J. Am. Chem. Soc. **1982**, *104*, 7181-7190

sample of (±)-dihydroaromatin, Dr. A. Romo de Vivar (Universidad Nacional Autonoma de Mexico) for copies of the NMR and IR spectra of (−)-aromatin, Professor R. H. Schlessinger (Rochester) for a comparison sample of **25b**, Dr. J. J. Piwinski for his contributions on the Cope–Claisen studies, and P. Demou and A. Pinto for recording high-field NMR spectra (NSF Northeast Regional NMR Facility, Yale University, Department of Chemistry.

Registry No. **2a** (M = Li), 81850-59-1; **2a** (M = Cu), 83573-02-8; **2b** (M = Li), 83562-41-8; **2c** (M = Li), 83562-42-9; **3c**, 74149-62-5; **3d**, 76156-81-5; **4**, 930-68-7; **5**, 930-30-3; **6**, 1120-73-6; (±)-**7**, 83562-43-0; (±)-**8**, 83562-44-1; **9a**, 73798-21-7; (±)-**9b**, 83562-45-2; **10a**, 73798-22-8; (±)-**10b**, 83562-46-3; (±)-**10c**, 83562-47-4; **10d**, 73798-26-2; **10e**, 73798-27-3; **10f**, 73798-28-4; **10g**, 73798-29-5; **10h**, 73798-30-8; **10i**, 73798-31-9; **11a**, 83562-48-5; (±)-**11b**, 83562-49-6; **12a**, 83602-29-3; (±)-**12b**, 83602-32-8; (±)-**12c**, 83562-50-9; (±)-**12d**, 83602-30-6; **12e**, 83562-51-0; (±)-**13a**, 76156-83-7; (±)-**13b**, 81939-03-9; (±)-**14**, 83602-31-7; (±)-**15**, 81875-17-4; (±)-**16**, 76156-87-1; (±)-**17**, 83562-52-1; (±)-**19a**, 76156-88-2; (±)-**19b**, 83562-53-2; (±)-**20a**, 76156-89-3; (±)-**21a**, 76156-90-6; (±)-**21b**, 76156-91-7; (±)-**22a**, 76156-92-8; (±)-**22b**, 76189-79-2; (±)-**23a**, 74645-42-4; (±)-**23b**, 74645-43-5; (±)-**24**, 76156-93-9; (±)-**25a**, 72341-86-7; (±)-**25b**, 72341-85-6; (±)-**26**, 60426-81-5; 1,3-propanedithiol, 109-80-8; (*E*)-2-methyl-2-butenal, 497-03-0; allyl bromide, 106-95-6.

Tandem Cope–Claisen Rearrangement: Scope and Stereochemistry[†]

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Contribution from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511. *Received March 4, 1982*

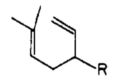
Abstract: The complete details of the seminal study on the tandem Cope–Claisen rearrangement are presented. The reaction uses an initial Cope rearrangement to trigger an irreversible Claisen rearrangement. In several cases, the Claisen step drives an unfavorable Cope equilibrium. Typically, vinyl ether **1c** provides aldehyde **3**, which, under certain conditions, can be transformed into the Conia products **4** and **5**. The stereochemical course of the rearrangement of the four 2-vinyl-3-isopropenylcyclohexyl vinyl ethers **8c**, **8d**, **9c**, and **9d** leading to aldehyde **18** is discussed. The Cope–Claisen rearrangement of **26b** and related isomers is studied in detail. The stereochemical consequences of the reaction are applied to the construction of an intermediate employed in the synthesis of the pseudoguaianolides aromatin and confertin.

The Cope rearrangement of unadorned 1,5-hexadienes suffers as a useful synthetic reaction for a number of reasons.[2] Foremost among them are the reversibility of the reaction and the preference for the formation of highly substituted olefins in the equilibrium mixture. Imaginative solutions to these difficulties have been realized by rendering the reaction irreversible through the formation of stable carbonyls (oxy–Cope),[3] enolates (alkoxy–Cope),[4] or other subsequent irreversible transformations.[5] In the latter context, we entertained the idea that the irreversible Claisen rearrangement could serve to trap, in the contrathermodynamic sense, unfavorable Cope equilibria. The union and utility of these reactions in the tandem mode has been realized in the elegant studies of Thomas[6] and Cookson[7] wherein the Claisen rearrangement precedes the Cope rearrangement (i.e., Claisen–Cope rearrangement). In such formulations, it is necessary for the Cope product to be judiciously chosen as the more highly substituted 1,5-hexadiene if the reaction is to have a favorable equilibrium. Intermediate Claisen products could be isolated in Cookson's studies since the lower activation energy process constituted the initial rearrangement. Accordingly, the lack of intermediates in most Cope–Claisen rearrangements was anticipated and confirmed.

This paper contains a complete account of our communicated studies on the tandem Cope–Claisen rearrangement.[8]

Results and Discussion

Our initial study focused upon an acyclic model. Alkylation of ethyl crotonate with 1-bromo-3-methyl-2-butene provided ester **1a**.[9] Thermolysis of ester **1a** at 266° C provided an 80/20 equilibrium mixture of **1a** and **2a** (K_{eq} **2a**/**1a** = 0.25). If ester **2a** were the desired product of such a rearrangement for the purpose of converting it into vinyl ether **2c** (via alcohol **2b**) for subsequent Claisen rearrangement, the sequence would have been rendered impractical, since the desired component is the minor constituent of the equilibrium mixture. Ester **1a** was successively



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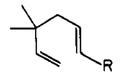

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a, R = $CO_2C_2H_5$; b, R = CH_2OH; c, R = $CH_2OCH{=}CH_2$

[†] Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

(1) Taken in part from the Ph.D. Thesis of J. J. P., Yale University, 1980.

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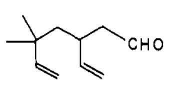
reduced with $LiAlH_4$ and vinylated to provide **1c**; thermolysis of this substance provided three identifiable products: **3**, **4**, and **5**.



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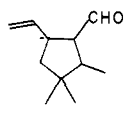

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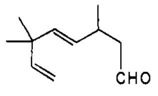

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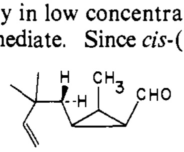
The principal product in each sealed-tube rearrangement was the Cope–Claisen aldehyde **3**. Lower temperatures required longer contact time for efficient conversion of the vinyl ether **1c** to products. Longer contact time produced more of aldehydes **4** and **5** at the expense of **3**. Resubmission of aldehyde **3** to the thermolysis conditions demonstrated that **4** and **5** were arising from **3**. Use of a flow reactor (high temperature, short contact time) virtually eliminated the products **4** and **5**.

On the basis of NMR data and literature precedent, these substances were identified as arising from subsequent Conia rearrangement[10] of the Cope–Claisen product **3**. Whereas cyclopentane carboxaldehyde **4** arises from the enol of aldehyde **3** interacting with the distal double bond, dienic aldehyde **5** invokes the proximate double bond undergoing Conia rearrangement with the enol of aldehyde **3**. This latter process requires the formation, ostensibly in low concentration, of the *all-cis*-cyclopropane **6** as an intermediate. Since *cis*-(2-methylcyclopropanecarboxaldehydes are known to undergo a 1,5-H shift (retro-Conia rearrangement) to the olefinic aldehyde,[11] aldehyde **6** has the option of reverting to starting material or of producing **5** by effecting a 1,5-H shift between the aldehyde and the methylene group. The presence of the *E* olefin in **5** requires the olefin residue of the side chain to be remote from the methyl group in the transition state for the rearrangement. Since the trans isomer **7** would be expected to be thermodynamically more stable than its all-cis counterpart **6**, its existence can be inferred; its only mode of reaction is a reversible return to the Cope–Claisen product **3**.



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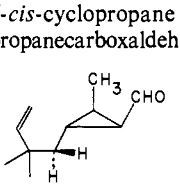


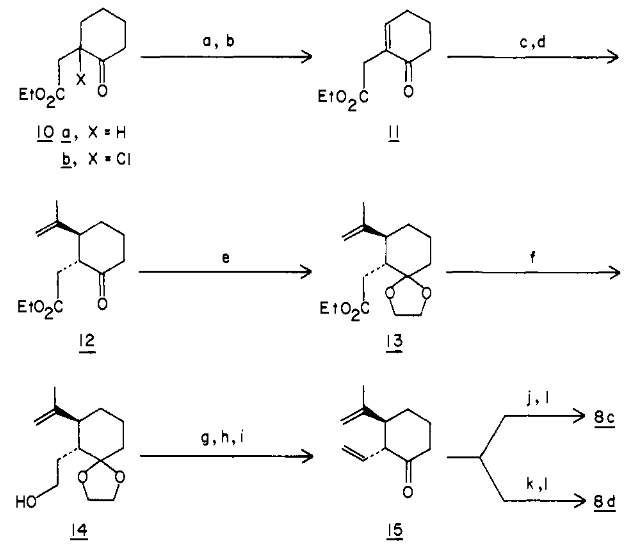
7

Rearrangement products of this type are not new and are often referred to as abnormal Claisen products. They were first observed in the phenyl ether series by Lauer and Filbert (1936) and in the vinyl ether series by Hurd and Pollack (1939).[12] These elegant structural studies predated modern considerations of the mechanism of these thermal rearrangements.

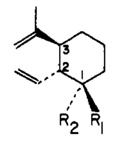
This preliminary study established the viability of the tandem reaction, demonstrating that an unfavorable Cope equilibrium could be channeled to the less substituted double-bond product by an irreversible Claisen rearrangement.

However, not all Cope-rearrangement equilibriums favor the more substituted double-bond structure. It is well recognized that (*E*,*E*)-1,5-cyclodecadiene[13] and (*E*,*Z*)-1,5-cyclodecadiene[14] isomerize under relatively mild conditions to *trans*- and *cis*-1,2-divinylcyclohexane, respectively. These equilibriums manifest themselves in natural-products chemistry in the elemane–germacrane class of sesquiterpenes. The success of the tandem Cope–Claisen rearrangement in this instance would, in principle, permit the chiral synthesis of several sesquiterpenes from the readily available enantiomers of carvone. The stereoisomers of 2-vinyl-3-isopropenylcyclohexyl vinyl ether (**8c** TT),[15] **8d** (CT), **9c** (TC), and **9d** (CC)) were prepared to assess the scope and stereochemistry of the tandem sequence in this class of compounds.

Scheme I



(a) SO_2Cl_2; (b) DBU, hexane; (c) $(i\text{-}C_3H_5)_2CuLi$, DMS, Et_2O; (d) $NaOC_2H_5$, C_2H_5OH; (e) $(CH_2OH)_2$, p-TsOH, C_6H_6; (f) $LiAlH_4$, Et_2O; (g) o-$NO_2C_6H_4SeCN$, n-Bu_3P, THF; (h) H_2O_2; (i) AcOH, H_2O, 45 - 55 °C; (j) Li, NH_3, -78 °C; (k) $LiH(n\text{-}Bu)_3B$, THF; (l) $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$.



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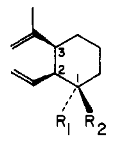

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a, $R_1 = OH$, $R_2 = H$; b, $R_1 = H$, $R_2 = OH$; c, $R_1 = OCH{=}CH_2$, $R_2 = H$; d, $R_1 = H$, $R_2 = OCH{=}CH_2$

The isomers **8c,d** (TT, CT) were prepared from ethyl 2-oxocyclohexylacetate (**10a**) as illustrated in Scheme I. Several comments on the syntheses are warranted. Enone **11** had been prepared previously by dehydrohalogenation of chloro ketone **10b** in refluxing collidine.[16] However, the product was found to be contaminated with approximately 25% of the exocyclic isomer of **11**. Although greater than 75% of the dehydrohalogenation product was the exocyclic isomer when 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) (35 °C, 10 min, cyclohexane) was employed in place of collidine, the thermodynamic enone **11** could be obtained cleanly by refluxing the solution. The trans relationship of the two substituents was established by base-catalyzed equilibration of the cuprate adduct to form **12**. The stereochemistry of **12** was confirmed by the appearance in the NMR spectrum of **15** of a one-proton triplet (δ 2.99, J = 10 Hz) for the methine proton adjacent to the ketone. Finally, the structure of alcohol **8a**, formed by metal–ammonia reduction of **15**, was confirmed as the TT isomer by the appearance of the hydroxyl methine proton at δ 3.28 as a triplet (10 Hz) of doublets (4 Hz). On the other hand, the lithium–Selectride reduction of ketone **15** provided the isomeric alcohol **8b**. The hydroxyl methine proton of this isomer appeared at δ 3.99 as a quartet (J = 3 Hz) requiring an axial hydroxyl group in the ground-state chair confirmation.

Access to the vinyl ether **9c** (TC) was achieved as illustrated in Scheme II. Hydroxy ketone **17** was obtained as a single diastereomer under conditions of kinetic protonation of the cuprate product. NMR spectroscopy failed to assign unequivocally the

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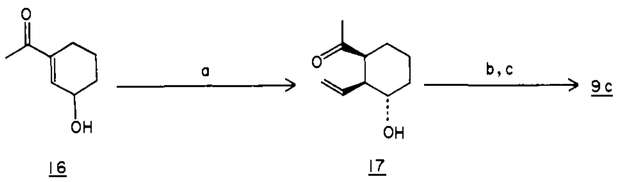
Scheme II



(a) $(CH_2{=}CH)_2CuLi$, DMS, THF, Et_2O; (b) $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$; (c) $(C_6H_5)_3P{=}CH_2$, THF.

Table I. High-Temperature Thermolysis of Vinyl Ethers 8c, 8d, and 9c

				% yield of products		
entry	vinyl ether	temp, °C	time, min	**18**	olefins	other aldehydes
1[a]	9c (TC)	292	270	55	12	9
2[b]	8c (TT)	312	180	21	43	11
3[b]	8d (CT)	312	180	26	40	11
4[b]	9c (TC)	312	180	70	18	12
5[b]	8c (TT)	378	3	9	33	5
6[b]	8d (CT)	377	3	18	45	7
7[b]	8c (TC)	379	3	61	34	11

[a] GC yield of distilled material. [b] GC yield of undistilled material using 1,2,3,4-tetrahydronaphthalen-1-ol as internal standard; detector response, **18**/THN = 1.23.

stereochemistry of this substance. Base-catalyzed (CH_3ONa–CH_3OH) epimerization provided an 86/14 mixture of isomers in which a new isomer predominated. The major component clearly contained a diequatorial disposition of the acetyl and vinyl groups about the cyclohexane ring, since the methine hydrogen adjacent to the ketone appeared at δ 2.43 as a double of triplets (J = 4 and 11 Hz) in its NMR spectrum. Methylenation of hydroxy ketone **17** with methylenetriphenylphosphorane in dimethyl sulfoxide[17] provided a mixture of diolefins in a 75/25 ratio. The major component was shown to be **8a**, identical with the alcohol derived from the Li–NH_3–C_2H_5OH reduction of ketone **15**. The problem of epimerization[18] was readily circumvented by converting hydroxy ketone **17** into its vinyl ether followed by Wittig methylenation in THF–hexane, thereby providing vinyl ether **9c** (TC) without contamination.[19]

The foregoing chemical proof of the structure of hydroxy ketone **17** was confirmed by single-crystal X-ray analysis.[20]

With three of the four possible diastereomers in hand, the thermolysis of these substances was studied. The results of high-temperature (>290 °C) thermolyses are detailed in Table I.

The only substance identifiable as arising from the Cope–Claisen rearrangement of either **8c** (TT), **8d** (CT), or **9c** (TC) was (Z,Z)-8-methyl-2,7-cyclodecadiene-1-acetaldehyde (**18**). The presence of infrared absorption bands at 748 and 725 cm^{-1} indicated the presence of Z-disubstituted olefins[21] while the absence of absorption bands between 1000 and 900 cm^{-1} precluded the presence of an E-disubstituted olefin or an E-trisubstituted olefin.[21,22] The NMR spectrum (270 MHz) of **18** was in accord with the gross structural assignment. The appearance of a vinylic methyl group at δ 1.69 argued for a Z configuration of the trisubstituted olefin, since methyl groups in related systems resonate farther downfield (δ 1.67) than their E counterparts (δ 1.61).[22,23] The C_3 H appeared at δ 5.33 as a triplet of doublets, coupled to the C_2 H and C_4 H_β (J = 11 Hz, t) and C_4 H_α (J = 4 Hz, d). This observation reconfirmed the presence of a Z-disubstituted olefin. The signal for the C_2 H and C_7 H appeared as a complex multiplet centered at δ 5.05. Irradiation of the methylene group adjacent to the aldehyde caused the aldehyde triplet to collapse to a singlet; the C_1 H multiplet at δ 2.82 was simplified to a triplet of doublets caused by coupling to the C_2 H and C_{10} H_α (J = 11 Hz, t) and the C_{10} H_β (J = 2 Hz, d). The NMR coupling constants and the known preference for (Z,Z)-1,6-cyclodecadiene to exist in the armchair conformation[24] support **18** as the ground-state conformation of the Cope–Claisen product.

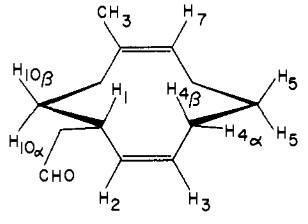


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Table II. Low-Temperature Thermolysis of Vinyl Ethers 8c, 8d, and 9c

				product ratios[a]					
entry	vinyl ether	temp, °C	time, min	18	8c (TT)	8d (CT)	9c (TC)	9d (CC)	other aldehydes
1	8c (TT)	255	180		53	47			
2	8d (CT)	255	180		56	44			
3	9c (TC)	255	180	58			24	9	9
4	9c (TC)	207	150				75	25	

[a] Relative yields as determined by GC.

Two other aldehydic materials with the same molecular weight as **18** could be detected in ≈10% yield. These substances displayed no vinylic methyl signals in their NMR spectra and were excluded as being geometric double-bond isomers of **18**. No definitive structural assignments could be made.

Five isomeric olefins (M^+ 148) derived from the thermolytic elimination of acetaldehyde from the vinyl ethers were obtained. Three of these olefins were tentatively assigned structures **19**, **20**, and **21** on the basis of their NMR spectra, which exhibited proton patterns typical of conjugated vinyl, ethylidene, and 1,3-butadienyl moieties, respectively.

The results detailed in Table II are informative. At all temperatures studied, the *trans*-divinyl isomers **8c** (TT) and **8d** (CT) consistently gave lower yields of the Cope–Claisen product **18** and more of the olefinic products relative to the cis isomer **9c** (TC).

Low-temperature thermolysis helped to clarify the course of these rearrangements. Thermolysis (Table II, entries 1 and 2) of either **8c** (TT) or **8d** (CT) at 255 °C produced an ≈1:1 equilibrium mixture of the two isomers *without the formation of elimination products or Cope–Claisen product* ***18***.

Under identical conditions (entry 3), the cis-isomer **9c** (TC) was still present, *in addition to the formation of the Cope–Claisen product* ***18***, *the presence of the heretofore unrealized vinyl ether*

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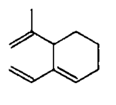

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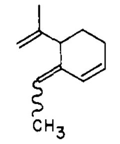

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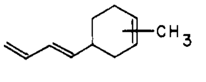

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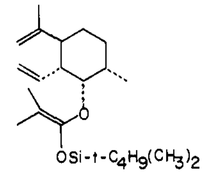


22

***9d** (CC), and the lack of olefinic byproducts.* The Cope–Claisen process was not detected in the thermolysis of **9c** (TC) at 207 °C, but facile equilibration of **9c** (TC) and **9d** (CC) was effected.

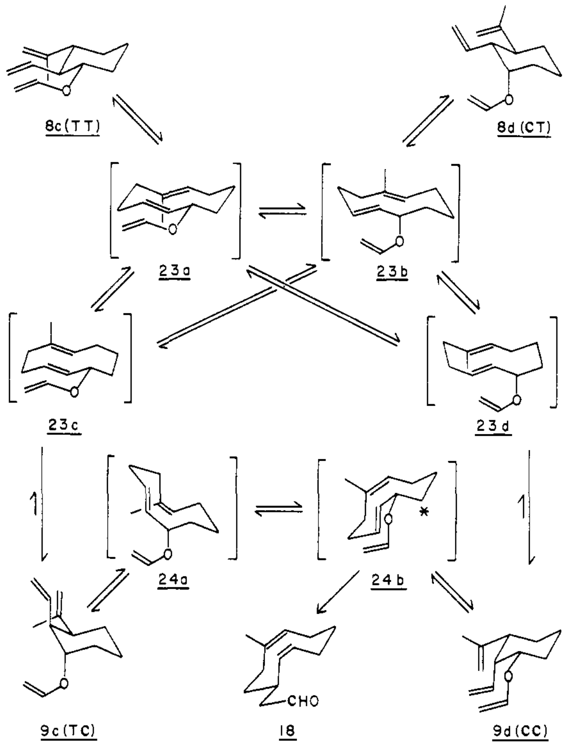
The thermal interconversion of *trans*-divinylcyclohexanes has been reported.[25] In the present instance, the fact that $(\Delta G^{\ddagger}_{\text{trans}} > \Delta G^{\ddagger}_{\text{cis}})_{\text{Cope-Claisen}}$ is apparent. In **8c** (TT) and **8d** (CT), $\Delta G^{\ddagger}_{\text{retro-Cope}} < \Delta G^{\ddagger}_{\text{Claisen}}$, while $\Delta G^{\ddagger}_{\text{retro-Cope}} \cong \Delta G^{\ddagger}_{\text{Claisen}}$ for **9c** (TC) and **9d** (CC). The preference for kinetic control in these processes is witnessed in the Cope–Claisen studies of Raucher[26] employing (silyloxy)ketene silyl acetal **22**, wherein the (*E*,*E*)-1,6-cyclodecadiene has been trapped by effectively lowering the activation energy of the Claisen step in the trans series. When the propionate-derived ketene acetal was employed, a mixture of products was obtained in which a major component showed evidence for a trans-disubstituted olefin. The acetate-derived ketene acetal rearrangement yielded no identifiable Cope–Claisen products. These observations are in accord with the increase in the rate of ketene silyl acetal Claisen rearrangements with successive increases in the substitution of the termini of the olefins and with the lower activation energy for ketene silyl acetal Claisen rearrangements compared to those of vinyl ether rearrangements.[27] The successful trapping of the (*E*,*E*)-1,5-cyclodecadiene in the rearrangement of **22** is clearly indicative of the lowering of the Claisen-rearrangement activation energy.

Entry 3 (Table II) demonstrates that the Cope–Claisen product **18** is more accessible through the *cis*-divinyl isomers **9c** (TC) and **9d** (CC) under conditions where the trans isomers only undergo equilibration.

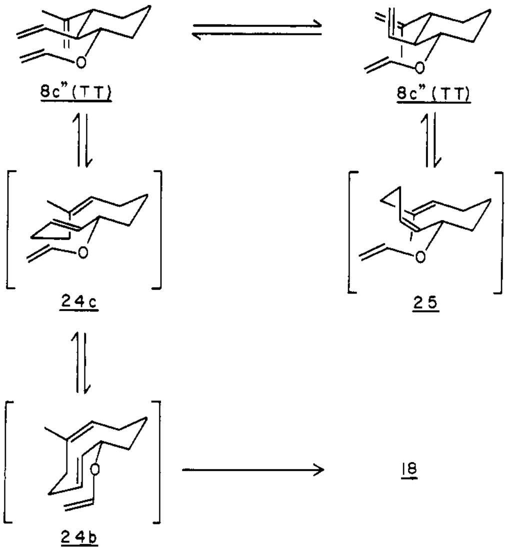
These data suggest that the trans isomers are channeled through the cis manifold and that an appreciable energy barrier separates the trans and cis series. This barrier accounts for the higher ratio of olefins/**18** in the high-temperature thermolysis of the trans isomers **8c** (TT) and **8d** (CT) relative to the cis isomer **9c** (TC) (Table II), the elimination of acetaldehyde being competitive with crossover to the cis series. The crossover process is effectively irreversible ($\Delta G^{\ddagger}_{9c\rightarrow 8c,d} > \Delta G^{\ddagger}_{9c\rightarrow 18}$); no **8c** (TT) or **8d** (TC) is detectable in the thermolysis of **9c** (TC).

Scheme III outlines one interpretation of these data.[28] At lower temperatures, isomers **8c** (TT) and **8d** (CT) interconvert through a chairlike transition state vis (*E*,*E*)-1,5-cyclodecadiene vinyl ether conformers **23a** and **23b**, respectively. Conformers **23a** and **23b** interconvert by two endocyclic double-bond rotations (EDBR) of 180°, from one crossed-double-bond conformer to the other.

Scheme III



Scheme IV



Conformation **23a** would be able to undergo Claisen rearrangement since it has the alkyl–oxygen bond overlapping with the π framework; conformation **23b** does not have such overlap. Passage of conformations **23a,b** to **23c,d** involves a single EDBR. Rotation of the trisubstituted olefin accomplishes the transforms **23a** → **23c** and **23b** → **23d**. Alternatively, rotation of the disubstituted olefin provides **23a** → **23d** and **23b** → **23c**. The single EDBR process initially provides **23c,d** having the original six cyclohexane carbons of **8c** (TT) and **8d** (CT) in a twist-boat conformation. This conformation has the reactive termini of the two olefins too remote for bonding. The conformations represented by **23c,d** (with the six aforementioned carbons in a boat conformation) permit the olefins to interact, leading to the cis manifold through **9c** (TC) and **9d** (CC), respectively. Cope rearrangement of **9c** (TC) and **9d** (CC) through chairlike transition states provide conformations **24a** and **24b**, respectively. The reduced strain of **24** (*E*,*Z*)[29] vs. **23** (*E*,*E*) permits the Claisen rearrangement to

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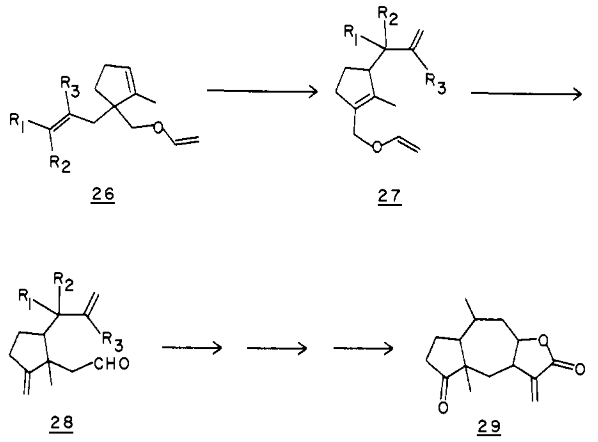
[25] Rao, A. S.; Paul, A.; Sadgopal, Bhattacharyya, S. C. *Tetrahedron* **1961**, *13*, 319. Mabry, T. J. *Chem. Commun.* **1967**, 1235. Jones, R. V. H.; Sutherland, M. D. *Ibid.* **1968**, 1229. Morikawa, K.; Hirose, Y. *Tetrahedron. Lett.* **1969**, 869. Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Ibid.* **1970**, 841. Takeda, K.; Horibe, I. *J. Chem. Soc., Perkin Trans. 1* **1975**, 870 and earlier papers in this series. Lange, G. L.; Huggins, M. A.; Neidert, E. *Tetrahedron. Lett.* **1976**, 4409. Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267. Williams, J. R.; Callahan, J. F. *J. Chem. Soc.* **1979**, 404.

[26] Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. D. *J. Am. Chem. Soc.* **1981**, *103*, 1853.

[27] Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

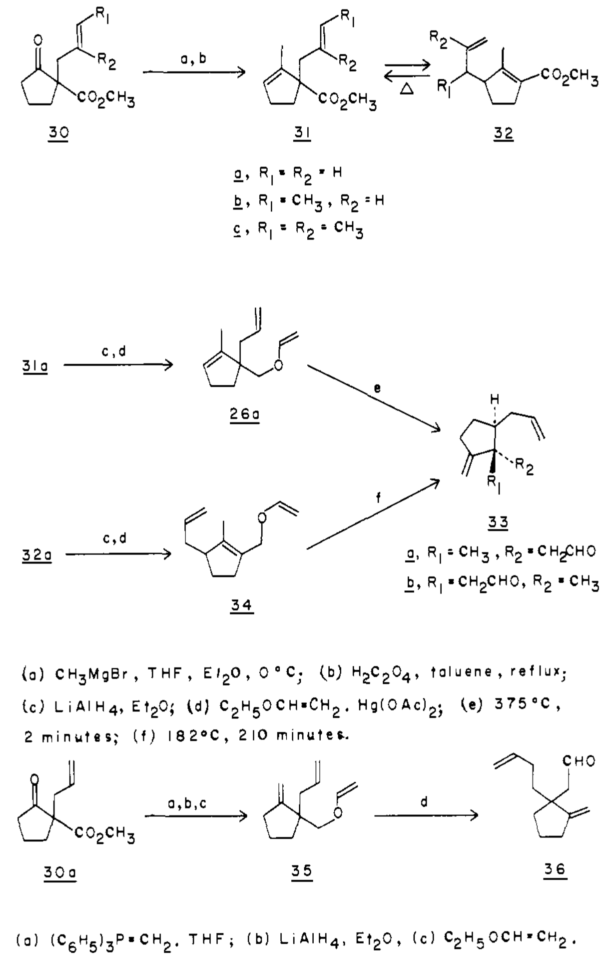
[28] Throughout the text, ground-state geometries have been employed when transition states are intended in order to conserve space. A single enantiomer is represented.

Scheme V



a, R$_1$ = R$_2$ = R$_3$ = H; b, R$_1$ = CH$_3$, R$_2$ = R$_3$ = H; c, R$_1$ = R$_3$ = CH$_3$, R$_2$ = H; d, R$_1$ = R$_2$ = CH$_3$, R$_3$ = H

Scheme VI



a, R$_1$ = R$_2$ = H
b, R$_1$ = CH$_3$, R$_2$ = H
c, R$_1$ = R$_2$ = CH$_3$

a, R$_1$ = CH$_3$, R$_2$ = CH$_2$CHO
b, R$_1$ = CH$_2$CHO, R$_2$ = CH$_3$

(a) CH$_3$MgBr, THF, Et$_2$O, 0 °C; (b) H$_2$C$_2$O$_4$, toluene, reflux; (c) LiAlH$_4$, Et$_2$O; (d) C$_2$H$_5$OCH=CH$_2$, Hg(OAc)$_2$; (e) 375 °C, 2 minutes; (f) 182 °C, 210 minutes.

(a) (C$_6$H$_5$)$_3$P=CH$_2$, THF; (b) LiAlH$_4$, Et$_2$O, (c) C$_2$H$_5$OCH=CH$_2$, Hg(OAc)$_2$; (d) 382 °C, 10 seconds.

proceed in vinyl ether **24b**. The Claisen rearrangement of **24b** proceeds through a chairlike transition state having the starred carbon axial in the chairlike transition state. This situation is abnormal in acyclic rearrangements; however, the constraints of the ten-member ring require these circumstances.

An alternative analysis for the crossover process invokes two possible boatlike transition states for the Cope rearrangement of **8c** (TT) (Scheme IV); an identical argument can be made for **8d** (CT)). Conformation **8c′** leads to a transition state that provides the (*E*,*Z*)-1,5-cyclodecadienyl vinyl ether as conformation **24c**, which, by conformational inversion to **24b**, gives rise to **18** upon Claisen rearrangement. The other boatlike conformation, **8c″**, would be expected to provide a transition state energetically similar to that derived from **8c′** which gives rise to the (*Z*,*E*)-1,5-cyclodecadienyl vinyl ether **25**. The formation of the *E*,*E* isomer of **18** from **25** (if formed at all) must be slower than reversal to **24c** through **8c″**.

The invocation of boatlike transition states has been employed in rationalizing the stereochemistries of the elemols derived from thermolysis of the four isomeric hedycaryols.[30]

Another potent application of the tandem Cope-Claisen rearrangement lies in the vicinal appending of functionalized alkyl chains to carbocyclic rings. An appropriately designed system entails the creation and control of three contiguous asymmetric centers. Scheme V illustrates this principle. The Cope rearrangement of **26** would establish the relative configuration in **27** by way of a chair- or boatlike transition state. Subsequent Claisen rearrangement to **28** raises the question of relative stereochemistry at the asymmetric ring carbons. Four possible diastereomers can arise in this tandem rearrangement. Since a significant number of pseudoguaianolides exist of known stereochemistry, they would serve to confirm the course of the rearrangement by permitting the conveniently functionalized aldehyde **28b** to be transformed into one of these natural substances.

Our initial study in this area of the tandem Cope-Claisen rearrangement employed the prototypical substrate **26a**, which was expected to provide evidence concerning the stereochemical course of the Claisen rearrangement. The preparation of vinyl ether **26a** (Scheme VI) was readily achieved by employing keto ester **30a** as the starting material. Methylmagnesium bromide selectively added to the ketone function, providing diene **31a** upon dehydration; the exocyclic olefin could not be detected. Subsequent LiAlH$_4$ reduction and vinylation with ethyl vinyl ether in the presence of Hg(OAc)$_2$ provided vinyl ether **26a**.

Thermolysis of vinyl ether **26a** at 375 °C produced a 56/44 mixture of Cope-Claisen products **33**. Although at this juncture of our investigations we were unable to assign the relative stereochemistries of these isomers, subsequent correlation of the chemical shifts of the aldehyde proton and quarternary methyl group with isomers whose structures were to be rigorously proved demonstrated that there was a slight bias toward formation of **33a**. This result was as anticipated; the carbon-carbon-bond-forming step of the Claisen rearrangement should occur on the face of the cyclopentane ring remote from the propenyl chain. Since an improvement in stereoselectivity was desirable, the rearrangement was explored at substantially lower temperature. This goal was readily accomplished since the ester **31a**, when subjected to Cope rearrangement, afforded a favorable equilibrium mixture of **32a**/**31a** (19/1). The ester mixture was converted to vinyl ether **34**, which is the putative intermediate in the Cope-Claisen sequence. When the rearrangement of **34** was conducted at 182 °C, the same ratio of aldehydes was produced as was observed in the tandem rearrangement at 375 °C.[31] The lack of temperature dependence on $\Delta\Delta G^{\ddagger}$ for the formation of the two diastereomers in closely related systems is not unprecedented in sigmatropic rearrangements.[32]

In a related case, vinyl ether **35** underwent facile rearrangement to a single aldehyde **36**. However, the thermolysis had to be conducted with short contact times to avoid further transformation of the product to a number of unidentified byproducts, Conia products being a distinct possibility.

The lack of appreciable selectivity in the rearrangement of **26a** prompted consideration of the consequences of the thermolysis

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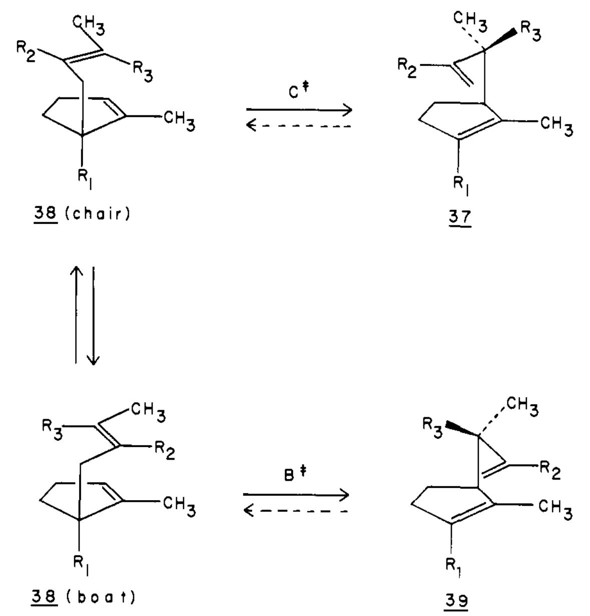
(29) (a) The disubstituted olefin is noted first. (b) Traynham, J. G.; Hirsh, H. H. *Tetrahedron Lett.* **1969**, 3905. Buemi, G.; Zuccarello, F.; Favini, G. *J. Mol. Struct.* **1974**, *21*, 41.

(30) Kodama, M.; Yokoo, S.; Matsuki, Y.; Ito, S. *Tetrahedron. Lett.* **1979**, 1687.

(31) Rearrangement of the ketene silyl acetal analogue of **34** gives ~1:1 ratio of isomers. Private communcation from G. Stork (Columbia).

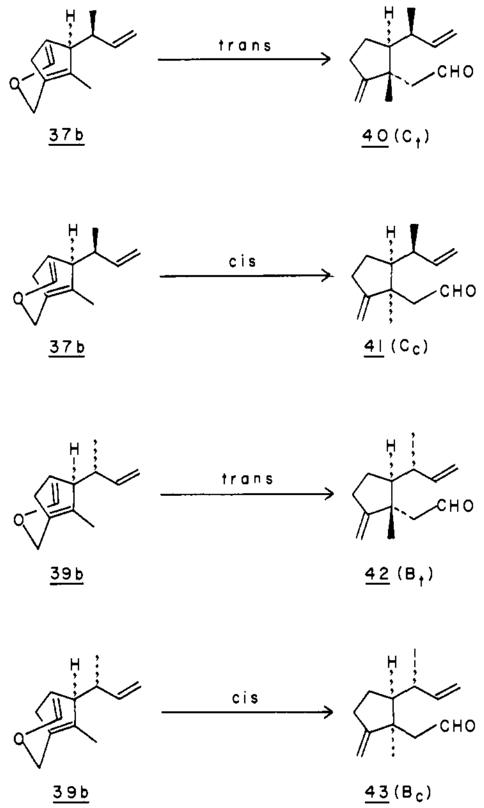
(32) Chan, K.-K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.

Scheme VII



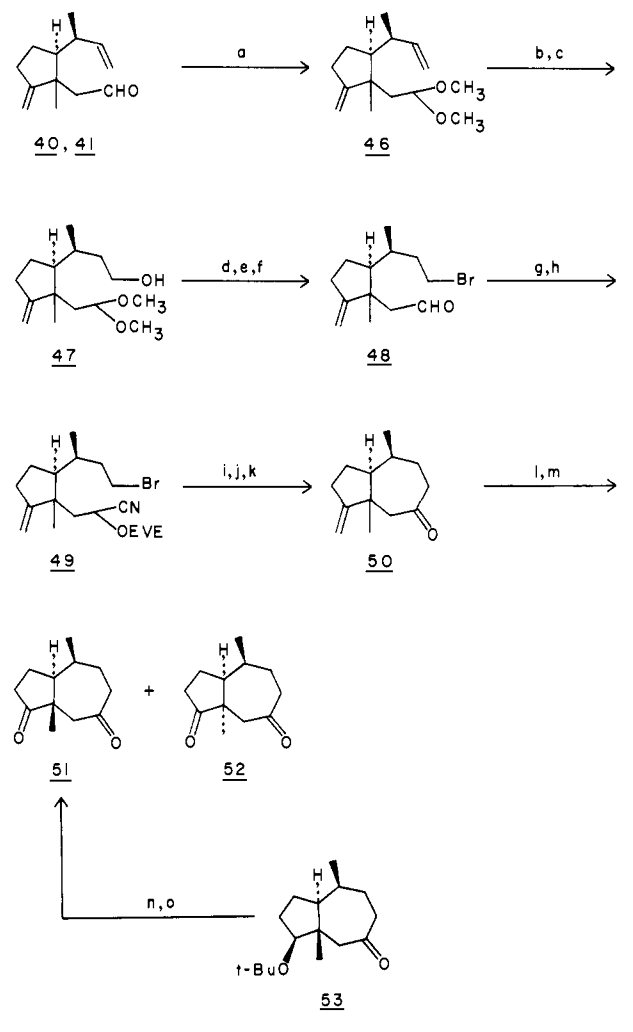
a, $R_1 = CO_2CH_3$, $R_2 = R_3 = H$; b, $R_1 = CH_2OCH{=}CH_2$, $R_2 = R_3 = H$, c, $R_1 = CO_2CH_3$, $R_2 = CH_3$, $R_3 = H$; d, $R_1 = CH_2OCH{=}CH_2$, $R_2 = CH_3$, $R_3 = H$; e, $R_1 = CH_2OCH{=}CH_2$, $R_2 = H$, $R_3 = CH_3$

Scheme VIII



of congener **26b** (**38b**). The Cope rearrangement of **26b** (**38b**) would introduce a new stereochemical problem since two diastereomers could arise in the initial rearrangement from either a chair- (C) or a boatlike (B) transition state (Scheme VII). Moreover, the Claisen rearrangement would be expected to be more selective toward a higher trans (t)/cis (c) ratio (acetaldehyde chain vs. 1-methyl-3-butenyl group) because of the secondary substitution pattern of the olefinic side chain. A total of four diastereomers could arise from such a rearrangement (Scheme VIII).

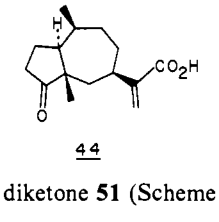
Scheme IX



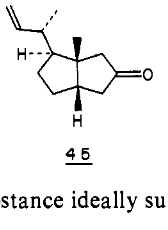
(a) HC(OCH$_3$)$_3$, CH$_3$OH, p-TsOH; (b) (sia)$_3$BH, THF; (c) H$_2$O$_2$, aq. NaOH; (d) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C; (e) LiBr, 2,6-lutidine, acetone, reflux; (f) AcOH, H$_2$O; (g) KCN, AcOH, C$_2$H$_5$OH; (h) C$_2$H$_5$OCH=CH$_2$, Et$_2$O, p-TsOH; (i) LDA, THF, $-78\ °C \rightarrow 25\ °C$; (j) H$_3O^+$; (k) aq. KOH; (l) O$_3$, AcOH, CH$_2Cl_2$, 0 °C; (m) DMS; (n) CF$_3CO_2$H; (o) CrO$_3$·C$_5H_5$N·HCl, CH$_2Cl_2$.

Vinyl ether **26b** (**38b**) was prepared by the same procedure as was described for the desmethyl analogue **26a**. Thermolysis of **26b** (**38b**) provided two Cope–Claisen products. The reaction showed a temperature dependence on the product ratio: 377 °C (70/30, 1.5 min), 306 °C (77/23), 30 min), and 257 °C (81/19, 337 min). The structures of these two isomers were proved by a detailed chemical analysis.

Lansbury and his co-workers[33] have synthesized damsinic acid **44** from **53**. In addition, the Buffalo group has converted ketone **53** into diketone **51** (Scheme IX), a substance ideally suited as



44



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[33] Lansbury, P. T.; Serelis, A. K. *Tetrahedron Lett.* **1978**, 1909. Lansbury, P. T.; Serelis, A. K.; Hengeveld, J. E.; Hangauer, D. G., Jr. *Tetrahedron* **1980**, *36*, 2701.

a relay to correlate the structures of the major and minor rearrangement products (**40**–**43**).

An efficient synthesis of diketone **51** appeared to be through intramolecular hydroacylation of olefins with tris(triphenylphosphin)rhodium(I) chloride (Wilkinson's catalyst). Since cyclopentanones have been formed from 4-pentenals bearing a monosubstituted double bond, the question became one of whether ring size or olefin substitution would dominate.[34] Unfortunately, the principal product of the reaction of the major isomer **40** (C_t) was cyclopentanone **45**; diketone **51** was not detected.

An 85/15 mixture of the two isomers (**40**/**41**) from the thermolysis of **26b** (**38b**) was transformed as outlined in Scheme IX to give an 85/15 mixture of two isomeric diketones **51** and **52**, respectively.[35] The identity of **51** prepared by the two routes was established by 270-MHz NMR, IR, and GC/MS. These data established the major isomer of the Cope–Claisen rearrangement of vinyl ether **26b** (**38b**) as aldehyde **40** (C_t). This stereochemistry requires the Cope rearrangement to proceed through a chairlike transition state followed by a Claisen rearrangement, which preferentially provides a trans relationship of the two side chains.

The identity of the minor diketone of Scheme IX was most reasonably assigned to structure **52** and ultimately derived from aldehyde **41** (C_c). The assignment could be inferred from the formation of **33a** and **33b**, wherein the diastereomeric differences were due to the Claisen rearrangement. This is a reasonable assumption since the lower activation energy Claisen rearrangement should trap any chairlike-transition-state Cope product. Proof that **41** (C_c) was indeed formed through a chairlike transition state required the independent generation of boatlike-transition-state Cope–Claisen products, namely, **42** (B_t) and/or **43** (B_c).

Thermolysis of ester **31b** (**38a**) at 266 °C rapidly established an equilibrium mixture of **31b** (**38a**) and **32b** (60/40). Structure **32b** was shown to be a mixture of diastereomers (**37a**/**39a**) whose ratio changed with time (235 °C, 6 h, 95/5; 266 °C, 0.5 h, 93/7; 266 °C, 1 h, 89/11; 263 °C 2 h, 82/18; 266 °C, 4 h, 75/25) as analyzed by the increase in the high-field methyl doublet (270 MHz) at δ 0.83 (**39a**) relative to the same signal in the spectrum of its isomer (**37a**) at δ 1.06. The new component was being formed through the intercedence of the higher energy boat transition state. No Z isomer of **38a** (**31b**) could be detected in the equilibrium mixture, thereby excluding reversal of **37a** through a boatlike transition state and **39a** through a chairlike transition state. Both of these situations would require a highly unfavorable axial methyl group in the transition state. Although the energy difference between diastereomers **37a** and **39a** should be negligible, it was not possible to reach a near 50/50 mixture because decomposition of the isomers occurred.

The 60/40 [**38a**/(**37a** + **39a**)] mixture of esters was reduced and vinylated to provide a 60/40 [**38b**/(**37b** + **39b**)] mixture of vinyl ethers, which was separable by gas chromatography. The major component consisted of the normal starting material of the Cope–Claisen rearrangement **38b** (**26b**) while the minor component was comprised of a 79/21 (**37b**/**39b**) mixture of the intermediate in the Cope–Claisen rearrangement and its diastereomer, respectively. Whereas Cope–Claisen rearrangement of **38b** (**26b**) provided an 85/15 mixture of two aldehydes whose protons were displayed as triplets att δ 9.67 and 9.72, respectively, the mixture of **37b** and **39b** (79/21), when subjected to Claisen rearrangement at 180 °C, produced a mixture of three detectable (NMR) aldehydes. Two of these aldehydes were those previously observed in the Cope–Claisen route while the third displayed its aldehyde proton as a doublet of doublets at δ 9.64. Irradiation of the NMR absorption of the CH_2 group adjacent to the aldehyde collapsed the δ 9.64 signal to a singlet. This new material must have ultimately arisen from a boatlike Cope rearrangement of **39b**. Since the side-chain stereochemistry of **37b** and **39b** should not appreciably influence the trans/cis ratio of the Claisen rearrangement, the new aldehyde should be **42** (B_t) while the minor component from the original Cope–Claisen rearrangement must be **41** (C_c). This analysis requires the nonreversal of vinyl ethers **37b** and **39b** to **38b** (**26b**) prior to their rearrangement to products. The lack of reversibility was confirmed in two ways. Vinyl ether **38b** (**26b**) did not undergo Cope–Claisen rearrangements at a detectable rate at 180 °C; thermolysis of **37b** and **39b** at 180 °C for only 2 h (38% conversion to products) showed the presence of the three aldehydes, the vinyl ethers **37b** and **39b**, and no retro-Cope product **38b** (**26b**).

If the rate of the Cope–Claisen rearrangement of **38b** (**26b**) were appreciable at 180 °C, the extrapolated (ln **40**/**41** vs. $1/T$) ratio of **40** (C_t)/**41** (C_c) would be 88/12. On the basis of the previously stated, reasonable assumption that the trans/cis ratio is not greatly affected by the side-chain stereochemistry, the calculated distribution of products **40** (C_t): **41** (C_c):**42** (B_t):**43** (B_c) should be 70 (88 × 79):9 (12 × 79):18 (88 × 21):3 (12 × 21). These values are in good agreement with the integrated NMR resonances of the aldehyde signals **40** (C_t, 67%), **41** (C_c, 14%), and 42 (B_t, 19%). The isomer **43** (B_c) was presumably formed but could not be detected by NMR or GC.

It is possible to effect Cope–Claisen rearrangements that generate dimethylamides as opposed to aldehydes. The alcohol formed by reduction of ester **31b** (**38a**) with $LiAlH_4$ was heated at 302 °C with dimethylacetamide dimethyl acetal to provide a 46% yield of a 75/25 mixture of the amides corresponding to aldehydes **40** (C_t) and **41** (C_c). The reactive (dimethylamino)methoxy ketene acetal intermediate can be formed under equilibrium conditions in the presence of generated methanol in a sealed tube to accomplish the rearrangement. It is necessary for the alcohol to bear no α-hydrogens, thereby avoiding an elimination reaction that is more facile than the Cope rearrangement.

The silyl ketene acetal Claisen rearrangement was found to be effective in this series.[26,27] The alcohol derived from ester **31b** (**38a**) by $LiAlH_4$ reduction was acetylated, followed by conversion of the acetate into its *tert*-butyldimethylsilyl ketene acetal. Thermolysis at 305 °C for 75 min afforded a mixture of products, which, upon hydrolysis with 75% aqueous acetic acid gave a 75/25 mixture of two acids in 60% yield. In analogy with the amide acetal rearrangement, the stereochemistries were assigned as the C_t and C_c isomers, respectively.

With a firm understanding of the stereochemical course of the tandem rearrangements of this general type, a study of the rearrangement of vinyl ether **26c** (**38d**) was undertaken. The anticipated major product from this rearrangement was expected to play an important role in the synthesis of pseudoguaianolides.

The general method employed thus far for the synthesis of this class of vinyl ethers was found wanting when applied to the preparation of **26c** (**38d**). The dehydration of the tertiary alcohol derived from methylmagnesium bromide addition to **30c** was complex; double-bond migration and lactonization were observed. An alternative method for the preparation of **31c** (**38c**) involved alkylation of β,γ-unsaturated ester **55**, which could be prepared by high-temperature thermolysis (540 °C, flow system, hexane) of the readily available cyclopropylacrylic ester **54** (Scheme X).[36]

Rearrangement of vinyl ether **26c** (**38d**) at 306 °C for 40 min afforded an 85% yield of aldehydes **56** and **57** in a 78/22 ratio, respectively. These structural assignments were made by comparison of the chemical shifts of the aldehyde and methyl protons of these isomers with those of the isomers **40** (C_t), **41** (C_c), and **42** (B_t). From these tabulated data, the major component from the rearrangement of **26c** (**38d**) could be assigned structure **56** (C_t).

Since the chairlike Cope transition state was the exclusive pathway in the rearrangement of **26b** (**38b**), it is less likely for the boatlike transition state **26c** (**38d**) to be operative because of 2,5-dimethyl interactions (bow–stern). In addition, thermolysis of ester **31c** (**38c**) at 266 °C showed the initial appearance of a

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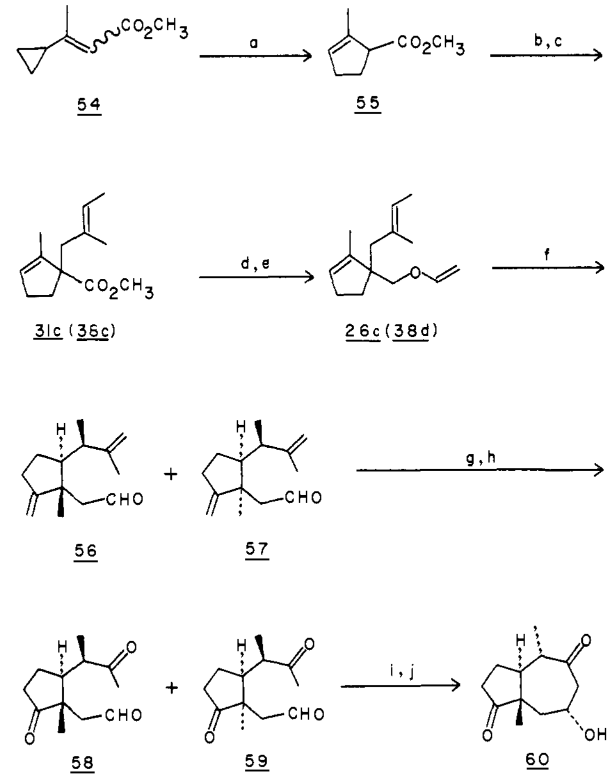
[34] Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287. Larock, R. C.; Oertle, K.; Potter, G. T. *J. Am. Chem. Soc.* **1980**, *102*, 190.

[35] In the strictest sense, an overall yield should be attained that does not permit the original major component to become the minor-product component due to a difference in reaction rate between the two isomers in one or more of the intervening steps.

[36] Jorgenson, M. J.; Leung, T. *J. Am. Chem. Soc.* **1968**, *90*, 3769.

Scheme X



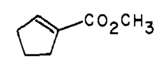
(a) 540 °C, hexane, flow system; (b) LDA, THF, -78 °C, (c) (E)-$(CH_3)CH{=}C(CH_3)CH_2Br$; (d) $LiAlH_4$, Et_2O; (e) $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$; (f) 306 °C, 40 minutes; (g) O_3, CH_3OH, CH_2Cl_2, -78 °C; (h) DMS; (i) KOH, H_2O, CH_3OH; (j) Chromatography.

methyl doublet at δ 1.04 in the NMR spectrum of **37c**, followed by the gradual formation of the boatlike-transition-state-product **39c** displaying a methyl doublet at δ 0.83. These observations are in agreement with the results obtained with ester **31b** (**38a**).

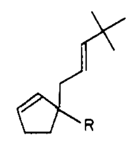
The diolefin **56** proved to be an important synthetic intermediate. The 78/22 mixture of diolefins **56** and **57** was ozonized to afford a mixture (79/21) of tricarbonyl compounds **58** and **59**. It was not necessary to separate the isomers at this point since exposure of the mixture to aqueous potassium hydroxide provided, after chromatography, the aldol product **60**. The Cope–Claisen route provides an alternative pathway to this substance, which has been prepared by a different sequence and converted to the pseudoguaianolides, aromatin and confertin.[37]

Vinyl ether **26d** (**38e**), prepared by the alkylation of ester **55** with 3-methyl-2-butenyl bromide followed by reduction and vinylation, when thermolyzed at 377 °C for 1.5 min, was only 46% converted to a mixture of nine products (GC), one of which was tentatively identified as the Cope–Claisen product. Higher temperatures resulted in extensive decomposition. The inability of this structural type to undergo facile rearrangement is apparent from the transition state for the Cope rearrangement that arises from chair conformation **38e** (**26d**). A 1,3-diaxial interaction between the vinylic methyl (R_3) and the ring methyl group severely retards the reaction.

The thermal rearrangement of vinyl ether **62c**, prepared by alkylation[9] of ester **61**[38] followed by reduction and vinylation, was investigated as a model study for a different synthetic program. Thermolysis of the vinyl ether at 375 °C for 1.5 min resulted in a mere 17% conversion to products. Two of the reaction products,



61



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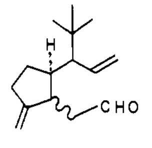
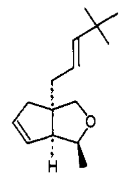
a, R = CO_2CH_3; b, R = CH_2OH; c, R = $CH_2OCH{=}CH_2$

on the basis of NMR analysis of a GC-collected sample, were determined to be aldehydes **63**, derived from the Cope–Claisen rearrangement. Under identical reaction conditions, **26b** (**38b**)



63



64

was totally converted to Cope–Claisen products. A third component of the reaction mixture was identified as the ene rearrangement product **64**. The similarity of the NMR spectrum of this substance with that of the vinyl ether **62c** was pronounced; the vinyl ether hydrogens had disappeared while a methyl doublet at δ 1.19 (J = 7 Hz) and a one-proton quintet at δ 3.89 (J = 7 Hz) appeared. The coupling constant of the δ 3.89 signal and preferred-transition-state analysis require the stereochemistry present in structure **64**. Since an ≈1/1 mixture of **63**/**64** was obtained, the *tert*-butyl group retards the Cope rearrangement step, allowing the ene process to proceed at a competitive rate.

When the rearrangement was conducted at 375 °C for 18 min, the starting material was completely consumed, although the Cope–Claisen-to-ene product ratio was 1/4. Since the two pathways are noninterconvertible, the Cope–Claisen product undergoes competitive decomposition during the duration of the experiment.

In conclusion, the Cope–Claisen rearrangement provides a method for executing Cope rearrangements that are thermodynamically unfavorable by way of an irreversible Claisen rearrangement. The resultant multiple functionality and stereochemical control hold promise for the application of this method to a variety of synthetic problems.

Experimental Section

The experimental section contains representative procedures for the preparation of intermediates in this study in addition to thermolysis procedures for significant products.

Ethyl 5-Methyl-2-vinyl-4-hexenoate (1a). To a solution containing 9.50 mL (67.8 mmol) of distilled diisopropylamine in 50 mL of dry THF at 0 °C (N_2) was added 27.5 mL of 2.4 M (66 mmol) *n*-BuLi in hexane. After 10 min, the mixture was cooled to −78 °C, and 13.0 mL (74.7 mmol) of dry HMPA was added. After another 30 min, 8.00 mL (4.4 mmol) of distilled ethyl crotonate was added dropwise, followed by, after 15 min, 12.2 g (81.9 mmol) of 3-methyl-2-butenyl bromide. The reaction mixture was quenched after 1.5 h with 10 mL of methanol. The mixture was warmed to 25 °C, water was added, and the mixture was extracted with ether. The organic layer was isolated and washed three times with 5% aqueous hydrochloric acid and three times with water. The combined aqueous portions were extracted three times with ether, and the combined extracts were subjected to standard workup. GC analysis (C, 100–150 °C) revealed the presence of several byproducts, which were removed by repeated distillation to give 7.81 g (66%) of ester **1a**: bp 39–44 °C (0.1 mmHg); IR (neat) 1729, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.91–5.76 (m, 1 H), 5.17–5.00 (m, 3 H), 4.13 (q, J = 7 Hz, 2 H), 3.01 (q, J = 7 Hz, 1 H), 2.52–2.17 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.24 (t, J = 7 Hz, 3 H). An analytical sample was isolated by GC.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.45; H, 9.98.

Cope Rearrangement of Ethyl 5-Methyl-2-vinyl-4-hexenoate (1a). Ethyl 5,5-Dimethyl-2,6-heptadienoate (2a). Ester **1a** (40 μL) was placed in a 20-mL pyrolysis tube, which was evacuated (≈0.2 mmHg), degassed, and sealed. The tube was heated at 262 ± 2 °C for 43 min, after which it was broken and its contents washed out with ether. GC analysis of the

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[37] Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *J. Am. Chem. Soc.*, preceding paper in this issue.

[38] Rhoads, S. J.; Chattopadhyay, J. K.; Walli, E. E. *J. Org. Chem.* **1970**, *35*, 3352.

product revealed the mixture to consist of 80% of the starting material **1a** along with 20% of another compound, which was isolated by GC and identified as ester **2a**: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.97–6.84 (m, 1 H), 5.86–5.74 (m, 2 H), 4.99–4.91 (m, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 2.18 (d, *J* = 7 Hz, 2 H), 1.29 (t, *J* = 7 Hz, 3 H), 1.03 (s, 6 H). Longer reaction times did not alter the product ratio.

5-Methyl-2-vinyl-4-hexen-1-ol (1b). To a suspension of 2.5 g (66.0 mmol) of LiAlH$_4$ in 40 mL of dry THF at 0 °C (N$_2$) was added dropwise 7.48 g (41.0 mmol) of ester **1a**. The reaction mixture was refluxed for 1 h, after which time it was cooled to 0 °C and quenched with a saturated aqueous solution of Na$_2$SO$_4$. Filtration, workup, and distillation gave 5.17 g (90%) of alcohol **1b**: IR (neat) 3350, 1638 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 5.73–5.59 (m, 1 H), 5.15–5.06 (m, 3 H), 3.59–3.53 (m, 1 H), 3.48–3.40 (m, 1 H), 2.45 (br s, 1 H), 2.29–1.91 (m, 3 H), 1.69 (s, 3 H), 1.60 (s, 3 H).

Anal. Calcd for C$_9$H$_{16}$O: C, 77.09; H, 11.50. Found: C, 77.02; H, 11.55.

5-Methyl-2-vinyl-4-hexen-1-yl Vinyl Ether (1c). A mixture of 2.70 g (19.3 mmol) of alcohol **1b** and 5.37 g (16.9 mmol) of Hg(OAc)$_2$ in 225 mL of freshly dried ethyl vinyl ether was refluxed for 21 h (N$_2$). The mixture was cooled to 25 °C, and 0.25 mL of glacial acetic acid was added. After being stirred for 4 h at 25 °C, the mixture was washed four times with 5% aqueous KOH. The aqueous portions were combined and extracted three times with ether. The combined organic phases were dried over Na$_2$SO$_4$, worked up, and distilled to give 2.46 g (77%) of vinyl ether **1c**: bp 33–34 °C (0.1 mmHg); IR (neat) 1637, 1611, 1204 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.46 (dd, *J* = 14, 7 Hz, 1 H), 5.80–5.66 (m, 1 H), 5.15–4.99 (m, 3 H), 4.15 (dd, *J* = 14, 2 Hz, 1 H), 3.96 (dd, *J* = 7, 2 Hz, 1 H), 3.60 (d, *J* = 6 Hz, 2 H), 2.49–2.35 (m, 1 H), 2.27–2.16 (m, 1 H), 2.11–2.02 (m, 1 H), 1.69 (s, 3 H), 1.60 (s, 3 H).

Anal. Calcd for C$_{11}$H$_{18}$O: C, 79.46; H, 10.92. Found: C, 79.46; H, 10.95.

Thermolysis of 5-Methyl-2-vinyl-4-hexen-1-yl Vinyl Ether (1c). A 500-mg sample of vinyl ether **1c** was prepared for thermolysis (vide supra). Analysis by GC revealed the presence of three products, which were separated by GC and identified as 5,5-dimethyl-3-vinyl-6-heptenal (**3**), 2,3,3-trimethyl-5-vinylcyclopentane-1-carboxaldehyde (**4**), and (*E*)-3,6,6-trimethyl-4,7-octadienal (**5**).

3: IR (CCl$_4$) 2710, 1726, 1638 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.65 (t, *J* = 2 Hz, 1 H), 5.84–5.63 (m, 2 H), 5.04–4.88 (m, 4 H), 2.79–2.68 (m, 1 H), 2.44–2.36 (m, 2 H), 1.53–1.33 (m, 2 H), 1.03 (s, 3 H), 1.02 (s, 3 H).

Anal. Calcd for C$_{11}$H$_{18}$O: C, 79.46; H, 10.92. Found: C, 79.23; H, 10.96.

4: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.80 (d, *J* = 3 Hz, 1 H), 5.82–5.67 (m, 1 H), 5.13–4.87 (m, 2 H), 3.23–3.05 (m, 1 H), 2.76–2.65 (m, 1 H), 2.14 (dd, *J* = 10, 8 Hz, 1 H), 1.79 (dd, *J* = 12, 8 Hz, 1 H), 1.53–1.33 (m, 1 H), 1.01 (s, 3 H), 0.97 (d, *J* = 8 Hz, 3 H), 0.82 (s, 3 H).

5: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.71 (br s, 1 H), 5.79 (dd, *J* = 18, 10 Hz, 1 H), 5.46 (d, *J* = 16 Hz, 1 H), 5.29 (dd, *J* = 16, 7 Hz, 1 H), 4.98–4.84 (m, 2 H), 2.80–2.67 (m, 1 H), 2.44–2.32 (m, 2 H), 1.10–1.02 (overlapping s and d, 9 H).

(1*R,2*R**,3*S**)-3-Isopropenyl-2-vinylcyclohex-1-yl Vinyl Ether (8c, TT).** A mixture of 159 mg (0.956 mmol) of alcohol **8a** and 877 mg (2.76 mmol) of recrystallized Hg(OAc)$_2$ in 16 mL of freshly dried and distilled ethyl vinyl ether was refluxed (N$_2$) for 21.5 h. The mixture was cooled to 25 °C, taken up in ether, and washed three times with 5% aqueous KOH. The aqueous portions were combined and extracted twice with pentane. The combined organic fractions were washed once with brine and worked up. Distillation (Kugelrohr, 60–70 °C, 0.05 mmHg) gave 147 mg (80%) of the vinyl ether as an oil: IR (CCl$_4$) 1644, 1632, 1607, 1193, 1179 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.28 (dd, *J* = 14, 7 Hz, 1 H), 5.56–5.41 (m, 1 H), 5.09–4.98 (m, 2 H), 4.72–4.65 (m, 2 H), 4.24 (dd, *J* = 14, 1.5 Hz, 1 H), 3.93 (dd, *J* = 7, 1.5 Hz, 1 H), 3.51 (td, *J* = 10, 4 Hz, 1 H), 2.20–1.22 (m, 8 H), 1.63 (br s, 3 H); GC/MS (70 eV), *m/e* (rel intensity) 192 (M$^+$, 0.6), 164 (10.6), 149 (26.7), 148 (22.9), 133 (15.1), 124 (11.2), 121 (12.7), 107 (47.9), 105 (18.0), 95 (58.3), 94 (12.3), 93 (86.4), 91 (42.5), 83 (11.5), 81 (100.0), 80 (25.5), 79 (74.9), 77 (31.8). An analytical sample was prepared by GC.

Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.20; H, 10.48. Found: C, 81.08; H, 10.50.

Thermolysis of the (1*RS*,2*RS*,3*SR*)-, (1*RS*,2*SR*,3*RS*)-, and (1*RS*,2*RS*,3*RS*)-3-Isopropenyl-2-vinylcyclohex-1-yl Vinyl Ethers (8c,TT; 8d,CT; and 9c,TC). (2*Z*,7*Z*)-8-Methyl-2,7-cyclodecadiene-1-acetaldehyde (18). A weighed amount (35–100 mg) of the designated vinyl ether was placed in a 20-mL pyrolysis tube and prepared (vide supra) for thermolysis. Thermolysis was conducted for the time and at the temperature specified in Tables I and II. The major individual products were isolated by GC and identified as (2*Z*,7*Z*)-8-methyl-2,7-cyclodecadiene-1-acetaldehyde (**18**), 3-isopropenyl-2-vinylcyclohex-1-ene (**19**), 3-ethylidene-4-isopropenylcyclohex-1-ene (**20**), and 1-methyl-4(or 5)-((*E*)-butadienyl)cyclohex-1-ene (**21**).

18: IR (neat) 2707, 1721, 748, 725 cm^{-1}, no absorption at 970 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.64 (t, *J* = 2 Hz, 1 H), 5.33 (td, *J* = 11, 4 Hz, 1 H), 5.13–4.97 (m, 2 H), 2.92–2.73 (m, 1 H), 2.60–2.12 (m, 3 H), 2.33 (dd, *J* = 7, 2 Hz, 2 H), 1.89–1.17 (m, 7 H), 1.69 (br s, 3 H); GC/MS (70 eV), *m/e* (rel intensity) 192 (M$^+$, 7.0), 149 (23.8), 140 (100.0), 133 (56.9), 124 (44.5), 109 (33.0), 107 (36.7), 105 (35.8), 95 (28.1), 93 (55.1), 91 (49.0), 81 (72.5), 80 (64.1), 79 (64.0).

Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.20; H, 10.48. Found: C, 81.13; H, 10.46.

Olefins **19** and **20** could not be separated from each other. Their individual NMR data were extracted from one NMR spectrum.

19: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.23 (dd, *J* = 18, 11 Hz, 1 H), 5.90 (t, *J* = 4 Hz, 1 H), 4.99 (d, *J* = 18 Hz, 1 H), 4.86 (d, *J* = 11 Hz, 1 H), 4.64 (br s, 1 H), 4.59 (br s, 1 H), 3.02–2.96 (m, 1 H), 2.18–1.49 (m, 6 H), 1.81 (br s, 3 H).

20: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.08 (d, *J* = 10 Hz, 1 H), 5.67–5.57 (m, 1 H), 5.45 (q, *J* = 7 Hz, 1 H), 4.85 (br s, 1 H), 4.81 (br s, 1 H), 3.27–3.20 (m, 1 H), 2.18–1.49 (m, 4 H), 1.81 (br s, 3 H), 1.60 (d, *J* = 7 Hz, 3 H).

19 and **20**: GC/MS (70 eV), *m/e* (rel intensity) 148 (M$^+$, 47.4), 133 (60.3), 119 (26.6), 106 (23.4), 105 (98.9), 91 (100.0), 79 (41.6), 77 (25.5).

21: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 6.41–6.24 (m, 1 H), 6.07 (dd, *J* = 15, 10 Hz, 1 H), 5.72 (dd, *J* = 15, 7 Hz, 1 H), 5.42–5.35 (m, 1 H), 5.11 (d, *J* = 17 Hz, 1 H), 4.98 (d, *J* = 10 Hz, 1 H), 2.39–1.23 (m, 7 H), 1.66 (br s, 3 H); GC/MS (70 eV), *m/e* (rel intensity) 148 (M$^+$, 26.2), 94 (61.9), 93 (10.5), 91 (16.0), 80 (82.5), 79 (100.0), 77 (14.7).

(1*RS*,5*RS*)- and (1*RS*,5*SR*)-5-(2′-Propen-1′-yl)-1-methyl-2-methylenecyclopentane-1-acetaldehyde (33a and 33b). Thermolysis of 99.8 mg (0.56 mmol) of vinyl ether **26a** was accomplished in a sealed tube (vide supra) at 375 ± 2 °C for 2 min. The product was distilled (Kugelrohr) to give 86.5 mg (87%) of a 56/44 ratio of aldehydes **33a** and **33b**, respectively: IR (CCl$_4$) 2725, 1719, 1638 cm^{-1}; ^{1}H NMR (CDCl$_3$, 90 MHz) 9.76–9.61 (2t, 1 H), 6.00–5.51 (m, 1 H), 5.16–4.74 (m, 4 H), 2.60–0.80 (m, 7 H), 2.44 (d, *J* = 3 Hz, 2 H), 1.22 (s, 1.32 H), 0.98 (s, 1.68 H); ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.69 (t, *J* = 3.3 Hz, 0.5 H), 9.66 (dd, *J* = 2.5, 2.4 Hz, 0.5 H); GC/MS (70 eV), *m/e* (rel intensity) 178 (M$^+$, 0.1), 134 (12.3), 119 (17.4), 107 (11.6), 95 (100.0), 93 (31.2), 91 (17.6), 79 (17.9), 77 (12.4).

Further confirmation of the structure of these aldehydes came from their LiAlH$_4$ derived alcohols. Reduction (LiAlH$_4$) of 84 mg of the aldehydes gave upon distillation (Kugelrohr, 125–130 °C, 0.03 mmHg) 60 mg (71%) of a 57/43 ratio (determined by NMR integration of the methyl singlets) of (1*RS*,5*RS*)- and (1*RS*,5*SR*)-2-[5′-(2″-propen-1″-yl)-1′-methyl-2′-methylenecyclopent-1′-yl]ethanol, respectively; IR (CCl$_4$) 3625, 1638 cm^{-1}; ^{1}H NMR (CDCl$_3$, 90 MHz) δ 6.04–5.51 (m, 1 H), 5.17–4.71 (m, 4 H), 3.65 (t, *J* = 7 Hz, 2 H), 2.60–0.98 (m, 7 H), 1.75 (t, *J* = 7 Hz, 2 H), 1.08 (s, 1.30 H), 0.89 (s, 1.70 H). An analytical sample of the mixture was prepared by GC.

Anal. Calcd for C$_{12}$H$_{20}$O: C, 79.94; H, 11.18. Found: C, 79.69; H, 11.18.

(1*RS*,5*RS*,3′*RS*)- and (1*RS*,5*SR*,3′*SR*)-5-(1′-Buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetaldehyde (40, C$_t$ and 41, C$_c$). The vinyl ether **26b** (613 mg, 3.19 mmol) was placed in a 120-mL pyrolysis tube and prepared as described. The tube was heated at 308 ± 2 °C for 45 min. Distillation (Kugelrohr, 80–85 °C, 0.03 mmHg) gave 500 mg (82%) of a 84/16 ratio of aldehydes **40** and **41**, respectively: IR (CCl$_4$) 2725, 1718, 1646 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.72 (t, *J* = 3.0 Hz, 0.16 H), 9.67 (t, *J* = 3.0 Hz, 0.84 H), 5.78–5.62 (m, 1 H), 5.00–4.77 (m, 4 H), 2.60 (d, *J* = 3.0 Hz, 1.68 H), 2.52–2.16 (m, 3.32 H), 1.88–1.30 (m, 3 H), 1.31 (s, 0.48 H), 1.08 (s, 2.52 H), 1.10 (d, *J* = 7.0 Hz, 0.48 H), 1.07 (d, *J* = 7.0 Hz, 2.52 H); GC/MS (70 eV), *m/e* (rel intensity 192 (M$^+$, 0.3), 133 (14.2), 107 (14.9), 105 (10.2), 95 (100.0), 94 (11.7), 93 (37.3), 91 (26.1), 81 (16.6), 79 (22.7), 77 (21.9), 67 (20.1), 55 (14.4). An analytical sample of the mixture was prepared by GC.

Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.20; H, 10.48. Found: C, 80.99; H, 10.33.

The isomer **40** could be enriched by HPLC. The fractions containing the major isomer were combined, concentrated in vacuo, and distilled (Kugelrohr, 65–70 °C, 0.01 mmHg) to give 95% pure **40**: IR (CCl$_4$) 2720, 1719, 1636 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.67 (t, *J* = 3.0 Hz, 1 H), 5.78–5.64 (m, 1 H), 5.00–4.77 (m, 4 H), 2.59 (d, *J* = 3.0 Hz, 2 H), 2.53–2.15 (m, 3 H), 1.86–1.30 (m, 3 H), 1.08 (s, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H).

Methyl (3*RS*,3′*RS*)- and (3*RS*,3′*SR*)-3-(1′-Buten-3′-yl)-2-methyl-1-cyclopentene-1-carboxylate (37a and 39a). Ester **31b** (1.148 g, 5.91 mmol) was placed in each of two 120-mL pyrolysis tubes, which were subsequently evacuated (≈0.2 mmHg), degassed, and sealed. The tubes were then heated at 266 ± 2 °C for 2 h. The tubes were cooled to 25 °C and their contents washed out with ether. The combined extracts were concentrated in vacuo and distilled to give 1.81 g (79%) of a product that gave rise to two peaks on GC in the ratio of 60/40. The constituents of each peak were isolated via GC. The major peak was shown to be starting material. The minor peak consisted of an 83/17 mixture (determined by NMR integration of their methyl doublets at δ 1.06 and 0.83, respectively) of esters **37a** and **39a**, respectively: IR (CCl$_4$) 1714, 1645 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 5.91–5.77 (m, 0.17 H), 5.75–5.60 (m, 0.83 H), 5.08–4.93 (m, 2 H), 3.73 (s, 0.50 H), 3.71 (s, 2.50 H), 2.88–2.44 (m, 4 H), 2.08 (br s, 3 H), 1.92–1.75 (m, 1 H), 1.68–1.54 (m, 1 H), 1.06 (d, J = 7 Hz, 2.50 H), 0.83 (d, J = 7 Hz, 0.50 H). An analytical sample of **37a** and **39a** was prepared by GC.

Anal. Calcd for C$_{12}$H$_{18}$O$_2$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.16.

Claisen Rearrangement of (3*RS*,3′*RS*)- and (3*RS*,3′*SR*)-1-[3-(1′-Buten-3′-yl)-2-methyl-1-cyclopenten-1-yl]methyl Vinyl Ether (37b and 39b). (1*RS*,5*RS*,3′*RS*)-, (1*RS*,5*SR*,3′*SR*)-, and (1*RS*,5*RS*,3′*SR*)-5-(1′-Buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetaldehydes (40,C$_t$; 41,C$_c$; and 42,B$_t$). The vinyl ethers **37b** and **39b** (79/21), respectively) (9.7 mg) were heated at 180 ± 10 °C for 14.3 h as described. The product was shown by its NMR spectrum to consist of three aldehydes, which were integrated at their aldehyde resonances to determine their relative amounts. They were identified as the previously observed aldehydes **40** (C$_t$, 67%) and **41** (C$_c$, 14%). The third aldehyde was assigned as (1*RS*,5*RS*,3′*SR*)-5-(1′-buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetaldehyde (**42**, B$_t$, 19%). These isomers could not be separated by GC but were distilled (Kugelrohr, 125–130 °C, 0.04 mmHg) to give 8.6 mg (89%) of the mixture of isomers: IR (CCl$_4$) 2732, 1722, 1649, 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.72 (t, J = 3.0 Hz, 0.14 H), 9.67 (t, J = 3.0 Hz, 0.67 H), 9.64 (dd, J = 4.0, 2.0 Hz, 0.19 H), 5.78–5.60 (m, 1 H), 5.05–4.77 (m, 4 H), 2.75 (dd, J = 16.0, 4.0 Hz, 0.19 H), 2.60 (d, J = 3.0 Hz, 1.34 H), 2.57–2.16 (m, 3.47 H), 1.98–1.28 (m, 3 H), 1.31 (s, 0.42 H), 1.08 (s, 2.01 H), 1.02 (s, 0.57 H), 1.10 (d, J = 7.0 Hz, 0.42 H), 1.07 (d, J = 7.0 Hz, 2.01 H), 0.99 (d, J = 7.0 Hz, 0.57 H); GC/MS (70 eV), *m/e* (rel intensity) 192 (M, 0.2), 133 (13.3), 107 (14.7), 95 (100.0), 94 (11.1), 93 (36.5), 91 (25.8), 81 (16.4), 79 (23.7), 77 (22.9), 67 (22.4), 55 (15.9), 53 (10.2). An analytical sample of the mixture was prepared by GC.

Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.20; H, 10.48. Found: C, 81.31; H, 10.33.

(1*RS*,5*RS*,3′*RS*)- and (1*RS*,5*SR*,3′*SR*)-*N*,*N*-Dimethyl-5-(1′-buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetamide. A mixture of the alcohol, 1-[(*E*)-2′-buten-1′-yl]-1-hydroxymethyl-2-methyl-2-cyclopentene (81 mg, 0.49 mmol), and 165 mg (1.24 mmol) of 1,1-dimethoxy-1-(dimethylamino)ethane was heated at 302 ± 2 °C for 1 h as described. After the tube was cooled to 25 °C, it was broken and the contents were dissolved in ether. The ether solution was washed four times with 5% aqueous hydrochloric acid, one with a saturated solution of NaHCO$_3$, and once with brine and subjected to a standard workup. Distillation (Kugelrohr, 145–150 °C, 0.01 mmHg) gave 53 mg (46%) of a 75/25 mixture of (1*RS*,5*RS*,3′*RS*)- and (1*RS*,5*SR*,3′*SR*)-*N*,*N*-dimethyl-5-(1′-buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetamide, respectively: IR (CCl$_4$) 1649 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 5.78–5.62 (m, 1 H), 4.97–4.57 (m, 4 H), 3.00 (s, 3 H), 2.91 (s, 3 H), 2.65–1.10 (m, 8 H), 1.35 (s, 0.75 H), 1.08 (s, 2.25 H), 1.10 (d, J = 7 Hz, 0.75 H), 1.06 (d, J = 7 Hz, 2.25 H); GC/MS (70 eV), *m/e* (rel intensity) 235 (M$^+$, 3.2), 180 (18.4), 149 (27.0), 133 (12.4), 107 (15.3), 93 (22.2), 91 (20.3), 88 (13.6), 87 (100.0), 79 (22.2), 77 (18.9), 72 (96.8), 55 (16.6).

(1*RS*,5*RS*,3′*SR*)- and (1*RS*,5*SR*,3′*RS*)-5-(2′-Methyl-1′-buten-3′-yl)-1-methyl-2-methylenecyclopentane-1-acetaldehydes (56 (C$_t$) and 57 (C$_c$)). Vinyl ether **26c** was heated at 306 ± 2 °C for 40 min. Distillation (Kugelrohr, 95–100 sC, 0.05 mmHg) gave 754 mg (85%) of a 78/22 mixture (GC) of the aldehydes: IR (CCl$_4$) 2732, 1723, 1645 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.72 (t, J = 3.0 Hz, 0.22 H), 9.67 (t, J = 3.0 Hz, 0.78 H), 5.03–4.57 (m, 4 H), 2.67 (d, J = 3.0 Hz, 1.56 H), 2.56–2.10 (m, 3.44 H), 1.88–1.15 (m, 3 H), 1.63 (br s, 3 H), 1.36 (s, 0.66 H), 1.06 (s, 2.34 H), 1.13 (d, J = 7.0 Hz, 0.66 H), 1.09 (d, J = 7.0 Hz, 2.34 H). An analytical sample of the mixture was prepared by chromatography (Florisil, pentane → ether).

Anal. Calcd for C$_{14}$H$_{22}$O: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.79.

Thermolysis of Vinyl Ether 62c. 5-(2′,2′-Dimethyl-4′-penten-3′-yl)-2-methylenecyclopentane-1-acetaldehydes (63) and (1*RS*,4*SR*,5*SR*)-4-Methyl-1-[(*E*)-4′,4′-dimethyl-2′-penten-1′-yl]-3-oxabicyclo[3.3.0]oct-6-ene (64). A weighed amount of vinyl ether **62c** was heated as described for the specified time at 375 ± 2 °C. The ratio of the products was determined by GC. The products were isolated by GC collection.

63: IR (CCl$_4$) 2719, 1727 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 9.79 (t, J = 2 Hz, 1 H), 5.83–5.68 (m, 1 H), 5.17–4.70 (m, 4 H), 2.70–1.39 (m, 9 H), 0.90 and 0.89 (2 s, 9 H); GC/MS (70 eV), *m/e* (rel intensity) 220 (M$^+$, 1.6), 176 (31.7), 164 (14.8), 149 (17.7), 146 (14.5), 135 (12.1), 131 (30.7), 123 (36.9), 122 (19.0), 121 (24.7), 120 (100.0), 119 (18.2), 118 (10.2), 117 (17.2), 107 (16.7), 105 (34.5), 95 (24.7), 94 (36.5), 93 (28.8), 92 (14.4), 91 (34.2), 81 (41.5), 80 (17.9), 79 (45.3), 77 (24.7).

64: IR (CCl$_4$) no carbonyls; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 5.75–5.69 (m, 1 H), 5.57–5.47 (m, 2 H), 5.26 (dt, J = 15, 7 Hz, 1 H), 3.89 (quin, J = 7 Hz, 1 H), 3.71 (d, J = 9 Hz, 1 H), 3.54 (d, J = 9 Hz, 1 H), 2.86–2.79 (m, 1 H), 2.50–2.17 (m, 4 H), 1.19 (d, J = 7 Hz, 3 H), 0.99 (s, 9 H); GC/MS (70 eV), *m/e* (rel intensity) 220 (M$^+$, 8.8), 133 (12.5), 122 (27.6), 121 (21.7), 120 (17.5), 119 (16.0), 105 (14.8), 98 (10.2), 93 (10.0), 92 (17.0), 91 (25.0), 83 (32.4), 80 (10.5), 79 (100.0), 78 (16.5), 77 (31.4).

An analytical sample of the mixture (80/20 ratio of **64/63**, respectively) was prepared by GC.

Anal. Calcd for C$_{15}$H$_{24}$O: C, 81.76; H, 10.98. Found: C, 81.65; H, 11.04.

wt of starting material, mg	time, min	temp, °C	product ratio (GC) of **62c/63/64**	distilled yield, %
39	1.5	375	83/9/8	
50	9	376	21/31/48	60
34	12	375	17/25/58	
73	18	376	0/20/80	55

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Supplementary Material Available: Additional experimental details are available (22 pages). Ordering information is given on any current masthead page.