Silicon-Mediated Skipped Diene Synthesis. Application to the Melon Fly Pheromone[1]

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The 1,4-diene unit is a key structural feature of many fatty acid derived natural products including arachidonic acid, several of the leukotrienes, and a variety of insect pheromones. In this paper substituted [2-[(trimethylsilyl)methyl]cyclopropyl]carbinols are demonstrated to cleave readily, upon treatment with acid or upon conversion to the corresponding mesylates, to give mono- and disubstituted 1,4-pentadienes. Stereoselective formation of cis and trans olefins from diastereomeric carbinols has been examined. Control of configuration at the olefin derived from the trimethylsilyl-bearing terminus of the cyclopropane system was found to be only moderate while the olefin derived from the carbinol terminus of the cyclopropane system was produced with high trans stereoselectivity. From these results it is concluded that the cleavage of the cyclopropane ring is neither significantly accelerated by, nor strongly coupled to, cleavage of the carbon–silicon bond. The high stereoselectivity observed for the formation of the trans configuration at the olefin derived from the carbinol terminus has been applied to the synthesis of a constituent of the melon fly pheromone.

The 1,4- or "skipped" diene unit **1** represents a key feature of many biologically active natural products. For example, arachidonic acid (which serves as the starting material for biosynthesis of the leukotrienes[2]) contains two consecutive "skipped" diene units having the all *Z* configuration.

$$\underset{\mathbf{1}}{RCH{=}CHCH_2CH{=}CHR_1}$$

The "skipped" diene unit is also found in many insect pheromones. Dienes of the type **1** are pheromones of the potato tuberworm moth (*Phtorimaea operculella*),[3] the southern armyworm moth (*Spodoptera eridiana*),[4] the almond moth (*Cadra cautella*), the India meal moth (*Plodia interpunctella*), and several other insects.[5] Macrocyclic lactones containing a *Z,Z* "skipped" diene have been isolated and identified[6] as the aggregation pheromones of the grain beetles *Cryptolestes turcicus*, *Oryzaephilus mercator*, *O. mercator* and *C. pusillus*. A γ-butyrolactone with a "skipped" diene substituent has been isolated as a component of the pheromone "smoke" emitted by the male melon fly (*Dacus curcurbitae Coquillett*).[7]

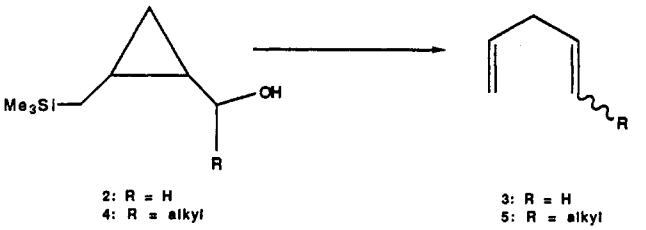
The general "skipped" diene **1** can exist in four isomeric forms, *E,E*, *E,Z*, *Z,E*, and *Z,Z*. Each isomer, having a different shape, might ellicite a different biological response. Control of geometry of the double bonds in the 1,4-diene unit is therefore of paramount importance in the synthesis of bioactive compounds.

Classical methods[8] for the control of olefin geometry depend heavily on relatively few strategies. The stereospecific reduction of 1,4-diynes by catalytic hydrogenation over Lindlar catalyst[9] or reduction with sodium in liquid ammonia gives the *Z,Z*- or *E,E*-1,4-dienes, respectively. Dienes of mixed olefin configuration (*E,Z* or *Z,E*) have been synthesized via reduction of the 1,4-enynes or modifications of the Wittig reaction.

Our interest in the synthesis of analogues of arachidonic acid led us to consider the development of a synthon capable of delivering, in a stereoselective fashion, the 1,4-diene function. This synthon could potentially be applied to the synthesis of insect pheromones as well.

Silicon is known to stabilize carbocation formation at a carbon atom β to it when a leaving group is present on that atom. The departure of the leaving group is, in general, accompanied by the cleavage of the carbon–silicon bond to generate the corresponding olefin. This forms the basis for the well-known Peterson olefination reaction. There is a strong stereoelectronic preference for the antiperiplanar relationship of the trimethylsilyl group and the departing leaving group.

A logical extension of the Peterson reaction[10] is the formation of "skipped" dienes from parent compound **2**. The elimination, under appropriate conditions, of the trimethylsilyl and hydroxyl groups with scission of the more substituted cyclopropane bond would then provide the parent 1,4-pentadiene **3**.[11]



2: R = H
4: R = alkyl

3: R = H
5: R = alkyl

(1) Previously presented in part: Zucker, P. A.; Wilson, S. R. *New Methodology for the Synthesis of Arachidonic Acid Analogues*; 188th ACS National Meeting, Philadelphia, PA, August 26–31, 1984; ORGN110.

(2) For a review, see: Green, R. H.; Lambeth, P. F. *Tetrahedron* **1983**, *39*, 1687–1721.

(3) Voerman, S.; Rothschild, G. H. L. *J. Chem. Ecol.* **1978**, *4*, 543–549.

(4) Jacobson, M.; Redfern, R. E.; Jones, W. A.; Aldrich, M. H. *Science (Washington, D.C.)* **1970**, *170*, 542.

(5) (a) Kuwahora, Y.; Hara, H.; Ishii, S.; Fukami, H. *Science (Washington, D.C.)* **1971**, *171*, 801. (b) Brady, V. E.; Tumlinson, J. H.; Brownlee, R. G.; Silverstein, R. M. *Science (Washington, D.C.)* **1971**, *171*, 802.

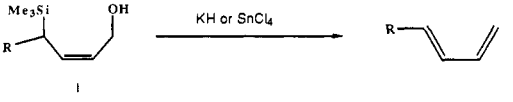
(6) (a) Millar, J. G.; Pierce, J. D., Jr.; Pierce, A. M.; Oehlschlager, A. C.; Borden, J. H. *J. Chem. Ecol.* **1985**, *11*, 1071–1081. (b) Pierce, A. M.; Borden, J. H.; Oehlschlager, A. C. *Environ. Entomol.* **1983**, *12*, 1367.

(7) Ohinata, K.; Jacobson, M.; Kobayashi, R. M.; Chambers, D. L.; Fujimoto, M. S.; Higa, H. H. *J. Env. Sci. Health* **1982**, *A17(2)*, 197.

(8) For reviews of the synthesis of insect pheromones with examples of these methods, see: (a) Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, pp 1–184. (b) Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845–1899.

(9) For an example, see: Nicolaou, K. C.; Hernandez, P. E.; Ladduwhetty, T.; Randall, J. L.; Webber, S. E.; Li, W. S.; Petasis, N. A. *J. Org. Chem.* **1983**, *48*, 5404–5406.

(10) The vinylogous extension of the Peterson reaction has also been reported. Clive and Angoh have studied the cleavage of compounds of the type i and have found that these compounds readily cleave under acidic or basic conditions to give exclusively the (*E*)-1,3-diene.



i

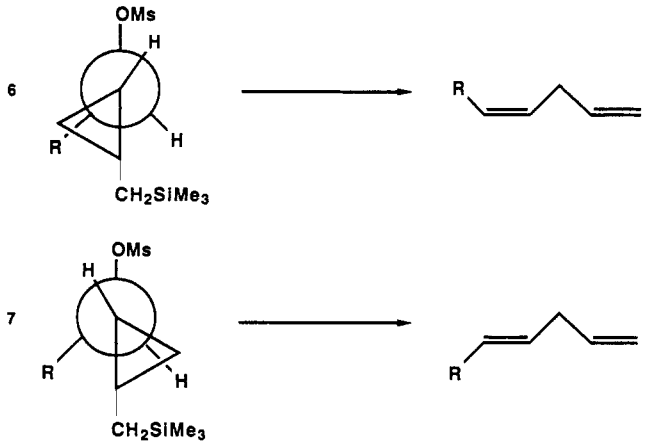
Angoh, A. G.; Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1984**, 535–536.

0022-3263/88/1953-4682$01.50/0

The cleavage of a more highly substituted compound such as **4** could, in principle, deliver two isomeric diene products **5**.

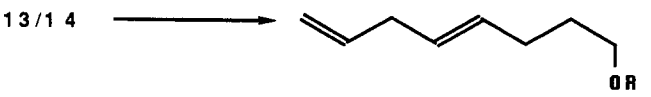
Results and Discussion

We began our study of the stereochemical outcome of the solvolysis reaction with compounds **4** (R = alkyl), substituted only at the carbinol end of the parent alcohol **2**, in order to determine whether the configuration of the monosubstituted pentadiene product was controlled by starting material configuration. The prospects for this control seemed hopeful on the basis of the following analysis. In the Julia synthesis[12] of trans allylic bromides, the high stereoselectivity for the formation of the trans doubled bond configuration is rationalized by nucleophilic attack by the C_1–C_2 bond of the cyclopropane ring on the carbon bearing the leaving group from the more stable conformer. Since the trimethylsilyl group is known to direct the formation and collapse of carbonium ions,[13] we felt that the double-bond geometry of the product of ring opening of the diastereomeric mesylates **6** and **7** would be determined by the configuration of the starting material and not its conformation. Thus mesylate **6**, upon solvolysis, would give the cis olefin and the corresponding mesylate **7** the trans olefin.



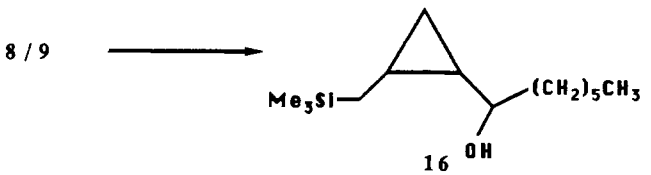
Synthesis and Reactions of 1-(Hydroxyalkyl)-cyclopropanes. The synthesis of the appropriate substrates for examination of the solvolysis of the diastereomeric mesylates is outlined in Scheme I. A 60:40 mixture of the known[14] trans and cis cyclopropyl esters, **8** and **9**, respectively, was readily obtained by the copper-catalyzed reaction of ethyl diazoacetate with allyltrimethylsilane. Separation by preparative HPLC on silica gel gave the pure cis and trans isomers. Quantitative LAH reduction of the trans isomer **8** to alcohol **10** followed by PCC oxidation (77%) gave the corresponding aldehyde **11**. This aldehyde was then treated with the anion **12b** derived from the corresponding halide **12a** and *tert*-butyllithium to provide a 1:1 mixture of the diastereomers **13**/**14** in an approximately 1:1 ratio (61% yield from **10**).

Treatment of either **13** or **14** with methanesulfonyl chloride (1.2 equiv) in the presence of an excess of triethylamine provided the diene **15a**, which was assigned the trans configuration on the basis of the IR spectrum. Solvolysis of both diastereomers gave the same mixture of products. When either **13** or **14** was treated with a catalytic amount of perchloric acid, elimination occurred to give the known dienol **15b**[35] (vide infra) in quantitative yield (GC).



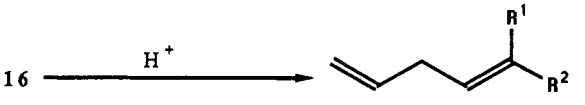
15a : R = TBDMS
15b : R = H

To avoid complications that might be introduced by the *tert*-butyldimethylsiloxy substituent, the reactions of the corresponding alkyl-substituted cyclopropanes **16** were studied. Since our initial studies of **13** and **14** indicated that both diastereomers formed the same product mixture, the cyclopropanes **16** were synthesized from the more conveniently available mixture of cis and trans cyclopropyl esters **8** and **9**. Thus the mixture of **12** and **13** was reduced to the corresponding mixture of alcohols and oxidized to the aldehydes with pyridinium chlorochromate in methylene chloride, and the crude aldehydes were treated with hexylmagnesium bromide in ether to give the cyclopropyl carbinols **16** as a mixture of all four possible stereoisomers. This mixture was purified by distillation in 51% overall yield from the alcohols.



Determination of the cis/trans ratio of the cleavage products of **16** required an analytic method. Selective epoxidation, with *m*-chloroperbenzoic acid, of the more nucleophilic disubstituted olefin in the product dienes provided[15,16] the cis and trans monoepoxides, which are readily resolved and analyzed by capillary GC.[17]

Treatment of the mixture of isomers **16** in ether, at room temperature or at 0 °C, with a catalytic amount of 70% perchloric acid resulted in a 96% yield of crude product, which upon distillation gave a 60% yield of a single diene (^{13}C) **17a**. Epoxidation of these products on a small scale and analysis by capillary GC showed only a trace of the *cis*-epoxide.



17a : R^1 = H, R^2 = n-hexyl
17b : R^1 = n-hexyl, R^2 = H

(11) Precedent for the acid-catalyzed cleavage of **2** was provided by the observation that cyclopropyl ketones of the type ii readily undergo cleavage to the corresponding γ,δ-unsaturated ketones iii in high yields.

Ochiai, M.; Sumi, K.; Fujita, E. *Chem. Lett.* **1982**, 79–80.

(12) Julia, M.; Julia, S.; Tchen, S.-Y. *Bull. Soc. Chim. Fr.* **1961**, 1849.

(13) For a general discussion, see: Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth's: London, 1981; pp 117–122. For a specific example in the norbornyl series, see: Fleming, I.; Michael, J. P. *J. Chem. Soc., Chem. Commun.* **1978**, 245.

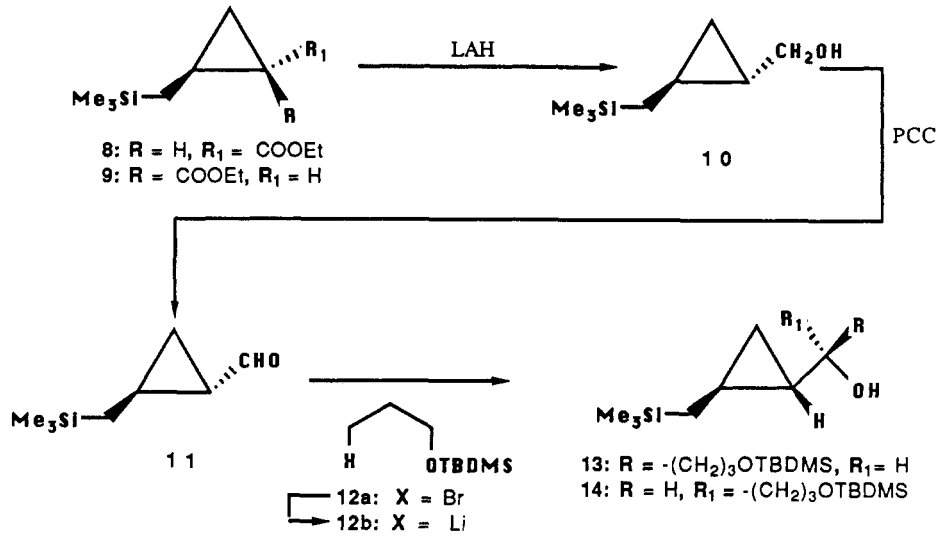
(14) D'yakonov, I. A.; Golodnikov, G. V.; Repinskaya, I. B. *J. Org. Chem. USSR* **1965**, *35*, 2169–2176.

(15) This method has been used previously for the quantitative analysis of mixtures of *E* and *Z* olefin isomers: Smith, R. G.; Daves, D., Jr. *J. Org. Chem.* **1975**, *40*, 1593–1595.

(16) The terminal olefin undergoes epoxidation only sluggishly: Swern, D. *J. Am. Chem. Soc.* **1947**, *69*, 1692–1698.

(17) Comparison with an independently synthesized standard *cis*-epoxide allowed the assignment of the two GC peaks (see the Experimental Section).

Scheme I



Treatment of **16** with methansulfonyl chloride under the conditions described for the elimination of **13** and **14** gave an 85% yield of the olefin **17a** contaminated with small amounts of side products. Epoxidation of a sample of this mixture also showed only a small amount of cis isomer **17b**.

These results suggest that the reaction proceeds through an intermediate with a sufficient lifetime to allow stereochemical equilibration at the carbinol carbon before collapse to the olefin occurs. The observed isomer ratio is the thermodynamic ratio: preferential formation of the trans olefin is normally observed in the solvolysis of secondary cyclopropyl carbinols.[18]

Determination of the mechanism for loss of stereochemical integrity at the hydroxyl-bearing carbon is not possible from these experiments. We propose, however, that formation of a carbonium ion intermediate[19] allows racemization at the hydroxyl-bearing carbon. The trimethylsilyl group, under these conditions, therefore does not provide sufficient acceleration toward the final collapse to diene product to circumvent loss of stereochemical integrity.

This result, while disappointing from the standpoint of a stereocontrolled *cis*-diene synthesis, does give a double bond synthesis with high trans stereoselectivity. It may be possible to find conditions that would accelerate collapse to the olefin before processes leading to the loss of stereochemical integrity at the hydroxyl-bearing carbon could occur.[20]

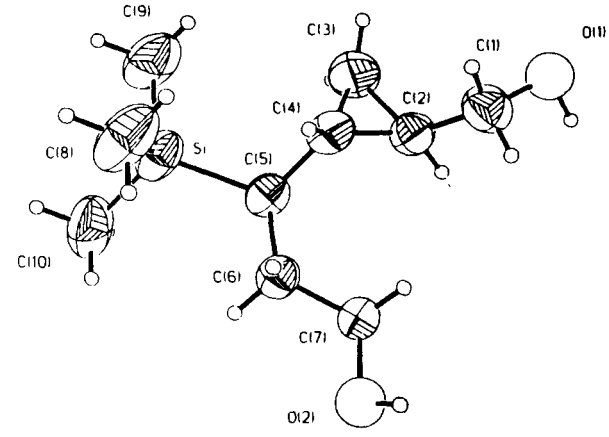
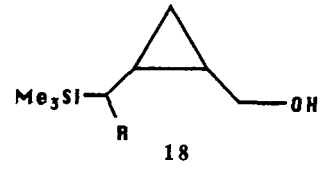


Figure 1. ORTEP drawing of diol **25**.

Synthesis and Reactions of 1-[(Trimethylsilyl)alkyl]cyclopropanes. We next examined the effect of the configuration at the silicon-bearing carbon (cf. **18**) on the configuration of the double bond in the elimination product.



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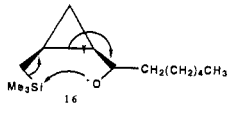
The synthesis of the appropriate silanes is outlined in Scheme II. Reduction of the (trimethylsilyl)propargyl alcohol **19** with LAH in ether gave the corresponding allylic alcohol[21] **20** quantitatively, which was then treated with triethyl orthoacetate and a catalytic amount of propionic acid at 140 °C[22] to give the intermediate ketene acetal, which is subjected to in situ Claisen rearrangement to provide carbethoxyallylsilane[23] **21** (67%). Reduction of

(18) For reviews, see: (a) Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 577–588. (b) Hanack, M.; Schneider, H. J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 666.

(19) Richey, H. G., Jr.; Richey, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 4971–4974.

(20) Attempts to effect the base-induced cleavage of **16** (cis isomer) with sodium hydride in THF or KH/HMPA were unsuccessful, leading to recovery of starting material. Since fluoride ion is known to assist in the cleavage of carbon–silicon bonds, an attempt was made to provide an aprotic source of fluoride ion. The mesylate and tosylate of **16** (cis and trans) eliminated spontaneously upon formation and thus could not be isolated and subsequently eliminated under aprotic conditions. The 3,5-dinitrobenzoate of **16** did not undergo elimination in the presence of fluoride ion in refluxing THF. At the suggestion of a referee, **16** was treated with NaH followed by treatment of the sodium alkoxide with methanesulfonyl fluoride. The alkoxide was inert to these conditions with only starting material being recovered after 24 h at reflux.



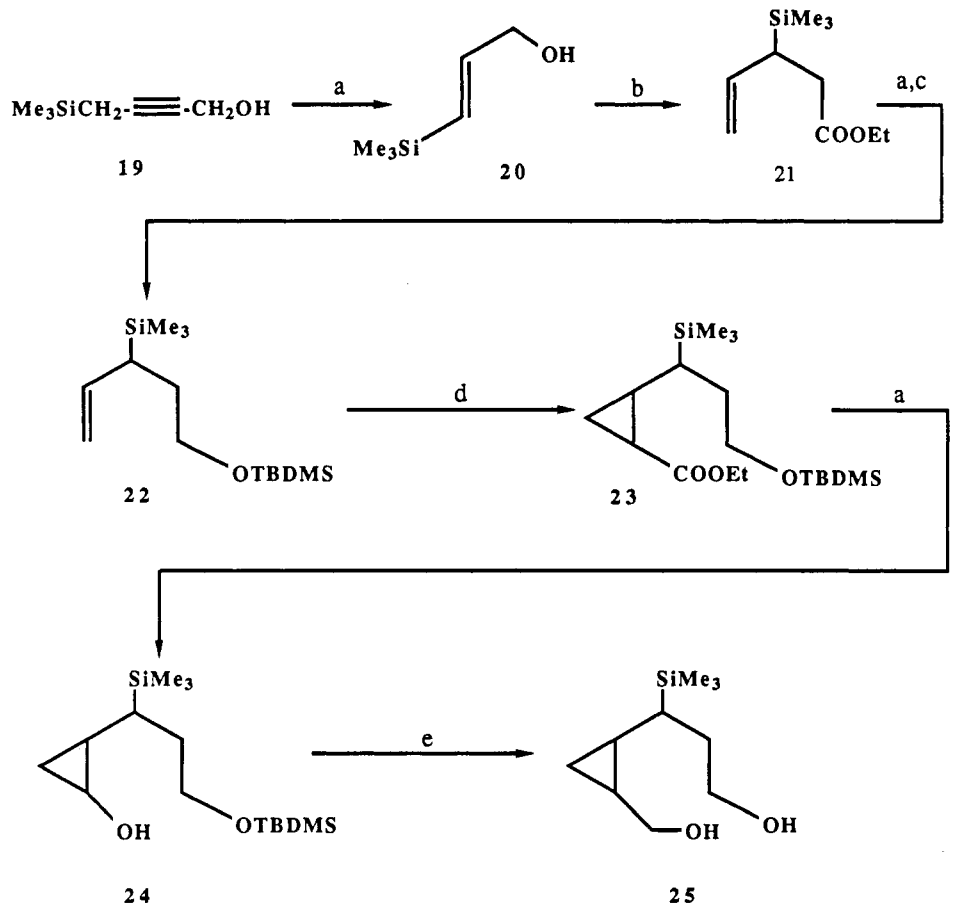
16

(21) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684–3686.

(22) (a) Miles, D. H.; Loew, P.; Johnson, W. S.; Kluge, A. F.; Meiwald, J. *Tetrahedron Lett.* **1972**, 3019. (b) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, J. J.; Lee, T.; Fulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(23) Related compounds have been synthesized via the corresponding rearrangement of the amide acetals: Jenkins, P. R.; Wetter, R. G. H.; Eschenmoser, A. *Helv. Chim. Acta* **1979**, *62*, 1922–1931.

Scheme II[a]

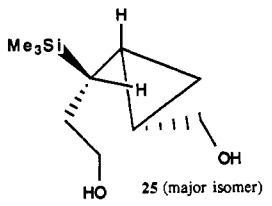


[a] (a) LAH; (b) $(EtO)_3CH$, H^+, Δ; (c) TBDMSCl, imidazole; (d) $EtOOCCHN_2$, Cu^{2+}, Δ; (e) $Bu_4N^+F^-$.

21 with LAH followed by protection as the corresponding *tert*-butyldimethylsilyl ether provided **22** in 75% overall yield after chromatography. Treatment of **22** with ethyl diazoacetate (3.0 equiv) in the presence of copper bronze and anhydrous copper sulfate at 118 °C provided a mixture of the four isomeric esters **23** (59%).

The mixture of esters **23** was reduced with LAH to the mixture of alcohols **24** (87%). Alternatively the crude reduction product was treated with tetra-*n*-butylammonium fluoride to give a 75% overall yield of the mixture of diols **25**.

The mixture of esters **23** consisted of an approximately two to one mixture of two major isomers and smaller amounts of two minor isomers. Preparative HPLC with shaving of the peak for the mixture of isomers **23** allowed separation into fractions containing varying ratios of the two major isomers (see the Experimental Section). The fraction of higher R_f value, accounting for 41% of the total diol, was a mixture of the three minor isomers. The fraction of lower R_f, accounting for 59% of the mixture of diols, proved to be a single crystalline diol. On the basis of steric considerations, and the structural studies discussed below, we have assigned the structure of the diol of lower R_f as **25**.



25 (major isomer)

Table I. Addition of Diazoalkanes to Vinylsilane 32

33	R	34/35	yield, % isolated
a	H	98/trace	98 (ref 28)
b	CH_3	68/32	84 (ref 28)
c	$(CH_2)_5CH_3$	56/44	89
d	$CH(CH_3)_2$	41/59	84

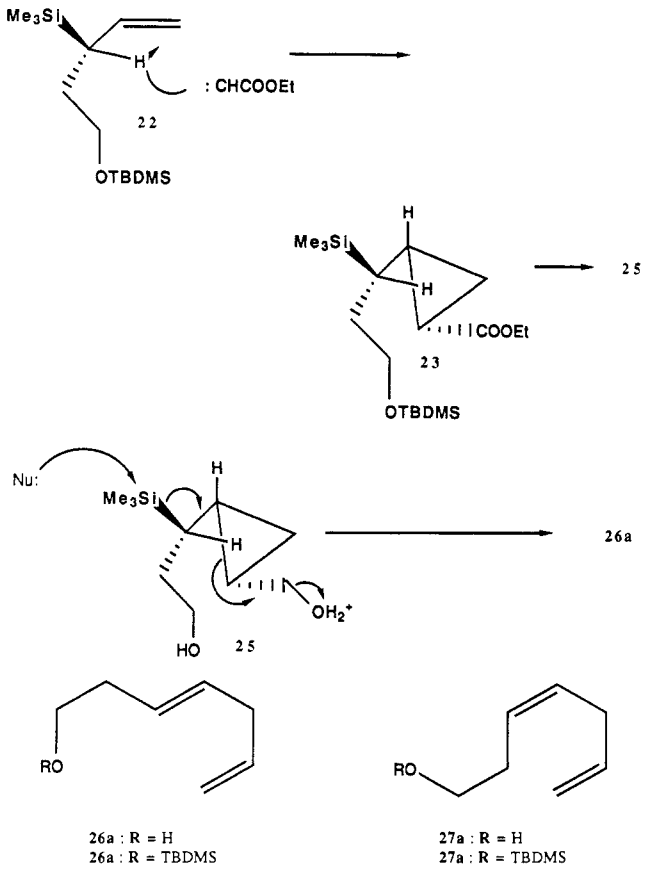
We assigned the configuration at the trimethylsilyl-bearing carbon of the major stereoisomer **25** on the expectation that it is produced as the major product as a result of diastereofacial selectivity[24] in the addition of the carbenoid derived from ethyl diazoacetate to the less hindered face of the olefin **22** in the conformation pictured.[25] If one assumes that the trimethylsilyl group is large relative to the alkyl substituent, the preferred direction of attack would then be the bottom face of the olefin to give diastereomer **23**. This compound upon reduction and deprotection provides diol **25**. This assignment has been confirmed by single-crystal X-ray diffraction.[26]

Diol **25** would, upon solvolysis, be expected to yield the trans olefin **26a** if elimination occurred with the usual antiperiplanar arrangement of the trimethylsilyl and leaving groups.

(24) For a review of acyclic diastereoselection, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3–72.

(25) This argument assumes that the allylic hydrogen atom preferentially occupies the plane defined by the double bond and that this represents the correct conformation as the transition state for the addition of the carbenoid to the allylsilane **22** is approached. See: Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 146–170.

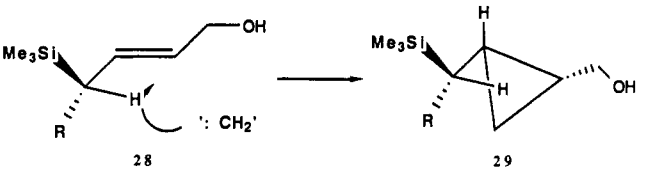
(26) We thank Dr. Paul Williard of Brown University, Providence, RI, for determining the X-ray structure of diol **33**.



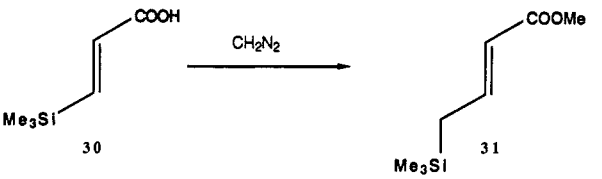
Solvolysis Studies. When the mixture of four stereoisomeric alcohols **24** was treated in the usual manner with methanesulfonyl chloride, a 58% yield, after chromatography, of a 68:32 mixture of two isomeric *tert*-butyldimethylsiloxy dienes **26b** and **27b** was isolated. The trans isomer **26b** had lower and the cis isomer **27b** higher retention time on the capillary GC. When varying mixtures of the two major isomers of **24** (vide infra) were treated with methanesulfonyl chloride (see the Experimental Section), varying ratios of the two olefinic isomers were obtained. As the proportion of the minor of the two isomeric alcohols **24** increased so did the relative amount of the *cis*-diene isomer **27b**. The proportion of cis isomer, however, did not increase as much as would be expected on the basis of the relative amounts of the two esters in the starting material, indicating that, although some control of product olefin geometry by the configuration at the carbon bearing the trimethylsilyl group was observed, it was not complete.

Treatment of a small sample of crystalline diol **25** with a trace of perchloric acid in deuteriochloroform led cleanly to the formation of the known[27] dienol **26a**, which showed two doublet of triplets (δ 5.62, 5.46) for the internal olefinic protons. Decoupling experiments indicate that these protons are trans to each other. Integration of the olefinic protons with respect to the trimethylsilyl protons indicated a quantitative yield of **26a**. No signals corresponding to the *cis*-diene **27a** were observed. Conversion of this alcohol to the *tert*-butyldimethylsilyl ether (TBDMSCI, DMAP, methylene chloride) **26b** and comparison by capillary GC showed that the diene corresponding to the peak of lower retention time was the *trans*-diene. Treatment of the more mobile mixture of diols with perchloric acid followed by conversion to the corresponding silyl ethers gave a mixture of diene ethers **26b** and **27b** in which only a very small amount of the cis olefin was present, indicating that loss of stereochemical control had occurred under these conditions.

Trimethylsilyl-Directed Diastereofacially Selective Cyclopropanation. The solvolysis results are consistent with the predominant formation, during cyclopropanation, of the stereoisomer at the trimethylsilyl-bearing carbon, which is expected to produce the trans olefin. The less predominant isomer, which produces the *cis*-diene, presumably results from addition to the top face of **22**. This analysis also suggests that a selective synthesis of a compound with the correct configuration to generate the *cis*-diene might be devised. Thus addition of "methylene" to an allylsilane already containing the hydroxymethyl group from the least hindered face of **28** would result in preferential formation of the isomer **29**. On solvolysis, **29** would be expected to provide the *cis*-diene as the predominant product of reaction.



This approach was made possible by the independent discovery in our laboratory of a little known reaction first described by Cunico.[28] As part of another project we attempted to prepare the methyl ester of **30** by treatment with an excess of diazomethane. To our surprise the product of this reaction was the ester **31**. A methylene unit had obviously been inserted into the carbon–silicon bond. The reaction has proven to be general, and a variety of diazoalkanes have been shown to undergo the reaction to give the corresponding α-substituted allylsilanes.



The silylacrylate **32** was readily available in large quantities via the $Co_2(CO)_8$-acatalyzed reaction[29] of trimethylsilane and methyl acrylate. This reaction provided **32** in 47% yield after distillation. The higher diazoalkanes were readily prepared by known methods.[30] The results of the reaction of **32** with diazoalkanes **33a–d** are presented in Table I. The reactions were carried out at 0 °C titrimetrically, adding small portions of **32** at intervals of several minutes until the deeply colored diazoalkane solution became pale. Immediately upon addition of a portion of **32**, nitrogen evolution was observed at 0 °C. After the endpoint had been reached, the solution was allowed to stand for 20 min and then the excess diazoalkane was destroyed by addition of a few drops of acetic acid. Concentration followed by distillation of chromatography provided the pure products as a mixture or

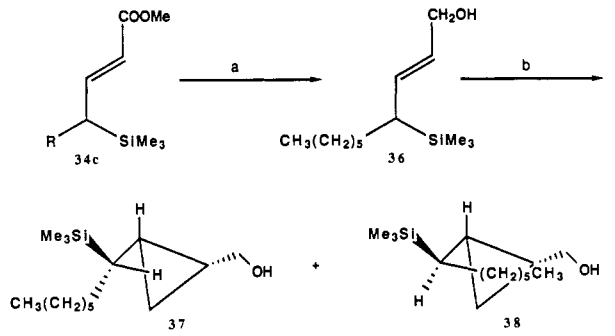
(27) (a) Snider, B. B.; Phillips, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 1114–1116. (b) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826–830.

(28) (a) Cunico, R. F.; Lee, H. M.; Herbach, J. *J. Organomet. Chem.* **1973**, *52*, C7–C10. (b) Cunico, R. F.; Lee, H. M. *J. Am. Chem. Soc.* **1977**, *99*, 7613–7622.

(29) Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1983**, 1193.

(30) Meader, A. L., Jr.; Wilds, A. L. *J. Org. Chem.* **1948**, *13*, 763–779.

Scheme III[a]

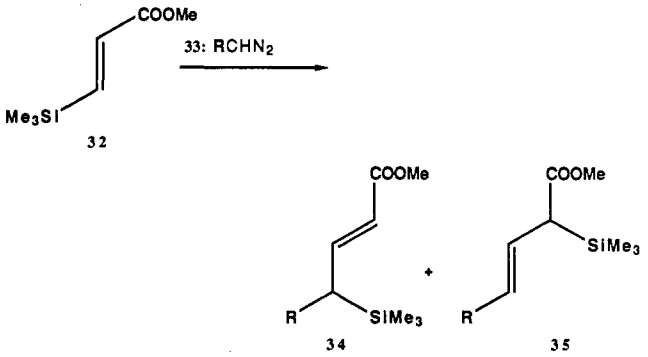


[a] (a) AlH_3, Et_2O; (b) $Zn(Et)_2$, CH_2I_2.

Table II. Stereoselectivity of Cyclopropane Ring Opening in 37/38 (Scheme III)

conditions	17a/17b
MsCl	38/62
$HClO_4$	67/33

separate isomers. Gram quantities were readily prepared by this procedure.



Direct insertion to form **34a–c** generally predominated, however, with an increase in steric bulk of the diazoalkane R group, increasing amounts of the β–γ unsaturated isomers **35b–d** were formed.[31] The isomers **35b–d** proved surprisingly stable for compounds bearing a trimethylsilyl group on a doubly activated methylene, surviving both distillation and chromatography on silica gel. The proton on the carbon bearing the trimethylsilyl group in the isomers **35** was readily identified as a doublet at δ 2.8–2.7 in the NMR spectrum. The double bonds in compounds **34a–d** and **35b–d** were trans based on the measured coupling constants of ~15 Hz.

With ready access to compounds of type **34**, the stereoselective synthesis of a compound having the relative configurations of **29** was explored. This synthesis is outlined in Scheme III. Chromatography of **34c/35c** provided the isomer **34c** (R = $(CH_2)_5CH_3$). Reduction with AlH_3 in ether[32] gave the crude allylic alcohol **36** in 96% yield. Treatment of this allylic alcohol with diethylzinc and diiodomethane according to the modified procedure of Furukawa et al.[33] provided a 55% yield of an 85:15 ratio of two cyclopropane isomers to which we have assigned the configurations **37** and **38**, respectively.

Treatment of small samples of this mixture of isomers with either perchloric acid in ether or methanesulfonyl chloride in the methylene chloride provided mixtures of the *trans*-diene **17a** and its cis isomer **17b**. Epoxidation

$$37/38 \rightarrow 17a/17b$$

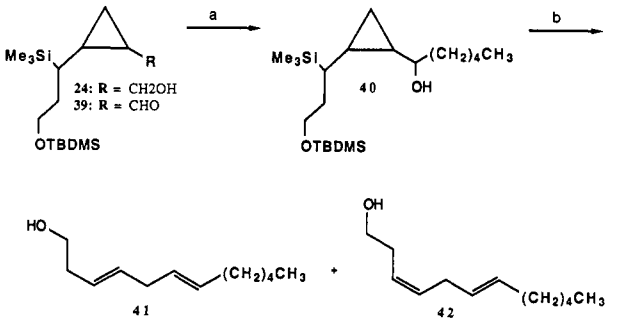
of the olefin mixtures and comparison with the *cis*-epoxide standard by capillary GC and GC–MS allowed determination of the ratios of the olefins formed (Table II).

These results demonstrate that the stereochemical outcome of the reaction depends upon the conditions used for the elimination reaction. Under either condition, partial loss of expression of starting material stereochemistry is observed. The loss is much more extensive, however, in the case of acid-catalyzed cleavage. This suggests that conditions might be found that would allow the reaction to be completely stereospecific. Although the mechanism for the loss of expression of the stereochemistry of the starting material in the product is uncertain, it may involve the formation of cationic species with sufficient lifetimes to undergo interconversions of configuration before collapsing to products.

Synthetic Applications. As an example of how compounds substituted on the carbon bearing the trimethylsilyl group might be used to generate synthetically useful intermediates, the synthetic pathway shown in Scheme IV was followed. Thus the mixture of alcohols **24** was oxidized with pyridinium chlorochromate in methylene chloride to the crude aldehydes **39**. These aldehydes, without further purification, were treated with pentylmagnesium bromide in ether to afford, after chromatography, a 55% yield (from **24**) of the isomeric alcohols **40**, which were treated with perchloric acid in ether to give a 58% yield of the two isomeric hydroxy dienes **41** and **42**.

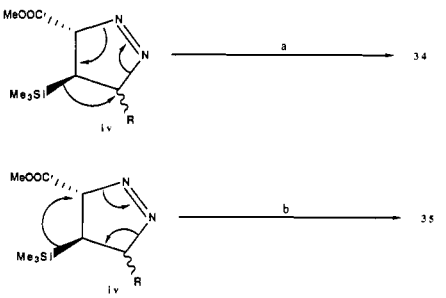
Conversion of a sample of this isomeric mixture to the corresponding *tert*-butyldimethylsilyl ethers and GC analysis indicated a ca. 80–20 ratio of **41** and **42**, respectively. This was confirmed by the ^{13}C spectrum of the mixture. Only traces of the other two isomers were detected. These compounds are isomers of the known *Z,Z*-diene, which has been used in the synthesis of leukotrienes

Scheme IV[a]



[a] (a) $CH_3(CH_2)_4MgBr$; (b) H_3O^+.

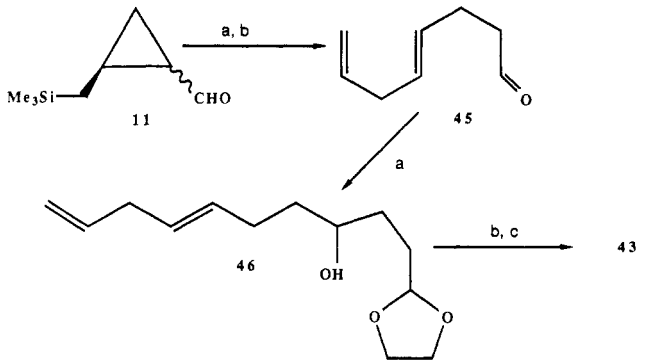
(31) The reaction has been formulated[28] as proceeding through an unusually unstable pyrazoline v, which can decompose, with 1,2-migration of the trimethylsilyl group, via two pathways, a or b, to give products of the type **34** or **35**, respectively. Apparently substitution by a trimethylsilyl group accelerates the decomposition of the intermediate pyrazoline.



(32) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314–6319.

(33) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353–3354.

Scheme V[a]

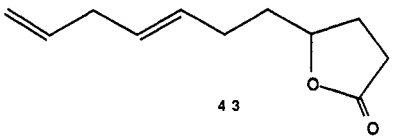


[a] (a) (1,3-Dioxolan-2-ylethyl)magnesium bromide (**44**), THF; (b) H_3O^+; (c) CrO_3, H^+.

and analogues of arachidonic acid.[34]

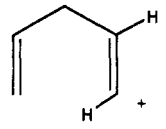
More promising, from a synthetic point of view, was the outcome of the acid-catalyzed elimination of the mixture of stereoisomers **16**. These results suggest that the high stereoselectivity observed for the formation of the trans olefin from the carbinol terminus may be synthetically useful.

The γ-butyrolactone **43** contains a trans monosubstituted 1,4-pentadiene attached to the lactone ring. this compound was isolated as a component of the pheromone "smoke" emitted by the male melon fly (*Dacus curcurbitae Coquillett*).[7] Mature male melon flies emit a "smoke" at dusk, starting from the time that they reach maturity, which is attractive to female melon flies. This "smoke" consists of 65% inorganic phosphates along with large amounts of pentacosane, heptacosane, and nonacosane. A small amount of a compound assigned the structure **43** was also isolated and has been subject to one previous synthesis.[35]



Our synthesis of compound **43** is outlined in Scheme V. Treatment of the mixture of aldehydes **11** with 1.5 equiv of the Grignard reagent **44**[36] gave a quantitative yield (GC) of the crude addition product, which was dissolved in acetone and treated with a catalytic amount of *p*-toluensulfonic acid, followed by treatment with THF and 6 N HCl under reflux for 5 h to effect complete hydrolysis to the aldehyde **45**. This procedure provided a 56% overall yield of the aldehyde **45** after the addition–elimination–hydrolysis sequence. Treatment of the aldehyde with 1.5 equiv of the Grignard **44** gave the alcohol **46** (69%), which was hydrolyzed with THF/6 N HCl followed by treatment of the resulting hydroxy aldehyde with Jones reagent in acetone, at room temperature. The oxidation of the intermediate hydroxy aldehyde to the lactone **43** presumably via the oxidation of the lactol form present, in the aqueous acidic medium, in equilibrium with it. The lactone **43** was thus obtained in 70% overall yield from **46** as a viscous liquid with a sweet, waxy odor. The spectral characteristics of **43** matched those previously reported.[35]

Thus the mixture of trans and cis aldehydes **11** formally represent the (*E*)-1,4-pentadienyl cation synthon **47**.



47

We have thus accomplished the stereoselective synthesis of 1,4-dienes and demonstrated the utility of this method in the synthesis of natural products. In addition, the stereoselective synthesis of cyclopropanes has been achieved via the use of the steric bulk of an allylic trimethylsilyl group to direct carbene addition to one of the diastereotopic faces of an olefin.

Experimental Section

General Procedures. All reactions were carried out under a nitrogen atmosphere. Melting points were determined in a Thomas capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian EM-360, Bruker WP-200SY, or General Electric QE-300 spectrometers with $CDCl_3$ as solvent. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. GC–MS analyses were obtained with a Hewlett-Packard 5992B GC–MS system equipped with a capillary column. Exact masses were obtained from the NIH Rockefeller Mass Spectrometry Biotechnology Resource at Rockefeller University, New York, NY, by use of negative ($^-$OH) chemical ionization (CI). Gas chromatographic (GC) analyses were performed on a Varian Model 3700 gas chromatograph (flame ionization detector) with use of $^1/_8$ in. columns packed with 2% OV-101, 0.2% Carbowax on Chromosorb G. Two lengths of column were used: (A) 6 ft and (B) 3 ft. The standard temperature program (60 °C at 1 min, 20 °C min^{-1}, to 320 °C) was used unless otherwise specified. Capillary GC analyses were performed on a fused silica column (OV-101, 25 m). Retention times where presented in text are denoted as (t_R) and are reported in minutes (min).

Dry tetrahydrofuran and ether were obtained by distillation from lithium aluminum hydride immediately before use. Other reagents and chemicals used were of commercial purity unless the method of purification is specified.

8/9: According to the procedure of Dyankov et al.,[14] 4.5 mL (0.5 equiv, 0.04 mol) of ethyl diazoacetate was dissolved in 2 mL of allyltrimethylsilane. A few drops of this solution was added under nitrogen to a refluxing solution of 5 mL of allyltrimethylsilane containing 140 mg of copper bronze and 140 mg of anhydrous copper sulfate. After reaction was initiated, as evidenced by the vigorous evolution of nitrogen, the remainder of the diazo ester solution was slowly added dropwise. After addition was complete, the mixture was refluxed for an additional 0.5 h. The solution was then cooled to room temperature and filtered through Celite to provide a slightly brown liquid (contaminated by small amounts of diethyl fumarate and maleate) pure enough for further use as a 2:1 mixture of cis (**9**) and trans (**8**) isomers. Distillation (102–105.5 °C, 20 Torr) provided a 55% yield of the pure mixture of esters as a colorless liquid. Partial chromatographic separation of the two cyclopropanes could be achieved on silica gel, eluting with 90:1 ethyl acetate–hexane to give pure cis and trans cyclopropanes. GC (B, OV-101): **8**, **9**, 4.67 min. TLC: silica gel, 5% ethyl acetate–hexane, R_f 0.30 (trans), 0.39 (cis). ^1H NMR (**8**): δ 4.15 (q, 3 H), 1.3 (t superimposed on m), 0.70 (7), 0.1 (s, 9 H). ^1H NMR (**9**): δ 4.25 (q, 3 H), 1.52 (m, 1 H), 1.2 (t superimposed on mt), 1.1–0.2 (m), 0.1 (s, 9 H). IR (neat, **8**): 3000 (m), 2980 (s), 2910 (m), 1740 (s), 1445 (m), 1400 (m), 1385 (m), 1325 (m, sharp), 1260 (m), 1250 (m, sharp), 1190 (s), 1170, 1162 (s, broad), 855 (s, broad). IR (neat, **9**): 3000 (m), 2980 (s), 2910 (m), 1740 (s), 1445 (m), 1405 (s), 1380 (s), 1365 (w), 1250 (s), 1210 (m), 1190 (m, shoulder), 1160 (s, broad), 840, 855 (s). GC–MS (relative abundance): 200 (M^+, 1), 185 (6), 157 (7), 155 (11), 119 (18), 103 (13.2), 82 (31), 75 (32), 73 (100), 54 (18), 45 (16).

10: The trans ester **8** (410 mg, 2.05 mmol) was dissolved in 10 mL of dry ether and added dropwise to a stirred solution of LAH (130 mg, large excess) in 10 mL of ether at 0 °C under a positive pressure of nitrogen. After the addition had been completed, the mixture was stirred at 0 °C for 30 min. The mixture was then

(34) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Laduwhetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400–5403.
(35) Voaden, D. J. *Synth. Commun.* **1984**, *14*(1), 55–63.
(36) Buchi, G.; Wuest, H. *J. Org. Chem.* **1984**, *49*, 1122.

quenched with saturated ammonium chloride (1.4 mL), and the salts were filtered and washed well with ether. The combined organic solutions were concentrated to give a quantitative yield (320 mg) of alcohol **10** pure enough for further use. Similar treatment of the mixture of isomers **8** and **9** gave a 100% crude yield of product. Distillation of the crude material gave an 86% yield of the mixture of alcohols **10** (bp 96.5–98.5 °C, 18 Torr). GC (B, OV-101): **10**, 3.54 (trans), 3.78 min (cis). TLC: silica gel, 30% ether–hexane, R_f 0.21. ^{1}H NMR: δ 3.5 (dd, 1 H), 3.3 (dd, 1 H), 1.8 (s, broad, ~1 H), 0.9–0.1 (m, 6 H), 0.0 (s, 9 H). IR (neat): 3385 (s, broad), 3015 (w), 2990 (s), 2910, 2900 (m), 1420 (m, broad), 1260 (s, sharp), 1160, 1140, 1120 (m), 860, 845 (s). GC–MS (relative abundance): 158 (M^+, not observed), 140 (6), 75 (84), 73 (100), 68 (37), 67 (53), 53 (11), 45 (24), 43 (14).

11:[37] The trans alcohol **10** (200 mg, 1.27 mmol) was dissolved in 5 mL of dry methylene chloride, and the solution was cooled to 0 °C. PCC (412 mg, 1.5 equiv, 1.91 mmol) was added, and the solution was stirred at 0 °C until TLC indicated complete disappearance of starting material. The mixture was then diluted with 10 volumes of ether, and the resulting suspension was filtered through Celite. This solution was concentrated to give 152 mg (77%) of aldehyde **11**, a slightly yellow liquid of sufficient purity for ruther use. Similar treatment of the mixture of isomers **10**(cis) and **10**(trans) gave a 78% crude yield of product. Distillation of the crude material gave a 71% yield of the mixture of aldehydes **11** (bp 78–82 °C, 18 Torr). GC (B, OV-101): **11**(cis) 3.06 min, **11**(trans) 3.38 min. TLC: silica gel, 30% ether–hexane, R_f 0.49. ^{1}H NMR (200 MHZ): δ 9.0 (d), 5.25 (s), 3.5 (broad m), 1.7–0.2 (m, 6 H), 0.0 (s, 9 H). IR (neat): 3600 (w, broad), 3100 (s), 3050 (s), 2850 (m), 1730 (s), 1450 (m, broad), 1400 (m), 1380 (7), 1250 (s, sharp), 1175 (m), 1160 (m), 1020 (7, broad), 920, 910 (m), 860, 840 (s, broad), 755 (m), 690 (m). GC–MS (relative abundance): 156 (M^+, 4), 155 (14), 141 (27), 75 (65), 73 (100), 59 (12), 45 (23), 43 (14).

12a:[38] Imidazole (1.47 g, 1.0 equiv, 22 mmol) was dissolved in 15 mL of dry DMF, and this solution was cooled to 0 °C under a nitrogen atmosphere. *tert*-Butyldimethylsilyl chloride (3.25 g, 1.0 equiv, 22 mmol) was added in small portions, and the resulting solution was allowed to stir for 20 min. 3–Bromo–1–propanol (3.0 g, 22 mmol) in 5 mL of DMF was added dropwise to this solution. After 1.5 h of stirring, this solution was poured into 200 mL of water and extracted with 4 × 100 mL of pentane. These combined extracts were washed with water and dried ($MgSO_4$). Concentration gave the crude product, which was distilled at 12 Torr, collecting the material boiling at 85–90 °C to give 4.8 g (86%) of **12a** as a colorless liquid. GC (B, OV-101): 4.35 min. ^{1}H NMR: δ 3.8 (t, 2 H), 3.55 (t, 2 H), 2.15 (m, 2 H), 1.075 (s, 9 H), 0.2 (s, 6 H). IR (neat): 3120 (s), 3020 (s), 1500 (ms), 1450, 1420, 1380 (m), 1260 (s), 1110 (s), 1060 (m), 960, 945 (m), 840 (s, broad), 780 (s, broad). GC–MS (relative abundance): 253 (M^+, not observed), 197, 195 (12), 169, 167 (18), 139, 137 (43), 115 (27), 75 (25), 73 (32), 57 (41), 45 (57), 41 (100).

12b, 13, 14: *tert*-Butyllithium in pentane (8.02 mL of a 2.3 M solution, 18.44 mmol) was added to 4 mL of THF at −78 °C. The halide **12a** (2.71 g, 10.72 mmol) in 29.5 mL of THF was then added dropwise. This solution was allowed to stir at −78 °C for 3 h.[39] The crude aldehyde **11**(trans), obtained from oxidation of the alcohol **10**(trans) (844 mg, 5.36 mmol), was dissolved in 17 mL of THF, and the solution was added dropwise. After the addition was complete, stirring was continued for an addition 10 min. The mixture was then quenched by addition of saturated ammonium chloride. Aqueous ethereal workup gave the crude diastereomeric alcohols in an approximately 1:1 ration (TLC). Flash chromatography (15% ether–hexane) provided a total yield of 1.08 g (61% from alcohol) of the two diastereomers **13** (R_f 0.18) and **14** (R_f 0.28) as clear oils. GC (B, OV-101): **13**, **14** 8.46 min. TLC: silica gel, 20% ether–hexane, R_f 0.18, 0.28. ^{1}H NMR (R_f 0.18): δ 3.75 (m, 2 H), 3.0 (m, broad, 1 H), 2.35 (s, broad, 1 H), 1.9–1.1 (m), 0.98 (s, 9 H), 0.6 (m), 0.15 (2 s, 15 H). ^{1}H NMR (R_f 0.28): δ 3.75 (m, 2 H), 3.0 (m, broad, 1 H), 2.35 (s, broad, 1 H), 1.9–1.1 (m), 0.98 (s, 9 H), 0.6 (m), 0.15 (2 s, 15 H). IR (neat, R_f 0.18) 3520 (s, broad), 3000, 2950 (s), 1470, 1450, 1380 (m), 1250 (s, sharp), 1090 (s, broad), 1050 (m, broad), 860, 835 (s, broad), 770 (s, broad). IR (neat, R_f 0.28) 3520 (s, broad), 3000, 2950 (s), 1720 (mw), 1470, 1450, 1380 (m), 1250 (s, sharp), 1090 (s, broad), 1050, 1020 (m, broad), 860, 835 (s, broad), 770 (s, broad). GC–MS (relative abundance): 330 (M^+, not observed), 157 (2.1), 79 (8.4), 75 (43), 73 (100), 67 (23), 57 (8), 55 (12), 45 (27), 41 (20). Exact mass (R_f 0.28, neg Cl, M − H) calcd for $C_{17}H_{38}O_2Si_2$ 329.2330, obsd 329.2332.

Compound 15a via the Mesylate. The more mobile isomer of the mixture **13**/**14** (250 mg, 0.76 mmol) was dissolved in 10 mL of dry methylene chloride, and the solution was cooled to 0 °C. Triethylamine was added (4.0 equiv, 307 mg, 423 μL), followed by dropwise addition of methanesulfonyl chloride (104 μL, 1.2 equiv, 0.912 mmol). The mixture was stirred at 0 °C for 20 min and then at room temperature of 1 h. It was then poured into 20 mL of ether, and the resulting solution was washed with water and brine and dried (Na_2SO_4). Concentration followed by flash chromatography of the residue (silica, 5% ether–hexane) provided 198 mg (108%) of impure diene **15a**. This material showed a single spot on TLC. GC indicated small amounts of impurities of higher retention time (T_R 6.54, 8.10 min) and a single peak accounting for 80% of the total area for the diene **15a**. Similar results were obtained when the less mobile material was treated under the same conditions. The NMR spectra of both products were identical. The ^{13}C spectra showed several olefinic impurities in both, in addition to the peaks for the desired product. GC (B, OV-101): **15a**, 5.86 min. TLC: silica gel, 20% ether–hexane, R_f 0.57. ^{1}H NMR (partial): δ 5.8 (m), 5.45 (m), 5.05–4.9 (m), 3.5 (t), 2.7 (m, =CHCH_2CH=), 0.9 (s), 0.05 (s). In addition to the peaks for the diene, signals suggesting remaining trimethylsilyl group and cyclopropane protons were evident in the NMR. IR (neat): 3050, 2950 (s), 1650 (w), 1480, 1440, 1420 (7), 1250 (s), 1100 (s), 960 (m), 840 (s), 770 (s). GC–MS (relative abundance): 240 (M^+, not observed), 183 (4), 155 (3), 107 (6), 89 (14), 81 (12), 79 (21), 77 (13), 75 (88), (73 (23), 67 (21), 59 (28), 57 (34), 45 (25), 41 (100).

Compound 15b via Acid-Catalyzed Reaction. The more mobile isomer of the mixture **13**/**14** (90 mg, 0.273 mmol) was dissolved in 5 mL of dioxane, and 3 drops of 70% aqueous $HClO_4$ was added. This mixture was stirred at room temperature for 30 min. Saturated $NaHCO_3$ solution (3 mL) was then added, and the mixture was poured into water and extracted with ether. The ethereal solution was washed with saturated $NaHCO_3$, dried, and concentrated. The GC showed a single peak (100% yield) for the crude product. The TLC showed two very minor impurities of higher R_f. Flash chromatography of the crude product gave the known alcohol **15b**.[35] Similar treatment of the less mobile isomer gave the same product. GC (B, OV-101): **15b**, 3.26 min. TLC: silica gel, 17% acetone–hexane, R_f 0.27. ^{1}H NMR: δ 5.8 (m, 1 H), 5.45 (m, 2 H), 5.075–4.9 (m, 2 H), 3.65 (t, 3 H), 2.75 (m, 2 H), 1.5 (m, 2 H). IR (neat) 3630 (s, broad), 3050 (s), 1650 (m), 1430 (m), 1040 (s, broad), 980 (m), 955 (s), 900 (s). GC–MS (relative abundance): 126 (M^+, not observed), 108 (5.9), 98 (15), 97 (11), 93 (57), 91 (33), 82 (27), 80 (52), 79 (100), 77 (47), 67 (67), 54 (36), 41 (57).

16: The crude aldehydes **11** (obtained from PCC oxidation of 2.2 g (13.92 mmol) of the mixture of cis and trans alcohols **10**) in 10 mL of ether was added dropwise, under a positive pressure of nitrogen, at room temperature to an excess of Grignard reagent prepared from hexyl bromide (5.86 mL, 6.89 g, 42 mmol) and magnesium (1.42 g, 58 mmol) in 60 mL of dry ether. After the addition was complete, the mixture was allowed to stir for an additional 15 min. Saturated ammonium chloride was added to quench, and the salts were filtered and washed well with ether. The combined ethereal solutions were concentrated to give the crude product as a mixture of isomers containing some *n*-dodecane. Distillation of the crude product at 2.2 Torr, collecting the material boiling at 114.5–125 °C, provided 1.72 g (51% for two steps) of the pure mixture of diastereomeric cyclopropanes **16** as a colorless oil. GC (A, OV-101): **16**, 8.92, 9.04 min. TLC: silica gel, 20% ethyl acetate–ligroin, R_f 0.48, 0.58, 0.71 (trace). ^{1}H NMR (partial): δ 3.26 (m), 2.92 (m). IR (neat) 3600 (s, broad), 3050, 3100 (s), 1480, 1425 (m, broad), 1250 (s, sharp), 1190 (w), 1050, 1025 (m), 905 (m), 865, 835 (vs, broad), 780, 755 (m), 690 (m). GC–MS (relative

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(38) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–9192. (b) Silylations on a small scale were performed with (TBDMSCI/DMAP in CH_2Cl_2): Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99–102.
(39) Misra, R. Ph.D. Thesis, 1980, Indiana University, Bloomington, IN.

abundance): 242 (M^+, not observed), 157 (4), 119 (2), 117 (47), 75 (20), 73 (100), 55 (11), 45 (11), 43 (11). Anal. Calcd: C, 69.35; H, 12.47. Found: C, 69.42; H, 12.67.

Compound 17a via Acid-Catalyzed Reaction. The mixture of diastereomers **16** (250 mg, 1.03 mmol) was dissolved in 6 mL of ether, and the solution was cooled to 0 °C. Aqueous $HClO_4$ (70%, 4 drops) was added, and the mixture stirred for 6 min. GC showed the reaction had gone to completion. The mixture was poured into 50 mL of ether and washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Bulb-to-bulb distillation (100 °C) at 20 Torr gave pure diene **17a**[40] 94 mg (60%) as a colorless liquid. The pot residue contained additional slightly impure **17a** (23.4 mg). The total yield of diene was 77%. When the elimination reaction was carried out at room temperature, a 96% yield of crude product was obtained. This product showed essentially identical spectral features with the exceptions that the NMR spectrum showed a small amount of silicon-containing impurity and the IR spectrum showed additional bands at 1250 (w), 850, 785, 765 (m, broad). Epoxidation by the standard procedure and anaylsis by capillary GC showed that a trace of the cis isomer had formed (vide infra). GC (A, OV-101): **17a**, 5.68 min. ^1H NMR: δ 5.62 (m, 1 H), 5.471 (m, 2 H), 5.15–4.95 (m, 2 H), 2.779 (m, 2 H), 2.041 (m, 2 H), 1.4 (s, broad, 8 H), 0.95 (t, 3 H). ^{13}C NMR: δ 137.54, 131.88, 127.61, 114.73, 36.87, 32.71, 31.89, 29.62, 28.99, 22.76, 14.15. IR (neat) 3050, 2950 (s), 1655 (mw), 1460, 1430 (m), 1080 (m, broad), 985 (m), 965 (s), 908 (s). GC–MS (relative abundance): 152 (M^+, 23), 124 (12), 110 (15), 109 (11), 96 (21), 95 (25), 82 (46), 81 (72), 79 (40), 77 (14), 67 (99), 54 (96), 41 (100).

Compound 17a via Mesylate. The diastereomeric carbinols **16** (300 mg, 1.24 mmol) were dissolved in 8 mL of methylene chloride, and the solution was cooled to 0 °C under a positive pressure of nitrogen. Triethylamine (4.47 mmol, 452 mg, 623 μL) was added via syringe followed by dropwise addition of methanesulfonyl chloride (1.49 mmol, 171 mg, 115 μL). After being stirred 5 min, the solution was warmed to room temperature, and stirring was continued for 20 min. The mixture was then poured into water and extracted with ether. The combined extracts were washed with water, 10% HCl, and brine, dried ($MgSO_4$), and concentrated. Epoxidation (vide infra) of a small sample of this mixture showed the usual trace of cis olefin. The crude NMR, however, showed olefinic impurities in addition to the signals for the expected diene. The crude mixture was purified by radial chromatography (2 mm of silica, hexane), collecting the most mobile UV-absorbing material. This provided 160 mg (85%) of the diene **17a** contaminated with olefinic impurities. GC(A, OV-101): **17a**, 5.68 min. TLC: silica gel, hexane, R_f 0.64. NMR showed the expected peaks for the trans diene (see above) but showed peaks for olefinic impurities. IR (neat): 3050, 2950 (s), 1655 (mw), 1480, 1460, 1430 (m), 1250 (m), 1140 (w), 1080 (m, broad), 985 (m), 965 (s), 908 (s), 855, 835 (s). GC–MS (relative abundance): 152 (M^+, 23), 124 (12), 110 (15), 109 (11), 96 (21), 95 (25), 82 (46), 81 (72), 79 (40), 77 (14), 67 (99), 54 (96), 41 (100).

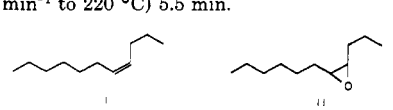
21: The allylic alcohol **20**[21] (500 mg, 3.85 mmol) was dissolved in 4.9 mL of triethyl orthoacetate in a flask fitted with a short-path distillation head. Five drops of propionic acid were added, and the flask was slowly heated to 140 °C under a positive pressure of nitrogen. It was maintained at this temperature for 25 min until 0.2 mL of ethanol was collected. The flask was then cooled, and most of the excess triethyl orthoacetate was distilled at aspirator pressure. The residue was heated, with stirring, at 140 °C overnight. The mixture was cooled and then purified by flash chromatography (silica, 30% ethyl acetate–hexane) to give 512 mg (67%) of suitably pure rearranged product **21**. This material contained a trace of a lower boiling impurity, which could be removed by distillation (92 °C, 18 Torr). GC (B, OV-101): **21**, 4.30 min. TLC: silica gel, 30% ethyl acetate–hexane, R_f 0.54. ^1H NMR: δ 5.76 (m, 1 H), 4.8–4.9 (m, 2 H), 4.13 (q, 2 H), 2.42 (d, 2 H), 2.1 (dd, 1 H), 1.2 (t, 3 H), 0.0 (s, 9 H). IR (neat): 3050, 2950 (s), 1750 (s), 1645 (m), 1445 (7), 1375 (7, sharp), 1250 (s), 1175 (s), 1115, 1085, 1035, 1000 (m), 995 (mw), 845 (s, broad), 750, 688 (m). GC–MS (relative abundance): 200 (M^+, 6), 157 (5), 119 (15), 82 (20), 75 (34), 73 (100), 54 (27), 45 (17). Exact mass (neg Cl, M – H) calcd for $C_{10}H_{19}O_2Si$ 199.1153, observed 199.1139. Anal. Calcd: C, 59.94; H, 10.06. Found: C, 59.68; H, 10.15.

22: The ester **21** (1.17 g, 5.84 mmol) was dissolved in 12 mL of dry ether and added dropwise to a solution of LAH (464 mg) in 30 mL of dry ether at 0 °C over the course of 20 min. The solution was allowed to warm to room temperature and stirred for an additional 45 min. Saturated NH_4Cl (6.42 mL) was added dropwise to quench. The solution was filtered, and the salts were washed well with ether. The combined ethereal solutions were concentrated to give the crude alcohol (t_R 3.62 min, R_f 0.17, 30% ether–hexane). This residue was added, in 1 mL of DMF, to a solution of silylating agent (previously prepared from imidazole (440 mg, 6.33 mmol) *tert*-butyldimethylsilyl chloride (954 mg, 6.33 mmol) in k mL of DMF, 0 °C, 20 min) at 0 °C. The mixture was stirred for an additional 15 min and then warmed to room temperature and stirred for 45 min. The mixture was then poured into 150 mL of ether. This ethereal solution was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude silyl ether was purified by flash chromatography on silica, eluting with 20% ether–hexane, to give 1.19 g (75%) of the silyl ether **22** as a colorless liquid containing ~5% of an impurity of lower retention time on GC. This material was of suitable purity for further use. Analytically pure **22** could be obtained by careful distillation of the material to 45 °C (0.5 Torr) to remove the impurity followed by distillation at 50 °C. GC (B, OV-101): **22**, 5.72 min. TLC: silica gel, 20% ether–hexane, R_f 0.61. ^1H NMR: δ 5.55 (m, 1 H), 4.9–4.7 (m, 2 H), 3.73 (m, 1 H), 3.52 (m, 1 H), 1.8–1.55 (m, 3 H), 0.93 (s, 9 H), 0.1–0.0 (2 s, 6 H, 9 H). IR (neat): 3000 (s), 1620 (m), 1450 (s), 1360 (m), 1250 (s), 1060 (s), 980 (m), 920 (m), 880 (s), 770 (s). GC–MS (relative abundance): 272 (M^+, not observed), 215 (19), 148 (16.3), 147 (100), 127 (10), 73 (58).

23: The silyl ether **22** (750 mg, 2.76 mmol) was placed along with 20 mg of copper bronze and 20 mg of anhydrous copper sulfate in a flask equipped with a reflux condenser and a inlet capped with a rubber septum. The mixture was then heated to 118 °C in an oil bath. Ethyl diazoacetate (3.0 equiv, 943 mg, 870 μL, 8.28 mmol) was added slowly dropwise, via syringe, at such a rate that nitrogen evolution had ceased between each addition of a drop. The mixture was then allowed to remain at 118 °C for 20 min. The mixture was cooled and filtered through Celite to remove solids. The solids were washed with ether, and the washings were combined with the filtrate and concentrated. Flash chromatography of this residue (silica, 10% ether–hexane) gave the isomeric mixture **23**, 463 mg, along with recovered **22**, 153 mg (59% on the basis of conversion of starting material). This material was a mixture of two major and two minor isomers (see solvolysis studies). On a larger scale, the same procedure was followed except that excess ethyl diazoacetate was added until starting material had disappeared (GC). Distillation to 110 °C (20 Torr) to remove diethyl fumarate and maleate provided the the pot residue as a dark liquid, which appeared pure enough for further use (95%). GC (B, OV-101): **23** (mixture), 8.42, 8.54. Capillary GC (100 °C at 1 min, 15 °C min^{-1}, to 320 °C): t_R 34.2 (52%), 36.5 (27%), 35.7 (16%), and 35.9 min (~5%). TLC: silica gel, 10% ether–hexane, R_f 0.37. ^1H NMR (partial): δ 5.4–3.2 (several m, 4 H), 0.95 (s, 9 H), 0.15 (s, 15 H). IR (neat): 3050, 2980, 2960, 2920, 2880 (m), 1742 (s), 1475, 1465, 1380, 1310, 1265, 1185, 1155, 845 (s). GC–MS (relative abundance): 358 (M^+, not observed), 343 (<5), 313 (6), 301 (45), 183 (15), 160 (16), 147 (25), 133 (21), 117 (43), 109 (11), 81 (20), 75 (37), 73 (100), 59 (10), 45 (14).

24: The mixture of esters **23** (200 mg, 0.63 mmol) in 3 mL of dry ether was added dropwise to a stirred solution of LAH (60 mg, 1.3 mmol) in 10 mL of ether. The resulting solution was

(40) Diene **23b** was synthesized via the catalytic hydrogenation over Lindlar catalyst of 1-undecen-4-yne as previously reported: Bosshardt, H.; Schlosser, M. *Helv. Chim. Acta* **1980**, *63*, 2393–2403. In our hands, however, this procedure resulted in some overreduction at the terminal olefin. This contaminant could not be removed, and the mixture of the mono-olefin and i was used in the next reaction. This resulted in a contaminant of ii in the *cis*-epoxide standard. The presence of ii, however, did not interfere in the analysis of product mixtures. The GC data for ii are as follows. GC (A, OV-101): 6.88. Capillary GC (100 °C at 1 min, 5 °C min^{-1} to 240 °C): 20.40 min. GC–MS (capillary): (60 °C at 1 min, 16 °C min^{-1} to 220 °C) 5.5 min.



stirred for 20 min, and then saturated NH_4Cl solution was added dropwise. The salts were filtered and washed well with ether. The combined ether solutions were concentrated to give the crude alcohol mixture **24** showing two spots on TLC. The higher R_f material (impurity) was present in minor amount. This material was purified by flash chromatography (silica, 10% ether–hexane) to give the mixture of alcohols **24** (150 mg, 87%). Later fractions were increasingly contaminated with impurities of lower retention time (GC). These were probably due to deomposition on the column. GC (B, OV-101): **24**, 7.42, 7.54 min. TLC: silica gel, 15% ether–hexane, R_f 0.12. ^1H NMR (220 MHz, mixture): δ 3.78–3.55 (7), and 3.4 (d) (total 4 H), 0.85 (s, 9 H), 0.05 to −0.05 (s, 15 H). IR (neat): 3610 (s, broad), 3000 (s), 1360 (m), 1245 (m), 1020 (s, broad), 855 (s), 770 (s). GC–MS (relative abundance): 316 (M^+, not observed), 241 (7), 169 (11), 147 (30), 95 (45), 93 (11), 89 (19), 79 (10), 75 (55), 73 (100), 67 (31), 45 (15).

25: The crude product of reduction, **24**, of 1.0 g of the esters **23** (2.8 mmol) was dissolved in 5 mL (1.8 equiv) of 1 M tetra-*n*-butylammonium fluoride. After TLC showed complete reaction (4 h), the mixture was poured into 40 mL of saturated $NaHCO_3$ solution and the mixture was extracted with ether. The ether layers were dried ($MgSO_4$) and concentrated to give the crude diols **25**. Flash chromatography on silica (30% acetone–methylene chloride) provided two fractions. The less mobile material weighed 245 mg, and the more mobile material 172 mg. The total yield of **25** was 417 mg (75% from ester). The isomer of lower R_f formed crystalline plates and was recrystallized from ether–pentane (mp 62–64 °C). GC (B, OV-101) (mixture of diols): 3.98 (minor), 4.58 min. TLC: silica gel, 30% acetone–methylene chloride, R_f 0.17, 0.39. ^1H NMR (R_f 0.17, **25**): δ 3.78–3.62 (m, 3 H), 3.03 (dd, 1 H), 1.82–1.7 (m, 1 H), 1.64–1.45 (m, 1 H), 0.8 (m, 2 H), 0.48 (m, 1 H), 0.35 (m, 1 H), 0.12 (m, 1 H), 0.02 (s, 9 H). ^{13}C NMR: δ 67.15, 62.66, 33.96, 28.94, 21.97, 19.21, 10.25, −2.03. IR (KBr, FT): 3245 (s), 1454 (m), 1242 (s), 1058 (s), 1043 (s), 1026 (s), 1001 (s), 866 (s), 833 (s). GC–MS (relative abundance): 200 (M^+, not observed), 185 (8.3), 142 (100), 100 (36), 58 (6), 44 (7), 41 (11). Exact mass (neg Cl, M − H): calcd for $C_{10}H_{21}O_2Si$ 201.1309, obsd 201.1253.

Solvolysis Studies. Capillary GC (100 °C at 1 min, 15 °C min^{-1}, to 320 °C) showed that the esters **23** were present as a mixture of two major (t_R 34.2 (52%), 36.5 min (27%)) and two minor isomers (t_R 35.7 (16%), and 35.9 min (~5%)). Preparative HPLC (silica, 120:1 ethyl acetate–hexane) with recycling and shaving of the trailing edge of the peak for the mixture of isomers provided a 1:1 mixture (A) of the two major isomers **23**. Cuts from the leading edge of the peak provided mixture B enriched in the major isomer (74/36). A small amount of mixture B was reduced with LAH in the usual manner and treated with methanesulfonyl chloride (see general procedure B for the cleavage of **27b**) to give a mixture of the two olefins **26b** and **27b** in a 4.6 to 1 ratio, respectively, by capillary GC (60 °C at 1 min, 5 °C min^{-1}, to 320 °C): **26b**, t_R 46.2 min, **27b**, t_R 46.8 min. Reduction of a sample of mixture A provided the corresponding mixture of alcohols. This mixture was converted to the mixture of mesylates according to the general procedure and showed an increase in the proportion of the cis olefin **27b**. By capillary GC (conditions as above), the ratio of **26b** to **27b** was 1.6 to 1. Conversion of the single diene alcohol **26a** obtained from acid-catalyzed cleavage of diol **25** (vide infra) to the TBDMS–ether (TBDMSCl, CH_2Cl_2, DMAP) showed that the isomer of lower retention time (**26b**, t_R 46.2 min) possessed the trans configuration at the internal olefin. Similar treatment of the mixture of diols of higher R_f, followed by silylation, let to a mixture of **26a** and **27a** in a 2.6 to 1 ratio, indicating some loss of stereocontrol under these conditions. Capillary GC–MS (60 °C at 1 min, 10 °C min^{-1}, to 230 °C): **26a**, **27a**, t_R 7.6 min (separation of less than 0.1 min.) clearly established the isomeric nature of these olefins.

Acid-Catalyzed Solvolysis of 25 (26a). The pure diol **25** (10 mg) was dissolved in 0.5 mL of deuteriochloroform. A trace of 70% $HClO_4$ was added, and the tube was shaken. After the mixture was allowed to stand for 20 min, the 300-MHz NMR spectrum was recorded. Decoupling showed a trans coupling constant of 15.3 Hz for the internal olefin. The only identifiable product was the diene. The solution was then poured into saturated $NaHCO_3$ and ether, and the layers were separated. The ether layer was dried ($MgSO_4$) and concentrated to give the crude product, the known dienol **26a**[27] GC (B, OV-101): **26a**, 2.34 min. TLC: silica gel, 30% ethyl acetate–hexane, R_f 0.24. ^1H NMR (crude): δ 5.85 (m, 1 H), 5.62 (dt, J = 6.3, 15.3 Hz, 1 H), 5.46 (dt, J = 6.6, 15.3 Hz, 1 H), 5.16–4.95 (m, 2 H), 3.68 (t, 2 H), 2.81 (m, 2 H), 3.25 (m, 2 H). IR (crude): 3550 (s), 3050 (s), 1650 (mw), 1450 (m), 1420 (m), 1380 (m), 1250 (s), 1040 (vs, broad), 970 (s), 910 (s), 840 (vs, broad). GC–MS (relative abundance): 112 (M^+, not observed), 94 (11), 81 (23), 79 (100), 68 (13), 67 (27), 53 (24), 41 (29).

26b, 27: The mixture of alcohols **24** (69 mg, 0.22 mmol) was dissolved in 3 mL of methylene chloride, and triethylamine (1.1 mmol, 140 μL) was added, followed by the dropwise addition of methanesulfonyl chloride (2 equiv, 39 μL, 0.55 mmol). When the GC of an aliquot showed no remaining starting material, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with ether. The combined ether extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. This material was purified by preparative TLC (silica, 20% ether–hexane) to give 29 mg (58%) of the material of highest R_f. The GC–MS of this material showed two peaks for the isomeric olefins **26b** and **27b** (68:32, respectively). GC (B, OV-101): **26b**, **27b**, 3.34 min. TLC: silica gel, 20% ethyl acetate–ligroin, R_f 0.54. ^1H NMR: δ 5.8 (m, 1 H), 5.4 (m, 2 H), 5.08–4.9 (m, 2 H), 3.6 (t, 2 H), 2.85 (2 overlapping m, 2 H), 2.2 (2 overlapping m, 2 H), 0.85 (s, 9 H), 0.02 (s, 6 H). GC–MS (relative abundance: 226 (M^+, not observed), 211 (<3), 169 (75), 141 (37), 139 (20), 101 (25), 89 (35), 75 (100), 73 (44), 59 (18), 41 (17).

General Procedure. Preparation of Diazoalkane 44c and Reaction with Silyl Acrylate 32[29] (R = $(CH_2)_5CH_3$). KOH (20 mL of a 40% solution) and methanol (20 mL) were placed in a 250-mL Erlynmeyer flask along with 90 mL of ether, and the mixture was cooled to 0 °C in an ice bath. Crude $CH_3(CH_2)_6N(NO)COOEt$ (prepared according to the procedure of Meader and Wilds[30]) (4.0 g, ~18.5 mmol) was added dropwise, and the resulting mixture was allowed to stand at 0 °C for 40 min with periodic swirling. The intensely yellow ether layer containing **33c** was decanted into a clean flask, and KOH pellets were added. The solution was allowed to stand at 0 °C for 2 h and then decanted into a clean flask, washing the pellets with additional fresh ether. Anhydrous $CaCl_2$ pellets were added, and the mixture was allowed to stand at 0 °C for 1 h. The solution was then decanted into a clean Erlynmeyer flask. A total of 2.0 g (12.7 mmol) of the silylacrylate **32** was added titrimetrically in small portions in intervals of several minutes until the solution was pale yellow in color. The solution was then allowed to stand for 20 min, at which time nitrogen evolution ceased. Glacial acetic acid was then added dropwise until nitrogen evolution ceased. The solution was concentrated and subjected to preliminary purification by flash chromatography (silica, 2% ethyl acetate–hexane) to give 2.9 g (89%) of a mixture of the allylic isomers in a 56:44 ratio of **34c** to **35c**. The α,β-unsaturated isomer was purified by preparative HPLC (silica, 2% ethyl acetate–hexane), with shaving and recycling to give the lower R_f material containing 5% of **35c** as an impurity. GC (A, OV-101): **34c**, 8.90 min, **35c**, 8.62 min. TLC: silica gel, 2% ethyl acetate–ligroin (one spot), R_f 0.32. ^1H NMR (**34c**): δ 6.95 (dd, 1 H, J = 10.2, 15.6 Hz), 5.65 (d, 1 H, J = 15.6 Hz), 3.55 (s, 3 H), 1.78 (dt, 1 H), 1.7–1.0 (m, 10 H), 0.85 (t, 3 H), 0.15 (s, 9 H). IR (neat, **34c**): 3000 (s), 2950 (m), 1710 (s), 1620 (m), 1350, 1320 (m), 1400, 1350, 1325, 1180, 1160, 1110, 1060, 1025, 980 (m), 860 (s), 840 (s). GC–MS (relative abundance, **34c**): 256 (M^+, 5.1), 241 (4), 185 (18), 152 (11), 146 (3), 108 (12), 81 (100), 73 (44), 59 (12), 53 (11), 45 (17). Exact mass (neg Cl, M − H) calcd for $C_{14}H_{27}O_2Si$ 255.1779, obsd 255.1751.

34/35d: Treatment of the silyl acrylate with isopropyldiazomethane **33d** gave a ratio of **34d:35d** of 41:59 (GC). Flash chromatography (silica, 2% ethyl acetate–hexane) provided an 84% yield of the mixture of allylic isomers. Small amounts of the pure isomers could be obtained by shaving; **34d** showed the following spectral features. GC (A, OV-101): **34d**, 7.60 min. TLC: silica gel, 2.5% ethyl acetate–ligroin, R_f 0.34. ^1H NmR δ 7.03 (dd, 1 H, J = 11.4, 15.3 Hz), 5.69 (d, 1 H, J = 15.3 Hz), 3.75 (s, 3 H), 2.02 (m, 1 H), 1.73 (dd, 1 H, J = 11.4, 5.4 Hz), 1.1–0.95 (2 d, total 6 H), 0.02 (s, 9 H). IR (neat) 3080 (s), 1700 (s), 1640 (w), 1460 (m), 1430 (m), 1300 (m), 1250, 1140 (s), 1075 (m), 970 (m), 900 (w), 870, 840 (s, broad), 755, 735 (w). GC–MS (relative abundance): 214 (M^+, 3), 199 (11), 110 (22), 95 (100), 73 (30), 67 (12), 59 (10), 45 (11). Exact mass (**34d** and **35d**, neg Cl, M − H) calcd for

$C_{11}H_{22}O_2Si$ 213.13096, obsd 213.1309. The allylic isomer **35d** showed the following spectral characteristics. GC (A, OV-101): **35d**, 6.80 min. TLC: silica gel, 2.5% ethyl acetate–ligroin, R_f 0.37. ^1H NMR: δ 5.61 (dd, 1 H, J = 10.2, 15.6 Hz), 5.27 (dd, 1 H, J = 6.9, 15.6), 3.65 (s, 3 H), 2.85 (d, 1 H, J = 10.2 Hz), 2.31 (m, 1 H), 1.09 (2 d, total 6 H), 0.02 (s, 9 H). IR (neat) 3080 (s), 1745 (s), 1650 (m), 1460 (m), 1430 (m), 1300 (m), 1250, 1180 (s), 1140 (s), 1030 (m), 900 (w), 870 (m), 840 (s, broad), 755, 735 (w). GC–MS (relative abundance): 214 (M^+, 11), 199 (14), 110 (20), 95 (100), 73 (29), 67 (11), 59 (10), 45 (11).

36:[32] The ester **34c** (400 mg, 1.56 mmol) in 4 mL of dry ether was added dropwise at 0 °C to stirred solution of alane (AlH_3, prepared from $AlCl_3$ (139 mg, 1.04 mmol) and $LiAlH_4$ (119 mg, 3.14 mmol) in 10 mL of dry ether, 0 °C, 15 min). After the addition was complete, the mixture was stirred at 0 °C for 40 min, and then saturated NH_4Cl solution was added dropwise to quench. Salts were filtered and washed well with ether. The combined ether solutions were concentrated to give crude allylic alcohol **36** (334 mg, 94%) pure enough for further use. GC (A, OV-101): **36**, 8.32 min. TLC: silica gel, 20% ethyl acetate–hexane, R_f 0.44. ^1H NMR: δ 5.5 (m, 2 H), 4.09 (s, broad, 2 H), 1.55–1.2 (m, 12 H), 0.85 (t, 3 H), 0.0 (s, 9 H). IR (neat) 3450 (s), 3000, 2920 (s), 1670 (w), 1450 (m), 1250 (s, sharp), 1080 (m), 980, 960 (m), 858, 835 (vs). GC–MS (relative abundance): 228 (M^+, not observed), 138 (25), 110 (32), 96 (42), 81 (44), 75 (55), 73 (87), 67 (57), 54 (100), 45 (34), 43 (30), 41 (31).

37/38:[33] The allylic alcohol **36** (300 mg, 1.32 mmol) was dissolved in pentane (20 mL), and 2.5 mL of diethylzinc in toluene (13% by weight) was added via syringe. Then 500 μL of diiodomethane (1.62 g, 6 mmol) were added dropwise via syringe followed by injection of 2 mL of air. The mixture was then refluxed for 4 h. After cooling, saturated NH_4Cl was added, and the mixture poured into ether and washed with water, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (silica, 10% ethyl acetate–hexane) to give the purified cyclopropane **37** (175 mg, 55%). Acetylation of a small amount of this material (CH_2Cl_2, Ac_2O, DMAP) showed, by GC analysis (A, OV-101: **38**(acetate), t_R 7.80 min, **37**(acetate), t_R 8.00 min), a 16% impurity of isomeric **38**. GC (A, OV-101): **37**(acetate), **38**(acetate) 9.24 min. TLC: silica gel, 10% ethyl acetate–hexane, R_f 0.23. ^1H NMR (partial): δ 3.779 (dd, J = 5.4, 10.8 Hz, 1 H), 3.216 (dd, 1 H, J = 8.4, 10.8 Hz, 1 H), 1.75–0.25 (m, 19 H), 0.0 (s, 9 H). ^{13}C NMR (**37**): δ 67.28, 32.01, 31.47, 30.70, 30.03, 29.47, 22.84, 21.30, 18.76, 14.22, 11.47, −1.69; (**38**) 67.44, 31.75, 30.81, 29.83, 22.35, 19.07, 10.66, −1.85. IR (neat): 3450 (s), 3050, 3000 (s), 1450 (s), 1255 (m), 1250 (s), 1050 (s), 835 (s, broad), 748 (m), 685 (m). GC–MS (relative abundance): 242 (M^+, not observed), 169 (17), 95 (11), 82 (20), 81 (27), 75 (40), 73 (100), 68 (29), 67 (31), 54 (30), 45 (20), 43 (18), 41 (20). Exact mass (neg Cl, M − H) calcd for $C_{14}H_{30}OSi$ 241.1986, obsd 241.1996. Anal. Calcd: C, 69.35; H, 12.47. Found: C, 69.42; H, 12.67.

General Procedure (A). Acid-Catalyzed Cleavage of 37. Approximately 5 mg of the carbinol **37** were dissolved in 2 mL of ether, the solution was cooled to 0 °C, and 1 drop of 70% $HClO_4$ added. This mixture was stirred for 5 min. GC showed complete reaction to give a single peak for the olefins. This mixture was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The crude residue was taken up in 1 mL of dry methylene chloride, and an excess of MCPBA was added. This solution was stirred until disappearance of starting material was detected by GC. Ether was added, and the solution was washed with 10% Na_2SO_3, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Capillary GC analysis of the crude mixture of epoxides, by comparison with the *cis*-epoxide standard,[40] demonstrated a ratio of **17a** to **17b** of 67% to 33%, respectively. Analysis by GC–MS confirmed the assignment of these two peaks to the *trans*- and *cis*-epoxides, respectively.

General Procedure (B). Cleavage via the Mesylate of 37. Approximately 5 mg of the carbinol **37** was dissolved in 2 mL of dry methylene chloride. Triethylamine (15 drops) was added followed by 2 drops of methansulfonyl chloride. This mixture was allowed to stand for 20 min at room temperature and then poured into water. This aqueous mixture was extracted with ether, and the combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in CCl_4, and the solvent was removed on the rotary evaporator. The crude residue was taken up in 1 mL of dry methylene chloride, and a small amount (excess) of MCPBA was added. This solution was stirred until disappearance of starting material was detected by GC. Ether was added, and the solution was washed with 10% Na_2SO_3, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Capillary GC analysis of the crude mixture of epoxides, by comparison with the standard *cis*-epoxide,[40] demonstrated a ratio of **17a** to **17b** of 38% to 62%, respectively. Analysis by GC–MS confirmed the assignment of these two peaks to the *cis*- and *trans*-epoxides. GC (A, OV-101): *cis*-epoxide, 6.76 min, *trans*-epoxide, 6.52 min. Capillary GC (100 °C at 1 min, 5 °C min^{-1}, to 240 °C): *cis*-epoxide, 19.70 min, *trans*-epoxide, 18.70 min. GC–MS (capillary) (60 °C at 1 min, 16 °C min^{-1}, to 220 °C): *cis*-epoxide, 5.3 min, *trans*-epoxide, 5.1 min.

41/42: The mixture of alcohols **24** (200 mg, 0.56 mmol) of was oxidized in the usual fashion (1.5 equiv of PCC, methylene chloride) to give the crude aldehydes **39**, 192 mg, (R_f 0.58, 20% ethyl acetate–hexane, silica). GC (A, OV-101): t_R 9.92 min. This material was taken up in 4 mL of ether and added dropwise to a stirred 0.5 M solution of pentylmagnesium bromide (4 mL, 2 mmol, ~4 equiv), and the mixture was stirred for 5 min. Saturated ammonium chloride was added to quench, and the salts were filtered and washed well with ether. The combined ether solutions were concentrated, and the residue was purified by flash chromatography on silica, eluting with 15% ethyl acetate–hexane, to give 132 mg (55% from the alcohols) of the mixture of carbinols **40** (R_f 0.48, 0.53, 20% ethyl acetate–hexane, silica). GC (A, OV-101): t_R 12.32, 12.56 min containing several impurities of lower retention time suggesting that partial decomposition on silica had occurred. The IR spectrum of the alcohols **40** showed the following bands: 3500 (s, broad), 3000, 2950 (s), 1650 (vw), 1400 (m), 1250 (s), 1090 (s), 850, 830 (s), 770 (m). The mixture of alcohols **40** (95.6 mg, 0.22 mmol) was dissolved in 4 mL of ether, and the solution was cooled to 0 °C. Aqueous $HClO_4$ (70%, 2 drops) was added, and the mixture was stirred at 0 °C for 15 min. A few drops of saturated $NaHCO_3$ were added to neutralize the solution. The ether layer was decanted and concentrated. The residue was purified by flash chromatography on silica, eluting with 20% ethyl acetate–hexane to give 23.4 mg (58% from **40**) of the pure dienes **41/42** in 37% overall yield from the alcohols **24**. Silylation (TMSCl, pyridine, CH_2Cl_2)[38] of this diene mixture and analysis by capillary GC showed an approximately 2 to 1 ratio of dienes **41** to **42**, respectively. GC (A, OV-101): **41**, **42**, 8.16 min. TLC: silica gel, 20% ethyl acetate–hexane, R_f 0.30. ^1H NMR: δ 5.75–5.35 (m, 4 H), 3.8–3.6 (m, 2 H), 2.95–2.68 (m, 2 H), 2.5–2.25 (m, 2 H), 2.15–1.8 (m, 2 H), 1.8–1.2 (m, 7 H), 0.95 (t, 3 H). ^{13}C NMR (major diene, **41**): δ 132.60, 131.69, 128.07, 126.47, 62.17, 36.10, 35.78, 32.64, 31.54, 29.31, 22.64, 14.14; (minor diene, **42**) 131.39, 131.32, 128.00, 125.71, 62.38, 30.88, 30.65, other peaks coincide with those of the major diene. IR (neat): 3360 (s, broad), 3020 (m), 2960, 2912, 2870, 2860 (s), 1465, 1425, 1375 (m), 1040 (s, broad), 960 (s, sharp), 730 (m). GC–MS (relative abundance): 182 (M^+, 11), 164 (3), 109 (17), 107 (14), 95 (31), 93 (37), 81 (51), 79 (86), 67 (100), 55 (57), 41 (77).

45: The Grignard **44** was prepared according to the procedure of Buchi and Wuest[36] by dropwise addition of 2-(2-bromoethyl)-1,3-dioxane (2.611 g, 14.42 mmol, 1.5 equiv) in 20 mL of dry THF to a stirred suspension of 351 mg (14.42 mmol) of magnesium turnings in 5 mL of THF at such a rate that temperature of the solution did not exceed 35 °C. After the addition was complete, the mixture was stirred at room temperature for 1 h. The mixture of aldehydes **11** (1.5 g, 9.6 mmol) in 8 mL of THF were added dropwise at room temperature. After the addition was complete, the mixture was stirred for an additional 5 min, and then saturated ammonium chloride and ether were added to quench. The salts were filtered and washed well with ether. The combined ethereal solutions were concentrated. The GC and TLC of this material indicated an essentially quantitative yield of the addition product. This crude product was dissolved in 50 mL of acetone, and 280 mg (1.48 mmol) of *p*-toluenesulfonic acid was added. After 3 h of stirring at room temperature, a 1:1 mixture of the aldehyde **45** and the corresponding acetal were obtained (GC). Reflux failed to induce further deprotection. The mixture was concentrated and taken up in ether. This solution was filtered through Florisil and concentrated. The residue was taken up in 25 mL of THF, 14 mL of 6 N HCl was added, and

the mixture was then refluxed for 5 h. At this time hydrolysis was incomplete, with 10–15% of the dioxolane remaining; however, the mixture began to darken, indicating the formation of side products, and was poured into pentane, and the layers were separated. The aqueous phase was extracted with several portions of pentane. The combined organic solutions were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. This reddish residue was distilled at ~18 Torr, collecting the material boiling at 70–73 °C (reported bp 6.–72 °C, 18 Torr), to give 669 mg (56%) of **45** as a clear, mobile liquid, which contained traces of the dioxolane and other impurities. This material was, however, suitable for further use. The spectral characteristics of this material were identical with those previously reported for **45**.[35] GC (B, OV-101): **45**, 2.74 min, dioxolane, 4.78 min. TLC: silica gel, 10% ethyl acetate–ligroin, R_f 0.42. ^1H NMR: δ 9.8 (t, 1 H), 5.82 (m, 1 H), 5.50 (m, 2 H), 5.06 (m, 2 H), 2.76 (m, 2 H), 2.54 (m, 2 H), 2.40 (m, 2 H). IR (neat): 3050, 2950 (s), 2750 (m), 1730 (s), 1625 (m), 1420, 1400 (s), 980 (s), 960 (s), 910 (s). GC–MS (relative abundance): 124 (M^+, 1), 123 (1.5), 95 (24), 83 (17), 80 (100), 79 (87), 77 (17), 68 (18), 67 (50), 65 (17), 55 (44), 54 (31), 53 (34), 51 (13), 42 (11), 41 (80).

46: The aldehyde **45** (500 mg, 4.03 mmol) in 10 mL of THF was added dropwise at room temperature, with stirring, to a solution of Grignard reagent **44** (1.5 equiv, 6.05 mmol) in THF. After the addition was complete, the mixture was stirred for an additional 5 min, and then saturated ammonium chloride and ether were added to quench. The salts were filtered and washed well with ether. The combined ethereal solutions were concentrated to give the crude alcohol **46**. Flash chromatography of this residue (silica, 30% ethyl acetate–ligroin) gave pure **46**, 625 mg (69%). GC (B, OV-101): decomposes. TLC: silica gel, 30% ethyl acetate–ligroin, R_f 0.23. ^1H NMR: δ 5.79 (m, 1 H), 5.44 (m, 2 H), 4.99 (m, 2 H), 4.87 (t, 1 H), 3.90 (m, 4 H), 3.61 (s, broad, 1 H), 2.71 (s, 2 H), 2.4–1.4 (m, 9 H). ^{13}C NMR: δ 131.1, 125.0, 122.0, 108.7, 98.3, 64.8, 58.8, 58.7, 31.0, 30.5, 25.2, 23.9, 22.7. IR (neat): 3550 (s, broad), 3000 (s), 1650 (m), 1450, 1410 (s), 1140 (s), 1020 (s, broad), 970 (s), 905 (s), 785, 765 (m). GC–MS (relative abundance): 226 (M^+, 0.3), 225 (0.9), 165 (1), 164 (3), 146 (1), 135 (2), 131 (4), 120 (4), 102 (5), 99 (10), 86 (12), 80 (17), 79 (23), 73 (100), 69 (14), 58 (12), 55 (14), 45 (39), 43 (13), 41 (26). Exact mass (neg Cl, M – H) calcd for $C_{13}H_{21}O_3$ 225.14895, obsd 225.1461.

43: The dioxolane **46** (200 mg, 0.89 mmol) was dissolved in THF (6 mL), and 6 N HCl (3 mL) was added. After 3.5 h a trace of the dioxolane remained, but no further hydrolysis appeared to occur. Three product spots were apparent by TLC. The mixture was poured into pentane, and the layers were separated. The aqueous phase was extracted with several portions of pentane. The combined organic solutions were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The crude residue was purified from the trace amount of dioxolane **46** remaining by flash chromatography (silica, 30% ethyl acetate–ligroin) to give two fractions, a mixture of two more mobile spots (102 mg) and the less mobile spot (21 mg). Initially, a single GC peak (t_R 4.70 min) was observed for the material of higher R_f value. On standing in wet ether solution, both the low and high R_f materials equilibrated to the same mixture by TLC. This coincided with the appearance of new peak (t_R 6.06 min), in the GC spectrum of the higher R_f material. The GC–MS of this mixture showed two peaks, having very similar mass spectra but widely different retention times (Δt_R 1.6 min). The total yield of material was 123 mg (84%). GC (B, OV-101): 4.70 min. TLC: silica gel, 30% ethyl acetate–ligroin, R_f 0.33 (minor), 0.60, 0.67 (major). GC–MS (relative abundance): 164 (M^+, 4), 136 (2), 135 (7), 133 (6), 122 (9), 121 (10), 107 (16), 105 (13), 95 (19), 94 (23), 93 (19), 91 (25), 83 (21), 82 (19), 81 (71), 80 (49), 79 (100), 71 (27), 69 (39), 67 (46), 66 (23), 55 (35), 53 (36), 41 (90).

43: The product of the preceding reaction (102 mg, 0.62 mmol) was dissolved in acetone (4 mL), and Jones reagent was added titerimetrically. After the endpoint had been reached, stirring was continued for an additional 15 min. The mixture was then poured into ether and filtered through Florisil. The tarry residue was triturated with ether, and the ethereal solution was filtered through Florisil. The combined ethereal solutions were concentrated to give the crude lactone **43**. The GC of the crude product showed a single peak. TLC showed only traces of impurities, which were removed by flash chromatography (silica, gradient elution: 5 to >30% ethyl acetate–ligroin). This provided lactone **43** (93 mg, 83%) whose spectral properties were identical with those reported previously. An analytical sample was prepared by Kugelrohr distillation (bp 172 °C, 18 Torr, reported bp 100 °C, 0.1 Torr[34]). GC (B, OV-101): **43**, 6.70 min. TLC silica gel, 30% ethyl acetate–ligroin, R_f 0.27. ^1H NMR: δ 5.77 (m, 1 H), 5.42 (m, 2 H), 4.95 (m, 2 H), 4.46 (m, 1 H), 2.71 (dd, 2 H), 2.49 (dd, 2 H), 2.29, 2.13, 1.80, 1.64 (m, 6 H total). IR (neat): 3600 (w, overtone), 3000 (s), 1810 (s), 1650 (m), 1470, 1430 (m), 1350 (m), 1160 (s), 980 (s), 955 (m), 910 (s), 800 (w). ^{13}C NMR: δ 176.95, 137.1, 129.7, 129.2, 115.1, 80.3, 37.0, 35.5, 28.9, 28.4, 28.0. GC–MS (relative abundance) 180 (M^+, 0.2), 165 (1), 152 (1), 112 (4), 111 (7), 105 (5), 95 (3), 93 (9), 91 (9), 85 (23), 81 (14), 80 (100), 79 (53), 77 (8), 67 (12), 54 (10), 55 (13), 53 (11), 41 (25). Exact mass (neg Cl, M – H): calcd for $C_{11}H_{15}O_2$ 179.1071, obsd 179.1034.

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