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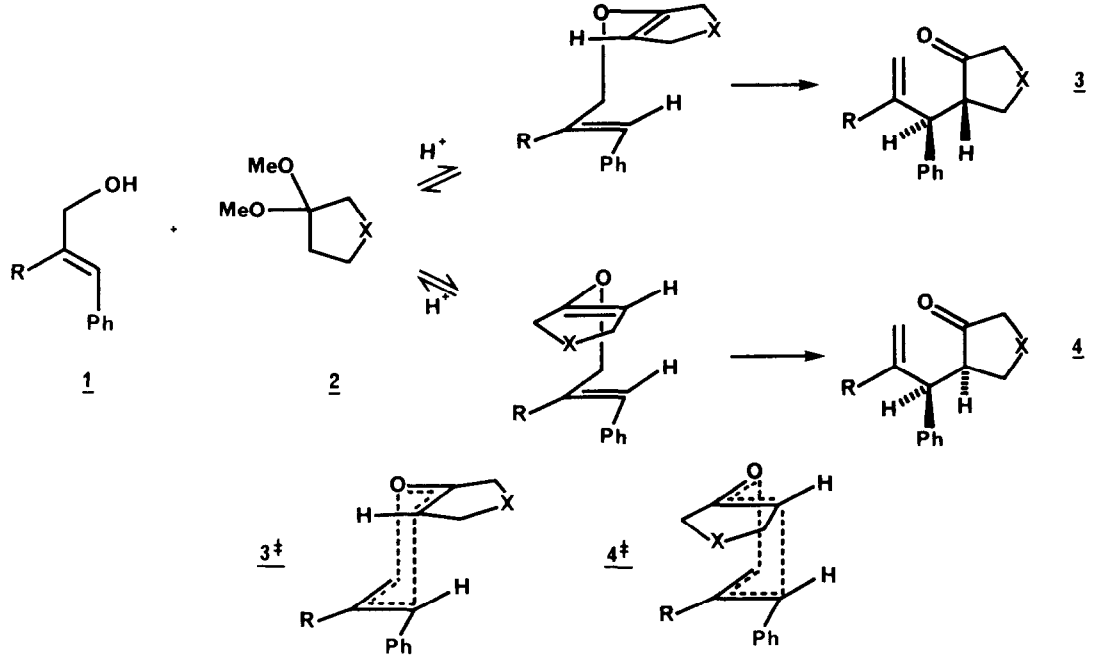
THE STEREOSELECTIVITY OF KETAL CLAISEN REARRANGEMENTS WITH KETALS OF SIMPLE CYCLIC KETONES

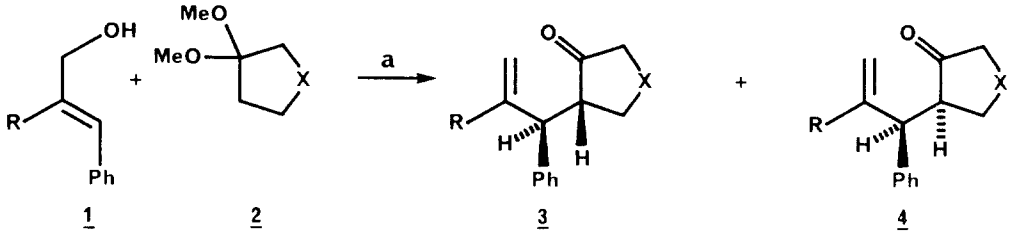
G. William Daub* and David A. Griffith

Department of Chemistry, Harvey Mudd College, Claremont, California 91711

Summary: Claisen rearrangements of the ketals of cyclopentanone, cyclohexanone and cycloheptanone give mixtures of syn and anti products favoring the syn isomer by as much as 19:1. The selectivity is attenuated by enolization processes in the 5- and 6-membered ring systems.

The ketal Claisen rearrangement[1] of an appropriate allylic alcohol (1) and the ketal of a simple cycloalkanone (2) can give rise to a mixture of diastereomeric[2] products (3 and 4) as indicated below. The syn product arises through a chair-like transition state ($3^{\ddagger}$) whereas the anti isomer is obtained via a boat-like transition state ($4^{\ddagger}$). While the chair transition state is typically more stable,[3] the boat transition state can effectively compete in cases where the allylic alcohol is contained in a cyclic framework.[4] Ziegler has examined the Claisen rearrangement involving ortho butyrolactones with acyclic allylic alcohols and has shown the chair transition state to be the predominant reaction pathway in that system.[5] We wish to report the ketal Claisen rearrangements of two allylic alcohols with the dimethyl ketals of cyclopentanone, cyclohexanone, and cycloheptanone. The reactions proceed in good yield to give the syn isomer





1 2 3 4

a) 2.0 equiv. ketal, 0.15 equiv. propionic acid, 125°C.

Table I

example	X	R	Intrinsic selectivity[1]	Ratio 3:4 after 24 hrs.[2]	yield
a	CH_2	H	80:20	52:48	78
b	CH_2	CH_3	91:9	64:36	80
c	$(CH_2)_2$	H	86:14	59:41	64
d	$(CH_2)_2$	CH_3	93:7	82:18	62
e	$(CH_2)_3$	H	90:10	85:15	83
f	$(CH_2)_3$	CH_3	95:5	95:5	68

Table II

example	X	R	Reaction Time (hrs.)	Ratio 3:4[2]	yield
a	CH_2	H	6	65:35	75
b	CH_2	CH_3	7	68:32	77
c	$(CH_2)_2$	H	15	66:34	75
d	$(CH_2)_2$	CH_3	17	85:15	70
e	$(CH_2)_3$	H	6	87:13	84
f	$(CH_2)_3$	CH_3	4	95:5	86

1 Ratio of 3:4 after reaction time of one hour (see reference 6).

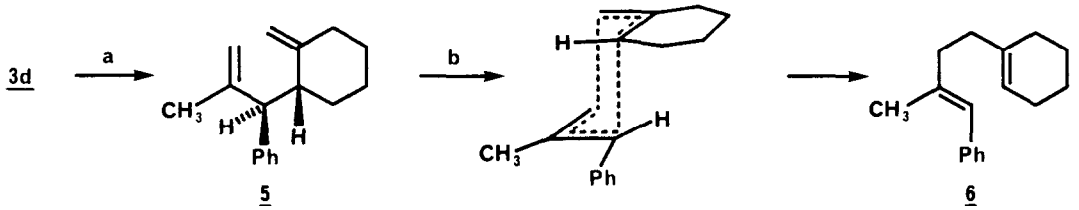
2 Selectivities have uncertainties of ± 1%.

as the major reaction product.

The results of this study are summarized in Table I above.[6] All reactions showed fair to excellent syn:anti selectivity in the initial stages, but the selectivity of the cyclohexanone ketal and in particular the cyclopentanone ketal reactions dropped as the reaction progressed. Control experiments indicated that enolization was responsible for the changes in the syn:anti ratios. Specifically, when pure 3d was resubjected to reaction conditions, a 93:7 mixture of 3d and 4d was obtained. In a similar fashion, pure 3b and pure 4b afforded 75:25 and 41:59 mixtures of 3b and 4b respectively when resubjected to the reaction conditions.

As Table I indicates, however, the initial or intrinsic selectivity[7] in most cases was quite good, especially in the $R=CH_3$ series. This is consistent with previous observations which show that a 2-methyl substituent in the allylic alcohol induces significant diastereoselectivity in the ortho ester Claisen rearrangement.[8] In the present case, a serious non-bonded interaction between the carbocyclic ring and the vinyl methyl substituent develops in the boat transition state ($4^{\ddagger}$). As a result the syn/anti selectivity improves when the methyl group is introduced.

While the diastereomeric products[9] typically displayed different retention times and ^1H and ^{13}C NMR spectra,[10] it was important to establish the identity of the major Claisen product by an independent method. To this end, pure 3d was subjected to Wittig olefination[11] and subsequent Cope rearrangement for 1 hour at 170°C in a sealed tube. Diene 5 cleanly afforded a single product (6).[9] ^1H NMR NOE experiments demonstrated that the acyclic trisubstituted olefin in 6 possessed the E configuration.[12] This conclusively establishes the relative stereochemistry



a) $CH_2=PPh_3$, Et_2O, 19 hrs., 25°C, 55% based on recovered 3d; b) 170°C, 1 hr., 100%.

in 3d to be syn, since the Cope rearrangement in similar systems has been shown to proceed almost exclusively via the chair transition state.[13]

Preparatively useful reaction products can be obtained in all six cases (Table II) when the reactions are allowed to run for less than 24 hours. Clearly the $R=CH_3$ series provides better selectivities and hence is more useful. It is worth noting that while the cyclopentanone ketal reactions are less selective, the syn and anti isomers in this series were readily separated by medium pressure chromatography. In contrast, the separation of the syn and anti isomers in the cyclohexanone series was tedious, and in the cycloheptanone series it proved impossible.

These results demonstrate that ketal Claisen rearrangements with the ketals of cyclic ketones proceed with fair to good diastereoselectivity. The overall yields are good and preparatively useful reaction products can be obtained in all the cases examined. We are currently

expanding the scope of the reaction in an attempt to achieve higher diastereoselectivity.

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(2) All structures, while drawn as a single enantiomer, represent racemates. The syn/anti stereostructural notation proposed by Masamune is used in this paper. Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. Angew. Chem. Int. Ed. Engl., **1980**, 19, 557.

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(6) In examples a-c and e-f (Table I) no starting alcohol could be detected and the % conversion is the same as the yield. In example d significant amounts of the mixed cyclohexanone ketal of methanol and 1 ($R=CH_3$) were isolated and the % conversion was 87%.

(7) Initial selectivities were determined by working up a reaction mixture aliquot after one hour and analyzing the reaction mixture by capillary gas chromatography or 200 MHz ^1H NMR.

(8) Daub, G. W.; Shanklin, P. L.; Tata, C. J. Org. Chem., **1986**, 51, 3402.

(9) (a) All compounds exhibited spectral characteristics (^1H and ^{13}C NMR, IR) and mass spectra consistent with the assigned structures. (b) Satisfactory combustion analyses were obtained for all new compounds.

(10) Syn and anti products exhibit some systematic differences in their ^1H NMR chemical shifts (δ). Vinyl CH_3 in syn isomers ($R=CH_3$): 3b, 1.65; 3d, 1.67; 3f, 1.62. Vinyl CH_3 in anti isomers ($R=CH_3$): 4b, 1.52; 4d, 1.52, 4f, 1.57. Single vinyl H in syn isomers (R=H): 3a, 6.19; 3c, 6.04; 3e, 5.95. Single vinyl H in anti isomers (R=H): 4a, 6.01; 4c, 5.87.

(11) Wittig, G.; Schoellkopf, U. Org. Syn. Col. Vol. V, **1973**, 751.

(12) Irradiation of the CH_2 (δ 2.25) cis to the vinylic H in the acyclic E olefin of 6 produced a 19% enhancement of the vinylic H resonance (δ 6.27). Irradiation of the vinylic CH_3 (δ 1.85) produced only an 11% enhancement of the same vinylic H resonance (δ 6.27).

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