Stereochemistry of Dialkylcuprate Additions to Cyclopropylacrylic Esters. An Application to the Synthesis of (±)-Eremophilone

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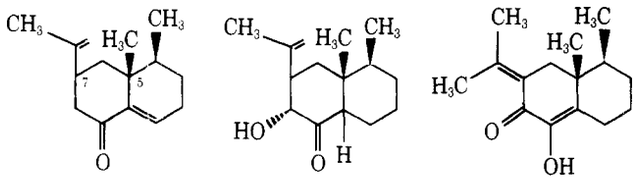
The details of the total synthesis of eremophilone (1) and its C-7 epimer **23** are discussed. The vicinal arrangement of cis dimethyl groups was achieved by the stereocontrolled addition of lithium divinylcuprate to 3,4-dimethylcyclohex-2-en-1-one. The C-7 center was created in a stereorandom fashion via a Claisen rearrangement one carbon removed from the nearest asymmetric site. This problem was solved in part by examining the stereochemistry of the addition of lithium diisopropenylcuprate to *syn*- and *anti*-cyclopropylacrylic esters **30b** and **36b**, respectively. The C-7 stereochemistry of the addition in the syn series was shown to favor the eremophilone stereochemistry (98/2), while the addition in the anti series was (85/15) in preference of the epieremophilone (**23**) stereochemistry. The stereochemical course of these reactions is discussed.

In 1932, Simonsen and co-workers[3a,4] reported the isolation of eremophilone (**1**), hydroxydihydroeremophilone (**2**), and hydroxyeremophilone (**3**) from the wood oil of *Eremophila mitchelli*, a tall shrub indigenous to the drier areas of New South Wales, Queensland, and South Australia. Adhering to the "inviolate" isoprene rule, Simonsen proposed the incorrect structure for eremophilone.[3a,b] Based upon a suggestion by Sir Robert Robinson that these substances might be nonisoprenoid compounds, Simonsen was able to propose and confirm the correct structure for eremophilone and its congeners.[3c-e] Some 15 years later Grant[5] confirmed the relative stereochemistry of hydroxydihydroeremophilone (**2**) by x-ray analysis. Shortly thereafter, Djerassi[6] provided the absolute stereochemistry of this trio by correlating hydroxyeremophilone (**3**) with material of known absolute stereochemistry. Since these three substances could be chemically interconverted, the absolute stereochemistry of the trio had been firmly established.



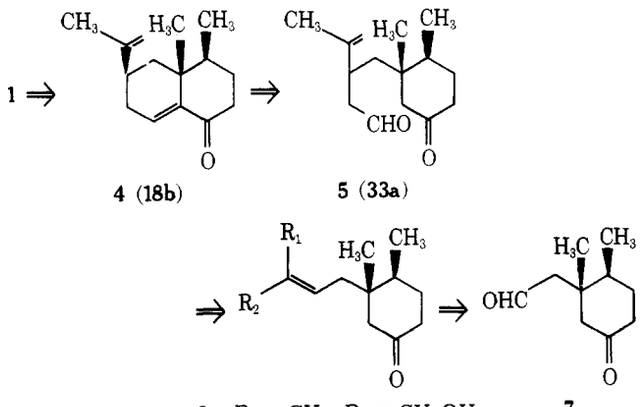
1 2 3

During the 1960's and early 1970's substantial effort went into developing methods for constructing the eremophilane and valencane (7-*epi*-eremophilane) ring systems. Many of these investigations culminated in the synthesis of members of these classes.[7] In 1974, we reported[8] a synthesis which produced both eremophilone and 7-*epi*-eremophilone. The following year, McMurry published[9] a stereoselective synthesis of eremophilone from 7-epinootkatone. This paper details the results of our previous investigation and presents a method for controlling the stereochemistry at the C-7 site.[10]

Results and Discussion

Our antithetical analysis (Scheme I) considered enone **4** as a target molecule, since the Wharton reaction[11] formally allows for the transposition of enones. The keto aldehyde **5** necessary to prepare enone **4** is capable of synthesis by either a Claisen rearrangement employing the vinyl ether of alcohol **6a** or via conjugate addition of an isopropenyl moiety to unsaturated ester **6b**. Both of these compounds would ultimately be derived from a keto aldehyde of structure **7**. Two main problems presented themselves at the outset. First, it was necessary to find a method which would cleanly produce the cyclohexanone **7** bearing the cis arrangement of methyl groups and, secondly, whether or not it is possible for stereochemistry at the *pro*-C-7 center to be controlled by the *pro*-C-5 asymmetry.

Scheme I

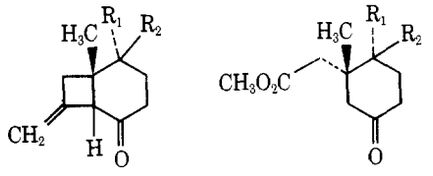


4 (18b) **5** (33a)

6a, $R_1 = CH_3$; $R_2 = CH_2OH$
b, $R_1 = H$; $R_2 = CO_2R$

7

The photoaddition of allene to cyclohex-2-en-1-ones has been applied successfully in polycyclic systems[12] with predictable stereochemistry as a means of formally adding acetaldehyde in a conjugate fashion. Corey has reported[13] the photoaddition of allene to cyclohexenone, providing the head-to-head adduct having an apparent cis-ring fusion, evidenced by the lack of epimerization upon prolonged exposure to pyridine. Irradiation of 3,4-dimethylcyclohexenone in the presence of allene at −78 °C provided a 4:1 mixture of photoadducts **8** (72% yield) displaying methyl singlets in their NMR spectrum at δ 1.23 and 1.12, respectively. The head-to-head regioselectivity was confirmed upon low-temperature ozonolysis in methanol, providing the methyl keto esters **9**, arising from Haller–Bauer cleavage of the intermediate cyclobutanone.[13] The high-field methyl singlets and doublets present in the NMR spectrum of keto esters **9** were in a ratio



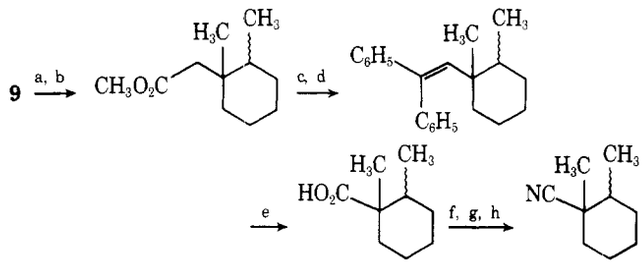
8 **9**

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

consistent with the photoadducts **8**, with the lower field signals predominating. The stereochemical assignments for these isomers were made by degradation of the keto esters to the

known isomeric *cis*- and *trans*-1,2-dimethylcyclohexylnitriles (Scheme II),[14] the cis isomer having been prepared from the

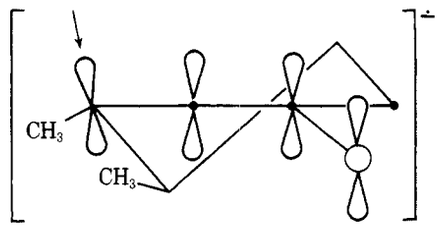
Scheme II



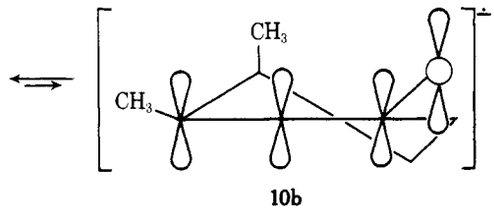
(a) KOH, NH_2NH_2, DEG; (b) CH_2N_2; (c) C_6H_5MgBr; (d) HOAc–H_2O, Δ (e) RuO_2, $NaIO_4$; (f) PCl_5; (g) NH_4OH; (h) $POCl_3$, Δ

Diels–Alder adduct of butadiene and tiglic acid.[15] NMR and VPC evidence indicated the same 4:1 ratio as in **8** and **9**, with the *trans*-1,2-dimethylcyclohexylnitrile being the major isomer.

Wiesner[16] has argued from evidence obtained from the photoaddition of allene and vinyl acetate to polycyclic cyclohexenones that the excited state of the enone has tetrahedral anionic character at the β position, being isoelectronic with the metal–ammonia reduction of similar species.[17] To our knowledge, no evidence has been brought to bare on this point concerning the stereochemistry in monocyclic systems.[18] It has been concluded[19] that the transition state radical anion from the metal–ammonia reduction of 3,4-dimethylcyclohexenone (84/16, trans/cis) is not completely sp^3 hybridized at the β position. The isomer ratios from the dissolving metal reduction (−33 °C) and the photoaddition (−78 °C) are similar, indicating a transition state with β-tetrahedral character (**10a**) lacking appreciable influence from $A^{1,2}$ interactions.[20]



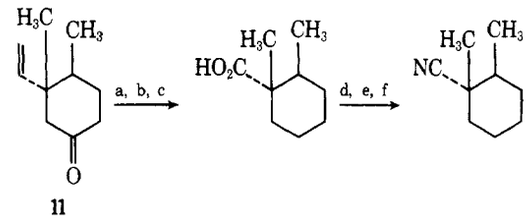
10a



10b

Since the photochemical route proved to be unsatisfactory for our needs, we sought another method which would solve this problem. The observation of Luong Thi and Riviere[21] that lithium diphenylcuprate adds to 4-methylcyclohexenone to provide a 97/3 mixture of *trans*- and *cis*-3-phenyl-4-methylcyclohexanone, respectively, taken in conjunction with evidence that cuprates add axially through a chair-like transition state[22] to cyclohexenones, argued that the 4-methyl group must be axially oriented in the transition state. Such an effect would lead to the conclusion that there would be appreciable $A^{1,2}$ interactions between the C(3)–H and C(4)–CH_3 if the latter were equatorial. Moreover, 3,4-dimethylcyclohexenone would be expected to provide a more selective reaction. This analysis proved to be correct, for when lithium divinylcuprate–tributyl phosphine complex[23] was reacted with 3,4-dimethylcyclohexenone a VPC homogeneous vinyl cyclohexanone **11** was obtained which had all the spectral attributes of a single diastereomer. In order to confirm the stereochemical integrity of this material, it was degraded as described in Scheme III, providing only *cis*-1,2-dimethylcyclohexylnitrile.

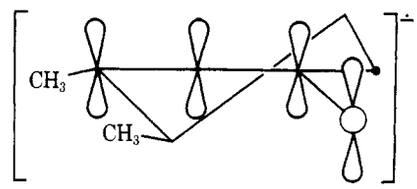
Scheme III



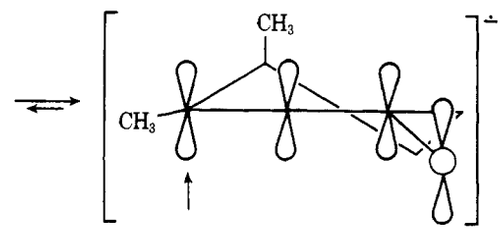
11

(a) KOH, NH_2NH_2, DEG; (b) O_3; (c) CrO_3; (d) PCl_5; (e) NH_4OH; (f) $POCl_3$, Δ

In striking contrast to the stereochemistry provided by the radical anion produced in the metal–ammonia reduction of 3,4-dimethylcyclohexenone, the cuprate addition, proceeding by an electron transfer process,[24] avoids $A^{1,2}$ interactions in a transition state **12b** with substantial sp^2 hybridization having the 4-methyl group axially oriented.



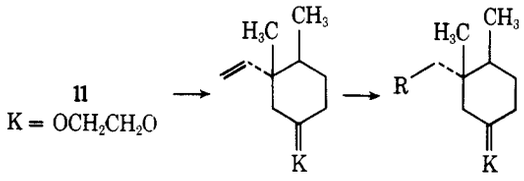
12a



12b

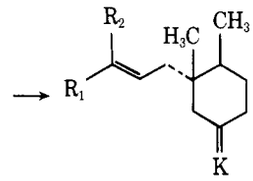
Having secured the methyl groups in the correct stereochemical arrangement, the elaboration of the vinyl group was accomplished by conventional ketalization of **11** followed by sequential hydroboration with disiamyl borane[25] and Collin's oxidation[26] to the desired ketal aldehyde[27] **14b**. Further confirmation for the diastereomeric purity of ketone **11** was obtained when alcohol **14a** was oxidized with Jones' reagent[28] followed by esterification with ethereal diazomethane to provide keto ester **9b**, whose NMR spectrum displayed a methyl singlet at δ 0.83 and a methyl doublet at δ 0.92, identical with the chemical shifts of the minor component in the diastereomeric keto esters **9** derived from the photochemical route.

We were now in a position to answer the question concerning stereochemical control at the *pro*-C-7 center. To this end, ketal aldehyde **14b** was subjected to a Wittig reaction with α-carbomethoxyethylidenetriphenylphosphorane to provide the unsaturated ester **15a** consisting of a 15/1 (*E*/*Z*) mixture of isomers. The ester was reduced with lithium aluminum hydride by inverse addition to provide the ketal allylic alcohol **15b**, since the normal mode of addition gave appreciable amounts of conjugate reduction products. When the allylic alcohol was heated at 110 °C for 18 h in ethyl orthoacetate[29] in the presence of a catalytic amount of pivalic acid, the ketal ester **16a** was produced, displaying for the isopropenyl unit a three-proton singlet at δ 1.73 (vinylic methyl) and

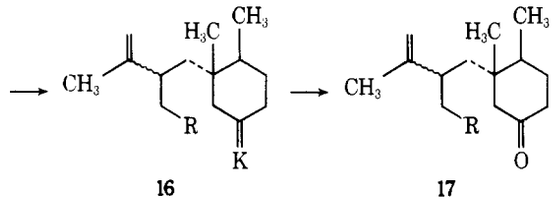


11
K = OCH_2CH_2O

13 14a, R = CH_2OH
b, R = CHO



15a, R_1 = CO_2CH_3; R_2 = CH_3
b, R_1 = CH_2OH; R_2 = CH_3
c, R_1 = $CH_2OCH{=}CH_2$; R_2 = CH_3
d, R_1 = $CO_2C_2H_5$; R_2 = H



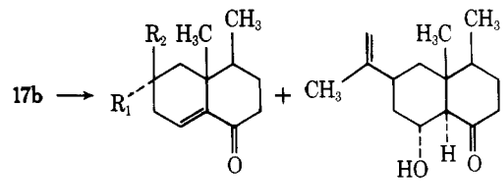
16 17

a, R = $CO_2C_2H_5$
b, R = CHO

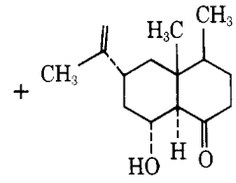
a two-proton multiplet centered at δ 4.88 (vinyl) along with the expected ethyl resonances, confirming the introduction of the requisite functionality. Dilute acid hydrolysis of the rearrangement product liberated the ketone function providing keto ester **17a**. The NMR spectrum of this material revealed two quaternary methyl singlets in a ratio of approximately 60/40. It was apparent that stereochemical control in the rearrangement was virtually nonexistent. Moreover, when ketal aldehyde **14b** was converted to unsaturated ester **15d** followed by treatment with lithium diisopropenylcuprate and subsequent acid hydrolysis, the keto ester **17a** was produced. The NMR spectrum of this material was virtually identical with the product from the Claisen route.

We chose at this juncture to examine the viability of the remaining stages of our synthetic plan (Scheme I) before reconsidering stereoselective development of the *pro*-C-7 center. To this end, mercuric acetate catalyzed exchange of allylic alcohol **15b** with *n*-butyl vinyl ether produced the vinyl ether **15c**, which upon heating at 175 °C for 12 min provided a diastereomeric mixture (~45/55) of ketal aldehyde **16b**. While this reaction was no more selective than the orthoacetate Claisen rearrangement, it conveniently provided the functionality necessary to accomplish the aldol condensation. Exposure of the ketals **16b** to aqueous acetic acid achieved deketalization without aldolization. Subsequent treatment of the keto aldehydes **17b** with sodium hydroxide in aqueous methanol provided a mixture of a single enone diastereomer **18** (1690 cm^{-1}, ~5%) and two hydroxy ketones (1710 cm^{-1}) **19** and **20** along with a variable minor amount of allylic alcohol **15b**, which was on occasion carried along when the crude Claisen product was utilized.

The aldol products proved to be resistant to or were destroyed by dehydration by traditional chemical means. However, when they were heated at 240–270 °C for 12 min a mixture of enones **18** was obtained with two distinct one-proton (enone vinyl) multiplets of nearly equal intensity in the NMR spectrum located at δ 6.40 and 6.18. The signal at δ 6.40 had the same chemical shift as the enone produced during the aldolization. Fractional crystallization of the



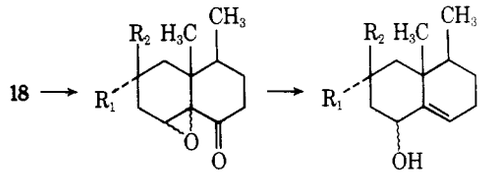
18a, R_1 = *i*-C_3H_5; R_2 = H
b, R_1 = H; R_2 = *i*-C_3H_5 19



20

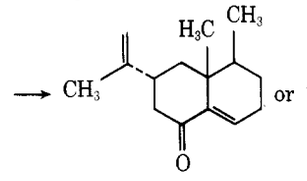
mixture of hydroxy ketones provided a single diastereomer, mp 94–95 °C, which displayed a doublet of triplets at δ 4.08 (J = 10 and 4 Hz) corresponding to the hydroxylmethine proton and consistent with an equatorial hydroxy group in either **19** or **20**. Upon thermolysis, this aldol provided the enone with the vinyl proton absorption at δ 6.18. Since no definitive information could be obtained at this point regarding the assignment of the stereochemistry of the isopropenyl group, it was necessary to explore the Wharton sequence to resolve this question by direct comparison with material from natural sources of known stereochemistry.

Reaction of the enone (δ 6.18) with alkaline hydrogen peroxide in aqueous methanol gave rise to an α,β-epoxy ketone **21** (1710 cm^{-1}), which upon exposure to hydrazine hydrate



21 22

a, R_1 = *i*-C_3H_5; R_2 = H
b, R_1 = H; R_2 = *i*-C_3H_5



23

in methanol–acetic acid gave a crude alcohol displaying a one-proton triplet at δ 5.56 (vinyl) in its NMR spectrum and the lack of carbonyl absorption in its infrared spectrum. Finally, oxidation under conditions which would not permit allylic isomerization, namely Collin's oxidation, provided eremophilone (**1**) (distinctly different from **18**) identical with a sample from natural sources[30] by thin layer chromatography, infrared, and NMR spectral comparison. The aldol product, mp 95–96 °C, could now be assigned structure **19** and its progeny **18b**, **21b**, and **22b**. Using the same synthetic sequence enone **18a** was transformed into 7-*epi*-eremophilone (**23**), different from eremophilone, but bearing gross spectroscopic similarities.

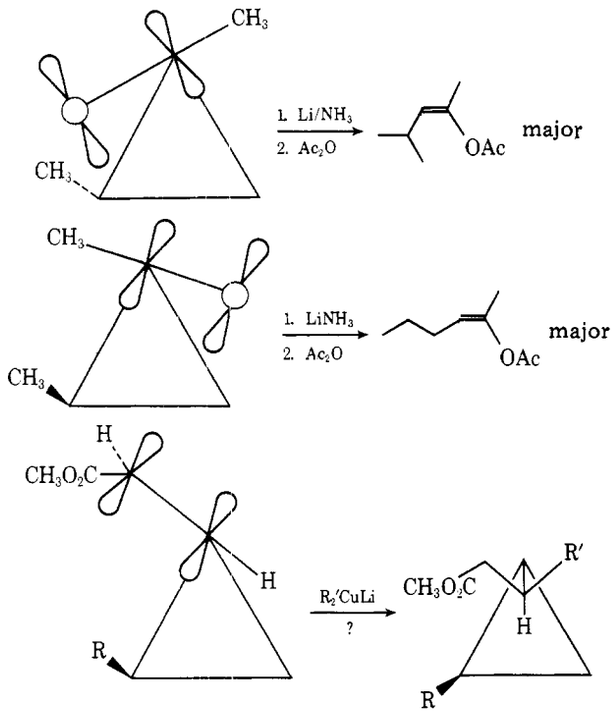
Although this approach allowed for eremophilone to be synthesized for the first time, a method was sought by which the stereochemistry at C-7 could be controlled employing the vinyl ketone **11**. It would not be necessary to convert synthetic material all the way to eremophilone (**1**) and 7-*epi*-eremophilone (**23**), since it was known that the enone **18b** had the vinyl hydrogen absorption at δ 6.18 and is converted to **1**, while

enone **18a** (δ 6.40) is transformed into **23**. These two intermediates could serve as relay compounds which would serve to define the stereochemical course of any new method.

The difficulty with the original synthesis was the failure of stereochemical control to be achieved at the *pro*-C-7 center. This was obviously due to the intercedence of the nonasymmetric center at *pro*-C-6. However, if the asymmetry at the *pro*-C-5 center could be used to generate the *pro*-C-6 center (i.e., a single diastereomer C-5, C-6), which could in turn be used to control the *pro*-C-7 center, a single diastereomer (C-5, C-7) would be achieved after the asymmetry has been removed at *pro*-C-6.

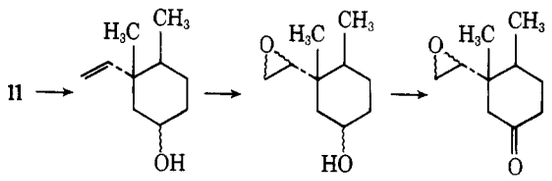
Dauben and Wolf[31] have shown that, when reduced with lithium–ammonia, methyl cyclopropyl ketones prefer a cisoid conformation in the transition state. Moreover, a cis alkyl group on the vicinal cyclopropane carbon alters the course of the bond cleavage (Scheme IV). Spectroscopic data indicates

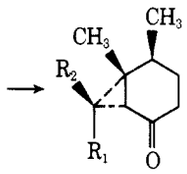
Scheme IV



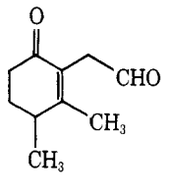
that the cisoid conformation of methyl cyclopropyl ketones is also preferred in the ground state,[32] while vinylcyclopropanes[33] and cyclopropylacrylic esters[34] prefer the transoid conformation. While the products from the methyl cyclopropyl ketone reductions are a reflection of the transition state geometry and not the ground state, it is imprudent to predict the course of kinetically controlled reactions from ground state geometries (Curtin–Hammett principle).[35] Given the generally high specificity in cuprate additions, the electron transfer process in both metal–ammonia reductions and cuprate additions,[24] and the similarity of ground and transition state geometries in the methyl cyclopropyl ketone reductions, it did not seem unreasonable that the mode of addition to a substituted cyclopropylacrylic ester would be as shown in Scheme IV. To test this possibility, a synthesis of the appropriate cyclopropylacrylic ester was undertaken.

Reduction of vinyl ketone **11** with ethereal lithium aluminum hydride gave the alcohols **24**, which were successively oxidized with *m*-chloroperbenzoic acid to epoxy alcohols **25** and with chromium trioxide–dimethyl pyrazole complex[36] to a mixture of keto epoxides **26**. This sequence was necessitated by the fact that direct epoxidation of **11** gave preferential Baeyer–Villiger products, while buffered epoxidations[37] were slow and erratic. The epoxidation of vinyl ketal **13** was uncomplicated, but removal of the ketal group resulted in a complex mixture of reaction products. The cyclopropanation[38] proceeded smoothly by the dropwise addition of the epoxy ketones to KO-*t*-Bu/HO-*t*-Bu at room temperature, providing the syn and anti alcohols **27a,b** in a ratio of ~2.5/1, respec-





27a, $R_1 = CH_2OH$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2OH$
c, $R_1 = CHO$; $R_2 = H$
d, $R_1 = H$; $R_2 = CHO$
e, $R_1 = E\text{–}CH{=}CHCO_2CH_3$; $R_2 = H$
f, $R_1 = H$; $R_2 = E\text{–}CH{=}CHCO_2CH_3$



28

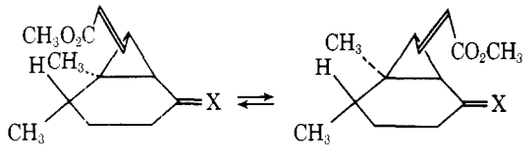
tively. The presence of the cyclopropane ring was confirmed by the appearance of a carbonyl frequency at ~1680–1675 cm^{-1} in both isomers. The syn–anti relationship was not able to be determined at this point with certainty, although the chromatographic polarity of the two alcohols was markedly different, the syn isomer presumably the less polar of the two compounds. On the assumption that the epoxide opening is S_N2-like, the isomer ratio would have been established at the epoxidation stage.

The stereochemistry of these isomers was placed on a firm foundation when the alcohols were oxidized to the cyclopropyl aldehydes with manganese dioxide.[39] The less polar alcohol provided an aldehyde which displayed an aldehyde proton (δ 9.70, d, J = 3 Hz), a three-proton doublet (δ 1.15, J = 6 Hz), a three-proton singlet (δ 1.20), and the remaining seven protons lying in the range δ 1.40–2.60. The more polar alcohol gave an aldehyde with an aldehyde proton doublet (δ 9.46, d, J = 4.5 Hz), the methyl singlet and doublet, and a five-proton array in the region δ 1.40–2.39. Shifted downfield from this area, in contrast with the other isomer, was a one-proton doublet (δ 2.47, J = 4.5 Hz) and a one-proton triplet (δ 2.84, J = 4.5 Hz). These latter resonances were assignable to the cyclopropane proton α to the ketone and aldehyde, respectively, in the anti isomer, each being deshielded by the other carbonyl. Irradiation of the aldehyde proton caused collapse of the triplet to a doublet, the doublet (δ 2.47) remaining unchanged. Alternatively, irradiation of the triplet caused the methine doublets to collapse to singlets. Attempts to interconvert the aldehyde isomers by epimerization resulted in decomposition of the substrates.

It is of interest that syn aldehyde **27c**[39] underwent partial thermal rearrangement upon VPC analysis (injection port 250 °C). Thermolysis of **27c** for 5 min at 250 °C under nitrogen produced aldehyde **28**, whose structure was assigned by NMR and IR spectroscopy. The presence of a three-proton doublet (δ 1.22, J = 7 Hz), a three-proton singlet (δ 1.92, vinylic

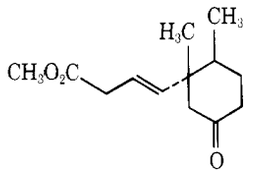
methyl), an unresolved two-proton singlet (δ 3.38, allylic methylene), and a one-proton triplet (δ 9.45, J = 2 Hz) in addition to carbonyl absorptions at 1770 (enone), 1725 (aldehyde), and 2720 cm^{-1} (aldehyde CH) was in full accord with the structural assignment. Such rearrangements are not without precedent,[40] although in this instance the initially formed tetrasubstituted double bond (C-3, C-4) migrates into conjugation with the ketone.

Since the syn alcohol **27a** was produced as the major and more readily available of the two isomers, the syn series was investigated first. Treatment of aldehyde **27c** with carbomethoxymethylenetriphenylphosphorane in methylene chloride at room temperature cleanly provided the unsaturated ester **27e** as a low-melting, crystalline solid. The α-olefinic proton (H_α) appeared in the NMR spectrum as a doublet (δ 5.89, J = 14.5 Hz), while the β-proton (H_β) appeared as a doublet of doublets (δ 6.76, $J_{\alpha,\beta}$ = 14.5 and $J_{\beta,\gamma}$ = 8 Hz) indicative of an E double bond and a transoid conformation of the side chain. Ethyl cyclopropylacrylate has been reported[34] to have a $J_{\beta,\gamma}$ = 9.4 Hz. While the coupling constant in this system arises from the weighted average[41] of $J_{trans} \cong$ 11–12 Hz and $J_{gauche} \cong$ 4 Hz,[42] the gauche conformations ($\theta_{\beta,\gamma}$ = 60°) and s-cis (θ = 0°) would all but be precluded from the syn ester conformations by interaction of the cyclohexane ring with the acrylic ester chain. Both half-chair conformations of the cyclohexane ring present transannular steric interactions between axial methylene hydrogens and H_β when the chain is maintained in the s-trans conformation ($\theta_{\beta,\gamma}$ = 180°). The major conformers which would account for the observed coupling constant of J_{obsd} = 8 Hz would have to have $J(\theta_{\beta,\gamma})$ equal to or just less than 8 Hz. These conformers **29a** and **30a** need not have the same angle θ or be equally populated.



29a, X = O (**27e**)
b, X = OCH_2CH_2O–

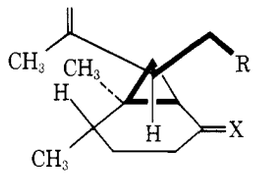
30a, X = O (**27e**)
b, X = OCH_2CH_2O–



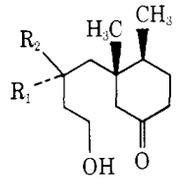
31

When the syn keto ester was reacted with lithium diisopropenylcuprate, a compound assigned structure **31** was obtained, displaying a ketone (1720 cm^{-1}) and a nonconjugated ester (1745 cm^{-1}) in its infrared spectrum. The NMR spectrum revealed the requisite methyl signals in addition to a broad two-proton singlet at δ 5.36 (vinyl H)[43] and 2.93 (allylic methylene). This type of reductive cleavage[44] is not unexpected in view of the electron transfer mechanism and is reminiscent of the course of the metal–ammonia reductions of methyl cyclopropyl ketones. In such a reaction, the conformation of the radical anion which effects cleavage would be related to ground state conformation **30a**, having the appropriate orbital overlap for reduction. In order to prevent reduction, it was considered necessary to mask the ketone as its ethylene glycol ketal[45] and, in addition, the ketal would be expected to favor conformer **30b**. The ketal, produced under carefully regulated conditions,[46] revealed a coupling constant of $J_{\beta,\gamma}$ = 10 Hz. This increase ($\Delta J_{\beta,\gamma}$ = 2 Hz) of the coupling constant is reasonable, since the ketal forbids conformations with small J values by restricting rotation about the C_β–C_γ bond and favors **30b** over **29b** (H_β/ketal interaction).

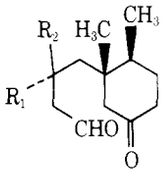
If the ketal function in **30b** were capable of accepting the role of the R group of the cyclopropylacrylic ester in our original proposal (Scheme IV), then the addition of the isopropenyl moiety to ketal **30b** should occur to provide adduct **32b**. When the cuprate addition was conducted followed by mild hydrolysis, a cyclopropyl keto ester (1686 and 1740 cm^{-1}), **32a** was obtained whose NMR spectrum displayed a



32a, R = CO_2CH_3; X = O
b, R = CO_2CH_3; X = OCH_2CH_2O
c, R = CH_2OH; X = O



33



34

a, R_1 = H; R_2 = i-C_3H_5
b, R_1 = i-C_3H_5; R_2 = H

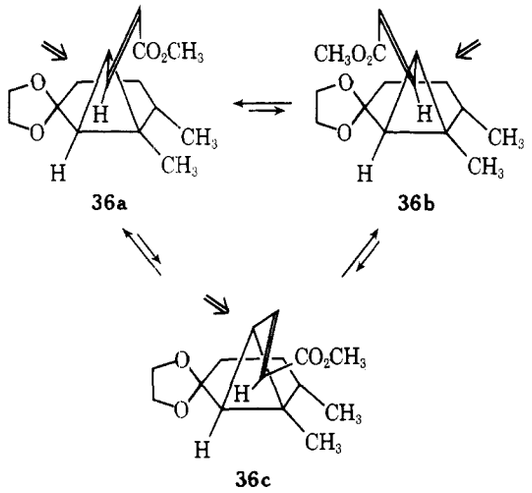
broadened two-proton singlet at δ 4.80 (H_2C=), three-proton singlets at δ 3.57 (CO_2CH_3) and 1.74 (vinylic CH_3), and a three-proton singlet and doublet (J = 7 Hz) both at δ 1.09. Although the chromatographic and spectroscopic evidence did not indicate diastereomers, it was necessary to convert this substance to either **18a** or **b** to confirm its purity.

Reduction of the crude ketal **32b** with lithium aluminum hydride followed by hydrolysis produced the cyclopropyl keto alcohol (3650–3390 and 1678 cm^{-1}) **32c**, which displayed the required methyl signals in its NMR spectrum. Reduction of the cyclopropyl ketone **32c** with lithium in liquid ammonia yielded a keto alcohol (3650–3200 and 1709 cm^{-1}) of gross structure **33** by the cleavage of the cyclopropyl bond overlapping with the ketone. Unraveling of the carbon framework as illustrated in **32** (bold lines) would give rise to the eremophilone stereochemistry. Collin's oxidation of **33a** provided the keto aldehyde **34a** [1725 cm^{-1} (br)], displaying a one-proton triplet (J = 3 Hz) at δ 9.22 in its NMR spectrum. Aldolization of the keto aldehyde followed by thermolysis gave enone **18b** in >98% isomeric purity by both NMR and VPC integration. Thus, as anticipated, the steric hindrance of the ketal allows for high selectivity in the cuprate addition step ($\Delta\Delta G^{\ddagger}_{273} > 2.1$ kcal).

The crystalline *anti*-cyclopropylacrylic ester **27f**, mp 93–94.5 °C, was prepared from the anti aldehyde by the method employed in the syn series. The NMR spectrum indicated a one-proton doublet of doublets at δ 6.59 (H_β, $J_{\alpha,\beta}$ = 15 Hz, $J_{\beta,\gamma}$ = 9 Hz), a one-proton doublet at δ 5.90 (H_α, $J_{\alpha,\beta}$ = 15 Hz), and a one-proton doublet of doublets at δ 2.60 (H_γ, $J_{\beta,\gamma}$ = 9 Hz, $J_{\gamma,\epsilon}$ = 4 Hz). The high-field signal for the cyclopropyl hydrogen was shifted downfield relative to the syn isomer, as was the case with the corresponding aldehydes. The β-proton experienced a slight ($\Delta\delta$ = 0.2 ppm) upfield shift relative to the syn isomer, which would be in accord with the larger coupling constant ($\Delta J_{\beta,\gamma}$ = 1 Hz) in the anti isomer, since the β-proton in the anti series would be in the shielding cone of the cyclopropane ring.[32a] Ketalization[47] of **27f** did not effect the value of $J_{\beta,\gamma}$, since the ketal group was sufficiently removed from the acrylate chain. The ketal was sequentially reacted with lithium diisopropenylcuprate, reduced with lithium aluminum hydride, and hydrolyzed to provide a cy-

clopropyl keto alcohol **35**. This material was reduced to the keto alcohol **33** with lithium ammonia, oxidized with Collin's reagent (**34**), aldolized, and thermolyzed to yield a 15/85 mixture of enones **18b** and **18a**. Structures **33b** and **34b** represent the stereochemistry of the predominant isomer derived from the *anti*-cyclopropyl ester ketal **36**.

If the transition state were to resemble the ground state in the addition reaction, the major stereoisomer would have to arise from the transoid conformation **36b** (or s-trans, $\theta_{\beta,\gamma}$ = 180°) or the gauche conformation **36c**, both presumably minor contributors to the ground state population. Conformation **36b** suffers from a peri-(H_β–CH_3) interaction, while **36c** has an incipient 1,6-H_β-cyclopropyl hydrogen interaction. If either **36b** or **36c** were involved in the product developing step it would be necessary for the rate constants for the reaction of these conformers to be significantly greater than for conformer **36a** to account for the observed product ratio. Such a difference would invariably be related to steric hindrance in **36a**. The fact that the hydrogen atoms of the ketal extend to the plane of cyclopropane ring, taken in conjunction with the bulk of the cuprate reagent, represent the only steric factors associated with **36a**.



On the other hand, if the transition state has tetrahedral character at C_β, then a transoid conformation would favor approach as in **36b** (relief of H_β–CH_3 interaction), while **36a** would develop such an interaction. It must be borne in mind that the ratio 15/85 only represents an energy difference of $\Delta\Delta G^{\ddagger}_{273} \sim 0.9$ kcal for the transition states in the anti series. Quite clearly the anti series has options open to it which are virtually excluded in the syn series.

The cuprate addition to these cyclopropylacrylic ester ketals allows for a stereoselective synthesis of eremophilone, since the syn alcohol **27a** is formed as the major stereoisomer and the syn ketal ester **30b** undergoes a highly selective cuprate addition. More importantly, the technique involving the cyclopropylacrylic esters introduces a method for controlling stereochemistry at isolated sites (i.e., no vicinal asymmetry) in carbon chains. The testing of this method in a natural products synthesis has also permitted the establishment of the stereochemistry of the reaction, information which would have been difficult to determine with simpler models.

Experimental Section

Melting points (corrected) were determined on a Fisher–Johns apparatus. Elemental analyses were performed by Atlantic Microlabs (Atlanta) and are within 0.3% of the theoretical composition. NMR spectra were determined on a Varian A-60 (60 MHz) or EM-360A (60 MHz), Perkin-Elmer R-32 (90 MHz), Jeolco Minimar (100 MHz), or Bruker HX-270 spectrometer. Chemical shifts are reported in δ (ppm) downfield from $(CH_3)_4Si$. IR spectra were recorded on a Perkin-Elmer 337 or Beckmann 4250 infrared spectrometer. Mass spectra were recorded on a Hitachi RMU-6E or AEI-MS-9 spectrometer. Gas chromatography was performed on a Varian 90-P(TC) using a 6 ft × ¼ in. 20% SE-30 on Anakrom 60/70 SD column or a Perkin-Elmer 3920 (FID) using a 5 ft OV-1 on Chrom W-HP (80–100) or 5 ft OV-225 GC-Q (100–120) column. Anhydrous magnesium sulfate was used for drying organic solutions, unless specified otherwise. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were dried by distillation from either $LiAlH_4$ or sodium benzophenone ketyl. Thick-layer chromatography was performed on Analtech 200 × 200 × 2 mm silica gel plates with fluorescent indicator.

Photoadducts 8. To a standard photochemical immersion unit[48] (Hanovia medium pressure 450-W lamp) equipped with a dry ice condenser was added 6.2 g (50 mmol) of 3,4-dimethylcyclohexenone[49] in 750 mL of ether. The reaction vessel was cooled in a dry ice–acetone bath followed by purging with N_2. The vessel was charged with ~15 mL of allene and irradiated for 22 h. After 4, 8, and 11 h, 15-mL portions of allene were added. The resulting solution was carefully concentrated and distilled [bp 62–64 °C (0.5 mm)] to provide a 4:1 mixture of photoadducts **8**. A sample collected by VPC showed: NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6 Hz), 1.12 (0.6 H, s), 1.23 (2.4 H, s), 3.21–1.09 (8 H, m), and 4.79 (2 H, m); IR (CCl_4) 1725 cm^{-1}.

Anal. ($C_{11}H_{16}O$): C, H.

Keto Esters 9. A solution of 3.68 g (24.4 mmol) of photoadducts **8** in 30 mL of CH_3OH was ozonized at −78 °C until the blue ozone color persisted. The solution was purged with N_2 and then treated with 3 mL of dimethyl sulfide[50] followed by warming to 25 °C over 4 h. The solvent was carefully removed and the residue taken up in ether. The organic solution was washed twice with water, dried, concentrated, and distilled to provide 3.3 g (69%) of the keto esters **9**: bp 86–88 °C (0.06 mm); IR (CCl_4) 1735 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (0.6 H, s), 0.92 (0.6 H, d, J = 7 Hz), 1.00 (2.4 H, d, J = 7 Hz), 1.07 (2.4 H, s), 2.62–1.37 (9 H, m), and 3.46 (3 H, s).

Degradation of Keto Esters 9 (Scheme II). To a mixture of 830 mg of potassium hydroxide and 2.2 g of 85% hydrazine hydrate in 10 mL of diethylene glycol maintained under N_2 was added 990 mg (5.0 mmol) of keto esters **9**. The mixture was brought to 130 °C for 30 min, during which time 2 mL of low-boiling liquid was removed. The remaining solution was heated for 3 h at 195–200 °C. The reaction mixture was cooled to 25 °C, poured into 25 mL of water, acidified with 3 N HCl, and extracted thoroughly with ether. The combined ether extracts were dried and treated with an excess of ethereal diazomethane. The excess diazomethane was decomposed after 5 min with HOAc and the ether solution was washed with saturated $NaHCO_3$ solution. The organic solution was dried, filtered, and concentrated to provide 800 mg (87%) of crude esters which were homogeneous by VPC: IR (CCl_4) 1735 cm^{-1}.

Phenylmagnesium bromide was prepared in the usual way from 1.57 g (10 mmol) of bromobenzene and 240 mg (10 mmol) of magnesium metal in 30 mL of dry ether. The crude esters, 800 mg (4.3 mmol), were dissolved in 5 mL of ether and added dropwise to the Grignard reagent over a period of 30 min. The reaction mixture was cautiously decomposed with saturated NH_4Cl solution after having stirred for 7 h. The phases were separated and the aqueous solution was thoroughly extracted with ether. The combined ether extracts were dried, filtered, and concentrated, affording a crude alcohol (IR (CCl_4) 3650–3200 and 3125–3050 cm^{-1}). The alcohols were dissolved in 12 mL of HOAc and 1 mL of H_2O, and the solution was refluxed for 10 h. The mixture was cooled to room temperature, diluted with ether, and washed with saturated $NaHCO_3$ until the washings were alkaline. The ether solution was dried, filtered, and concentrated to provide a crude residue exhibiting no hydroxy absorption in its infrared spectrum.

To a mixture of 80 mg of ruthenium dioxide in 10 mL of water was added 2.1 g of sodium metaperiodate in three portions over 10 min. To the stirred, clear yellow solution was added the crude dehydration product in 5 mL of acetone, producing an immediate black precipitate. Excess periodate was added as needed to maintain the yellow solution over a period of 60–70 h. The reaction mixture was filtered, the residue was washed with water and ether, and the resulting filtrates extracted three times with ether and once with chloroform. The combined organic fractions were extracted with 4 N NaOH solution and the extracts acidified with 3 N HCl. The acidic solution was extracted thoroughly with ether, dried, filtered, and concentrated to give 126 mg (0.8 mmol) of crude acids, which exhibited infrared absorptions at 3500–2300 and 1700 cm^{-1}.

The crude acids were added to 1.2 g (6 mmol) of phosphorus pentachloride in 5 mL of CH_2Cl_2 and stirred for 30 min. The mixture was cautiously poured onto 3 N NH_4OH at 0 °C. After 10 min, the layers were separated and the aqueous solution was extracted thoroughly with CH_2Cl_2. The combined extracts were dried, filtered, and con-

centrated. The residue was dissolved in 10 mL of ethylene dichloride containing 0.5 mL of $POCl_3$ and a trace of NaCl and refluxed for 18 h. The reaction mixture was cooled to 25 °C, washed with water, dried, filtered, and concentrated to afford 96 mg (14% overall) of a 4:1 mixture of *trans*- and *cis*-1,2-dimethylcyclohexylnitrile (IR 2245 cm^{-1}) having identical retention times (VPC) with authentic samples.[14]

Vinyl Ketone 11. To a stirred suspension of 28.5 g (0.15 mol) of cuprous iodide in 100 mL of dry ether maintained under N_2 at 0 °C was added 31.9 g (0.16 mol) of tri-*n*-butylphosphine at a rate such that the temperature did not exceed 20 °C. After the addition had been completed, the reaction mixture was allowed to stir at 25 °C until the milky CuI suspension was converted into a slightly cloudy yellow solution. The solution was cooled to −60 °C, followed by the addition of 150 mL (0.3 mol) of 2 M vinyllithium in THF (Ventron) via syringe at such a rate that the temperature did not exceed −30 °C. The resulting deep red-brown solution was cooled to −78 °C, stirred an additional 30 min, and followed by the addition of 12.6 g (0.1 mol) of 3,4-dimethylcyclohexenone in 50 mL of dry ether over a period of 45 min. After stirring the solution for an additional 1 h at −78 °C, the reaction mixture was allowed to warm to 25 °C and was subsequently poured into 200 mL of saturated NH_4Cl solution. After stirring for 1 h, the solution was thoroughly extracted with ether, dried, filtered, concentrated, and distilled to afford 15.0 g (98%) of ketone **11**, 95% pure by VPC analysis: bp 51–54 °C (0.3 mm); IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 0.88 (3 H, s), 0.91 (3 H, d, J = 6 Hz), 4.83 (1 H, d, J = 15 Hz), 4.89 (1 H, d, J = 10 Hz), and 5.62 (1 H, d, J = 10 and 15 Hz).

Anal. (VPC sample) $C_{10}H_{16}O$: C, H.

Degradation of Vinyl Ketone 11. Employing the conditions for the Wolff–Kishner reduction and ozonolysis of photoadduct **8**, 1.3 g (8.5 mmol) of vinyl ketone **11** was successively converted to the crude 1,2-dimethylcyclohexane carboxaldehydes (Scheme III): IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 9.35 (1 H, s). The crude aldehyde was dissolved in 10 mL of acetone at 0 °C, followed by the addition of 8 N Jones reagent[28] to the stirred solution until the reaction mixture gave a positive test with starch–iodide paper. After 30 min, the solvent was removed in vacuo and the residue taken up in water and thoroughly extracted with ether. The ether solution was extracted twice with 3 N KOH solution, the aqueous solution acidified with 3 N HCl, and thoroughly extracted with ether, dried, filtered, and concentrated to provide a crude acid: IR (CCl_4) 3500–3200 and 1700 cm^{-1}. The acid was transformed into the nitrile [IR (CCl_4) 2245 cm^{-1}] (vide supra) providing only *cis*-1,2-dimethylcyclohexylnitrile[14] (VPC) in 25% overall yield.

Keto Ester 9b. To a stirred solution of disiamylborane,[25] prepared from 240 mL (240 mmol) of 1 M borane in THF and 51 mL (480 mmol) of 2-methyl-2-butene in 300 mL of dry dimethoxyethane (DME) maintained at 0 °C under a N_2 atmosphere, was rapidly added 12.2 g (0.08 mol) of vinyl ketone **11** in 10 mL of DME. The reaction mixture was allowed to warm to 25 °C over 4 h, followed by cooling to 0 °C, and cautious treatment with 200 mL of 3 N aqueous NaOH solution followed by 120 mL of 30% H_2O_2. The solution was stirred overnight at 25 °C, poured onto 300 mL of water, and extracted thoroughly with ether. The ether extracts were dried, filtered, and concentrated.

The crude residue in 100 mL of acetone was added dropwise to a solution of 110 mL of 8 N Jones reagent in 400 mL of acetone at 0 °C. After the addition had been completed, the reaction mixture was stirred for 30 min and then concentrated in vacuo. The residue was thoroughly triturated with ether followed by extraction of the ether solution with 3 N NaOH. The aqueous solution was acidified with 3 N HCl, extracted with ether, dried, filtered, and partially concentrated (~100 mL) in vacuo. The ether solution was treated with a slight excess of ethereal diazomethane followed by removal of the solvent and distillation of the residue to provide 9.03 g (57%) of keto ester **9b**: bp 87–89 °C (1 mm); NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.92 (3 H, d, J = 7 Hz), and 3.47 (3 H, s).

Anal. ($C_{11}H_{18}O_3$): C, H.

Vinyl Ketal 13. A mixture of 14.50 g (0.095 mol) of vinyl ketone **11**, 11.8 g (0.19 mol) of ethylene glycol, and 910 mg (4.8 mmol) of *p*-toluenesulfonic acid in 400 mL of benzene was refluxed under nitrogen using a Dean–Stark trap. After 3 h, the solution was cooled to 25 °C, washed twice with 3 N NaOH, and once with water. The aqueous phase was extracted once with ether and the combined organic phases were dried, filtered, concentrated, and distilled to afford 16.8 g (90%) of vinyl ketal **13**: bp 71–73 °C (0.3 mm); IR (CCl_4) no carbonyl; NMR (CCl_4) δ 0.74 (3 H, d, J = 7 Hz), 0.95 (3 H, s), and 3.77 (4 H, s).

Anal. ($C_{12}H_{20}O_2$): C, H.

Ketal Aldehyde 14b. A stirred solution of 0.13 mol of disiamylborane in dry THF was prepared at 0 °C (vide supra). After 1 h, a solution of 16.8 g (0.086 mol) of vinyl ketal **13** in 30 mL of dry THF was added over a period of 5 min, after which the solution was allowed to warm to 25 °C and stirred for an additional 4 h. The solution was cautiously treated at 0 °C with 129 mL of 3 N NaOH followed by 100 mL of 30% H_2O_2 and allowed to warm to 25 °C over 18 h. The organic solvent was removed in vacuo and the aqueous solution was thoroughly extracted with ether. The ether solution was washed twice with water, dried, filtered, concentrated, and azeotroped in vacuo with benzene. The crude ketal alcohol **14a** (18.3 g, ~100%) had an NMR spectrum virtually identical with a sample of alcohol prepared in another experiment which had the following physical properties: bp 98–102 °C (5 μm); IR (CCl_4) 3650–3100 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 6 Hz), 0.91 (3 H, s) 3.73 (2 H, t, J = 7 Hz), and 3.86 (4 H, m).

Anal. ($C_{12}H_{22}O_3$): C, H.

Using purified solvents,[26b] 109.0 g (1.38 mol) of pyridine was added dropwise over a period of 5 min to a suspension of 68.8 g (0.69 mol) of chromium trioxide in 2.5 L of CH_2Cl_2. After stirring the mixture for 2 h at 25 °C, 18.3 g (0.086 mol) of the crude ketal alcohol **14a** in 50 mL of methylene chloride was added over a period of 5 min, after which the reaction mixture was stirred for 18 h. The solvent was removed followed by trituration of the residue with ether and filtration over Celite in vacuo. The residue was washed several times with ether and the combined ether fractions were concentrated and distilling providing 12.8 g (70%) of ketal aldehyde **14b**: bp 83–85 °C (5 μm); IR (CCl_4) 2725 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.96 (4 H, s), 2.38 (2 H, d, J = 4 Hz), and 9.95 (1 H, t, J = 4 Hz).

Anal. ($C_{12}H_{20}O_3$): C, H.

Ketal Ester 15a. A mixture of 4.35 g (20.5 mmol) of ketal aldehyde **14b** and 7.83 g (22.5 mmol) of α-carbomethoxyethylidenetriphenylphosphorane[51] in 100 mL of benzene was refluxed for 24 h. The cooled reaction mixture was concentrated in vacuo to a viscous oil, which crystallized upon trituration with 25 mL of hexane. The mixture was filtered and the residue washed thoroughly with hot hexane. The combined hexane fractions were concentrated and distilled to afford 5.77 g (91%) of a 15/1 (*E*/*Z*) mixture of ketal esters **15a**: bp 115–122 °C (6 μm); IR (CCl_4) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.81 (3 H, br s), 2.11 (2 H, br d, J = 8 Hz), 5.89 (0.06 H, br t, J = 8 Hz), and 6.75 (0.94 H, dt, J = 1.5 and 8 Hz) (irradiation at δ 1.81 causes collapse to a broad singlet).

Anal. ($C_{16}H_{26}O_4$): C, H.

Ketal Ester 15d. To a stirred suspension of 50 mL of dry DME containing 1.0 g (20 mml) of sodium hydride (50% dispersion in mineral oil), which had been washed twice with 5-mL portions of DME, maintained at 25 °C under N_2 was added dropwise 4.5 g (20 mmol) of ethyl diethylphosphonoacetate[52] in 25 mL of DME. To the resultant clear yellow solution was added 3.8 g (18.0 mmol) of ketal aldehyde **14b** in 15 mL of DME over 15 min (exothermic). The reaction mixture was stirred for 18 h at 25 °C and then concentrated in vacuo. The residue was dissolved in ether, washed with 3 N NaOH, dried, concentrated, and distilled to afford 4.7 g (90%) of ketal ester **15d**: bp 110–115 °C (8 μm); IR (CCl_4) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 2.11 (2 H, d, J = 8 Hz), 3.82 (4 H, m), 4.10 (2, H, q, J = 7 Hz), 5.69 (1 H, d, J = 16 Hz), and 6.82 (1 H, dt, J = 8 and 16 Hz).

Anal. ($C_{16}H_{26}O_4$): C, H.

Allylic Alcohol 15b. To a stirred solution of 5.1 g (18.0 mmol) of ketal ester **15a** in 100 mL of ether maintained under N_2 at 0 °C was added 800 mg (21 mmol) of lithium aluminum hydride in five portions over a period of 5 min. The reaction mixture was stirred at 25 °C for 22 h, followed by cooling to 0 °C and cautious decomposition with saturated Na_2SO_4 solution. The ether layer was separated and the aqueous layer extracted thoroughly with ether. The combined extracts were dried, concentrated, and distilled to afford 4.07 g (95%) of allylic alcohol **15b**: bp 115–120 °C (5 μm); IR (CCl_4) 3620–3100 cm^{-1}; NMR ($CDCl_3$) δ 1.64 (3 H, br s), 3.86 (4 H, m), 3.95 (2 H, br s), and 5.41 (1 H, br t, J = 8 Hz).

Anal. ($C_{15}H_{26}O_3$): C, H.

Keto Esters 17a (via orthoacetate Claisen rearrangement). A mixture of 2.1 g (8.3 mmol) of allylic alcohol **15b** and 40 mg (0.4 mmol) of pivalic acid was heated in 10 mL of ethyl orthoacetate at 110–120 °C for 18 h under an atmosphere of N_2 with the occasional removal of low-boiling solvent. The reaction mixture was cooled, diluted with ether, washed with saturated $NaHCO_3$ solution, dried, and concentrated in vacuo to afford 2.5 g (93%) of crude ketal ester **16a**: NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.73 (3 H, s), 3.96 (4 H, m), 4.17 (2 H, q, J = 7 Hz), and 4.88 (2 H, m).

A sample [1.1 g (3.4 mmol)] of the crude ketal was dissolved in 9 mL of ethanol and 3 mL of 0.3 N HCl and stirred for 24 h at 25 °C. The mixture was diluted with water, thoroughly extracted with ether, backwashed with saturated $NaHCO_3$ solution, dried, filtered, con-

centrated, and distilled affording 850 mg (86%) of keto esters **17a**: bp 110–115 °C (5 μm; Kugelrohr); IR (CCl_4) 1735 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (1.2 H, s), 0.73 (1.8 H, s), 0.78 (1.8 H, d, J = 6 Hz), 0.92 (1.8 H, d, J = 6 Hz), 1.20 (3 H, t, J = 7 Hz), 1.65 (3 H, s), 4.00 (2 H, q, J = 7 Hz), and 4.70 (2 H, m).

Anal. ($C_{17}H_{28}O_3$): C, H.

Keto Esters 17a (via cuprate). To a stirred suspension of 1.0 g (0.14 mol) of sliced lithium wire (1.1% Na) in 30 mL of dry ether maintained under an argon atmosphere at 25 °C was added, dropwise over a period of 1 h, 5.2 g (55.0 mmol) of 2-bromopropene.[53] After the addition had been completed, the mixture was stirred at RT for 18 h. The reaction mixture was transferred via syringe to a heavy-walled serum-capped centrifuge tube. The suspension was centrifuged and the supernatant solution was transferred to a second tube. The solution was standardized by NMR integration of the isopropenyl signals of a known volume aliquot against a weighted amount of benzene or biphenyl (1.1 M).

To a stirred suspension of 4.80 mg (2.5 mmol) of CuI in 25 mL of ether at 0 °C (under N_2) was added 4.5 mL (5.0 mmol) of 1.1 M isopropenyllithium. After 10 min, 282 mg (1.0 mmol) of ketal ester **15d** in 6 mL of ether was added dropwise over 5 min. After an additional 10 min, the solution was allowed to warm to 25 °C and poured onto an equal volume of saturated NH_4Cl solution. The mixture was stirred for 30 min and then thoroughly extracted with ether, dried, filtered, and concentrated. Deketalization (vide supra) provided a sample (VPC) of keto ester **17a** identical (NMR and VPC retention time) with the material prepared by the orthoacetate rearrangement.

Vinyl Ether 15c. A mixture of 1.5 g (5.9 mmol) of allylic alcohol **15b** and 30 mg of mercuric acetate were refluxed in 15 mL of butyl vinyl ether with occasional removal of the vapor head. Refluxing of the solution was continued for 18 h with the addition of 30-mg portions of mercuric acetate after 2 and 4 h. The reaction mixture was cooled, diluted with 30 mL of ether, and washed with 15 mL of cold saturated $NaHCO_3$ solution. The aqueous phase was backwashed with ether and the combined ether extracts were dried, filtered, concentrated, and distilled to provide 1.6 g (76%) of vinyl ether **15c**: bp 106–110 °C (5 μm); NMR ($CDCl_3$) δ 1.60 (3 H, br s), 1.96 (2 H, br d, J = 8 Hz), 3.80 (4 H, m), 4.27–3.85 (2 H, m), 5.42 (1 H, br t, J = 7 Hz), and 6.34 (1 H, dd, J = 7 and 14 Hz).

Anal. ($C_{17}H_{28}O_3$): C, H.

Enone 18a and Hydroxy Ketone 19. Vinyl ether **15c**, 5.0 g (17.8 mmol) (contaminated with 10–15% of **15b**), maintained under an atmosphere of N_2 was heated neat for 12 min at 175 °C. The crude product revealed the following spectroscopic data: IR (CCl_4) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (3 H, br s), 2.33 (1 H, m), 3.83 (4 H, m), 4.75 (2 H, m), and 9.50 (1 H, t, J = 3 Hz). The crude ketal aldehydes **16b** were stirred for 18 h in 72 mL of 80% aqueous HOAc. The solution was poured onto ice and carefully neutralized with 4 N NaOH while maintaining the temperature below 10 °C. The resulting solution was thoroughly extracted with ether, dried, filtered, and concentrated to give 3.1 g (74%) of crude keto aldehydes **17b**: IR (CCl_4) 1725 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 4.88–4.79 (2 H, m), 9.25 (0.5 H, t, J = 3 Hz), and 9.22 (0.5 H, t, J = 3 Hz).

The crude keto aldehydes **17b** were dissolved in 60 mL of methanol and 36 mL of 0.5 N aqueous NaOH at 0 °C under N_2. The initial yellow solution was allowed to warm to 25 °C over 18 h, by which time the solution had turned red. The solution was reduced to one-half its volume in vacuo and poured into an equal volume of water. The aqueous mixture was thoroughly extracted with ether, dried, filtered, and concentrated, providing 2.6 g of crude product. Chromatography of 1 g of this crude material on silica gel (35 g) using benzene as an eluent afforded three fractions.

The early eluents gave 50 mg (~5%) of enone **18a**: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.00 (3 H, d, J = 6 Hz), 1.75 (3 H, s), 4.73 (2 H, br s), and 6.40 (1 H, m).

The second material eluted was a mixture of hydroxy ketones **19** and **20** (600 mg): MS m/e 70 eV (rel intensity) 236 (32), 218 (40), 203 (22), 177 (42), 175 (32), 161 (32), 125 (100), 107 (38), 93 (34), 83 (54), 69 (60), and 55 (100). Trituration of this mixture with hexane afforded ketol **19**: mp 94–95 °C; IR (CCl_4) 3600–3200 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (3 H, s), 0.83 (3 H, d, J = 7 Hz), 1.68 (3 H, s), 4.08 (1 H, dt, J = 4 and 10 Hz), and 4.60 (2 H, br s).

Anal. ($C_{15}H_{24}O_2$): C, H.

The final eluent afforded 250 mg of allylic alcohol **15b**.

Enones 18. A 400-mg (1.7 mmol) sample of the ketol mixture **19** and **20** was heated under N_2 for 10 min at 250–270 °C (Wood's metal bath). The flask was cooled to 25 °C and the reaction mixture purified (TLC, double elution, C_6H_6) to afford 126 mg (34%) of enones **18a** and **18b** homogeneous on TLC and separable on VPC (OV-1): IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.06 (6 H, m), 1.73 (3 H, br s), 4.72 (2 H, br s), 6.18 (0.5 H, m), and 6.40 (0.5 H, m); MS m/e 70 eV (rel intensity), 218 (100), 203 (46), 177 (30), 176 (54), 164 (24), 163 (22), 162 (52), 148 (35), 136 (40), 134 (43), 119 (62), 107 (47), 105 (56), 93 (41), 91 (44), 79 (35), 77 (30), and 55 (36).

Anal. (evap dist/1μm) ($C_{15}H_{22}O$): C, H.

Epoxy Ketones 21. To a stirred solution of 126 mg (0.55 mmol) of enones **18** in 3 mL of CH_3OH maintained under N_2 at 15 °C was added 0.4 mL (3.3 mmol) of 30% H_2O_2. To this solution was added 0.05 mL (0.27 mmol) of 6 N aqueous NaOH in three portions over 30 min. The solution was stirred for 18 h at 25 °C and then poured into a solution of saturated Na_2SO_3 at 0 °C. The aqueous solution was extracted thoroughly with ether, dried, filtered, and concentrated to afford 123 mg (95%) of crystalline residue. The material was recrystallized to provide the epoxy ketones **21**: mp 56.5–58.5 °C (ether–hexane); IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.92–1.06 (6 H, m), 1.69 (3 H, s), 3.04 (0.5 H, d, J = 5 Hz), 3.24 (0.5 H, m), and 4.65 (2 H, br s).

Anal. ($C_{15}H_{22}O_2$): C, H.

Eremophilone (1) and 7-*epi*-Eremophilone (23). A stirred methanol solution of 127 mg (0.5 mmol) of epoxy ketones **21** maintained at 0 °C under N_2 was treated with 0.15 mL (4.0 mmol) of 85% hydrazine hydrate and 1 drop of acetic acid.[11] The solution was stirred for 8 h, during which time gas evolution was observed. The reaction mixture was diluted with ether, washed with water, dried, filtered, and concentrated to afford 115 mg of a yellow oil which was purified (TLC, C_6H_6) to provide 70 mg of allylic alcohols **22**: NMR ($CDCl_3$) δ 4.31 (1 H, m, >C**H**OH), 4.67 (2 H, br s), and 5.57 (1 H, m, =C**H**CH_2).

The crude alcohols in 1 mL of purified CH_2Cl_2[26b] were added to a stirred solution of 1.5 mmol of CrO_3·py complex in 6 mL of purified CH_2Cl_2 maintained under a N_2 atmosphere. After stirring for 1.5 h, the solvent was removed in vacuo and the residue was triturated with ether with subsequent filtration in vacuo through a Celite pad. The residue was thoroughly washed with ether, and the ether fractions combined and concentrated to afford 40 mg of an oil. The material was purified (TLC, C_6H_6), affording 15 mg of a mixture of enones **1** and **23**. Analytical thin layer chromatography [hexane (triple elution), 10% ethyl acetate–benzene, and benzene] showed the mixture to have the same R_f value as eremophilone obtained from natural sources:[30] IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.90–1.01 (6 H, m), 1.74 (3 H, m), 4.71 (2 H, m), 6.39 (0.5 H, t, J = 3 Hz), and 6.52 (0.5 H, t, J = 3 Hz);[54] MS m/e 70 eV ($C_{15}H_{22}O$), 218.16705 (calcd), 218.16643 (obsd).

The hydroxy ketone **19** was converted to eremophilone via the sequence **19** → **18b** → **21b** → **22b** → **1** in 15% overall yield.

Enone **18b**: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6 Hz), 0.91 (3 H, s), 1.75 (3 H, s), 1.10–2.62 (10 H, m), 4.73 (2 H, br s), and 6.18 (1 H, m).

Epoxide **21b**: IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.96 (1 H, d, J = 5 Hz) and 4.58 (2 H, br s).

Allylic alcohol **22b**: NMR ($CDCl_3$) δ 5.56 (1 H, t, J = 4 Hz).

Eremophilone (**1**): IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (6 H, m), 1.75 (3 H, s), 4.72 (2 H, m), and 6.56 (1 H, t, J = 3 Hz). The synthetic sample was identical with eremophilone (**1**) from natural sources by solution infrared and nuclear magnetic resonance spectroscopy.

Enone **18a** was converted to 7-*epi*-eremophilone **23** in 20% overall yield via the sequence **18a** → **21a** → **22a** → **23**.

Epoxy ketone **21a**: IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.03 (3 H, d, J = 6 Hz), 1.72 (3 H, s), 3.26 (1 H, d, J = 3 Hz), and 4.67 (2 H, m).

Allylic alcohol **22a**: NMR ($CDCl_3$) δ 4.30 (1 H, t, J = 2 Hz), 4.67 (2 H, br s), and 5.54 (1 H, t, J = 3 Hz).

7-*epi*-Eremophilone **23**: IR (CCl_4) 1690 cm^{-1}; NMR (CCl_4) δ 0.94 (6 H, m), 1.74 (3 H, s), 4.71 (2 H, br s), and 6.39 (1 H, t, J = 3 Hz).

Vinyl Alcohols 24. To a stirred suspension of 1.60 g (0.042 mol) of lithium aluminum hydride in 300 mL of dry ether was added dropwise 12.64 g (0.083 mol) of vinyl ketone **11** dissolved in 100 mL of dry ether over a period of 1 h. After the addition had been completed, the reaction mixture was stirred an additional 1 h, then cautiously decomposed with saturated aqueous Na_2SO_4, followed by the addition of anhydrous Na_2SO_4. The white granular suspension was filtered in vacuo through Celite, the filtrate concentrated and distilled to provide 11.08 g (86%) of vinyl alcohols **24**: bp 82–88 °C (1 mm); IR ($CHCl_3$) 3650–3100 cm^{-1}; NMR ($CDCl_3$) δ 0.68–1.00 (6 H, m), 2.74 (1 H, m), and 4.86–6.40 (3 H, m).

Anal. ($C_{10}H_{18}O$): C, H.

Epoxy Alcohols 25. To a stirred solution of 4.62 g (0.030 mol) of vinyl alcohols **24** in 200 mL of CH_2Cl_2 at 5 °C was added 7.24 g (0.032 mol) of 75% *m*-chloroperbenzoic acid. After the acid had dissolved, the solution was stirred at 25 °C for 21 h. The reaction mixture was

washed successively with 50 mL of 10% Na_2SO_3, 100 mL of 1% NaOH, and 100 mL of H_2O. The organic solution was dried, filtered, concentrated, and distilled (Kugelrohr) to provide 4.67 g (91%) of epoxy alcohols **25**: bp 90–100 °C (0.8 mm); IR ($CHCl_3$) 3700–3200 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (1 H, br s), and 2.46–2.83 (2 H, m, epoxide H).

Anal. ($C_{10}H_{18}O_2$): C, H.

Epoxy Ketones 26. To a stirred suspension of 9.30 g (0.093 mol) of CrO_3 in 310 mL of CH_2Cl_2 at 25 °C was added 8.90 g (0.093 mol) of 3,5-dimethylpyrazole.[36] After stirring the dark solution for 30 min, 6.10 g (0.036 mol) of epoxy alcohols **25** dissolved in 40 mL of CH_2Cl_2 was added dropwise over 20 min, followed by stirring for an additional 1.5 h. Isopropyl alcohol (8 mL) was added and the reaction mixture was stirred 5 min followed by concentration in vacuo at 25 °C. The crude residue was triturated with five 100-mL portions of boiling ether followed by in vacuo filtration of the extracts through Celite. The residue from the ether solution was triturated in the same manner with five 100-mL portions of petroleum ether. The crude residue was distilled (Kugelrohr) to afford 5.52 g (91%) of epoxy ketones **26**: bp 90–120 °C (1 μm); IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.83 (1 H, m, lowest field signal, epoxide H).

Anal. ($C_{10}H_{16}O_2$): C, H.

Cyclopropyl Keto Alcohols 27a (syn) and 27b (anti). Potassium, 1.40 g (0.036 mol), was dissolved in 100 mL of dry *tert*-butyl alcohol (CaH_2) under N_2. To the stirred solution maintained at 25 °C was added dropwise over a period of 30 min 5.50 g (0.033 mol) of epoxy ketones **26** dissolved in 40 mL of dry *tert*-butyl alcohol. After the addition had been completed, the yellow solution was stirred for an additional 1.25 h, and then poured into an equal volume of saturated brine. The mixture was extracted with four 50-mL portions of ethyl acetate, dried, filtered, concentrated, and distilled [Kugelrohr, bp 90–120 °C (6 μm)] to provide 4.55 g of keto alcohols. The distillate was subjected to medium pressure chromatography (50–100 psi, 20 × 1 in. column of E. Merck Silica Gel 60H, EtAc solvent, 3 mL/min, 6 mL/fraction) providing 2.31 g (42%) of syn keto alcohol **27a**, 710 mg (13%) of a mixture (~1:1) of **27a** and **27b**, and 890 mg (16%) of anti keto alcohol **27b**.

Keto alcohol **27a**: IR (CCl_4) 3600–3200 and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3 H, s), 1.17 (3 H, d, J = 6 Hz), 3.89 (2 H, m), and 3.22 (1 H, br s, shifts on dilution).

Anal. ($C_{10}H_{16}O_2$) (VPC): C, H.

Keto alcohol **27b**: IR (CCl_4) 3600–3130 and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (3 H, d, J = 6 Hz), 1.18 (3 H, s), and 3.69 (2 H, m).

Anal. ($C_{10}H_{16}O_2$) (VPC): C, H.

Syn Keto Aldehyde 27c. To a solution of 919 mg (5.47 mmol) of syn keto alcohol in 450 mL of dry benzene was added 11.35 g of air-dried MnO_2[55] and the mixture was stirred at 25 °C for 25 h. The reaction mixture was filtered in vacuo through a bed of Celite and washed with four 15-mL portions of warm $CHCl_3$. The combined filtrates were evaporated in vacuo and distilled to give 795 mg (88%) of keto aldehyde **27c**:[57] bp 75–78 °C (4 μm, Kugelrohr); IR ($CHCl_3$) 2750 and 1705 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 6 Hz), 1.20 (3 H, s), 1.40–2.60 (7 H, m), and 9.70 (3 H, d, J = 3 Hz).

Anti Keto Aldehyde 27d. In the manner described for the preparation of the syn keto aldehyde **27c**, 484 mg (2.88 mmol) of anti keto alcohol provided 396 mg (83%) of anti keto aldehyde **27d**: bp 75–80 °C (5 μm, Kugelrohr); IR ($CHCl_3$) 2755 and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.40–2.39 (5 H, m), 2.47 (1 H, d, J = 4.5 Hz), 2.84 (1 H, t, J = 4.5 Hz), and 9.46 (1 H, d, J = 4.5 Hz).

Anal. ($C_{10}H_{14}O_2$): C, H.

***syn*-Cyclopropylacrylic Ester 27e.** To a stirred solution of 1.73 g (0.0104 mol) of syn keto aldehyde **27c** in 150 mL of CH_2Cl_2 maintained under N_2 at room temperature was added dropwise a solution of carbomethoxymethylenetriphenylphosphorane[58] in 50 mL of CH_2Cl_2 over a period of 30 min. After 13 h, the solvent was removed in vacuo at 25 °C. The residue was triturated with ether and allowed to stand in the cold for several hours. The crystalline triphenylphosphine oxide was filtered in vacuo and discarded. The concentrated residue was chromatographed on silica gel (45 g) providing 1.90 g (82%) of syn acrylic ester **27e** from the benzene–15% ether/benzene eluent. The material crystallized on standing and was recrystallized from ether–pentane: mp 52.5–53 °C; bp 80–85 °C (5 μm; Kugelrohr); IR ($CHCl_3$) 1715 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.17 (3 H, d, J = 7 Hz), 3.64 (3 H, s), 5.89 (1 H, d, J = 14.5 Hz), and 6.76 (1 H, dd, J = 14.5 and 8 Hz).

Anal. ($C_{13}H_{18}O_3$): C, H.

***anti*-Cyclopropylacrylic Ester 27f.** In the manner described above, 933 mg (5.62 mmol) of keto aldehyde **27d** was converted to 666 mg (53%) of ester **27f**: mp 93–94.5 °C (ether–pentane); IR ($CHCl_3$) 1715 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7 Hz), 1.19 (3 H, s), 2.60 (1 H, dd, J = 9 and 4 Hz), 3.67 (3 H, s), 5.90 (1 H, d, J = 15 Hz), and 6.59 (1 H, dd, J = 15 and 9 Hz).

Anal. ($C_{13}H_{18}O_3$): C, H.

***syn*-Cyclopropyl Keto Alcohol 32c.** A stirred mixture of 1.54 g (6.9 mmol) of syn acrylic ester **27e**, 25 mg (0.13 mmol) of *p*-toluenesulfonic acid, and 1.30 g (21.0 mmol) of ethylene glycol in 395 mL of anhydrous benzene (azeotrope) was refluxed utilizing a direct return (nonsyphon) Soxhlet extractor containing ~10–15 g of Linde 4A molecular sieves. After 75 min of refluxing the solution, the reaction mixture contained ~85% of the desired ketal plus starting material and rearranged ketal.[46] The reaction mixture was cooled to 25 °C, treated with 5 drops of triethylamine, and poured onto ~50 mL of a vigorously stirred solution of cold 2% NaOH. The layers were separated. The organic phases were washed twice with cold 2% NaOH and the combined basic extracts backwashed with ether. The combined organic solutions were dried, filtered, and concentrated in vacuo to provide 1.97 g of clear oil. Due to the lability of the ketal (decomposition upon distillation at 1 μm), the crude material was used without further purification. IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (3 H, s), 3.87 (~4 H, s), 5.89 (1 H, d, J = 15 Hz), and 6.98 (1 H, dd, J = 15 and 10 Hz).

To a stirred mixture of 20 mL of anhydrous ether and 20 mL of dimethyl sulfide[59] under argon was added 3.32 g (0.017 mol) of cuprous iodide (Alfa-Ventron) followed by cooling to −78 °C in a dry ice–acetone bath. A solution of ethereal 2-lithiopropene (30 mL of 0.9 M and 10 mL of 0.8 M, i.e., 35 mmol) (vide supra) was added via the syringe-serum cap technique at such a rate that the temperature did not exceed −33 °C. After stirring the solution for 45 min, the crude ketal (1.97 g) in 35 mL of ether was added dropwise over 5–10 min. The mixture was stirred an additional 1 h below −60 °C and then allowed to come to 25 °C over 4 h. The reaction mixture was poured onto an equal volume of saturated NH_4Cl solution and stirred 30 min. The mixture was filtered in vacuo through a pad of Celite and the aqueous phase extracted thoroughly with ether. The combined organic extracts were washed with saturated brine, dried, filtered, and concentrated. The residue was triturated with pentane, filtered (to remove trace amounts of copper salts), and concentrated to give 2.55 g of crude ketal **32b** as a dark oil: NMR ($CDCl_3$) δ 0.99 (3 H, d, J = 6 Hz), 1.02 (3 H, s), 1.75 (3 H, s), 3.64 (3 H, s), 3.95 (4 H, br s), and 4.83 (2 H, s).

To a stirred suspension of 380 mg (10.0 mmol) of lithium aluminum hydride in 50 mL of ether was added dropwise 2.55 g of the crude ketal ester dissolved in 35 mL of ether followed by stirring of the mixture at 25 °C overnight. The reaction mixture was cautiously decomposed with saturated aqueous Na_2SO_4 solution. The white granular mass was dried with anhydrous Na_2SO_4, filtered, and concentrated.

The residue (2.18 g) was stirred for 45 min in 80 mL of 1:1 THF–3% aqueous HCl. The reaction mixture was diluted with water and extracted thoroughly with ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to afford 1.96 g of dark oil. The residue was subjected to medium pressure chromatography (vide supra, 3:1 ethyl acetate–hexane), providing 717 mg of keto alcohol **32c** (44% overall): IR (CCl_4) 3650–3390 and 1678 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (2 H, t, J = 6 Hz) and 4.80 (2 H, br s); MS m/e (70 eV) ($C_{15}H_{24}O_2$) 236.17775 (calcd), 236.18086 (obsd).

***anti*-Cyclopropyl Keto Alcohol 35.** Employing the reaction sequence used in the previous experiment, 438 mg (1.97 mmol) of *anti*-cyclopropylacrylic ester was converted to 522 mg (100%) of crude ketal: NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.93 (4 H, s), 5.98 (1 H, d, J = 16 Hz), and 6.80 (1 H, d, d, J = 16 and 9 Hz).

Cuprate adduct: NMR ($CDCl_3$) δ 1.70 (3 H, s), 3.57 (3 H, s), 3.87 (4 H, br s), and 4.65 (2 H, s).

Keto alcohol **35**: 74% overall; IR (CCl_4) 3640–3350 and 1679 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6 Hz), 1.13 (3 H, s), 1.70 (3 H, s), 3.60 (1 H, t, J = 7 Hz), and 4.78 (2 H, br s); MS m/e 70 eV ($C_{15}H_{24}O_2$) 236.17775 (calcd), 236.17970 (obsd).

Keto Alcohol 33a. Into a flask capped with a dry ice condenser was distilled 50 mL of liquid ammonia (from Na metal). The flask was cooled to −78 °C followed by the addition of 252 mg (36 mmol) of lithium wire cut into small pieces. After stirring the mixture for 1 h, 717 mg (3.0 mmol) of *syn*-cyclopropyl keto alcohol **32c** dissolved in 25 mL of anhydrous ether was added dropwise over 15 min, followed by stirring for an additional 75 min. The cold bath was removed and solid NH_4Cl was added cautiously to the reaction mixture until the blue color had discharged. The solvent was allowed to evaporate overnight. The residue was dissolved in H_2O and extracted thoroughly with ether. The combined organic extracts were washed with saturated brine, dried, filtered, concentrated, and distilled to give 628 mg (88%) of keto alcohol **33a**: bp <165 °C (2 μm, Kugelrohr); IR 3650–

3200 and 1709 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (3 H, s), 0.88 (3 H, d, J = 6 Hz), 1.68 (3 H, s), 3.29 (1 H, br s, OH), 3.50 (1 H, t, J = 6 Hz), and 4.77 (2 H, br s); MS m/e 70 eV ($C_{15}H_{26}O_2$) 238.19340 (calcd), 238.19280 (obsd).

Keto Alcohols 33. *anti*-Cyclopropyl keto alcohol **35** (554 mg, 2.35 mmol) gave 420 mg (75%) of keto alcohols **33**: bp < 165 °C (2 μm, Kugelrohr); IR (CCl_4) 3650–3200 and 1709 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (3 H, s), 0.91 (3 H, d, J = 6 Hz), 1.65 (~3 H, s), 3.57 (1 H, t, J = 6 Hz), and 4.81 (2 H, m); MS m/e 70 eV ($C_{15}H_{26}O_2$) 238.19340 (calcd), 238.19396 (obsd).

Enone 18b. To a stirred solution of 2.50 g (32 mmol) of pyridine and 30 mL of CH_2Cl_2 maintained at 0 °C was added 1.58 g (15.8 mmol) of chromium trioxide. After stirring the mixture for 45 min at 25 °C, 628 mg (2.6 mmol) of keto alcohol **33a** in 20 mL of CH_2Cl_2 was added over 5 min, followed by stirring of the reaction mixture for 30 min. The reaction mixture was poured into 250 mL of ether and filtered (Celite) in vacuo. The combined filtrates were washed with ice cold 3% HCl, ice cold 1% NaOH, ice cold 3% HCl, and finally saturated brine. The ether solution was dried, filtered, and concentrated to give 555 mg (88%) of crude aldehyde **34a**: NMR ($CDCl_3$) δ 9.22 (t, J = 3 Hz).

The aldehyde was aldolized and dehydrated as described (vide supra). The crude dehydration product showed <2% [NMR, VPC (OV-1, 140 °C)] of the epimer **18a**. The material was purified twice by thick-layer chromatography (5% EtAc–C_6H_6) to give 104 mg^{60} of pure enone **18b**: IR (CCl_4) 1688 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s), 0.93 (3 H, d, J = 6 Hz), 1.75 (3 H, s), 4.73 (2 H, br s), and 6.18 (1 H, m).

Anal. ($C_{15}H_{22}O$): C, H.

Enones 18a and 18b. In the manner described (vide supra), 420 mg (1.8 mmol) of keto alcohols **33** were converted to 147 mg of enones **18a** and **18b**.

Keto aldehydes **34**: NMR ($CDCl_3$) δ 9.24 (t, J = 3 Hz).

Enones **18a** and **18b**: IR (CCl_4) 1685 cm^{-1}; NMR ($CDCl_3$, normal amplitude) δ 0.96 (6 H, m), 1.75 (3 H, s), 4.75 (2 H, br s), and 6.40 (1 H, m). A high-amplitude spectrum of the region δ 6–7 showed signals at both δ 6.40 and 6.18 in an 85/15 ratio, respectively. This ratio was confirmed by VPC integration (OV-1, 140 °C).

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Registry No.—**1**, 53797-64-1; **8a**, 61847-10-7; **8b**, 61913-85-7; **9a**, 61847-11-8; **9b**, 61847-12-9; **11**, 53768-14-2; **13**, 61847-13-0; **14a**, 53768-21-1; **14b**, 53768-22-2; *E*-**15a**, 53768-23-3; *Z*-**15a**, 61913-86-8; **15b**, 53768-24-4; **15c**, 61913-87-9; **15d**, 61847-14-1; **16a**, 61847-15-2; **16b** isomer 1, 61847-16-3; **16b** isomer 2, 61913-88-0; **17a** isomer 1, 61847-17-4; **17a** isomer 2, 61913-89-1; **17b** isomer 1, 53768-13-1; **17b** isomer 2, 53834-80-3; **18a**, 53802-60-1; **18b**, 53768-26-6; **19**, 53768-28-8; **20**, 53768-27-7; **21**, 61847-18-5; **22**, 61847-19-6; **23**, 53797-63-0; **24** isomer 1, 61847-20-9; **24** isomer 2, 61847-21-0; **25**, 61847-22-1; **26** isomer 1, 61847-23-2; **26** isomer 2, 61913-90-4; **27a**, 61847-24-3; **27b**, 61847-25-4; **27c**, 61847-26-5; **27d**, 61847-27-6; **27e**, 61847-28-7; **27f**, 61847-29-8; **28**, 61847-30-1; **30b** isomer 1, 61847-31-2; **30b** isomer 2, 61913-91-5; **31**, 61847-32-3; **32a**, 61847-33-4; **32b**, 61847-34-5; **32c**, 61847-35-6; **33a**, 61847-36-7; **33b**, 61913-92-6; **35c**, 61847-37-8; 3,4-dimethylcyclohexenone, 1123-09-7; allene, 463-49-0; *cis*-9 deoxo, 61847-38-9; *trans*-9 deoxo, 61847-39-0; *cis*-9 alcohol analogue, 61847-40-3; *trans*-9 alcohol analogue, 61847-41-4; *cis*-1,2-dimethylcyclohexanecarboxylic acid, 61847-42-5; *trans*-1,2-dimethylcyclohexanecarboxylic acid, 61847-43-6; *trans*-1,2-dimethylcyclohexylnitrile, 61847-44-7; *cis*-1,2-dimethylcyclohexylnitrile, 61847-45-8; *cis*-1,2-dimethylcyclohexanecarboxaldehyde, 61847-46-9; *trans*-1,2-dimethylcyclohexanecarboxaldehyde, 61847-47-0; 2-methyl-2-butene 513-35-9; ethylene glycol, 107-21-1; α-carbomethoxyethylidenetriphenylphosphorane, 40467-01-4; ethyl diethylphosphonoacetate, 867-13-0; ethyl orthoacetate, 78-39-7; 2-bromopropene, 557-93-7; *m*-chloroperbenzoic acid, 937-14-4; carbomethoxymethylenetriphenylphosphorane, 2605-67-6.

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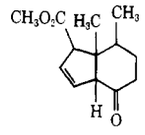

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Notes

Methyldialkylcyanodiazenecarboxylates as Intermediates for Transforming Aliphatic Ketones into Nitriles

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Several years ago we described[3] a method for converting aliphatic ketones into nitriles by the base-induced decomposition of methyl dialkylcyanodiazenecarboxylates. The method permits the in situ methylation and carbomethoxylation of the intermediate nitrile anions, thereby constituting a method for geminal substitution at the α carbonyl carbon.[4] This Note provides the experimental details for this reaction. The diazenes **1b–4b** were readily prepared as outlined in Scheme I. Generation of hydrogen cyanide in situ (KCN–NH_4Cl) gave somewhat lower yields than liquid HCN, due to water solubility of the products.

The decomposition of diazene **1b** with catalytic NaOMe in MeOH at 0 °C provided cyclohexylnitrile in 94% yield (VPC). When MeOH-d_1 was employed, cyclohexylnitrile-d_1 was obtained. The cleavage with methoxide also undergoes a degenerate methoxide exchange with the substrate. Evidence for this process was obtained by employing a two-phase system of ether and water, the yellow diazene being soluble in the former phase. When dilute aqueous NaOH was added slowly to the mixture at 0 °C, the aqueous phase turned yellow (diazenecarboxylate salt) as gas was evolved from the same phase. When gas evolution had ceased, the reaction mixture was colorless.

Diazene **2b** provided approximately an equal mixture of *cis*- (**5a**) and *trans*-2-methylcyclohexylnitrile (**5b**), while the 4-*tert*-butyldiazene **3b** gave rise to two nitriles in a ratio of 58/42 by VPC analysis. Rickborn and Jensen[7a] have shown that the equilibrium (*t*-BuOK/*t*-BuOH) of 4-*tert*-butylcyclohexylnitrile favors the equatorial nitrile **6b** over the axial isomer **6a** (**6b/6a** = 56/44). Subjection of the mixture to these conditions provides a thermodynamic mixture, the major component now becoming the minor component. Thus, the catalytic decomposition provides a kinetic mixture, wherein the axial nitrile **6a** predominates.

In order to permit alkylation of the nitrile anion, it was necessary to perform the reaction with stoichiometric quantities of methoxide and to employ an aprotic solvent. Anhydrous lithium methoxide was prepared in situ from anhydrous methanol and butyllithium (hexane) or methyllithium (ether) in dimethoxyethane (DME). When the diazene in the presence of an excess of methyl iodide was added dropwise at 0 °C to the base, the yellow diazene color was discharged and gas evolution occurred providing from diazene **1b** an 84% yield of products consisting of 1-methylcyclohexylnitrile 77%) and 1-carbomethoxycyclohexylnitrile (13%). This method of addition of the methyl iodide is necessary, since, if the diazene is added first and then the methyl iodide, upwards of 70% of the reaction mixture consists of 1-carbomethoxycyclohexylnitrile. This arises from the nitrile anion reacting with generated dimethyl carbonate or unreacted diazene. The concomitant addition procedure allows the alkylation to favorably compete with the acylation. An efficient procedure for the preparation of 1-carbomethoxycyclohexylnitrile was achieved by adding the diazene to the $LiOCH_3$/DME containing excess dimethyl carbonate.

The in situ methylation of the nitrile anion from diazene **2b** provided a diastereomeric mixture (**5c/5d** = 73/27) of methylated nitriles (63%) and a diastereomeric mixture of carbomethoxylated nitriles (25%). The identity of the minor methylated nitrile was confirmed by synthesis from the Diels–Alder adduct of tiglic acid and butadiene.[4b,7] A similar decomposition of diazene **3b** provided 1-methyl-4-*tert*-butylcyclohexylnitrile as a mixture of diastereomers (**6c/6d** = 76/24) in 70% yield along with 23% of carbomethoxylated product. House and Bare[8] have obtained a similar ratio (71/29)