10468-64-1; **2** ($R^5 = CH_3$), 593-75-9; **2** ($R^5$ = *t*-Bu), 7188-38-7; **3a**, 80242-76-8; **3b**, 80242-77-9; **3c**, 80242-77-9; **3d**, 80242-79-1; **3g**, 80242-80-4; **4b**, 80242-81-5; **5b**, 80242-82-6; **5d**, 66175-28-8; **6e**, 80242-83-7; **6f**, 80242-84-8; **7b**, 80242-85-9; **8b**, 80242-86-0.

**Supplementary Material Available:** Experimental details including IR and NMR spectral data and combustion analyses (5 pages). Ordering information is given on any current masthead page.

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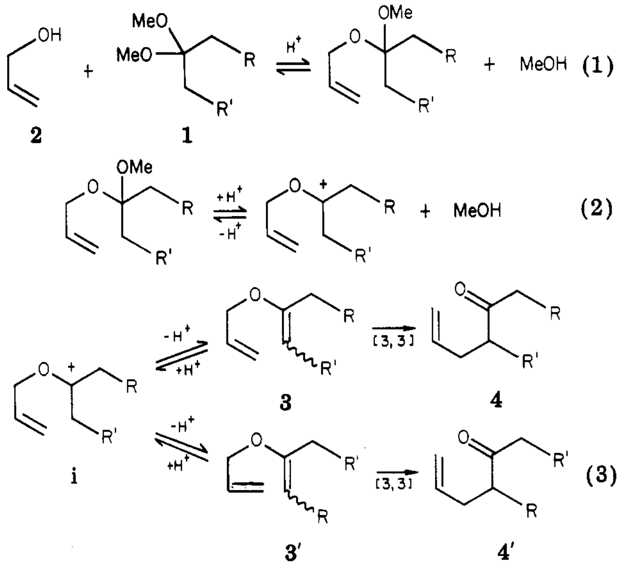
## Regioselectivity of the Ketal Claisen Rearrangement[1]

*Summary:* The ketal Claisen rearrangement with a simple unsymmetrical ketal exhibits a high degree of regioselectivity, which is attenuated by substitution of the $\alpha$- and $\beta$-carbon atoms of the ketal.

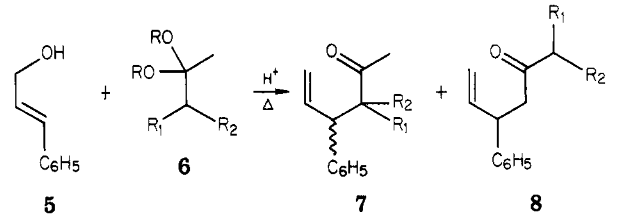
*Sir:* The Claisen rearrangement has emerged as a very general and powerful synthetic tool over the last 10 years.[2] In particular, enolate Claisen methods,[3] ortho ester/ketal exchange procedures,[4] and amide acetal reactions[5] have provided the synthetic chemist with convenient new methods for exploiting this historically important pathway to $\alpha,\beta$-unsaturated carbonyl compounds.

The ketal Claisen rearrangement has only been developed in a few specific cases. The work of Johnson and Faulkner[6-9] provide the only examples of the ketal Claisen rearrangement. The related enol-ether Claisen rearrangements from the work of Saucy[10] are also included in this discussion because they involve nearly identical reaction pathways. For the more general case, the reaction between an acyclic unsymmetrical ketal (**1**) and an allylic alcohol (**2**) can give rise to two isomeric ketonic products. Scheme I details the mechanistic scenario for this process during which the intermediate cation **i** can be reversibly partitioned along two different pathways. These different paths lead to isomeric allyl/vinyl ethers (**3** and **3′**) which irreversibly ($K_{eq} \simeq 10^6$) rearrange to the isomeric ketones **4** and **4′**. The ketal Claisen rearrangements developed by Johnson and Faulkner specifically avoid this problem, since one of the competing paths in each case is blocked.[11] Recent efforts in our laboratory have been designed to answer this regiochemical question, which is inherent in the ketal Claisen rearrangements of simple unsymmetrical ketals.

### Scheme I

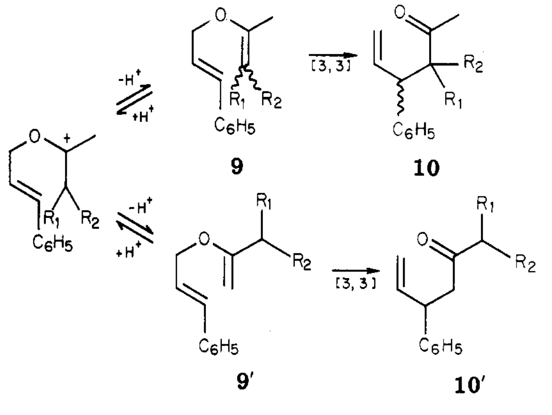


### Scheme II



| example | $R_1$ | $R_2$ | ketal | % yield | ratio 7:8 |
|---|---|---|---|---|---|
| a | Me | H | di-Et | 63 | 96:4 |
| b | Et | H | di-Et | 66 | 92:8 |
| c | Et | H | di-Me | 84 | 88:12 |
| d | *i*-Pr | H | di-Et | 74 | 67:33 |
| e | *t*-Bu | H | di-Me | 72 | 0:100 |
| f | *i*-Bu | H | di-Et | 62 | 96:4 |
| g | Me | Me | di-Et | 73 | 69:31 |
| h | Et | Me | di-Me | 81 | 74:26 |

### Scheme III



Our preliminary work has examined the ketal Claisen rearrangements of some simple unsymmetrical ketals with

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(10) Saucy, G.; Marbet, R. *Helv. Chim. Acta* **1967**, *50*, 2091.

(11) The three examples reported by Johnson and Faulkner (ref 6–8) lack hydrogens on one of the adjacent carbon atoms. The other example reported by Johnson (ref 9) effectively blocks the competing reaction path with a cyclopropyl group, which precludes the formation of an $sp^2$ carbon atom at one of the $\alpha$ sites. Saucy's enol ether (ref 10) is symmetrical.

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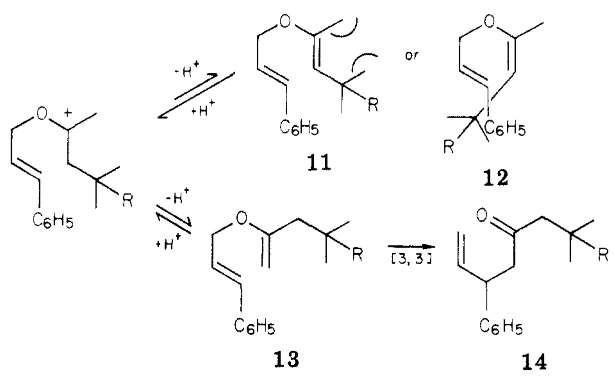
Scheme IV



R = H or $CH_3$

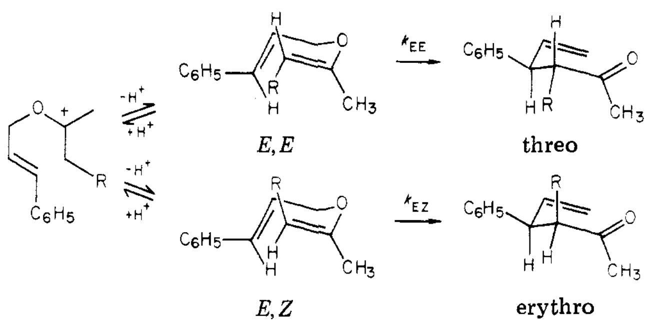
cinnamyl alcohol. The ketal (**6**, 3.0 equiv) and cinnamyl alcohol (**5**) are heated to 120 °C in the presence of a catalytic amount (0.15 equiv) of propionic acid for 24 h. Subsequent workup and column chromatography[12] on silical gel afford the isomeric reaction products. These products have been thoroughly characterized.[13] The results of this study are summarized in Scheme II.

The results in Scheme II present two significant trends. With the exception of example e, the more highly substituted (or "major") ketone (**7**) predominates over the less highly substituted (or "minor") one (**8**). The second trend is the decrease in regioselectivity as the $\alpha$ and $\beta$ carbons in the ketal (**6**) become more highly substituted. This effect is dramatically illustrated by the complete reversal of the selectivity in example e.

These trends can be accomodated in a reasonably simple model. The intermediate cation (Scheme III) is assumed to be in equilibrium with the isomeric allyl/vinyl ethers, which subsequently rearrange to the observed ketones. This assumption is quite reasonable, since one can show that the rate of protonation of the allyl/vinyl ethers is at least 2 orders of magnitude greater than the rate of the [3,3] sigmatropic rearrangement.[14] Consequently, there is a higher concentration of the more stable allyl/vinyl ether (**9**) and a greater proportion of the more highly substituted ketone (**10**).

Additional substitution at the $\alpha$ or $\beta$ carbons lowers the selectivity as seen in Scheme II. In the case of additional $\alpha$ substitution (examples g and h, Scheme II), this is presumably due to the reduced rate of the [3,3] rearrangement for the more highly substituted allyl/vinyl ether. The work of Cresson[15] shows that substitution on the allyl terminus slows down the rate of sigmatropic rearrangement. Similarly, substitution of the vinylic terminus would be expected to retard the rearrangement step. This allows the less highly substituted path to compete more favorably. Hence the "minor" ketone **10′** accounts for a larger proportion of the total product in examples g and h. Additional $\beta$ substitution develops unfavorable nonbonded interactions in the more highly substituted allyl/vinyl ethers (**11** and **12**, Scheme IV). This results in a less favorable equilibrium constant for their formation. The alternative allyl/vinyl ether (**13**) is unaffected by the additional methyl groups and an increased proportion of the "minor" ketone (**14**) is observed. This effect is so strong that in case e the "minor" ketone can be isolated in a 72% yield. When the additional alkyl groups are placed on the $\gamma$ carbon (example f), the original selectivity is restored.

Scheme V



The major product for all of the examples in Scheme II (except g) is obtained as a ca. 1:1 mixture of the erythro and threo diastereomers. These are formed from the *E,Z* and *E,E* allyl/vinyl ethers, respectively, as shown in Scheme V. The work of Schmid[14c] suggests that the threo isomer should predominate due to the enhanced rate of [3,3] sigmatropic rearrangement of *E,E* isomers over *E,Z* isomers ($k_{EE}/k_{EZ} = 3$). However, Schmid measured these rates for allyl/vinyl ethers in which the vinyl group was disubstituted. In the current work the vinyl group is trisubstituted and the erythro/threo ratios for our examples[16] range from 1.2:1 to 1:1. We have ruled out the possibility that acid-catalyzed equilibration of the threo and erythro isomers occurs during the reaction by subjecting a small amount of *erythro*-**7f**[17] to the reaction conditions. No *threo*-**7f** was detected by $^1$H NMR spectroscopy.[18]

These results demonstrate that ketal Claisen rearrangements with simple unsymmetrical ketals exhibit substantial selectivity and proceed in good yields. This selectivity may be as high as 25:1 in the most favorable cases. However, alkyl substitution on the $\alpha$ or $\beta$ carbons of the ketal attenuate this selectivity and may even reverse it in unusual cases. We are currently investigating the complete scope of this reaction and its application to the synthesis of polyfunctional molecules.

**Acknowledgment.** Financial support for this work was kindly provided by the Research Corporation (Grant C-1009 to G.W.D.), the National Science Foundation Undergraduate Research Participation Program (Grant to HMC Chemistry Department), and the Harvey Mudd College Chemistry Department.

**Registry No. 5**, 104-54-1; **6a**, 52752-16-6; **6b**, 80359-80-4; **6c**, 55904-98-8; **6d**, 80359-81-5; **6e**, 72409-07-5; **6f**, 80359-82-6; **6g**, 80359-83-7; **6h**, 72409-06-4; *erythro*-**7a**, 32096-07-4; *threo*-**7a**, 32252-97-4; *erythro*-**7b**, 80359-84-8; *threo*-**7b**, 80359-85-9; *erythro*-**7d**,

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[12] The products were purified by medium-pressure liquid chromatography.

[13] (a) All ketones exhibited $^1$NMR, IR, and low-resolution mass spectra that were consistent with their proposed structures. (b) Satisfactory combustion analyses were obtained for **7a**, **7g**, and **8g**.

[14] (a) The work of Salomaa[14b] allows for the approximation of the rate of protonation of the allyl/vinyl ether. The rate of protonation has a lower limit of 0.1 [allyl/vinyl ether] $s^{-1}$ at 120 °C. The work of Schmid[14c] allows for the approximation of the rate of sigmatropic rearrangement of the allyl/vinyl ether. This rate has an upper limit of $8.7 \times 10^{-4}$ [allyl/vinyl ether] $s^{-1}$ at 120 °C. (b) Kankaanperä, A.; Salomaa, P.; Juhala, P.; Aaltonen, R.; Mattsén, M. *J. Am. Chem. Soc.* **1973**, *95*, 3618. (c) Hansen, H. J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959.

[15] (a) Cresson, P.; Lecour, L. *C. R. Acad. Sci., Ser. C* **1966**, *262*, 1157. (b) Cresson, P.; Bancel, S. *C. R. Acad. Sci., Ser. C* **1968**, *266*, 409.

[16] The erythro/threo ratios were determined by $^1$H NMR spectroscopy. The diastereomeric methyl ketone groups displayed distinctly different chemical shifts due to the strong anisotropic effect of the aromatic ring. The threo isomer exhibited a singlet at $\delta$ 2.10 for the methyl ketone protons, while the erythro isomer showed a higher field singlet at $\delta$ 1.85.

[17] *erythro*-**7f** (99% pure by VPC) was obtained in selected fractions of the medium-pressure chromatography of **7f**/**8f**.

[18] The detection limits of $^1$H NMR spectroscopy for the presence of *threo*-**7f** were ±2%.

80359-86-0; *threo*-**7d**, 80359-87-1; *erythro*-**7f**, 80359-88-2; **7g**, 80359-89-3; *erythro*-**7h**, 80359-90-6; *threo*-**7h**, 80359-91-7; **8a**, 80359-92-8; **8b**, 80359-93-9; **8d**, 70245-09-9; **8e**, 80359-94-0; **8f**, 80359-95-1; **8g**, 80359-96-2; **8h**, 80359-97-3.

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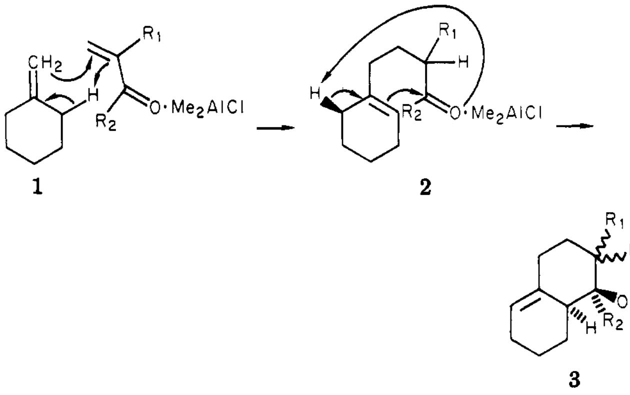
## Sequential Ene Reactions. A New Annelation Procedure

*Summary:* Alkylidenecycloalkanes react with $\alpha,\beta$-unsaturated carbonyl compounds in the presence of $Me_2AlCl$ to give bicyclic alcohols resulting from two sequential ene reactions.

*Sir:* The use of carbon–carbon double bonds as activating groups for the formation of new carbon–carbon bonds under mild conditions is a challenge to synthetic chemists. The ene reaction provides a potential solution to this problem.[1] We have found that Lewis acid catalyzed ene reactions with acrylate esters as the enophile occur at 25 °C and that the ene reactions of $\alpha$-substituted acrylate esters are regioselective and stereoselective, with the carboalkoxy group adding endo.[1b] Lewis acid catalysis offers significant advantages over the corresponding thermal ene reactions which occur at 200–300 °C. We have also shown that alkylaluminum halides are preferred catalysts for these reactions since the alkyl group functions as a proton scavenger.[2]

$\alpha,\beta$-Unsaturated ketones and aldehydes have seen very little use as enophiles.[3] Acrolein reacts with $\beta$-pinene at 140 °C[3b] or with $ZnBr_2$ catalysis at 25 °C.[4] Methyl vinyl ketone (MVK) reacts with $\beta$-pinene at 25 °C with $ZnBr_2$ catalysis[4] and has been reported to react with limonene with $AlCl_3$ catalysis.[5]

We report here that alkylidenecycloalkanes react with $\beta$-unsubstituted $\alpha,\beta$-unsaturated ketones or aldehydes in the presence of $Me_2AlCl$ to give a bicyclic alcohol resulting from two sequential ene reactions. For instance, methylenecyclohexane (**1**), acrolein, and $Me_2AlCl$ in $CH_2Cl_2$ at 0 °C for 20 min react to give a 63% yield of **3a**.[6,9] The initially formed ene adduct **2a** undergoes a second, intramolecular ene reaction with the complexed aldehyde functioning as the enophile. Loss of methane from the resulting alcohol–Lewis acid complex to give the aluminum alkoxide prevents proton-catalyzed side reactions or solvolysis of the alcohol. Cyclization of **2a** to **3a** is much faster than formation of **2a** since no **2a** could be detected, even when the reaction is run to low conversion at −78 °C.



a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$
c, $R_1 = \alpha\text{-}CH_3$, $R_2 = H$
d, $R_1 = \beta\text{-}CH_3$, $R_2 = H$
e, $R_1 = \alpha\text{-Br}$, $R_2 = H$
f, $R_1 = \beta\text{-Br}$, $R_2 = H$
g, $R_1 = H$, $R_2 = CH_3$, $4\alpha\text{-}CH_3$

Reaction of **1**, MVK, and $Me_2AlCl$ at −20 °C for 2 h gives a 39% yield of **2b** and a 4% yield of **3b**. The same reaction at 25 °C for 1 h gives a 9% yield of **2b** and a 49% yield of **3b**. Thus, at different reaction times, either **2b** or **3b** can be isolated as the major product. The successful isolation of **2b**, as opposed to **2a**, results from the dimished reactivity of the ketone carbonyl as an enophile.[10] The isolation of a teritary alcohol, **3b**, from a Lewis acid catalyzed reaction is due to its protection as an aluminum alkoxide.

Reaction of **1**, methacrolein, and $Me_2AlCl$ (0 °C, 1 h) gives a 66% yield of a 3:1 mixture of **3d** (mp 69–71 °C) and **3c** (mp 51.5–53.5 °C). The methyl group thus prefers to be equatorial, suggesting that ring formation is well ad-

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(1) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969,** *8,* 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980,** *13,* 426.

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(5) Mehta, G.; Reddy, A. V. *Tetrahedron Lett.* **1979,** 2625. We have been unable to repeat this reaction. Professor Mehta has indicated that "the yields are somewhat erratic and decrease enormously on scale up above 10 mmole." In addition the reported yield of 75% is based on recovery of 80% of the limonene. From the spectral data reported, there is no doubt that the ene adduct was obtained. However, our results make it clear that the ene adduct will not be stable to $AlCl_3$ for 12 h in benzene. The most likely explanation is that a partially hydrated, and therefore much less active, sample of $AlCl_3$ was used.

(6) All new compounds were characterized by IR, $^1H$, and $^{13}C$ NMR spectroscopy and gave satisfactory elemental analyses. The stereochemistry of hydroxyl and bromine substituents was established by the chemical shift and splitting pattern of the $\alpha$-protons. The stereochemistry of these substituents and methyl groups could be established by $^{13}C$ NMR spectroscopy. The reported $^{13}C$ spectra of 1,2,3,4,4a,5,6,7-octahydronaphthalene and 1*H*-2,3,3a,4,5,6-hexahydroindene[7] could be assigned using the spectra of 1-methylcyclohexene and 2-(methylmethylene)cyclohexane[8] as models. With shift values for equatorial and axial substituents on cyclohexanes and the shift values for equatorial and axial methyl substituents on methylenecyclohexane,[8] the expected $^{13}C$ spectra could be calculated for each possible isomer. In all cases agreement between the calculated and observed spectra was very good for all carbons.

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(8) Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1975,** *53,* 589.

(9) The detailed procedure given below is typical. Methylenecyclohexane (0.53 g, 5.5 mmol) was added to a solution of acrolein (distilled from $CuSO_4$; 0.28 g, 5.0 mmol) and $Me_2AlCl$ (4.16 mL of 1.14 M in heptane, 4.75 mmol) in 15 mL of $CH_2Cl_2$ at 0 °C. The mixture was stirred for 20 min at 0 °C and quenched by cautious addition of water and ether. The organic layer was removed and the aqueous layer was washed 3 times with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated to give 0.808 g of crude product. Evaporative distillation of 0.696 g (100 °C, 0.25 torr) gave 0.411 g (63%) of pure **3a**: mp 54.4–55.5 °C; NMR ($CCl_4$) $\delta$ 5.6 (br s, 1), 3.8 (br s, 1); $^{13}C$ NMR ($CDCl_3$) $\delta$ 136.0, 124.3, 71.3, 42.1, 34.8, 33.5, 26.4, 25.2, 21.9, 20.9; IR (KBr) 3370, 3050, 1670 cm$^{-1}$. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.79; H, 10.36.

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