaHCO_3$ (2 mL) and Et_2O (25 mL) were added, the mixture was separated, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (30% Et_2O/hexane, then 60% Et_2O/hexane) gave, in order of elution, the α-silyloxy ketone **24** (105 mg, 40%) and the α-hydroxy ketone **25** (68 mg, 39%).

Silyloxy ketone **24**: ^1H NMR (90 MHz) δ 7.30 (s, 5 H), 4.79 (d, J = 3 Hz, 1 H), 4.43 (d, J = 8 Hz, 1 H), 4.23 (d, J = 8 Hz, 1 H), 3.60 (s, 3 H), 2.77 (qd, J = 7, 3 Hz, 1 H), 0.93 (s, 9 H), 0.92 (d, J = 7 Hz, 3 H), 0.17 (s, 3 H), 0.07 (s, 3 H); IR (CCl_4) 1730 cm^{-1}; MS, *m/e* 319 (M^+ − MeO·). Anal. Calcd for $C_{19}H_{30}SiO_4$: C, 65.10; H, 8.63; Si, 8.01. Found: C, 65.23; H, 8.65; Si, 8.15.

Hydroxy ketone **25**: mp 103–104 °C (hexane); ^1H NMR (500 MHz) δ 7.42–7.32 (m, 5 H), 4.82 (d, J = 2.6 Hz, 1 H), 4.39 (d, J = 7.9 Hz,

(58) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(59) Cf.; Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, T. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

1 H), 4.36 (dd, J = 7.9, 3.3 Hz, 1 H), 3.69 (s, 3 H), 3.62 (d, J = 3.3 Hz, 1 H, D_2O exchange), 2.93 (qd, J = 7.2, 2.7 Hz, 1 H), 1.01 (d, J = 7.3 Hz, 3 H); IR ($CHCl_3$) 3600–3350, 1710 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.21; H, 6.98.

Reaction of Diene 14 and Benzaldehyde under Boron Trifluoride Catalysis with Early Quenching. To a cold (−78 °C) solution of benzaldehyde (106 mg, 1.0 mmol) and dimethyl diene **14** (220 mg, 1.1 mmol) in dry CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (125 μL, 1.0 mmol), dropwise, followed, after 5 min, by saturated $NaHCO_3$ solution (1 mL). The mixture was diluted with brine (5 mL) and separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (50% Et_2O/hexane) of the residue gave, in order of elution, a mixture of *trans*-pyrone **26** and *cis*-pyrone **27** (100 mg, 48%, 8:1 by NMR analysis) followed by a mixture of *threo*-**28** and *erythro*-**29** (110 mg, 46%). Rechromatography (2% MeOH/$CHCl_3$) of the hydroxy enone mixture gave, in order of elution, pure erythro isomer **29** (30 mg), mp 123–124 °C (hexane), and pure threo isomer **28** (70 mg), mp 108–109 °C (hexane).

Threo-hydroxy enone **28**: ^1H NMR (90 MHz) δ 7.30 (s, 5 H), 7.13 (q, J = 1 Hz, 1 H), 4.82 (dd, J = 7, 5 Hz, 1 H), 3.76 (s, 3 H), 3.32 (d, J = 5 Hz, 1 H, D_2O exchange), 3.28 (dq, J = 7, 7 Hz, 1 H), 1.69 (d, J = 1 Hz, 3 H), 1.04 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 3750–3400, 1630 br cm^{-1}; MS, m/e 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.63; H, 7.67.

Erythro-hydroxy enone **29**: ^1H NMR (90 MHz) δ 7.30 (s, 5 H), 7.17 (br s, 1 H), 5.02 (d, J = 3 Hz, 1 H), 4.06 (s, 1 H, D_2O exchange), 3.83 (s, 3 H), 3.10 (qd, J = 7, 3 Hz, 1 H), 1.70 (br s, 3 H), 1.08 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 3700–3400, 1635 br cm^{-1}; MS, m/e 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 7.65.

Repetition of the above experiment under identical conditions, except for a 45-min delay between catalyst addition and quenching, gave a mixture of *cis*- and *trans*-pyrones (94 mg, 46%, **27**:**26** = 9:1 (cis/trans)) and a mixture of the threo and erythro hydroxy enones **28** and **29** (104 mg, 44%, 1.6:1 threo/erythro).

Treatment of a $CDCl_3$ solution of *threo*-**28** with catalytic trifluoroacetic acid effected smooth cyclization to *trans*-**26**. Similar treatment of *erythro*-**29** gave *cis*-**27**.

Boron Trifluoride Mediated Cyclization of Hydroxy Enones 28 and 29. To a cold (−78 °C) solution of a mixture of *threo*-**28** and *erythro*-**29** (24.0 mg, 0.10 mmol, 1.6:1 threo/erythro) in dry CH_2Cl_2 (1 mL) was added $BF_3{\cdot}Et_2O$ (13 μL, 0.1 mmol). After 0.5 h, saturated $NaHCO_3$ solution (0.5 mL) was added, then brine (2 mL), and CH_2Cl_2 (10 mL). The mixture was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash chromatography (50% Et_2O/hexane) to give a mixture of *trans*- and *cis*-pyrones **26** and **27** (5.6 mg, 28%, 4:1 trans/cis by NMR) and recovered hydroxy enones **28** and **29** (15.0 mg, 67%, 1.2:1 erythro/threo by NMR).

Reaction of Monomethyl Dienes 19 and 20 with Benzaldehyde under Boron Trifluoride Catalysis. To a cold (−78 °C) solution of benzaldehyde (60 mg, 0.55 mmol) and a mixture of the monomethyl dienes **19** and **20** (114 mg, 0.50 mmol, 4:1 *E,Z*/*E,E*) in dry CH_2Cl_2 (5 mL) was added $BF_3{\cdot}Et_2O$ (63 μL, 0.50 mmol). After 2 h, the reaction was quenched by addition of saturated $NaHCO_3$ solution (0.5 mL) and brine (2 mL), the mixture separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in CCl_4 (5 mL), treated with trifluoroacetic acid (100 μL) at 25 °C, then diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ (2 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (40% Et_2O/hexane) gave, in order of elution, the *trans*-pyrone **23** (18 mg, 19%) and the *cis*-pyrone **22** (51 mg, 54%).

Pure (*E,E*)-monomethyl diene **20** (40 mg, 0.18 mmol) and benzaldehyde (26 mg, 0.25 mmol) under the above conditions gave *trans*-pyrone **23** (22 mg, 67%) and *cis*-pyrone **22** (7 mg, 21%).

Preparation of Prelog–Djerassi Lactone 34 and Erythronolide Fragment 48. Preparation of Dihydropyrone 38. A solution of silyloxy diene **14** (12.3 g, 55.0 mmol) and aldehyde **32** (6.7 g, 47.5 mmol) in CH_2Cl_2 (500 mL) was cooled to −78 °C under N_2. Boron trifluoride etherate (6.3 mL, 50 mmol) was added and the resulting solution stirred at −78 °C for 3 h and then poured into saturated $NaHCO_3$ solution (250 mL). Et_2O (500 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 400 mL); the combined organic layers were washed successively with H_2O (250 mL), brine (100 mL), and dried ($MgSO_4$). Removal of the solvents in vacuo left 13.9 g of a yellow oil, which was dissolved in THF (200 mL) and treated with 50 mL of trifluoroacetic acid at room temperature. After 2 h, saturated $NaHCO_3$ (100 mL) was added; then solid $NaHCO_3$ was added to neutrality. This solution was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL) and dried ($MgSO_4$). The solvents were removed in vacuo to give 14.3 g of a dark red oil, which was purified by silica gel chromatography. Elution with hexane/Et_2O (3:1) afforded 10.5 g (95%) of an oil that contained *trans*-**38** and *cis*-**39** dihydropyrone isomers. The minor *cis*-dihydropyrone isomer was removed by fractional recrystallization from hexane/ether to yield 8.8 g of an oil that was 94% *trans*-**38**.

Trans isomer **38**: IR ν ($CHCl_3$) 1658, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.34–7.14 (m, 6 H), 4.10 (dd, J = 4.5, 9 Hz, 1 H), 3.09 (dq, J = 4.5, 7 Hz, 1 H), 2.48 (qd, J = 7, 9 Hz, 1 H), 1.63 (s, 3 H), 1.38 (d, J = 7 Hz, 3 H), 1.17 (d, J = 7 Hz, 3 H); MS, m/e 230 (M^+).

Cis isomer **39**: IR ν ($CHCl_3$) 1665, 1623 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.20 (m, 4 H), 7.18–7.13 (m, 2 H), 4.29 (dd, J = 2.7, 11 Hz, 1 H), 3.10 (qd, J = 6.7, 11 Hz, 1 H), 2.00 (dq, J = 2.7, 7.4 Hz, 1 H), 1.67 (d, J = 1 Hz, 3 H), 1.41 (d, J = 6.7 Hz, 3 H), 1.01 (d, J = 7.4 Hz, 3 H); MS, m/e 230 (M^+), 125.

Preparation of Glycals 40. A solution of dihydropyrone **38** (190 mg, 0.83 mmol) in benzene (12 mL) was cooled (5 °C) under N_2. A solution of diisobutylaluminum hydride in toluene (1.2 mL, 1.7 mmol) was added dropwise. After 1.5 h the reaction was quenched with methanol (1 mL), then poured into saturated Na_2SO_4 (25 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to yield a clear oil, which was purified by silica gel chromatography. Elution with CH_2Cl_2 afforded 173 mg (90%) of a mixture of glycals **40**. The resulting oil was triturated with ether/hexane. The first several crops of crystals contained pure equatorial isomer **40e**, the resulting mother liquors crystallized to yield the axial isomer **40a**.

40a (axial hydroxy isomer): mp 96–97.5 °C; ^1H NMR (270 MHz) δ 7.38–7.17 (m, 5 H), 6.21 (br s, 1 H), 3.77 (m, 1 H), 3.71 (dd, J = 2.5, 10 Hz, 1 H), 3.00 (dq, J = 2.5, 7 Hz, 1 H), 1.86 (m, 1 H), 1.65 (s, 3 H), 1.52 (br s, 1 H, D_2O exchange), 1.27 (d, J = 7 Hz, 3 H). IR ($CHC6_3$) 1665 cm^{-1}; MS, m/e 232 (M^+), 127.

40e (equatorial hydroxy isomer): mp 92–94 °C; ^1H NMR (270 MHz) δ 7.32–7.16 (m, 5 H), 6.16 (s, 1 H), 3.72 (m, 2 H), 3.22 (dq, J = 5, 7 Hz), 1.81 (m, 1 H), 1.61 (s, 3 H), 1.50 (br d, J = 8 Hz, 1 H, D_2O exchange), 1.27 (d, J = 7 Hz, 3 H), 1.04 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 1665 cm^{-1}; MS, m/e 232 (M^+), 109.

Preparation of Pseudoglycal 41. A solution of glycals **40** (1.42 g, 6.1 mmol) in isopropyl alcohol (113 mL) was cooled (0 °C) under nitrogen. $TsOH{\cdot}H_2O$ (226 mg) was added and the mixture stirred at 0 °C overnight. The reaction was poured into saturated $NaHCO_3$ (100 mL). Extraction with Et_2O (3 × 300 mL) gave a combined organic phase that was washed with H_2O (2 × 50 mL) and then brine (50 mL). The organic phase was dried ($MgSO_4$) and evaporated to yield a yellow oil, which was purified by silica gel chromatography. Elution with CH_2Cl_2–hexane (1:2) afforded 1.60 g (96%) of unsaturated acetal **41**.

41: ^1H NMR (90 MHz) δ 7.41–7.10 (m, 5 H), 5.36 (s, 1 H), 4.71 (s, 1 H), 3.56 (dd, J = 3, 9 Hz, 1 H), 3.52 (septet, J = 6 Hz, 1 H), 3.04 (dq, J = 3, 6 Hz, 1 H), 2.32 (m, 1 H), 1.63 (s, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.00 (d, J = 3 Hz, 3 H), 0.94 (d, J = 3 Hz, 3 H), 0.54 (d, J = 6 Hz, 3 H); MS, m/e 274 (M^+), 98.

Preparation of Tetrahydropyran 42. To a solution of unsaturated acetal **41** (1.59 g, 5.79 mmol) in EtOAc (64 mL) was added 5% Pd/Al_2O_3 (1.6 g), and after evacuation and purging with H_2, the mixture was stirred for 7 h under H_2. Filtration through Celite and evaporation followed by silica gel chromatography (hexane/benzene, 5:1) afforded saturated acetal **42** (1.26 g, 79%).

42: ^1H NMR (270 MHz) δ 7.31–7.10 (m, 5 H), 4.55 (d, J = 2 Hz, 1 H), 3.46 (dd, J = 2, 10 Hz, 1 H), 3.10 (septet, J = 6 Hz, 1 H), 3.00 (dq, J = 2, 7 Hz, 1 H), 1.85–1.59 (m, 2 H), 1.44 (m, 1 H), 1.26 (d, J = 7 Hz, 3 H), 1.22 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H), 0.57 (d, J = 6 Hz, 3 H). MS, m/e 276 (M^+), 83.

Preparation of the Prelog–Djerassi Lactone 34. To a solution of saturated acetal **42** (318 mg, 1.15 mmol) in H_2O (8 mL) acetic acid (48 mL) was added trifluoroacetic acid (8 drops). Ozone in oxygen was passed through the solution for 4 h at room temperature. H_2O_2 (30%, 4 mL) in H_2O (7 mL) was added and the resulting solution stirred overnight. The volatiles were removed in vacuo and the residual oil was dissolved in H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 125 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). Evaporation and trituration with hexane/Et_2O yielded 113 mg (53%) of crystalline Prelog–Djerassi lactonic acid **34**.

34: mp 116–117 °C; ^1H NMR (270 MHz) δ 8.80 (br s, 1 H, D_2O exchange), 4.59 (dd, J = 2.3, 10 Hz, 1 H), 2.76 (dq, J = 2.3, 7 Hz, 1 H), 2.52 (m, 1 H), 2.02–1.81 (m, 2 H), 1.46 (m, 1 H), 1.29 (d, J = 7 Hz, 3 H), 1.20 (d, J = 7 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H); IR ($CHCl_3$) 3600–2400, 1725, 1720 cm^{-1}; MS, m/e 200 (M^+) 56.

Preparation of Prelog–Djerassi Lactone Aldehyde 35: To a solution of Prelog–Djerassi lactonic acid **34** (233 mg, 1.16 mmol) in benzene (5

mL) under N_2 was added oxalyl chloride (5 mL), and the mixture was stirred at room temperature for 5 h. The volatiles were removed in vacuo and the residue dissolved in toluene (4 mL). Pd/$BaSO_4$, 5% (63 mg), was added, and H_2 was bubbled through the solution while heating under gentle reflux for 1 h. The mixture was cooled and filtered through Celite. The filtrate was evaporated and the residue dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford 197 mg (92%) of lactonic aldehyde **35** as a pale yellow oil, homogeneous by TLC and NMR. The aldehyde was used immediately in the following reaction. ^1H NMR (90 MHz) δ 9.78 (s, 1 H), 4.58 (dd, J = 2, 10 Hz, 1 H), 2.70–2.30 (m, 2 H), 2.17–1.73 (m, 2 H), 1.43 (m, 1 H), 1.30 (d, J = 7, 3 H), 1.20 (d, J = 7 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H).

Preparation of Lactone Pyranone 44 under $ZnCl_2$ Catalysis. To a mixture of aldehyde **35** (37 mg, 0.20 mmol) and diene **14** (400 mg, 2.0 mmol) was added anhydrous $ZnCl_2$ (270 mg, 2.0 mmol) in THF (2 mL) and the mixture stirred at room temperature for 13 h; then saturated $NaHCO_3$ solution (2 mL) was added. After dilution with Et_2O (15 mL) and brine (15 mL), the mixture was separated and the aqueous layer extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography on silica gel (Et_2O/hexane, 4:1) gave, in order of elution, *cis*-pyrones **44** (24 mg, 43%) and **45** (16 mg, 19%). Crystals of **44** suitable for X-ray crystallographic analysis[53] were obtained by hexane/$CHCl_3$ phase diffusion recrystallization, mp 186–187 °C.

Isomer **44**: ^1H NMR (500 MHz) δ 7.27 (d, J = 1.1 Hz, 1 H), 4.37 (dd, J = 2.8, 10.3 Hz, 1 H), 3.94 (dd, J = 1.7, 10.3 Hz, 1 H), 2.58 (qd, J = 7.2, 2.8 Hz, 1 H), 2.51 (dqd, J = 12.7, 6.9, 6.0 Hz, 1 H), 2.20 (dqd, J = 10.3, 6.6, 1.7 Hz, 1 H), 1.99 (m, 2 H), 1.67 (d, J = 1.1 Hz, 3 H), 1.38 (m, J = 12.7 Hz, 1 H), 1.29 (d, J = 6.9 Hz, 3 H), 1.11 (d, J = 6.6 Hz, 3 H), 1.04 (d, J = 7.2 Hz, 3 H), 1.00 (d, J = 6.5 Hz, 3 H); IR ($CHCl_3$) 1730, 1664, 1620 cm^{-1}; MS, m/e 280 (M^+), 83.

Isomer **45**: ^1H NMR (500 MHz) δ 7.21 (s, 1 H), 4.46 (dd, J = 10.4, 2.6 Hz, 1 H), 4.43 (dd, J = 11.0, 0.9 Hz, 1 H), 2.51 (dqd, J = 13.0, 7.2, 6.5 Hz, 1 H), 2.41 (qd, J = 7.4, 2.6 Hz, 1 H), 2.15 (dqd, J = 10.4, 6.5, 0.9 Hz, 1 H), 1.98 (m, 2 H), 1.66 (s, 3 H), 1.44 (m, J = 13 Hz, 1 H), 1.30 (d, J = 7.2 Hz, 3 H), 1.05 (d, J = 7.4 Hz, 3 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H); IR ($CHCl_3$) 1725, 1660, 1620 cm^{-1}; MS, m/e 280 (M^+) 127.

Preparation of Lactone Pyrone 44 under BF_3·Et_2O Catalysis. To a solution of aldehyde **35** (46 mg, 0.25 mmol) and diene **14** (55 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C under N_2 was added BF_3·Et_2O (31 μL, 0.25 mmol). After 2 h, saturated $NaHCO_3$ solution (0.5 mL), CH_2Cl_2 (5 mL), and brine (2 mL) were added. The mixture was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL); then the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and evaporated. Purification of the residue by flash chromatography on silica gel (Et_2O/hexane, 2:1) gave, in order of elution, *trans*-pyrone **46** (15 mg, 21%) and the desired *cis*-pyrone **44** (8 mg, 11%).

trans-Pyrone **46**: ^1H NMR (270 MHz) δ 7.14 (q, J = 1.1 Hz, 1 H), 4.29 (d, J = 6.0 Hz, 1 H), 4.03 (dd, J = 9.8, 2.2 Hz, 1 H), 2.61 (qd, J = 7.0, 6.0 Hz, 1 H), 2.48 (dqd, J = 13.0, 7.3, 6.0 Hz, 1 H), 2.17 (dqd, J = 7.0, 7.0, 2.2 Hz, 1 H), 1.92 (m, 2 H), 1.66 (d, J = 1.1 Hz, 3 H), 1.37 (m, J = 13.0 Hz, 1 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.24 (d, J = 7.3 Hz, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 1725, 1660, 1620 cm^{-1}; MS, m/e 280 (M^+), 127.

Preparation of Formate Methyl Ester 48: A solution of dihydropyrone **44** (23.0 mg, 0.082 mmol) in methanol (2 mL) at −78 °C was treated with ozone in oxygen for 1 min. Excess ozone was removed by purging with dry N_2 at −78 °C; then the solution was treated with 10% hydrogen peroxide (1 mL) for 2.5 h at room temperature. The mixture was extracted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to yield 24 mg (100%) of crude formate acid **47**. The crude acid (13.0 mg, 0.0455 mmol) was dissolved in Et_2O (1 mL) and a solution of diazomethane in Et_2O added dropwise until a yellow color persisted. This solution was stirred for 15 min at room temperature; then the mixture was evaporated. The residual oil was purified by silica gel chromatography. Elution with hexane/EtOAc (3:1) provided 10.0 mg (73%) of formate methyl ester **48**.

48: ^1H NMR (270 MHz) δ 8.12 (s, 1 H), 5.51 ("t", J = 6.3 Hz, 1 H), 4.04 (dd, J = 1.6, 10.2 Hz, 1 H), 3.69 (s, 3 H), 2.89 (dq, J = 6.3, 7.1 Hz, 1 H), 2.49 (m, 1 H), 2.03 (ddq, J = 1.6, 6.3, 6.9 Hz, 1 H), 1.98–1.87 (m, 2 H), 1.38 (m, J = 12.5 Hz, 1 H), 1.27 (d, J = 7.1 Hz, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H); IR ($CHCl_3$) 1730 br cm^{-1}; MS, m/e 300 (M^+), 128.

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