Stereo- and Regiochemistry of the Claisen Rearrangement: Applications to Natural Products Synthesis

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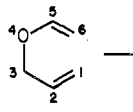
The Claisen rearrangement[1] of substituted allyl vinyl ethers (1 → 2) can formally be considered as the intramolecular S_N2' addition of a carbonyl enol to an allylic alcohol, forming a carbon–carbon σ bond ([3,3] sigmatropic rearrangement) with concomitant double-bond migration. The ready availability of allylic alcohols in organic chemistry, coupled with the generation of two functional groups, carbonyl (electrophilic) and olefin (nucleophilic), of different chemospecificity, allows for a diversity of selective transformations. Since the latent carbonyl residue (i.e., C_4–C_6) is appended to the allylic alcohol, its oxidation level, functionality, and substitution pattern can be conveniently altered by the judicious application of the appropriate carbonyl enol equivalent. The most common methods for preparing unsaturated aldehydes, ketones, amides, esters, and carboxylic acids are illustrated in eq 1–6. The reaction temperatures for these rearrangements can range from the vicinity of 200 °C (eq 2) to ambient temperatures (eq 6).



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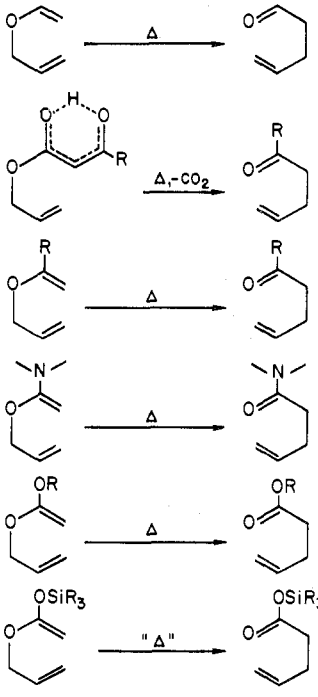

Burgstahler[2] (1)

Carroll[3] (Kimel-Cope); R = alkyl (2)

Saucy-Marbet;[4] R = H, alkyl (3)

Eschenmoser[5] (4)

Johnson[6] (5)

Ireland[7] (6)

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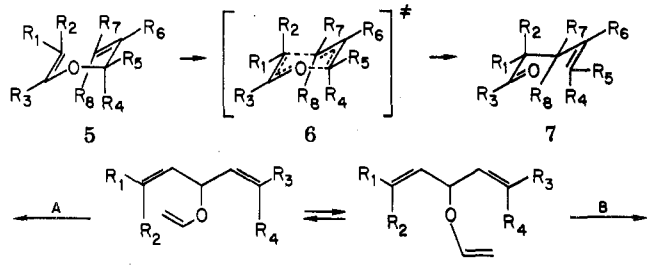
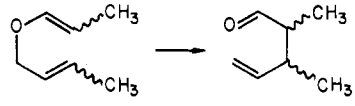
Scheme I



5 6 7

Substrate	% A	% B	Remarks
8, $R_3 = CH_3$; $R_1 = R_2 = R_4 = H$	66	33	allyl > (*E*)-propenyl
9, $R_4 = CH_3$; $R_1 = R_2 = R_3 = H$	95	5	allyl >> (*Z*)-propenyl
10, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$	78	22	(*E*)-propenyl > (*Z*)-propenyl
11, $R_3 = R_4 = CH_3$; $R_1 = R_2 = H$	100	0	allyl >> 2-methylpropenyl

Schmid and co-workers[8] have examined the kinetics and product stereochemistries of the rearrangement of the four crotyl propenyl ethers **3** to the aldehydes **4**.

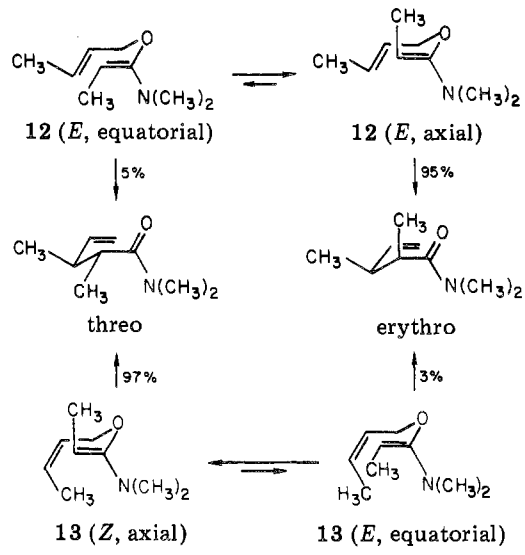


3 4

These experiments indicate that greater than 95% of rearrangement proceeds through a chairlike transition ($\Delta\Delta G^{\ddagger}$ = 2.5–3.0 kcal) rather than through a boatlike transition state. A negative entropy ($\Delta S^{\ddagger}$ = −10–15 eu) reflects the high degree of order in the transition state. Moreover, the *E,E* isomer is found to rearrange nine times faster than the *Z,Z* isomer, while the two *E,Z* isomers are intermediate in reaction rate. These data reveal that the most favorable stereochemistry for rearrangement is the *E,E* isomer, wherein the methyl groups in **6** ($R_1 = R_7 = CH_3$) are equatorially disposed

(1) L. Claisen, *Chem. Ber.*, **45**, 3157 (1912).
(2) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).
(3) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, **65**, 1992 (1943).
(4) (a) R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 1158, 2091 (1967); (b) *ibid.*, 2095 (1967).
(5) D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).
(6) W. S. Johnson, L. Werthemann, W. R. Bartlett, J. J. Brocksom, T. Lee, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
(7) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5898 (1972); R. E. Ireland, R. H. Mueller, and A. K. Willard, *ibid.*, **98**, 2868 (1976).
(8) P. Vittorelli, T. Winkler, J. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **51**, 1457 (1968); H. J. Hansen and H. Schmid, *Tetrahedron*, **30**, 1959 (1974).

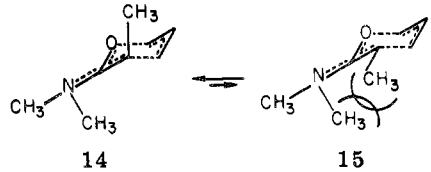
Scheme II



in the transition state (Scheme I).

Evidence for the relative reactivity of olefins has been obtained from competitive rearrangements. The series of bis(allyl) vinyl ethers **8–11** reveals that successive substitution of C_1 controls the rate of rearrangement such that allyl > (*E*)-propenyl > (*Z*)-propenyl > 2-methylpropenyl.[9] The stereochemistry of the resultant double bond in the rearrangement of the vinyl ethers of secondary allylic alcohols displays high selectivity (~90%) for the *E* isomer. The substituent at C_3 prefers the equatorial position R_5 (**6**) rather than R_4. This selectivity is higher (~99%) when R_3 is a group other than hydrogen, e.g., $R_3 = OC_2H_5$ or $N(CH_3)_2$. The greater selectivity arises from pseudo-1,3-diaxial interactions between R_3 and R_4[10] in the transition state.

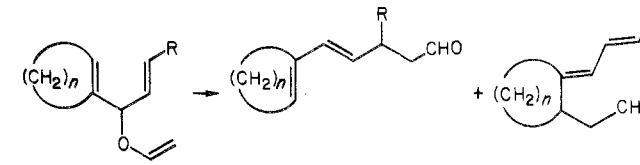
It might appear that substituents at carbon atoms C_1, C_3, and C_6, which are undergoing rehybridization, may always prefer to be equatorially disposed. This is not the case in the rearrangement of the dimethylamino vinyl ethers **12** and **13**[11] (Scheme II). The methyl substituent at C_6 is capable of isomerization by protonation–deprotonation during its formation. The equatorially situated methyl group provides a large steric interaction with the planar delocalized C_4–C_6 residue in the transition state (eq 7). In general, the



(7)

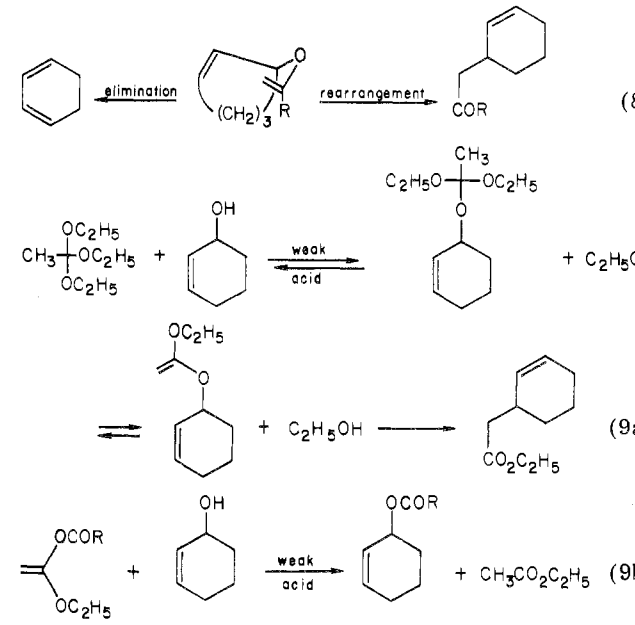
presence of heteroatoms at C_5 aids in lowering the activation energy of the rearrangement.

Thus far, consideration has been extended to systems which do not contain double bonds as part of a ring system. When C_1 and C_2 are contained in a ring, the rate of rearrangement is competitive with noncyclic allyl residues but dependent upon ring size and substitution patterns (**16–19**).[12]



16, R = H, *n* = 3	89%	11%
17, R = CH_3, *n* = 3	50%	50%
18, R = H, *n* = 4	88%	12%
19, R = CH_3, *n* = 4	65%	35%

A more serious problem arises when C_1–C_3 are contained in a ring. Under these circumstances, in order for the chairlike transition state to be maintained, C_5 must protrude above the ring and be subject to interactions with ring substituents.[13] Consequently, elimination to 1,3-dienes can be a serious side reaction (eq 8). In both the amino acetal (eq 4) and ketene



acetal (eq 5) rearrangements, the vinyl ether is prepared in situ from the allyl alcohol. While the former reagent employing amide acetals is capable of undergoing reversible exchange without the aid of a catalyst, the ketene acetal rearrangement requires a weak acid catalyst, such as propionic acid, to effect the reversible exchange of the allylic alcohol with the alcohol of the orthoacetate. The step which drives the reaction to completion is the irreversible rearrangement (eq 9a). When the rearrangement is relatively difficult, such as that which is illustrated in eq 8, esterification (propionylation) of the allylic alcohol can occur (eq 9b). This undesirable side reaction can be repressed by employing hindered weak acids, such as pivalic or perchlorohomocubanecarboxylic acid, or, alternatively, weak acids such as ammonium nitrate or 2,4-dinitrophenol.

Having considered the major stereo- and regiochemical aspects of the Claisen rearrangements, our

(9) P. Cresson and L. Lecour, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **262**, 1157 (1966); P. Cresson and S. Bancel, *ibid.*, **266**, 409 (1968).

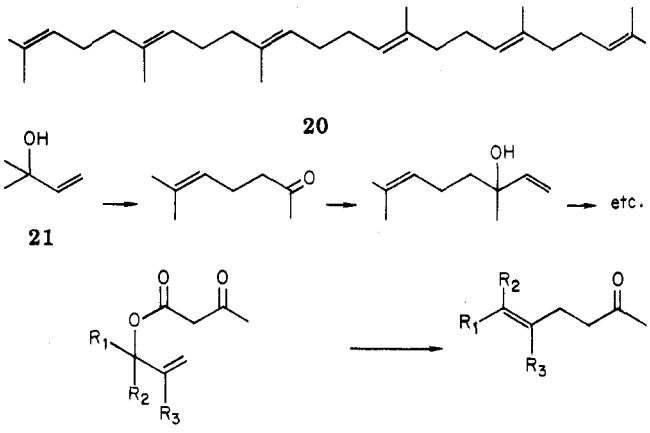
(10) (a) D. J. Faulkner and M. R. Petersen, *Tetrahedron Lett.*, 3243 (1969); (b) *J. Am. Chem. Soc.*, **95**, 553 (1973).

(11) W. Sucrow, *Angew. Chem., Int. Ed. Engl.*, 629 (1968); W. Sucrow and W. Richter, *Tetrahedron Lett.*, 3675 (1970); W. Sucrow, *ibid.*, 4725 (1970); W. Sucrow and W. Richter, *Chem. Ber.*, **104**, 3679 (1971); W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *ibid.*, **104**, 3689 (1971).

(12) S. Bancel and P. Cresson, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **268**, 1535 (1969).

(13) B. Lythgoe and D. A. Metcalfe, *Tetrahedron Lett.*, 2447 (1975).

Scheme III

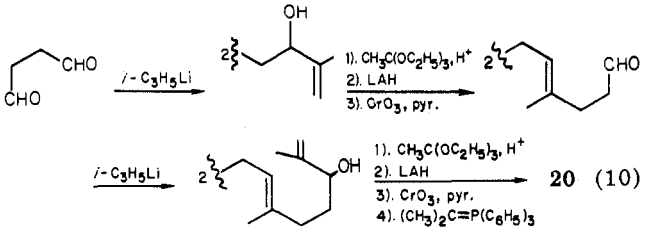


	E/*Z* (% yield)
22a, $R_1 = CH_3$; $R_2 = R_3 = H$	97/3 (76%)
22b, $R_1 = R_3 = CH_3$; $R_2 = H$	93/7 (85%)
c, $R_1 = CH_2CH_2CH{=}C(CH_3)_2$; $R_2 = CH_3$; $R_3 = H$	54/46 (67%)

attention can now be turned to the varied applications of this reaction in the area of natural products synthesis.

Synthetic Applications

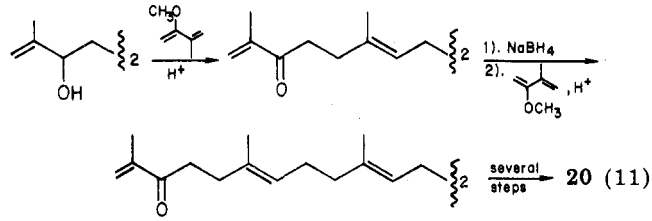
An area of natural products chemistry in which the Claisen rearrangement has been frequently employed is in the synthesis of polyisoprenoids, such as squalene (**20**) (Scheme III). Since the chain consists of a sequence of 1,5-hexadienes, it might be considered efficacious to start with alcohol **21** and proceed from terminus to terminus by an iteration process which successively introduces isoprene units after each cycle. High stereocontrol would be mandatory to avoid a host of olefin isomers. This mode of construction has been examined in the case of the allyl acetoacetates **22**.[14] Selectivity is acceptable in the case of secondary alcohols **22a** and **22b**. However, **22c**, with two substitutents at C_3, gives only a slight excess of the *E* isomer derived from the transition state having the larger group equatorial. There is virtually no free-energy difference between the conformations having R_1 or R_2 equatorial. An alternate analysis of the problem allows for the rearrangements to proceed from the center of the molecule toward the termini.[6] Because of symmetry, this route reduces the number of operations (eq 10). In

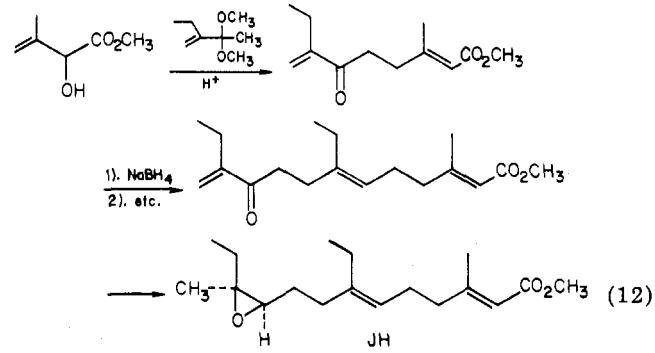


20 (10)

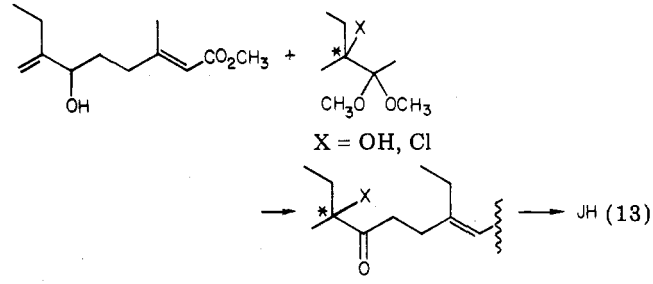
addition, the sequence employs secondary allylic alcohols which permit high stereochemical control. On first examination it may seem more reasonable to have employed the Burgstahler-type rearrangement (eq 1) to directly provide the aldehydes. However, such a pathway provides stereoselectivity on the order of 90%, whereas the orthoacetate rearrangement is selective by another order of magnitude, thereby justifying the additional chemical transformations.

A variation on the preceding theme does not depend upon isopropenyllithium to create each allylic alcohol, but rather incorporates the isopropenyl unit as an integral part of the rearrangement. This technique has been realized by employing 3-methoxyisoprene or its derived ketals in syntheses of squalene[6,10a] (eq 11) and the *Cecropia* juvenile hormones (JH)[10b,15] (eq 12).





The juvenile hormone is a chiral molecule by virtue of the asymmetry in the epoxide ring. The appropriate chirality can be introduced into the molecule during the rearrangement step by employing halo[16] or hydroxy[10b] ketals (eq 13). The resultant chiral ketone is reduced



nonstereospecifically to a mixture of diastereomeric chlorohydrins or diols, which can in turn yield the enantiomeric JH and its chiral diastereomer. It is to be noted that the chiral center is not directly involved in the bond-breaking and -forming processes.

As a direct consequence of the concerted nature and high stereospecificity of the rearrangement, it is possible to transfer chirality from C_3 to C_1.[17] In a synthetic study in the vitamin D series, Lythgoe and his collaborators[18] have effected rearrangement of the chiral alcohol **23** with methyl (*R*)orthocitronellate, which not

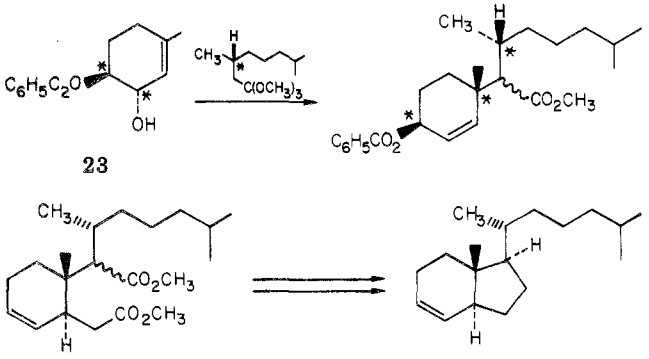
(14) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966).

(15) W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Lee, and D. J. Faulkner, *J. Am. Chem. Soc.*, **92**, 4463 (1970).

(16) P. Loew and W. S. Johnson, *J. Am. Chem. Soc.*, **93**, 3765 (1971); D. J. Faulkner and M. R. Petersen, *ibid.*, **93**, 3766 (1971).

(17) R. K. Hill and A. G. Edwards, *Tetrahedron Lett.*, 3239 (1964); R. K. Hill and M. E. Synerholm, *J. Org. Chem.*, **33**, 925 (1968); R. K. Hill, R. Soman, and S. Sawada, *ibid.*, **37**, 3737 (1972).

(18) I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc. C*, 2950 (1971).



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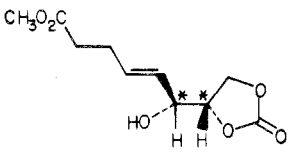
only transfers chirality at the reactive site but also transfers the noninteracting side-chain chirality. Moreover, the migration of the double bond creates a latent, chiral allylic alcohol which is ready for chiral iteration.

The stereochemistry at the asymmetric centers in **23** necessarily controls the introduction of the ester residues, which are appropriately arranged for Dieckmann cyclization. Upon reductive removal of the carbonyl group, the olefin remains as a handle for further chemical elaboration toward the desired goal.

The chiral induction technique has been elegantly employed in the synthesis of the prostaglandin (+)-15(*S*)-PGA_2 (**26**) starting with L-erythrose.[19] The three contiguous carbons bearing oxygen atoms in **24** con-



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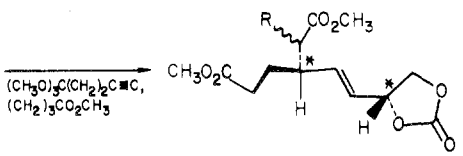

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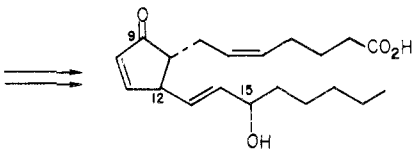

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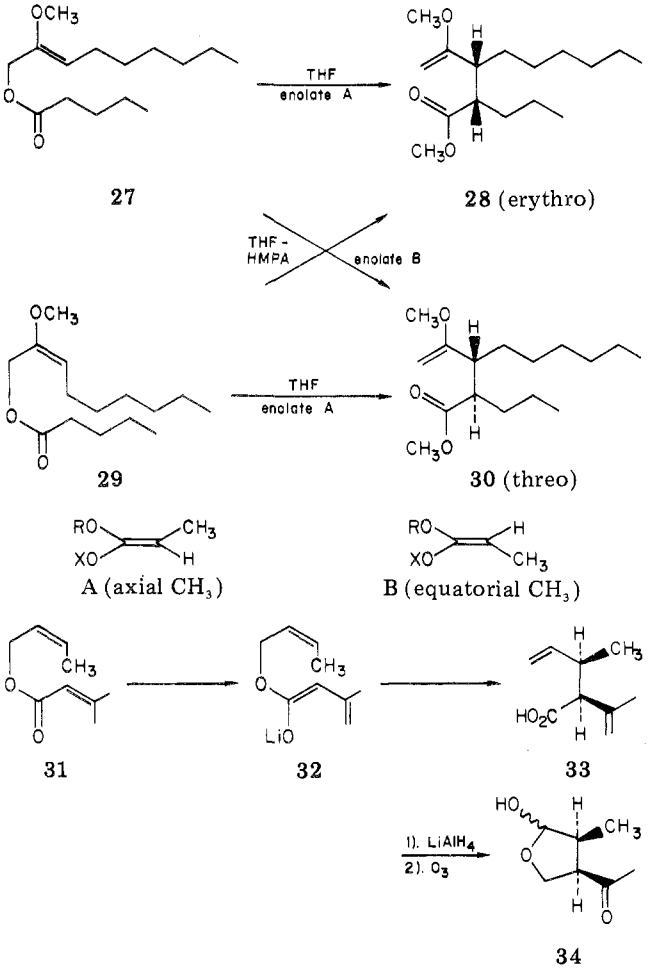
stitute the hydroxy-bearing atoms of the tetrose. The olefinic ester residue is itself introduced by the Claisen rearrangement, but, more significantly, chirality is transferred to the *pro*-C_{12} center (**25**) of PGA_2, in addition to introducing the necessary *E*-$\Delta^{13,14}$ double bond. The substituted adipate **25** allows for Dieckmann cyclization to the cyclopentanone, at which point the epimeric center present in **25** is erased. Although the carbon atom sequence C_9–C_8–C_{12}–C_{13}–C_{14} contains the basic structural entity of the Claisen rearrangement, a perceptive analysis of the structure is required for the design of the synthesis.

With a view toward employing the Claisen rearrangement in the synthesis of prostaglandins, Ireland[9] has expanded the ester enolate rearrangement.[20] The

(19) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976).

Scheme IV



27 28 (erythro) 29 30 (threo) A (axial CH_3) B (equatorial CH_3) 31 32 33 34

enolates are generated with a lithium dialkylamide followed by O-silylation to form the silylketene acetal. It is not uncommon, depending upon substitution patterns, for the half-life of the ketene acetal to be on the order of minutes at 32 °C. Moreover, the enolates A (THF) and B (THF–HMPA) can be prepared stereoselectively (4/1) by the appropriate choice of solvent. The resultant silyl esters are readily cleaved by methanol to provide methyl esters. Although the trimethylsilyl esters are too unstable to isolate, the *tert*-butyldimethylsilyl esters can be readily obtained. The acid unstable enol ether function in both **27** and **29** (Scheme IV) would preclude the use of the ortho-acetate route (acid catalysis). The silylketene acetal pathway to methyl esters allows for the rearrangement to be conducted under neutral to alkaline conditions at near-ambient temperatures.

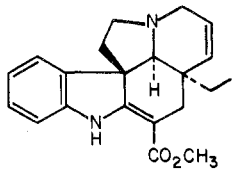
Upon retrosynthetic analysis it appears that the antibiotic and antileukemic agent botryodiplodin (**34**) might be prepared by sequential lithium aluminum hydride reduction and ozonolysis of acid **33**. The achievement of this end is realized[21] by treatment of (*Z*)-crotyl senecioate (**31**) with 2,2,6,6-tetramethylpiperidide in THF to provide the (*E*)-dienolate **32**.

(20) For earlier methods see R. T. Arnold and S. Searles, *J. Am. Chem. Soc.*, 71, 1150 (1949); R. T. Arnold, W. E. Parham, and R. M. Dodson, *ibid.*, 2439 (1949); K. C. Brannock, H. S. Pridgen, and B. Thompson, *J. Org. Chem.*, **25**, 1815 (1960); R. T. Arnold and C. Hoffman, *Syn. Commun.*, **27** (1972); J. E. Baldwin and J. A. Walker, *J. Chem. Soc., Chem. Commun.*, 117 (1973); S. Julia, M. Julia, and G. Linstrumelle, *Bull. Soc. Chim. Fr.*, 3499 (1976).

(21) F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.*, **95**, 7458 (1973).

Rearrangement of the (*Z*)-trimethylsilylketene acetal of **32** at reflux yields **33** with high stereoselectivity (91/9). In a similar fashion, the diastereomer of **33** can readily be prepared from (*E*)-crotyl senecioate.[22]

In this laboratory the Claisen rearrangement has been effectively utilized in the total synthesis of the Aspidosperma alkaloid, tabersonine (**35**).[21] Since the keto



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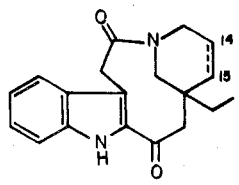
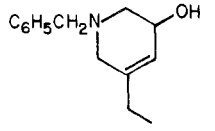


36a, 14,15-dihydro
b, 14,15-dehydro



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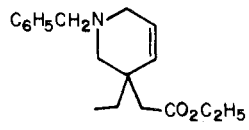
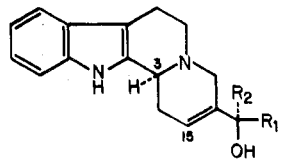


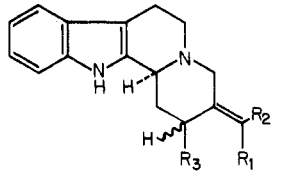
38

lactam **36a** had been previously prepared by us via a nine-membered-ring intramolecular acylation of the indole nucleus, it was apparent that its unsaturated counterpart **36b** would be a viable intermediate and might be accessible through the amino ester **38**. The rearrangement would not only introduce the requisite olefin but also serve to append the acetic acid residue necessary for cyclization. The amide–acetal rearrangement of allylic alcohol **37** provided the amide analog of **38** in 45% yield along with substantial elimination to, and disproportionation of dihydropyridines. On the other hand, the propionic acid catalyzed orthoacetate route provided minor amounts of rearrangement product **38** and principally the propionate ester of the alcohol. As discussed in the introduction, this side reaction can be repressed by utilizing pivalic acid, which, in this instance, provided the ester **38** in 74% yield.

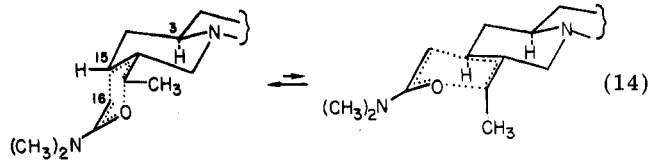
The Corynanthe alkaloid geissoschizine (**40a**) bears a substitution pattern accessible by the Claisen rearrangement except for the fact that the *E* configuration would not be expected to be produced. Nonetheless, dihydro derivatives could be realized by this route.[23] When two diastereomeric mixtures of alcohols **39a** and **39b** of known composition were subjected to the amide–acetal rearrangement, amides **40b** and **40c** were obtained in nearly the same ratios as were present in the diastereomeric mixtures of alcohols.[24] These data indicate high stereoselectivity in the rearrangement of each alcohol. The stereochemistry of the amides at C_3 and C_{15} was determined by further chemical transformations. The possible transition states for the rearrangement of alcohol **39a** (eq 14) and **39b** (eq 15) favor the presence of an equatorial methyl group and a chairlike conformation of the dehydropiperidine ring. Transition state $A^{\ddagger}$ is favored over $B^{\ddagger}$ in order to avoid the pseudo-1,3-diaxial interaction ($(CH_3)_2N/CH_3$) present in $B^{\ddagger}$. It is transition state $B^{\ddagger}$ which would have led to the correct stereochemistry in geissoschizine. Alcohol **39b** rearranges through $D^{\ddagger}$, which provides the



39a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = H$



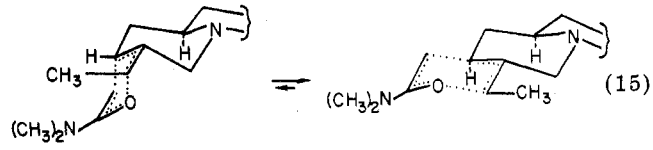
40a, $R_1 = CH_3$; $R_2 = H$; $R_3 = \beta\text{-}CH_3O_2CC{=}CHOH$
b, $R_1 = H$; $R_2 = CH_3$; $R_3 = \alpha\text{-}CH_2CON(CH_3)_2$
c, $R_1 = H$; $R_2 = CH_3$; $R_3 = \beta\text{-}CH_2CON(CH_3)_2$
d, $R_1 = R_2 = H$; $R_3 = \alpha\text{-}CH_2CON(CH_3)_2$



(14)

$A^{\ddagger}$, C-3,C-15 anti, ethylidene *Z*

$B^{\ddagger}$, C-3,C-15 syn, ethylidene *E*



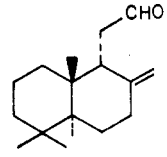
(15)

$C^{\ddagger}$, C-3,C-15 anti, ethylidene *E*

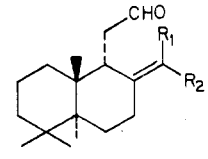
$D^{\ddagger}$, C-3,C-15 syn, ethylidene *Z*

desirable syn arrangement of hydrogens at C_3 and C_{15}, but has the incorrect (*Z*)-olefin stereochemistry. However, when the stereochemically controlling secondary methyl group is removed (i.e., **39c**), amide **40d** is produced. This result dictates that transition state $A^{\ddagger}$ ($CH_3 = H$) is favored over $B^{\ddagger}$ ($CH_3 = H$), since the latter encounters an incipient $A^{(1,3)}$ interaction[25] in the formation of the C_{15}–C_{16} bond.

A similar case appears in the construction of terpene synthons. The aldehyde **41**, having the α-axially or-



41

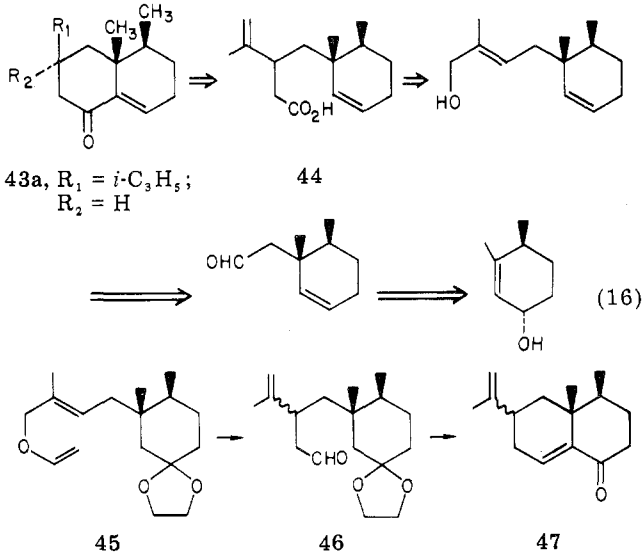


42a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = H$

iented acetaldehyde chain, was readily produced by rearrangement of the corresponding vinyl ether. The axial acetaldehyde chain is of the anticipated geometry, based upon the previous discussion. The aldehydes **42**, both having an axial acetaldehyde group, were produced from a presumed diastereomeric mixture of alcohols. In this case, both aldehydes would have to have been formed, the latter having an axial methyl group in the transition state. In such a situation, the buttressed quaternary methyl group apparently dominates any stereochemical control by the secondary methyl group, thereby preventing formation of the equatorially substituted product.[26]

(22) S. R. Wilson and R. S. Myers, *J. Org. Chem.*, **40**, 3309 (1975).
(23) F. E. Ziegler and J. G. Sweeny, *Tetrahedron Lett.*, 1097 (1969).
(24) F. E. Ziegler and J. G. Sweeny, unpublished observations.
(25) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965).
(26) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **27**, 1118 (1962); R. F. Church and R. E. Ireland, *ibid.*, **28**, 17 (1963). Since the vinyl ether related to **42** was produced in 66% yield while that of **41** was obtained in 91% yield, the possibility could exist that only one ether formed in the former case. The rearrangement providing **42** proceeded in 97% yield.

The nonisoprenoid sesquiterpene eremophilone **42a** had long defied the synthetic chemists' efforts. A retrosynthetic analysis (eq 16) considered in this labo-



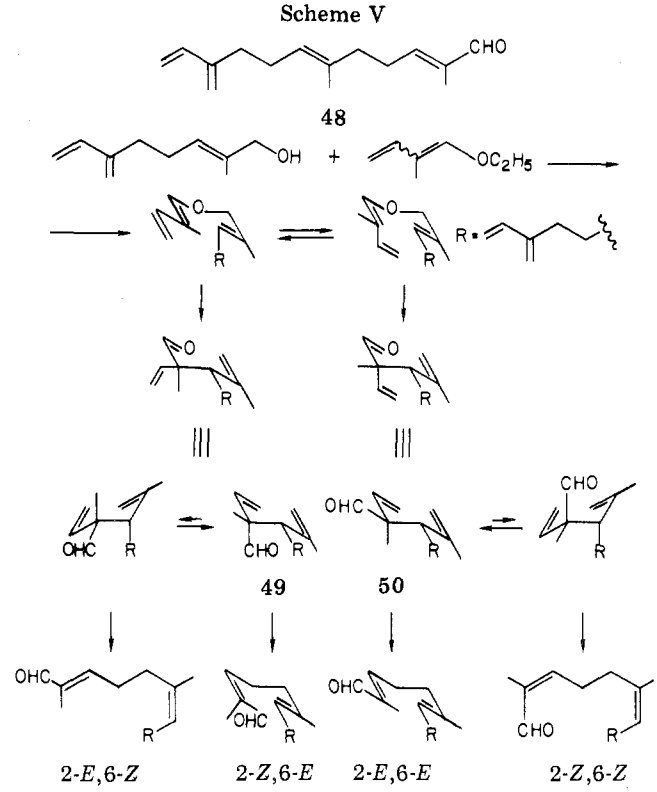
43a, $R_1 = i\text{-}C_3H_5$; $R_2 = H$ **44** (16)

45 **46** **47**

ratory invoked two Claisen rearrangements. The difficulties associated with such a scheme included the lack of viable methods for preparing pure cyclohexenols of the appropriate stereochemistry needed to control the vicinal methyl geometry in the initial rearrangement, the diastereomeric composition of acid **44** as a result of the second rearrangement, and the distinct possibility of competitive olefin cyclization in the ultimate step. The stereochemistry of the vicinal methyl groups was solved by employing dialkylcuprate chemistry. Thermolysis of vinyl ether **45** at 175 °C provided the ketal aldehyde **46**, albeit as a nearly equal mixture of diastereomers. The quaternary center has little if any influence in the control of the stereochemistry at the newly created asymmetric center. The enones **47**, prepared by aldol condensation, avoid the necessity of risking a questionable cationic cyclization so late in the sequence. By virtue of the Wharton rearrangement,[27] a reaction sequence which formally permits the transposition of enone moieties, the goal of eremophilone was eventually realized.[28]

Successive [3,3] sigmatropic rearrangements can be achieved when a 1,5-hexadiene is created after the initial rearrangement. Such rearrangements can be realized by first effecting an irreversible Claisen rearrangement, which is subsequently followed by a reversible Cope rearrangement which is driven to completion by the production of the more highly substituted double bond isomer. This process is exemplified by the synthesis by Thomas[29] of β-sinensal (**48**), a component

Scheme V



48 **49** **50**

2-*E*,6-*Z* 2-*Z*,6-*E* 2-*E*,6-*E* 2-*Z*,6-*Z*

of the essential oil of the Chinese orange (see Scheme V). Only the 2-*E*,6-*E* isomer is isolated in this rearrangement, indicating that the reaction must be funneled through intermediate **50** having an equatorial aldehyde in the Cope transition state. Although the intermediacy of **49** appears to have been excluded by the absence of the 2-*Z*,6-*E* isomer, related rearrangements have produced this isomer. It is imperative that the position α to the aldehyde be substituted to avoid conjugation of the β,γ double bond and thereby suffer short-circuiting of the sequence.

Conclusion

Because of space limitations, it has not been possible to deal with the many other reported applications of this reaction.[30] An attempt has been made to codify the expanse and kind of this rearrangement according to the author's own prejudices and experience. It can readily be seen that the Claisen rearrangement, with all its modifications, allows, through high stereoselectivity and diversity of functionality, a means for synthesizing a wide variety of chemical structures.

I wish to express my appreciation to my collaborators, Drs. Gregory Bennett, James Sweeny, and Paul Wender, who have played an integral part in the utilization of this reaction in this laboratory. I also wish to thank my colleague, Professor Richard Mueller,[7] for many stimulating discussions and the Division of General Medical Sciences for a Career Development Award (1973–1978), which has in part provided the time to prepare this Account.

(27) P. Wharton and D. Bohlen, *J. Org. Chem.*, **26**, 3615, 4718 (1961).
(28) F. E. Ziegler and P. A. Wender, *Tetrahedron Lett.*, 449 (1974); F. E. Ziegler, G. R. Reid, W. L. Studt, and P. A. Wender, *J. Org. Chem.*, in press.
(29) A. F. Thomas, *J. Am. Chem. Soc.*, **91**, 3281 (1969); see also A. F. Thomas, *Chem. Commun.*, 1657 (1968); *J. Chem. Soc. C*, 220 (1970). For other Claisen–Cope rearrangements, see B. Bowden, R. C. Cookson, and H. A. Davis, *J. Chem. Soc., Perkin. Trans. 1*, 2634 (1971), and R. C. Cookson and N. R. Rogers, *ibid.*, 2741 (1971).
(30) For a more complete literature survey of the Claisen and Cope rearrangements, see S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1, (1975).