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KETAL CLAISEN REARRANGEMENTS OF FUNCTIONALIZED KETALS

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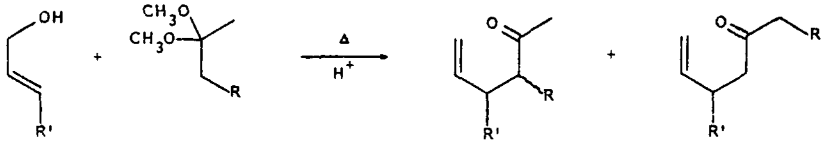
Summary: Functionalized ketals participate successfully in the acid-catalyzed ketal Claisen rearrangement to afford mixtures of the isomeric γ,δ-unsaturated ketones, with the more highly substituted isomer predominating by a factor of 2-4:1.

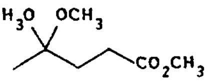
The ketal Claisen rearrangement using simple aliphatic ketals has previously been examined in order to establish the regioselectivity associated with the transformation.[1] Typically, the more highly substituted isomer (3) predominated over the less highly substituted one (4) in the product mixture. Substitution of the α or β carbons of the ketal attenuated this selectivity. In order to expand the scope of this reaction, this study was extended in order to examine the effects of additional functional groups on the selectivity and yield.



1 2 3 4

Previous studies by Johnson and Faulkner provide elegant examples of ketal Claisen rearrangements using functionalized ketals where synthetic design has precluded any regiochemical uncertainty in the reaction products.[2] The positioning of a functional group proximal to the allyl-vinyl ether moiety can make such rearrangements highly selective, as illustrated by the work of McCurry[3] and Denmark.[4] Our interest lay in determining the inherent regioselectivity in systems where the functional group was placed far enough away to preclude any electronic interactions. Such a reaction would allow for the efficient preparation of complex molecules.

We have examined the ketal Claisen rearrangements of methyl 4,4-dimethoxypentanoate (5),[5,6] methyl 5,5-dimethoxyhexanoate (6), and 5,5-dimethoxy-1-hexene (7) with cinnamyl alcohol (8), trans 2-hexen-1-ol (9), and 1-hexen-3-ol (10). The ketal (1.0 equiv.) and the allylic alcohol



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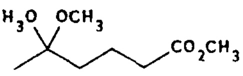

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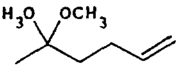

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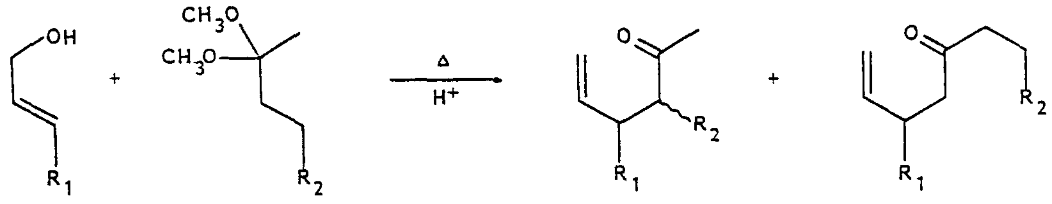
were heated to 120°C in the presence of a catalytic amount of propionic acid (0.15 equiv.) for 24 hours. Subsequent workup and column chromatography on silica gel afforded the isomeric reaction products (11-14).[7] These products have been characterized[6] and the results of this study are summarized in Tables I-II.

A comparison of the results in Tables I-II with the results obtained with simple aliphatic ketals provides two observations. First, the regioselectivity obtained for the functionalized ketals is comparable to that obtained for a simple aliphatic analog, 2,2-dimethoxypentane.[8] The reaction is sufficiently selective to be of practical utility. Second, while the yields are not exceptional, they are good enough to be synthetically useful in some of the examples.

Several of the products obtained in this study contain two chiral carbons. Unfortunately there appears to be no stereoselectivity in these reactions; the products 11a-f were obtained as a *ca.* 1:1 mixture of the *erythro* and *threo* diastereomers.[9] These results are consistent with the observations in aliphatic ketal Claisen rearrangements.[1] The possibility that acid-catalyzed equilibration of the *threo* and *erythro* isomers occurs during the reaction has been excluded for the aliphatic case.[1] Presumably it may be excluded in the current case as well.

Table I



8 $R_1 = C_6H_5$

9 $R_1 = n\text{-}C_3H_7$

11

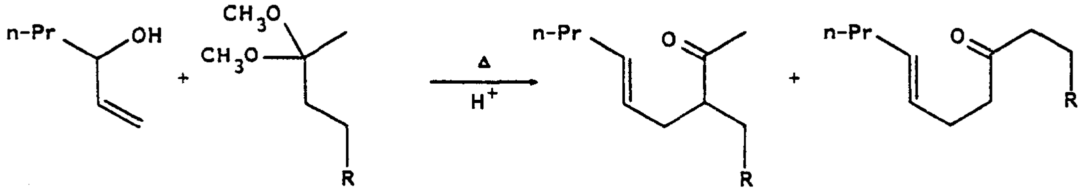
12

example	method[a]	R_1	R_2	% yield	ratio 11:12[b]
a	A	C_6H_5	CO_2CH_3	55	83:17
b	A	C_6H_5	$CH_2CO_2CH_3$	69	88:12
	B			55	83:17
c	A	C_6H_5	$CH{=}CH_2$	62	86:14
d	A	$n\text{-}C_3H_7$	CO_2CH_3	49	71:29
e	A	$n\text{-}C_3H_7$	$CH_2CO_2CH_3$	57	80:20
f	A	$n\text{-}C_3H_7$	$CH{=}CH_2$	47	82:18
	B			23	85:15

[a] Method A, 1.0 equiv. ketal; Method B, 2.0 equiv. ketal.

[b] See Reference 11.

Table II



10 13 14

example	method[a]	R	% yield	ratio 13:14[b]
a	A	CO_2CH_3	36	58:42
b	A	$CH_2CO_2CH_3$	68	62:38
c	A	$CH=CH_2$	45	58:42

[a] Method A, 1.0 equiv. ketal.

[b] See Reference 11.

The reactions could be conducted according to two protocols. Method A involved the use of 1.0 equivalent of ketal, while Method B utilized 2.0 equivalents. From a mechanistic point of view, one would expect the latter method to be preferable due to the presence of so many preliminary equilibria in the reaction sequence. Method A, however, proved superior in a practical sense. The parent ketones of the ketals used in this study are relatively non-volatile. Any excess ketal is hydrolyzed to the parent ketone during workup which complicates an already difficult chromatographic separation.

These results demonstrate that ketal Claisen rearrangements using ketals containing distal carbomethoxy or olefinic functions may exhibit substantial selectivity and proceed in fair to good yields. The selectivity may be as high as 88:12 with primary allylic alcohols. The use of secondary allylic alcohols, however, appears to decrease the selectivity.

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(5) The ketals were prepared according to the method of Johnson (reference 2c).

(6) Spectral data (^{1}H NMR, IR, and mass spectrum) are consistent with the assigned structures for all new compounds. ^{1}H NMR data ($CDCl_3$): 5 δ 1.20 (s,3H), 1.9 (m,2H), 2.4 (m,4H), 3.17 (s,6H), 3.63 (s,3H); 6 δ 1.23 (s,3H), 1.6 (m,4H), 2.3 (m,2H), 3.13 (s,6H), 3.65 (s, 3H); 7 δ 1.23 (s,3H), 1.6 (m,2H), 2.1 (m,2H), 3.17 (s,6H), 4.9 (m,2H), 5.8 (m,1H); 11a δ 1.77/2.20 (s/s,3H), 2.7 (m,2H), 3.3 (m,2H), 3.53/3.60 (s/s,3H), 5.0 (m,2H), 6.1 (m,1H), 7.27 (s,5H); 11b δ 2.0 (m,7H) including 1.73/2.11 (s/s), 3.0 (m,1H), 3.5 (m,4H) including 3.57/3.67 (s/s), 5.1 (m,2H), 6.0 (m,1H), 7.23 (s,5H); 11c δ 2.0 (m,5H) including 1.67/2.03 (s/s), 2.9 (m,1H), 3.40 (d of d,1H,J=10 and 8 Hz), 4.9 (m,4H), 5.8 (m,2H), 7.20 (s,5H); 11d δ 0.8 (m,3H), 1.2 (m,4H), 2.3 (m,7H) including 2.23/2.27 (s/s), 3.67/3.70 (s/s,3H), 4.9 (m,2H), 5.4 (m,1H); 11e δ 0.8 (m,3H), 1.2 (m,4H), 1.8 (m,2H), 2.2 (m,7H) including 2.10/2.17 (s/s), 3.67 (s,3H), 4.9 (m,2H), 5.4 (m,1H); 11f δ 0.8 (m,3H), 1.3 (m,4H), 2.4 (m,7H) including 2.06/2.10 (s/s), 4.9 (m,4H), 5.6 (m,2H); 12a δ 2.5 (m,4H), 2.80 (d,2H, J=7 Hz), 3.60 (s,3H), 3.91 (q,1H,J=7 Hz), 4.95 (d of t,1H,J_t=2 Hz and J_d=18 Hz), 5.02 (d of t,1H,J_t=2 Hz and J_d=10 Hz), 6.0 (m,1H), 7.23 (s,5H); 12b δ 1.6 (m,2H), 2.4 (m,4H), 2.81 (d,2H,J=7 Hz), 3.58 (s/3H), 3.89 (q,1H,J=7 Hz), 5.0 (m,2H), 6.0 (m,1H), 7.23 (s,5H); 12c δ 2.3 (m,4H), 2.77 (d,2H,J=7 Hz), 3.87 (q,1H,J=7 Hz), 4.9 (m,4H), 5.8 (m,2H), 7.20 (s,5H); 12d δ 0.9 (m,3H), 1.3 (m,4H), 2.1 (m,7H), 3.59 (s,3H), 4.9 (m,2H), 5.4 (m,1H); 12e δ 0.9 (m,3H), 1.3 (m,6H), 2.1 (m,7H), 3.60 (s,3H), 4.9 (m,2H), 5.3 (m,1H); 12f δ 0.9 (m,3H), 1.4 (m,4H), 2.4 (m,7H), 5.0 (m,4H), 5.6 (m,2H); 13a δ 0.87 (t,3H,J=7 Hz), 1.3 (m, 2H), 2.1 (m,10H) including 2.20 (s), 3.63 (s,3H), 5.3 (m,2H); 13b δ 0.87 (t,3H,J=6 Hz), 1.33 (6-plet,2H,J=6 Hz), 2.2 (m,12H) including 2.13 (s), 3.67 (s,3H), 5.3 (m,2H); 13c δ 0.87 (t,3H,J=7 Hz), 1.33 (6-plet,2H,J=7 Hz), 2.3 (m,10H) including 2.10 (s), 4.9 (m, 2H), 5.3 (m,2H), 5.8 (m,1H); 14a δ 0.87 (t,3H,J=7 Hz), 1.32 (6-plet,2H,J=7 Hz), 2.2 (m, 10H), 3.67 (s,3H), 5.4 (m,2H); 14b δ 0.83 (t,3H,J=6 Hz), 1.8 (m,14H), 3.67 (s,3H), 5.3 (m,2H); 14c δ 0.87 (t,3H,J=7 Hz), 1.37 (6-plet,2H,J=7 Hz), 2.2 (m,10H), 5.0 (m,2H), 5.4 (m,2H), 5.9 (m,1H).

(7) The procedures for workup and purification have been previously described in reference 1b.

(8) For the reaction between cinnamyl alcohol and 2,2-dimethoxypentane, the ratio of 3:4 ($R=Et$, $R'=C_6H_5$) is typically 94:6 (±2), see reference 1b.

(9) The erythro:threo ratios were estimated from the diastereotopic methyl ketone signals in the ^{1}H NMR spectra of compounds 11a-f.

(10) (a) Camille and Henry Dreyfus Teacher-Scholar, 1982-1987. (b) NSF-Undergraduate Research Participant, 1981; Shell Foundation Summer Research Fellow, 1982.

(11) The product percentages have uncertainties of ± 3%.

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