Structural Effects on [1,5]-Sigmatropic Hydrogen Shifts of Vinylallenes

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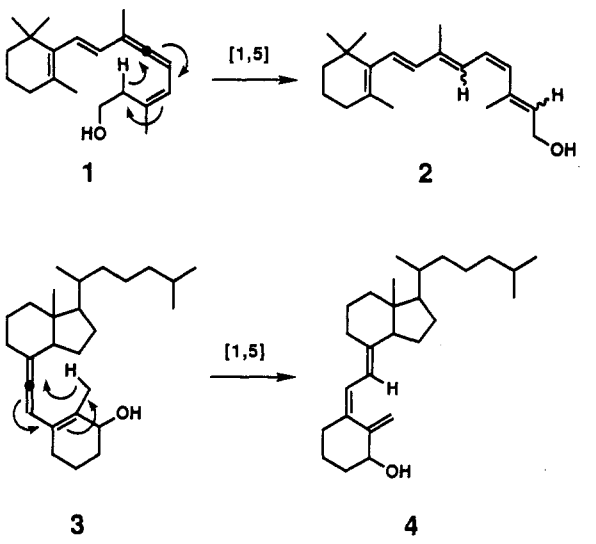
This study was directed toward developing a more quantitative understanding of ring size and sulfoxide anti-directing effects on the reactivity profile and/or stereochemical course of [1,5]-sigmatropic hydrogen shifts of vinylallenes. Regarding ring size effects, vinylallenes **13a–c** were synthesized and subjected to kinetic studies. The results were not in simple agreement with an earlier prediction from this laboratory that the ring size which influences the migrating hydrogen trajectory distance is the primary determinant in the rate of vinylallene isomerization to hexatrienes. It is apparent that additional factors such as ring strain have to be taken into account. Regarding substituent effects on the π-facial stereochemical course of [1,5]–shifts, vinylallenes with various terminal allenic substituents were studied and it is concluded that the anti–directing effect imparted by a sulfoxide group and enhancement of this effect by a geminal alkyl substituent are general. Of all the substituents studied previously and in this investigation (alkyl, sulfide, sulfoxide, sulfone, phosphine oxide, phosphonate, and carbonyl), the sulfoxide remains the only substituent which imparts significant π-facial selectivity.

Introduction

The thermally induced [1,5]-sigmatropic hydrogen shift[1] of vinylallenes[2] of the retinoid (vitamin A) and calciferol (vitamin D) types, **1** and **3**, respectively, has been demonstrated by this laboratory to be useful for synthesizing polyenes such as 11-*cis*-vitamin A isomers **2**[3] and vitamin D analogue **4**[4] (Scheme I). In light of the utility of vinylallenes in these syntheses, there is continuing interest in this laboratory to glean detailed information regarding quantitative structure–reactivity patterns in pericyclic processes involving allenes. In this manner, the versatility of allenes in other synthetic ventures could be more effectively realized.[5,6] This investigation concerns two structural effects characteristic of [1,5]–sigmatropic shifts: ring size effects[7,8] and the effects of a wider variety of allenyl substituents than heretofore examined in influencing the π-facial course of [1,5]–shifts of vinylallenes.[2b,c]

Scheme I



1 **2** **3** **4**

Table I. Results for the Thermal Rearrangement of Vinylallenes 10 at 40.0 °C

10	X	R	$\tau_{1/2}$, min	12/11
a	S(O)Ph	H	104	82/18
b	S(O)Ph	Me	147	92/8
c	S(O)Ph	Et	112	92/8
d	S(O)Ph	*i*-Pr	110	93/7
e	S(O)Ph	*t*-Bu	138	>98/2
f	*t*-Bu	H	6800	39/61
g	SPh	H	123	50/50
h	$S(O)_2Ph$	H	7	53/47

During studies of the syntheses of vitamin D analogues via [1,5]–hydrogen shifts, it was discovered that the thermal conditions needed to induce the [1,5]-hydrogen shift of the precursor vinylallenes were sensitive to A-ring size (Scheme II), cf., **5a–c**.[7] A dilute solution of the seven-membered A-ring vinylallene **5c** in isooctane was completely converted to products in 3 h at 100 °C.[7d] Under the same conditions, the corresponding six-membered ring

(1) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781. (b) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (c) Frey, H. M.; Walsh, R. *Chem. Rev.* **1969**, *69*, 103. (d) Gajewski, J. J. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 4, pp 1–54. (e) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic: New York, 1981.

(2) (a) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81 and references cited therein. (b) Shen, G.-Y.; Tapia, R.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 7499. (c) Okamura, W. H.; Shen, G.-Y.; Tapia, R. *J. Am. Chem. Soc.* **1986**, *108*, 5018. See also: (d) Skattebøl, L. *Tetrahedron* **1969**, *25*, 4933. (e) Heimgartner, H.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2924. (f) Crowley, K. J. *Proc. Chem. Soc.* **1964**, 17. (g) Crowley, K. J. *J. Org. Chem.* **1968**, *33*, 3679. (h) Minter, D. E.; Fonken, G. J.; Cook, F. T. *Tetrahedron lett.* **1979**, 711. (i) van Koeveringe, J. A.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 80. (j) Havinga, E. *Experientia* **1973**, *29*, 1181. (k) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459. (l) Mikolajczak, K. L.; Bagby, M. O.; Bates, R. B.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 2983.

(3) For a recent application in the vitamin A series, see: Shen, G.-Y.; de Lera, A. R.; Norman, T. C.; Haces, A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 2917 and references cited.

(4) For a recent vitamin D application, see: Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072 and references cited.

(5) Besides reference 2a, see: (a) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717. (b) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, *1*, 1. (c) Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034. (d) Elnagar, H. Y.; Okamura, W. H. *J. Org. Chem.* **1988**, *53*, 3060. (e) Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. (f) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487.

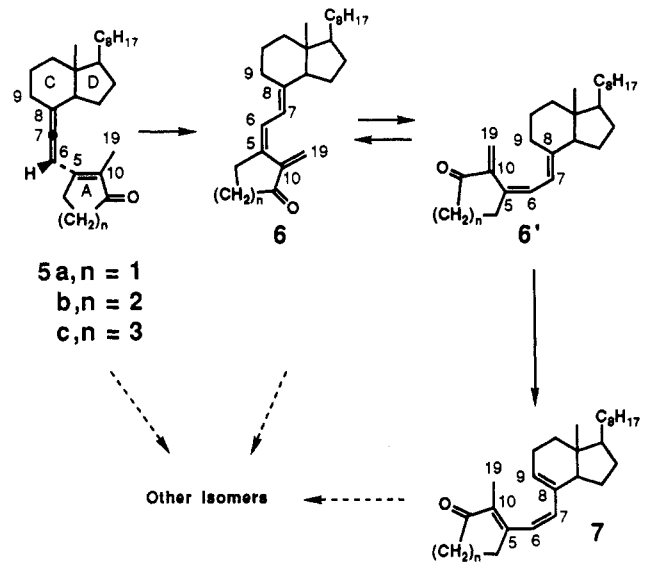
(6) For a recent example pertinent to the mechanism of cis–trans olefin isomerization, see: Palenzuela, J. A.; Elnagar, H. Y.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 1770.

(7) Ring-size effects in the vitamin D series: (a) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 5197. (b) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (c) Barrack, S. A.; Okamura, W. H. *J. Org. Chem.* **1986**, *51*, 3201. (d) Gerdes, J. M.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 4030.

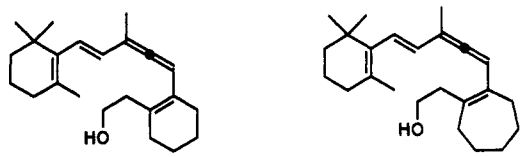
(8) Ring size effects in the vitamin A series: (a) Chandraratna, R. A. S.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6114. (b) Chandraratna, R. A. S.; Bayerque, A. L.; Okamura, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 3588. (c) Silveira, M. H.; Okamura, W. H. *J. Org. Chem.* **1985**, *50*, 2390.

0022-3263/90/1955-4381$02.50/0

Scheme II



vinylallene **5b** required 20 h.[7b,c] Finally, the five-membered ring analogue **5a** required considerably harsher conditions (24 h at 140 °C),[7a] but in this latter case, presumably because of the higher temperature required, other modes of isomerization became dominant. This reactivity trend was also observed for the vitamin A type vinylallenes 8 and 9.[8] The six-membered ring-fused vinylallene 8 was com-



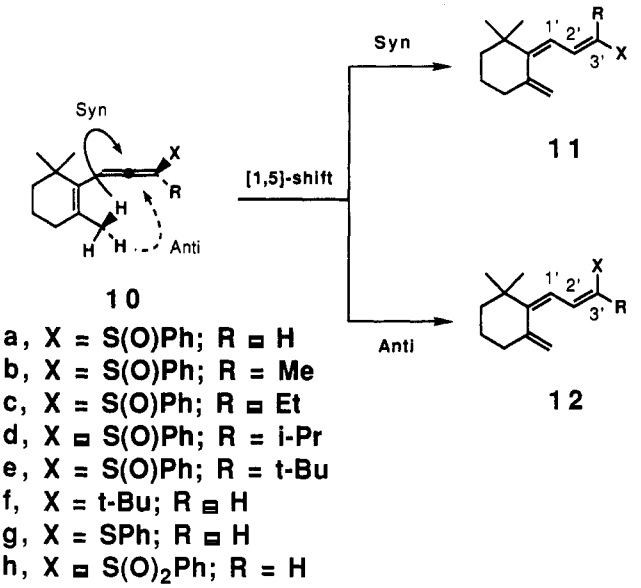
8 **9**

pletely isomerized via a [1,5]-shift at 69 °C in 4 h,[8a] but the thermal threshold for the same process for the seven-membered ring analogue **9** was much lower.[8b,c] The isomerization reaction of the latter substrate was observed to proceed even at room temperature!

The fact that the rate of thermal [1,5]-hydrogen shift follows the order seven-membered ring vinylallene > six-membered ring analogue > five-membered ring compound was attributed[7-9] to the increase in the distances between the migrating hydrogen termini (i.e., the C_{19}–C_7 distance for **5** in Scheme II). For simplicity, the C_{19}–C_7 distances (steroid numbering) were estimated using appropriate bond angle corrected Dreiding models assuming that a planar 5,6-s-cis conformation of vinylallenes **5** is involved.[9] These distances were measured to be 2.9, 2.6, and 2.4 Å for **5a**, **5b**, and **5c**, respectively. This ring size effect hypothesis, wherein the shorter trajectory facilitates the [1,5]-shift, offers a simple explanation for the qualitative trend in reactivity (7 > 6 > 5). An objective of this study was to quantitatively assess this hypothesis.

The [1,5]-sigmatropic shifts of vinylallenes have already been subjected to a limited set of substituent effect studies in this laboratory (Scheme III).[2b,c] In one such study, it was found that a sulfoxide substituent, but not simple alkyl groups, exerts a pronounced anti-directing effect on the hydrogen migrating trajectory (Table I). When the vinylallenes **10a–e** were warmed, the triene sulfoxides **12a–e**,

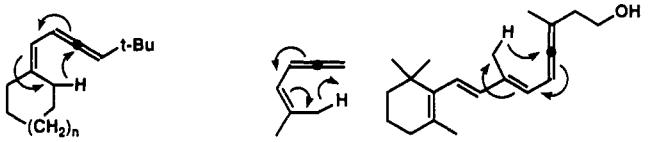
Scheme III



respectively, were the major products obtained with the hydrogen migrating anti to the sulfoxide substituent. An alkyl group geminal to the sulfoxide substituent can enhance this anti-directing effect, but alkyl groups alone have minimal effects. Further evaluation of the generality of the observed sulfoxide anti-directing effect and the ability of geminal alkyl substituents to enhance or attenuate the anti-directing effect was another objective of this study. Included in this study was a search for other substituents which might be capable of affecting the π-facial course of [1,5]-shifts.

Results and Discussion

Ring-Size Effects. Vinylallenes bearing various ring sizes such as **13** were selected for study in order to broaden the scope of the kinds of vinylallene substitution patterns subjected to mechanistic scrutiny. Previously, in connection with ring-size effects, only systems bearing an endocyclic orientation of the vinyl portion of the vinylallene unit had been studied in this laboratory in terms of [1,5]-sigmatropic shifts. For example, vitamin D based systems **5a–c**[7] (Scheme II) and retinoid derivatives **8** and **9**[8] bear on ring-size effects. Only Skattebøl's acyclic system **14**[2d] and the vitamin A systems **1**[2a] and **15**[10] of this laboratory represent vinylallenes not possessing a ring-fused π-framework.



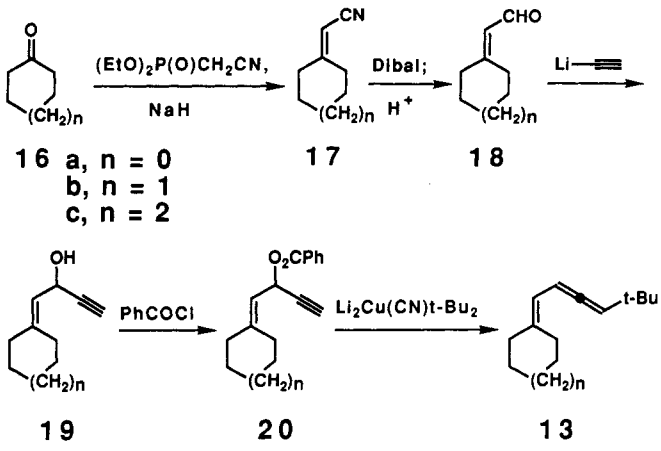
13 a, n = 0; b, n = 1; c, n = 2 **14** **15**

For the synthesis of **13** (Scheme IV), treatment of **16** with the sodium salt of diethyl (cyanomethyl)phosphonate afforded nitrile **17** (**a**, 89%; **b**, 92%; **c**, 91%),[11] which was reduced with diisobutylaluminum hydride (Dibal) followed by acid workup to give aldehyde **18** (**a**, 36%; **b**, 58%; **c**,

(9) Dr. Alberto Haces of this laboratory is acknowledged for first suggesting the distance effect rationale. For further discussion, see reference 16 below and the accompanying text.

(10) Sueiras, J.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6255.
(11) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.

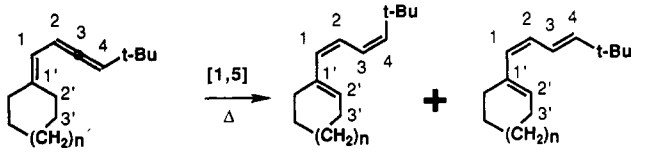
Scheme IV



16 a, n = 0
b, n = 1
c, n = 2

17 18 19 20 13

Scheme V



13 a, n = 0
b, n = 1
c, n = 2

21 22

Table II. Summary of the Results for the Thermal Rearrangement of Vinylallene 13 to Trienes 21 and 22 at 68.3 °C

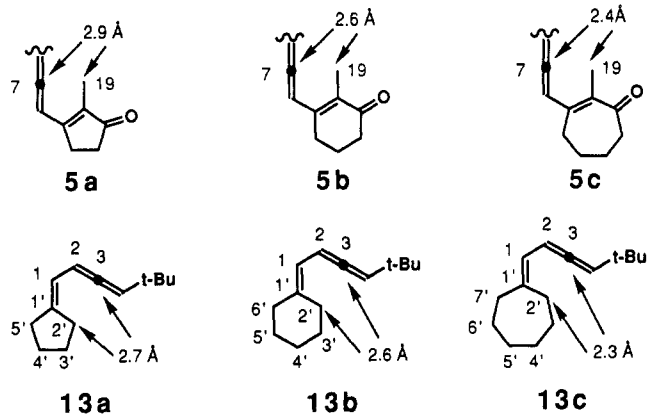
	$k \times 10^6$,[a] s^{-1}	$\tau_{1/2}$,[a] min	22/21[a]
13a	86.9 ± 1.3	133 ± 2	1.21 ± 0.05
13b	6.36 ± 0.20	1820 ± 60	1.82 ± 0.08
13c	400 ± 11	28.9 ± 0.8	1.99 ± 0.09

[a] The uncertainties are standard deviations (calculated from three independent runs).

89%).[12] Coupling of the aldehyde **18** with lithium acetylide[13] generated propargyl alcohol **19** (**a**, 72%; **b**, 96%; **c**, ~100%), which was treated with benzoyl chloride to furnish propargyl benzoate **20** (**a**, 97%; **b**, 92%; **c**, 92%). Finally, the desired vinylallene **13** was obtained in good yield (**a**, ~100%; **b**, ~100%; **c**, 78%) simply by treatment of the benzoate **20** with an ethereal solution of the Lipshutz type higher order mixed organocuprate reagent[3,14] dilithium di-*tert*-butylcyanocuprate at −78 °C. These vinylallenes were then subjected to thermally induced [1,5]-sigmatropic hydrogen migrations to yield trienes **21** and **22** (Scheme V), which were characterized individually after purification.

With *tert*-butylvinylallenes **13a–c** in hand, their thermally induced [1,5]-sigmatropic hydrogen shifts were studied kinetically (68.3 °C, benzene-d_6, ^{1}H NMR analyses)[15] in order to assess the relative reactivity of the substrates with one another (ring-size effect) as compared to the similarly substituted **10f** (Scheme III and Table I).

Chart I



From earlier investigations, it was shown that **10f** rearranged irreversibly to **11f** plus **12f** with $\tau_{1/2}$ ~275 min at 68.3 °C in benzene-d_6.[2b,c]

The rearrangement of **13** was followed by monitoring the signals assigned to the *tert*-butyl groups of starting vinylallene **13** and triene products **21** and **22**. ^{1}H NMR peak areas were determined by the cut and weigh method, and then the mole fraction of starting material remaining at various time intervals was computed. Assuming an irreversible first-order rate law, the kinetic results from three independent runs for each vinylallene could be obtained as summarized in Table II. The individual trienes **21** and **22** were found to be stable to the conditions of the kinetic experiments.[6]

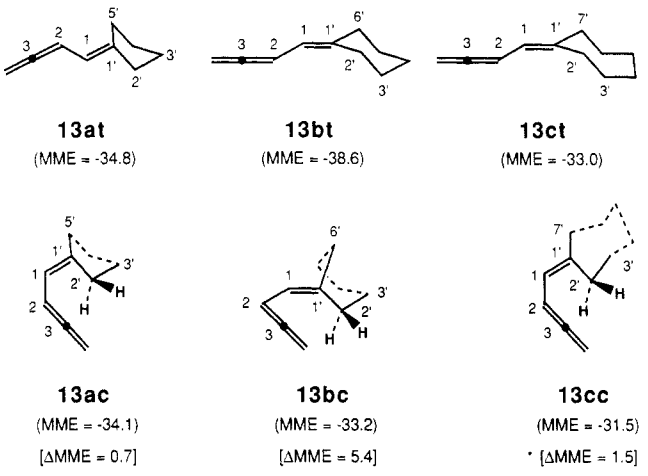
As indicated earlier, it has been qualitatively observed that the seven-membered ring vinylallene **5c** rearranges via a [1,5]-hydrogen shift faster than the six-membered ring derivative **5b**, which in turn rearranges faster than the five-membered ring compound **5a**.[7] It was reasoned that the shorter C_{19}–C_7 distance of 2.4 Å for **5c** rendered this substance the most reactive. The longer corresponding distances for **5b** (2.6 Å) and **5a** (2.9 Å) then accounts for their slower reaction rates.[9] Based on the distances measured for vinylallenes **13a–c** from bond angle corrected Dreiding models as shown in Chart I, one would expect that vinylallene **13c** (C_2–C_3 distance of 2.3 Å) should exhibit a faster isomerization rate than **13b** (2.6 Å) and that the latter should rearrange at a rate similar to **13a** (2.7 Å). The observation (Table II) that the seven-membered ring vinylallene **13c** rearranged 63 times faster than the six-membered ring vinylallene **13b** is in agreement with the distance effect hypothesis. However, that the five-membered ring vinylallene **13a** rearranged 14 times faster than the six-membered ring vinylallene **13b** is not consistent with this prediction.

This reactivity order however may be rationalized in the following way. It is proposed that although the distance effect hypothesis is valid (i.e., the reactivity order should be **13c** > **13b** ≈ **13a**), the rate of rearrangement of **13b** is exceptionally slow. If one assumes that at the time of the [1,5]-hydrogen rearrangement the vinylallene moiety of **13a–c** must assume a *coplanar conformation*, only **13b** develops significant strain. While the relatively flexible **13a** and **13c** can assume a planar orientation of the vinylallene moiety without developing significant strain, **13b**, which exists primarily as a relatively rigid chair conformation, must assume a higher energy, flexible twist-boat like conformation (see below).

The results of molecular mechanics calculations[16] (Chart

(12) Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627.
(13) (a) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250. (b) Midland, M. M.; McLaughlin, J. I.; Werley, R. T. *Org. Synth.* **1989**, *68*, 14.
(14) (a) Lipshutz, B. H. *Synthesis* **1987**, 325. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.
(15) The protocol used by Dr. G.-Y. Shen of this laboratory was adapted for this study. Besides ref 2b, see: Shen, G.-Y. Ph.D. Dissertation, University of California, Riverside, CA, August, 1986.

Chart II

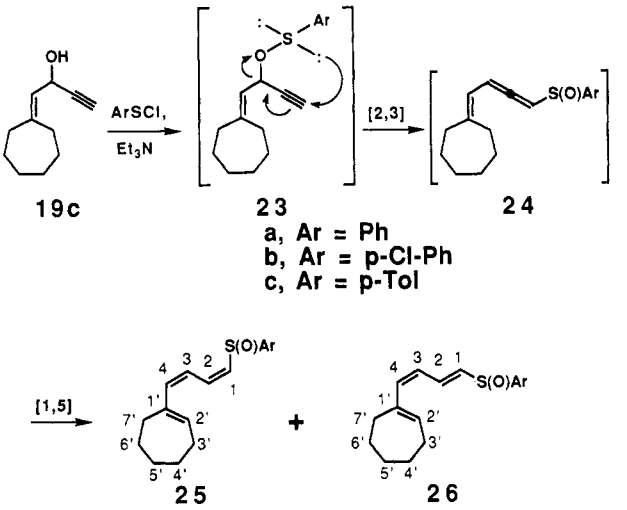


(MME = MM energy in kcal/mol for the lowest energy conformation computed)

II) are consistent with the explanation given above on the reactivity order for the rearrangement of vinylallenes **13a–c**. In order to facilitate the computation, the *tert*-butyl group was replaced by a hydrogen for the calculation. The most stable ground states of vinylallenes **13a–c** whose $\Delta^{1,2}$ single bonds are s-trans are depicted schematically in Chart II (**13at**, **13bt**, and **13ct**, respectively). The MM energies (MME) for the three systems were calculated to be −34.8 kcal/mol (**13at**), −38.6 kcal/mol (**13bt**), and −33.0 kcal/mol (**13ct**). For the **13ct** structure, an additional six structures were found which were within 3 kcal of the lowest energy structure. Two of these (−32.8 and −30.4 kcal/mol) had the $C_{3'}$, $C_{2'}$, $C_{1'}$, and $C_{7'}$ atoms nearly in a planar arrangement. In the remaining structures, the absolute values of the dihedral angles for these atoms ranged from 60° to 90°. Structures **13ac**, **13bc**, and **13cc** represent the conformers of **13a–c** which approximate the ground-state planar s-cis conformation leading to the putative transition state for the [1,5]-shift. Note that seven atoms, C_1, C_2, C_3, $C_{1'}$, $C_{2'}$, $C_{3'}$, and C_n (n = 5′ for **13ac**, 6′ for **13bc**, and 7′ for **13cc**), are located nearly in a plane in this model. The calculation results for **13ac** indicate one accessible low-energy conformation with an MME of −34.1 kcal/mol (with the following absolute values of the dihedral angles: ∠3′,2′,1′,5′ of 6.0° and ∠1′,1,2,3 of 1.6°). The MME of one accessible low-energy conformation obtained for **13bc** was calculated to be 33.2 kcal/mol (with the following absolute values of the dihedral angles: ∠3′,2′,1′,6′ of 9.3° and ∠1′,1,2,3 of 3.1°). Finally it was calculated that for the two accessible low-energy conformations of **13cc**, MME were −29.3 and −31.5° (with the following absolute values of the dihedral angles: ∠3′,2′,1′,7′ of 13.7° and 21.7°, respectively; ∠1′,1,2,3 of 11.0° and 8.5°; respectively). Thus by comparing the difference in MME (**13at** versus **13ac**; **13bt** versus **13bc**; and **13ct** versus the lowest MME of

(16) (a) Molecular mechanics calculations were performed using PCMODEL from Serena Software; π-calculations were performed on the butadiene portion of the vinylallene. For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; JAI Press: Vol. 2, in press. (b) Using PCMODEL, the $C_{2'}$–C_3 distances of the accessible lowest energy $\Delta^{1,2}$-s-cis conformers were calculated to be 3.0 ± 0.1 Å for all three cases. Thus, the PCMODEL $C_{2'}$–C_3 distances are quite different from the values obtained from Dreiding Models (2.7, 2.6, and 2.3 Å for five-, six-, and seven-membered ring vinylallenes, respectively). Note too that we are fully cognizant of the notion that activation energies should be used to predict the order of reaction rates. However PCMODEL is not designed to handle the transition state structure of [1,5]-sigmatropic hydrogen shifts. Higher level computations would of course be preferable, but for the time being, we are only able to address this problem by analysis of the cisoid ground-state conformation as a model for the [1,5]-shift.

Scheme VI



13cc), the five- and seven-membered ring vinylallenes **13a** and **13c** can easily assume a conformation approaching the transition-state structure with development of only a relatively small amount of strain energy (0.7 and 1.5 kcal/mol, respectively) compared to **13b**. The latter six-membered ring vinylallene **13b** must assume the higher energy twist-boatlike conformation and thus develops considerably more strain (5.4 kcal/mol of strain energy) on going from **13bt** to **13bc**.

It should be noted that in **5a–c**, the A-ring exocyclic methyl carbon and the reacting π-system can become planar without ring distortion. To reiterate, it is suggested that the distance effect factor provides a simple predictive model for the rate ordering **5c** > **5b** > **5a** and **13c** > **13a**, but that **13b** is slower than expected for the additional reason cited above.

Substituent Effects. As noted earlier (Scheme III and Table I), the phenyl sulfoxide (phenylsulfinyl, PhS(O)) group has been observed to be unique in its ability to impart an anti-directing effect on the trajectory of the suprafacial, [1,5]-sigmatropic shift. In order to test the generality of the anti-directing effect imparted by the sulfoxide moiety on the [1,5]-sigmatropic hydrogen shift in a ring system different from that represented by **10**, we selected for study the seven-membered exocyclic vinylallene system related to **13c**, namely **24a** (Scheme VI). This vinylallene sulfoxide was expected to be easily generated from the propargyl alcohol **19c** described above by treating it with PhSCl.[2b,c,17] Since **13c** rearranges to **21c** plus **22c** 10 times faster than **10f** to **11f** plus **12f** (68 °C),[2b,c] and since **10a** rearranges to **11a** plus **12a** ~140 times faster than **10f** to **11f** plus **12f** (40 °C),[2b,c] it was expected that **24a** would rearrange to **25a** plus **26a** at below room temperature. That is, the process shown in Scheme VI leading to **25a** plus **26a** would occur without detection of **23a** or **24a** by simply treating **19c** with PhSCl at room temperature. Indeed, in the event, treatment of **19c** with PhSCl/Et_3N produced **25a** and **26a** directly. Sulfenate ester **23a** was presumably formed first at low temperature (~−40 °C)[17b] and it rearranged to vinylallene sulfoxide **24a** via the usual [2,3]-sigmatropic shift upon warming to room temperature. Vinylallene sulfoxide **24a** is considered to

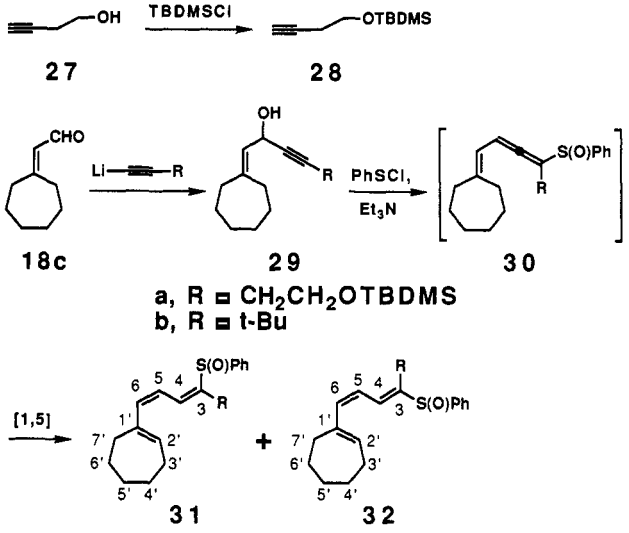
(17) (a) van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 1019. (b) VanRheenen, V.; Shephard, K. P. *J. Org. Chem.* **1979**, *44*, 1582. (c) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530. (d) Braverman, S.; Stabinsky, Y. *Isr. J. Chem.* **1967**, *5*, 125. (e) Evans, D.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (f) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

Table III. Observed Triene Product Ratios for Vinylallenes 24a–c and 10a

vinylallene	25/26[a]	12a/11a[b]
24a	2.8 ± 0.2/1.0	–
24b	2.8 ± 0.4/1.0	–
24c	3.1 ± 0.3/1.0	–
10a	–	3.5/1.0

[a] The average and standard deviations of three separate determinations (by ^{1}H NMR analysis, HPLC analysis and actual weight ratio of products). [b] One diastereomer of **10a** gave a **12a**/**11a** ratio of 82/18. The other one gave a **12a**/**11a** ratio of 75/25.

Scheme VII

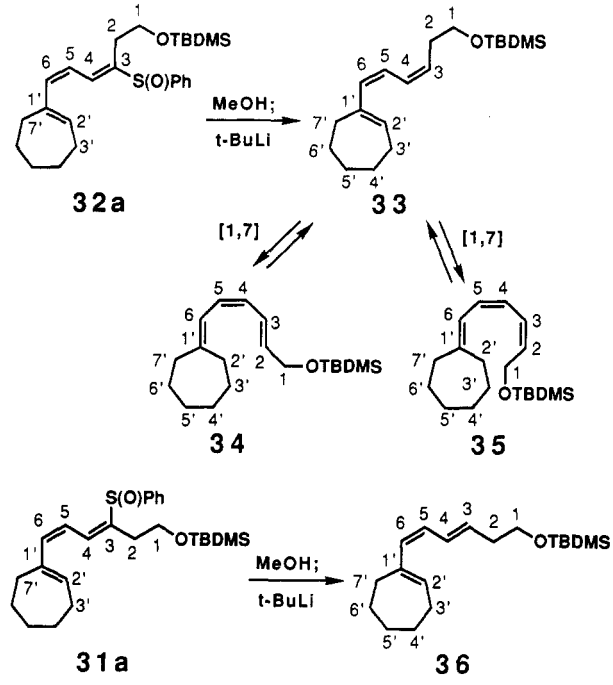


be transformed to triene sulfoxide **25a** and **26a** (81% yield) via a spontaneous [1,5]-sigmatropic hydrogen migration at room temperature. Vinylallene sulfoxides with a para-substituted electron-withdrawing group or electron-donating group on the benzene ring were also investigated. Treatment of propargyl alcohol **19c** with *p*-Cl-PhSCl and *p*-TolSCl presumably afforded vinylallene sulfoxides **24b** and **24c**, respectively, which upon standing at room temperature (without isolation or attempted detection) rearranged to the corresponding triene sulfoxides **25** plus **26** (73% and 72% yields, respectively). These triene products (**25a–c** and **26a–c**) were characterized individually after purification. In order to establish that the observed products **25** and **26** represent kinetic rather than thermodynamic products, the individual trienes were allowed to stand in C_6D_6 for at least 16 h at room temperature. No interconversion between **25** and **26** was observed.[6]

The ratio of products **25** and **26** from the rearrangement of **24** together with the corresponding data for the thermal rearrangement of sulfoxide **10a** described earlier (Scheme III and Table I) are compared in Table III. The anti-directing effect imparted by the sulfoxide group on the [1,5]-sigmatropic hydrogen migration of vinylallene sulfoxide **24** was similar to that observed for ring system **10a**. It can also be seen from Table III that a donor or acceptor substituent on the aryl group imparts no significant effect on π-facial selectivity. It was intended to further investigate whether an alkyl substituent geminal to the sulfoxide of **24** would enhance the anti-directing effect as was observed for **10b–e**.

Vinylallene sulfoxide **30a** (Scheme VII) substituted with a geminal alkyl group was easily generated from aldehyde **18c** in two steps. Treatment of **18c** with the lithium salt of protected alkynol **28**,[3] which in turn was readily obtained by protection of alcohol **27** with *tert*-butyldimethylchlorosilane (93%), afforded propargyl alcohol **29a** (71%).

Scheme VIII

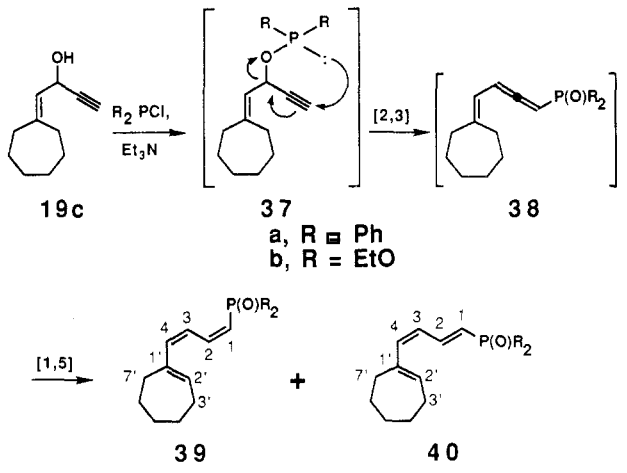


Reaction of alcohol **29a** with PhSCl and triethylamine in the usual fashion generated the desired sulfoxide **30a**, which at room temperature spontaneously rearranged to give two triene products **31a** and **32a**, which were characterized individually after purification, in a ratio of 82/18 (89%). Although the geminal substituted alkyl group still enhanced the anti-directing effect by the sulfoxide substituent, the enhancement observed in this system was somewhat reduced compared to the corresponding sulfoxide **10c**, which gave a *Z*/*E* ratio of 92/8. Further probing of this system geminally substituted with a *tert*-butyl and phenyl sulfoxide similar to **10e**, namely **30b**, in order to maximize the anti-directing effect, was explored. However, although **29b** could be readily prepared (Scheme VII), the reaction of **29b** with PhSCl under a variety of conditions led primarily to hydrocarbon, apparently a dienyne resulting from formal elimination of PhSOH. Accordingly, although small quantities of **31b** and **32b** appeared to be produced, this study had to be abandoned.

In order to confirm the assignments of **31a** and **32a**, the sulfoxides **32a** and **31a** were individually converted to the isomeric trienes **33** (36%) and **36** (71%), respectively, by replacing the sulfoxide substituent with a hydrogen with retention of configuration via a method developed in this laboratory[18] (Scheme VIII). The individual triene sulfoxides were premixed with MeOH, treated with an excess of *t*-BuLi at −78 °C, and then quenched at low temperature to give the corresponding reduced trienes. The triene **33** was thermally labile and it was shown to slowly rearrange to **34** and **35**, presumably via [1,7]-sigmatropic hydrogen migrations. This rearrangement reaction was monitored by ^{1}H NMR spectroscopy. At ~23 °C, a decrease in the amount of starting endocyclic triene **33** and an increase in the amount of rearranged exocyclic triene **34** was observed. The appearance of another minor product **35** assigned on the basis of an ^{1}H NMR signal at δ 4.38 (dd, J ~ 6.4, 1.7 Hz) [which is similar to the H_1 resonance (δ 4.26, dd, J ~ 5.2, 1.1 Hz) of **34**] was also detected. After 109 h, the three trienes appeared to approach an equilibrium

(18) (a) Theobald, P. G.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 741. (b) Theobald, P. G.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6565.

Scheme IX



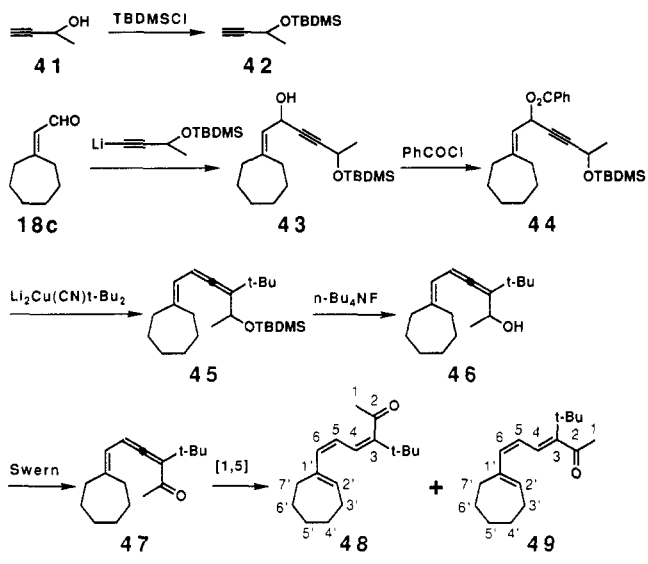
with a **33**/**34**/**35** ratio of 9/88/4. The **34**/**35** ratio remained relatively constant at 22 ± 3/1.0 during the course of the isomerization and the half-life for disappearance of **33** was ~15 h at ~23 °C. It is somewhat surprising that the exocyclic triene **34** proved to be thermodynamically more stable than the endocyclic isomer **33**. This may perhaps be attributed to the inability of the triene moiety of **33** to assume a planar, stabilized π-system because of the presence of two *Z*-double bonds.

In view of the ready availability of propargyl alcohol **19c**, attention was turned next to examine whether phosphorus substituents were capable of imparting significant π-facial selectivity on [1,5]-sigmatropic hydrogen migrations of vinylallenes. The two phosphorus substrates studied were vinylallenes **38a** and **38b** (Scheme IX), which were easily generated[19] in a manner similar to the preparation of vinylallene sulfoxides (cf. Scheme VII). Treatment of propargyl alcohol **19c** with either chlorodiphenylphosphine or diethyl chlorophosphite (Scheme IX) afforded directly upon standing at room temperature the trienes **39** and **40** (**a**, 89%; **b**, 77%). These were assumed to be formed by initial formation of **37** followed by a [2,3]-sigmatropic shift to **38** and then finally by the usual competing modes of [1,5]-hydrogen migrations. Both substituents [$P(O)Ph_2$ and $P(O)(OEt)_2$] gave no significant directing effects as indicated by the product ratios (**39a**/**40a** = 47/53; **39b**/**40b** = 40/60). In order to verify that these ratios represented a kinetic distribution of products, the individually purified trienes in benzene-d_6 were shown to not interconvert (room temperature, 23 h, **39a** and **40a**; 40 °C, 80 h, **39b** and **40b**).

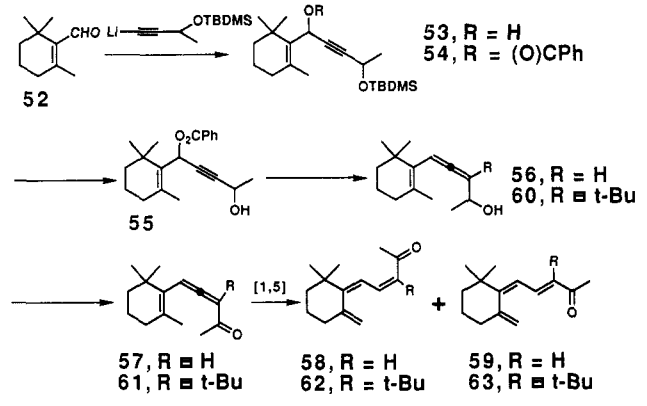
A final substituent investigated for possibly imparting π-facial selectivity on [1,5]-sigmatropic hydrogen migrations was the carbonyl group. As outlined in Schemes X and XI, vinylallene ketones could be easily prepared. The most significant steps involved in the synthesis of the substrates included the treatment of suitable propargyl benzoates with either a Lipshutz type "higher order" cuprate[14] reagent or samarium iodide (SmI_2) in the presence of a catalytic amount of $Pd(PPh_3)_4$.[20]

Treatment of aldehyde **18c** with alkynyllithium derived from protected alcohol **42**, obtained from alkynol **41** (72%), afforded a diastereomeric mixture of propargyl alcohol **43** (86%) (Scheme X). The latter was converted to propargyl benzoate **44** (92%), which was transformed into vinylallene

Scheme X

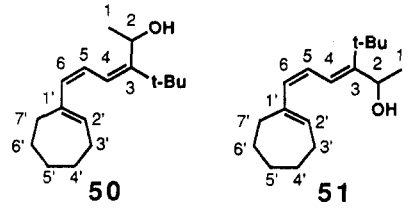


Scheme XI



45 (84%) by an S_N2' reaction of benzoate **44** with dilithium di-*tert*-butylcyanocuprate.[3,14] Vinylallene **45** was deprotected with *n*-Bu_4NF to give a diastereomeric mixture of vinylallenols **46**, which were separated and then individually oxidized with the Swern reagent[21] to the same vinylallenone **47** (61% total from **45**). Vinylallenone **47** was refluxed in CH_2Cl_2 under a nitrogen atmosphere for 12 h to give an inseparable mixture of trienones **48** and **49** (99% yield). ^1H NMR data indicated that the ratio of **48**/**49** was 63/37. In control experiments, the individually purified trienones **48** and **49** (obtained as described below) were subjected to the same thermal conditions for at least 15 h and were found to be stable.[6]

The inseparable mixture of **48** and **49** was subjected to hydride reduction ($NaBH_4$, $CeCl_3$) followed by HPLC separation to afford trienols **50** and **51** (88%). These



trienols were individually converted back to ketones **48** (77%) and **49** (12%), respectively, by MnO_2 oxidation. The structures assigned to trienones **48** and **49** were based primarily on the method of preparation and ^1H NMR data

(19) (a) Boisselle, A. P.; Meinhardt, N. A. *J. Org. Chem.* **1962**, *27*, 1828. (b) Altenbach, H.-J.; Korff, R. *Tetrahedron Lett.* **1981**, *22*, 5175. (c) Mark, V. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; John Wiley & Sons, Inc.: New York, 1969; Vol. 2, pp 319–437.

(20) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237.

(21) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

including NOE experiments.

Since the rearrangement of ring system **10** bearing a terminal allene carbonyl group had not been previously studied, and since a convenient method for introducing a carbonyl group at this position had now been developed, vinylallenones **57** and **61** (Scheme XI) were also synthesized and studied. Aldehyde **52** was reacted with the lithium salt of protected alkynol **42** to generate a diastereomeric mixture of propargyl alcohol **53** (86%), which was then converted to propargyl benzoate **54** (92%). The benzoate **54** was deprotected with n-Bu_4NF to afford alcohol **55** (92%), which was then treated with SmI_2 and s-BuOH in the presence of a catalytic amount of $Pd(PPh_3)_4$ to furnish a readily separable, ~1:1 diastereomeric mixture of vinylallenol **56** (81%).[20] This mixture was oxidized with Dess–Martin periodinane[22] to give vinylallenone **57**. A solution of vinylallenone **57** in C_6D_6 was thermolyzed in a sealed NMR tube at 68.5 °C for 0.5 h to afford two trienones **58** and **59** (36% of a 50/50 mixture from **56**) whose structural assignments were based on the method of preparation and ^1H NMR data including NOE experiments. The trienes **58** and **59** were subjected individually to the reaction conditions (C_6D_6, 68.5 °C, 1 h) and were found to be unchanged.[6]

Vinylallenone **61** was prepared (Scheme XI) in a manner similar to that used for the preparation of vinylallenone **47**. In an initial attempt, treatment of benzoate **54** with dilithium di-*tert*-butylcyanocuprate failed to afford the TBDMS ether of **60**, and it was noted that the silyl ether moiety was lost, possibly as a consequence of a competing displacement of the (*tert*-butyldimethylsilyl)oxy group via an S_N2 or S_N2' process. The problem was readily solved by treatment of propargyl alcohol **55** with the same higher order cyanocuprate at −78 °C, which afforded a diastereomeric mixture of vinylallenol **60** (52%). The latter was oxidized under Swern conditions[21] to furnish the desired vinylallenone **61** (62%). Thermolysis of a benzene solution of vinylallenone **61** at 68.5 °C for 17.5 h afforded two trienones **62** and **63** (90% yield of a 61/39 mixture). The trienones **62** and **63** were also subjected to the same thermal conditions for 20 h and were found to be stable under these conditions.[6] Their geometries were assigned on the basis of the method of preparation and analysis of their ^1H NMR spectra including NOE studies.

As regard the π-facial selectivity imparted by the allenyl substituent, the results for the rearrangement of the phosphorus derivatives **38a** and **38b** and the carbonyl derivatives **47**, **57**, and **61** are summarized in Table IV. Although a small preference for the *Z,Z*-triene product was observed for **47** and **61** (but not **57**), by comparing the results from the thermolyses of **13c** and **10f** (Tables III and I, respectively), it is concluded that the carbonyl substituent, like alkyl groups, sulfide (PhS), sulfone [$PhS(O)_2$], phosphine oxide [$Ph_2P(O)$], and phosphonate [$(EtO)_2P(O)$], is an ineffective π-facial directing group. Only the arylsulfoxide group has thus far proven effective in affording *Z,Z*-selectivity.

Summary and Conclusions

In the first part of this study, there was described a quantitative evaluation of the effect of ring size in systems of the type **13** in their [1,5]-sigmatropic hydrogen shifts. Experimentation revealed that the relative rate of rearrangement followed the ring size order 7 > 5 > 6 (**13c** > **13a** > **13b**). This reactivity order was not in simple congruence with our prediction based on a ring size, distance effect hypothesis described earlier. The intrinsic reactivity of **13b** (six-membered ring) is considered to be lowered by virtue of the need for the relatively rigid six-membered ring chair (cyclohexyl) of **13b** to adopt a higher energy boatlike conformation before it can adopt the assumed flat vinylallene framework necessary for the suprafacial [1,5]-sigmatropic shift.

Table IV. Results from Thermal Rearrangement of Vinylallenes 38a, 38b, 47, 57, and 61

	vinylallene				
	38a	**38b**	**47**	**57**	**61**
Z,Z/*Z,E* ratio	**39a/40a** 1.0/1.1[a]	**39b/40b** 1.0/1.5[a]	**48/49** 1.7/1.0[b]	**58/59** 1.0/1.1[a]	**62/63** 1.5/1.0[a]

[a] The average of three separate determinations (^1H NMR analysis, HPLC analysis, and by actual weight ratio of products) as described in the Experimental Section. [b] The ratio was obtained from ^1H NMR analysis. Similar ratios were obtained by reducing the trienone mixture to an HPLC separable mixture of trienols (64/36 by HPLC, 68/32 by weight).

The second part of this investigation concerned: an evaluation of the generality of the anti-directing effect imparted by the phenylsulfinyl group previously observed for the thermal [1,5]-sigmatropic rearrangement of vinylallenes **10a–e**; a study of the effect of acceptor (chlorine) or donor (methyl) substituents on the benzene ring of the phenylsulfinyl group on the magnitude of the anti-directing effect; and investigations of other substituents such as phosphine oxide, phosphonate, and carbonyl as to their π-facial directing effect ability. Of all the substituents examined, including those of the previous study (alkyl, sulfide, sulfoxide, sulfone, phosphine oxide, phosphonate, and carbonyl), only the sulfoxide substituent exerts significant π-facial selectivity on the course of the hydrogen migration trajectory of the thermal [1,5]-sigmatropic hydrogen migration. The anti-directing effect imparted by the sulfoxide group is general and the magnititude of this effect can be enhanced by a geminal alkyl substituent to varying degrees. The arylsulfinyl group is only a modest director, but all of the other substituents are not particularly effective if at all. This phenomenon is not yet fully understood, but it is hoped that the results described herein will stimulate efforts toward developing a theoretical evaluation of this phenomenon. Equally importantly, in the area of stereoselective polyene syntheses, it would be desirable to identify more effective π-facial directing groups.

Experimental Section[23]

1-Cyclopentylidene-5,5-dimethylhexa-2,3-diene (13a). A suspension of CuCN (260 mg, 2.90 mmol) in anhydrous ether (1.4 mL) was stirred under N_2 and cooled to −78 °C, and a solution of *t*-BuLi in pentane (3.41 mL, 1.70 M, 5.80 mmol) was added dropwise. After 30 min, the mixture was allowed to warm to 0 °C for 10 min and was recooled to −78 °C. A solution of propargyl benzoate **20a** (251 mg, 1.04 mmol) in anhydrous ether (1.4 mL) was added dropwise via cannula. Additional anhydrous ether (2 × 0.7 mL) was used to further rinse the benzoate into the solution containing the copper reagent. After 2.5 h, the reaction mixture was warmed up to 0 °C and then the reaction was quenched with H_2O (5.8 mL). The mixture was extracted with ether, and the organic solution was washed with 5% aqueous $NaHCO_3$ and brine

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(23) General experimental procedures and spectral data and a detailed description of the kinetic studies are given in the supplementary material. For workup procedures, organic solutions were dried over $MgSO_4$ and solvent evaporation was performed on a rotatory evaporator unless otherwise indicated. All new compounds were judged to be of satisfactory purity by a combination of HPLC and ^1H and ^{13}C NMR spectral analyses before mass spectral determination. Satisfactory combustion analyses were also obtained for selected compounds.

and then dried. Solvent evaporation followed by Chromatotron purification (silica gel, 100% pentanes) gave the desired vinylallene **13a** as a pale yellow liquid in essentially quantitative yield. The vacuum-dried material was spectroscopically (^1H and ^{13}C NMR analyses) homogeneous, but the high volatility of the material resulted in losses.

1-Cyclohexylidene-5,5-dimethylhexa-2,3-diene (13b). Vinylallene **13b** was prepared from propargyl benzoate **20b** (as described above for preparation of **13a**) in essentially quantitatively yield. The vacuum-dried material was spectroscopically (^1H and ^{13}C NMR analyses) homogeneous, but some care should be taken to prevent evaporation losses.

1-Cycloheptylidene-5,5-dimethylhexa-2,3-diene (13c). Vinylallene **13c** was obtained from **20c** as described above for preparation of **13a** in 78% yield after chromatotron purification (silica gel, 100% hexanes).

General Procedure for the Kinetic Studies of 13. Reactions were monitored by ^1H NMR spectroscopy in benzene-d_6 at 68.3 ± 0.1 °C, and the results are summarized in Table II in the text. The details are presented in the supplementary material.

Cyclopentylideneacetonitrile (17a). Sodium hydride (2.96 g, 60% in mineral oil, 74.0 mmol) was washed with dry hexanes (6 mL) twice under N_2. After the hexanes was removed, anhydrous ether (150 mL) was added. A solution of diethyl cyanomethylphosphonate (13.4 g, 74.0 mmol) in anhydrous ether (37 mL) was added dropwise to the suspension via cannula at 0 °C. After the evolution of H_2 had stopped, cyclopentanone (5.65 g, 67.2 mmol) was added via syringe to the reaction flask. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water (336 mL), the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic solution was washed with water and brine and then dried. After solvent evaporation, the residue was subjected to fractional distillation (83–84 °C, 12 mm) to give the known[24] nitrile **17a** (6.44 g, 89%) as a colorless liquid.

Cyclohexylideneacetonitrile (17b). By use of a procedure similar to that used for preparing **17a**, the known[24b] nitrile **17b** was obtained in 92% yield as a colorless liquid (bp 86–88 °C, 10 mm).

Cycloheptylideneacetonitrile (17c). Cycloheptanone (**16c**) was transformed to the known[24b] nitrile **17c** (91%, bp 94–95 °C, 6 mm) as a colorless liquid as described above for preparing **17a**.

Cyclopentylideneacetaldehyde (18a). To a solution of **17a** (1.295 g, 12.08 mmol) in dry pentanes (60 mL, distilled over CaH_2) was added diisobutylaluminum hydride (24.16 mL, 1.0 M in hexanes, 24.16 mmol) by a syringe in one portion at −60 °C under N_2 with stirring. The stirring was continued at −60 °C for 30 min and at 0 °C for 5 h. Ethyl formate (0.98 mL) was added dropwise, and the stirring was continued for another hour. Saturated NH_4Cl (24.2 mL) was added dropwise, and the mixture was allowed to warm to room temperature. After 1 h, 1 M aqueous H_2SO_4 (48.5 mL) was added. The organic layer was separated, and the aqueous solution was extracted with ether (20 mL × 3). The combined organic solution was washed with 5% $NaHCO_3$ and brine and then dried. After solvent evaporation, the residue was subjected to Chromatotron purification (silica gel, 20% Et_2O/hexanes) to give the known[25] aldehyde **18a** (486 mg, 36%) as a volatile, pale yellow liquid.

Cyclohexylideneacetaldehyde (18b). The known[25,26] aldehyde **18b** was obtained from **17b** as a colorless liquid (58%, bp 52–54 °C, 2 mm) using the same procedure as for preparing **18a**.

Cycloheptylideneacetaldehyde (18c). By use of the procedure for preparing **18a**, the known[26] aldehyde **18c** was obtained in 89% yield as a pale yellow liquid after flash chromatography (silica gel, 20% ether/hexanes).

1-Cyclopentylidenebut-3-yn-2-ol (19a). An acetylene solution (1.4 mL in 5 mL of THF at −78 °C) was transferred into THF (14 mL) at −78 °C under N_2 by cannula, and *n*-butyllithium (6.03 mL, 1.56 M in hexanes, 9.41 mmol) was slowly added dropwise. After 10 min, a solution of aldehyde **18a** (690.5 mg, 6.27 mmol) in THF (2 mL) at −78 °C under N_2 was transferred to the lithium acetylide solution by cannula. THF (2 × 1 mL) was used to further rinse the residual aldehyde to the mixture, and the resulting mixture was stirred at −78 °C for 20 min, warmed to room temperature, and quenched with water (4.7 mL). K_2CO_3 was added until the aqueous layer became pasty. The organic layer was separated from the aqueous layer, and the latter was extracted with ether. The combined organic solution was dried. Solvent evaporation followed by flash column purification (silica gel, 30% Et_2O/hexanes) and then vacuum drying gave the desired propargyl alcohol **19a** (615 mg, 72%) as a pale yellow oil.

1-Cyclohexylidenebut-3-yn-2-ol (19b). The propargyl alcohol **19b** was obtained from **18b** as a colorless oil (96%, bp 51–54 °C, 0.03 mm) using a procedure similar to that used for preparing **19a**.

1-Cycloheptylidenebut-3-yn-2-ol (19c). By use of the procedure for preparing **19a**, the aldehyde **18c** was converted to the propargyl alcohol **19c** as a pale yellow oil in essentially quantitative yield after flash column chromatography (silica gel, 30% ether/hexanes).

1-Cyclopentylidenebut-3-yn-2-yl benzoate (20a). To a solution of propargyl alcohol **19a** (333 mg, 2.44 mmol) in pyridine (2.4 mL) was added benzoyl chloride (0.30 mL, 2.6 mmol) dropwise under N_2. The mixture was stirred for 5 min, and pyridine (2 × 1 mL) was used to rinse the flask. Stirring was continued for 5 min, the reaction was quenched with 5% $NaHCO_3$ (9.6 mL), and the resulting mixture was extracted with ether (3 × 10 mL). The combined, dried organic solution was concentrated. Chromatotron purification (silica gel, 20% Et_2O/hexanes) followed by vacuum drying gave the desired propargyl benzoate **20a** (567 mg, 97%) as a viscous liquid, which was sufficiently pure for use in the next step.

1-Cyclohexylidenebut-3-yn-2-yl benzoate (20b). Propargyl alcohol **19b** was converted to the desired propargyl benzoate **20b** in 92% yield as a viscous liquid by the method described immediately above.

1-Cycloheptylidenebut-3-yn-2-yl benzoate (20c). Propargyl benzoate **20c** was obtained as a viscous liquid in 92% yield by using the method described above for preparing **20a**.

(1*Z*,3*Z*)-1-(Cyclopenten-1′-yl)-5,5-dimethylhexa-1,3-diene (21a) and Its 1*Z*,3*E* Isomer 22a. Into an NMR tube were introduced vinylallene **13a** (59 mg, 0.33 mmol) and C_6D_6 (0.5 mL). The solution was cooled to dry ice temperature under a nitrogen atmosphere, and then the NMR tube was evacuated and sealed. The mixture was heated at 68.3 ± 0.1 °C in an NMR probe, and the reaction was monitored by NMR. Two geometric isomers, (1*Z*,3*Z*)-**21a** and (1*Z*,3*E*)-**22a** were produced in a ratio of 44/56. The kinetic study of this isomerization is described in the supplementary material. For characterization purposes, the vinylallene **13a** (460 mg, 2.6 mmol) in benzene (3 mL) was sealed in two separate ampoules under vacuum in a manner similar to that described above and subjected to the same thermal conditions for 18 h. The solvent was carefully evaporated, and the residue was subjected to HPLC separation (Partisil, 100% hexanes) to afford in order of elution, the 1*Z*,3*Z* isomer **21a** (less polar, minor isomer A) and the 1*Z*,3*E* isomer **22a** (more polar, major isomer B). Solvent evaporation gave the two expected products as volatile, colorless liquids. It was not possible to determine the true isolated yield ratio due to product volatility problems.

(1*Z*,3*Z*)-1-(Cyclohexen-1′-yl)-5,5-dimethylhexa-1,3-diene (21b) and Its 1*Z*,3*E* Isomer 22b. A solution of vinylallene **13b** (47 mg, 0.25 mmol) in C_6D_6 (0.5 mL) in a sealed NMR tube was prepared as described immediately above. The vinylallene solution was maintained at 68.27 ± 0.04 °C in an oil bath. The reaction, monitored by NMR, revealed the formation of two geometric isomers, (1*Z*,3*Z*)-**21b** and (1*Z*,3*E*)-**22b**, in a ratio of 35/65. The kinetic study of this isomerization is described in the supplementary material. In a preparative experiment, a solution of vinylallene **13b** (520 mg, 2.7 mmol) in benzene (3 mL) was divided and then sealed into two separate ampoules in a manner similar to that described above. The solution was heated under the same condition for 264 h, and then the resulting mixture was subjected to HPLC separation (Partisil, 100% hexanes) to afford in order

(24) (a) Wheeler, O. H. *J. Org. Chem.* **1961**, *26*, 4755. (b) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.

(25) Ono, N.; Miyake, H.; Tanikaga, R.; Kaji, A. *J. Org. Chem.* **1982**, *47*, 5017.

(26) Clive, D. L. J.; Farina, V.; Beaulieu, P. L. *J. Org. Chem.* **1982**, *47*, 2572.

of elution, (1*Z*,3*Z*)-**21b** (less polar, minor isomer A) and (1*Z*,3*E*)-**22b** (more polar, major isomer B). Solvent was evaporated to give the expected isomers as volatile, colorless liquids. Due to their volatility, the isolated yields could not be accurately determined.

(1*Z*,3*Z*)-1-(Cyclohepten-1′-yl)-5,5-dimethylhexa-1,3-diene (21c) and Its 1*Z*,3*E* Isomer 22c. A solution of vinylallene **13c** (49 mg, 0.24 mmol) in C_6D_6 (0.5 mL) in a sealed NMR tube was prepared and thermolyzed at 68.3 ± 0.1 °C in an NMR probe as described above for **13a**, and the reaction was also monitored by NMR. Thermolysis of the vinylallene gave two geometric isomers, (1*Z*,3*Z*)-**21c** and (1*Z*,3*E*)-**22c**, in a ratio of 34/66. The kinetic studies of the rearrangement are described in the supplementary material. For characterization purposes, a solution of the vinylallene (1 g, 5 mmol) in benzene (3 mL), divided into two portions, was sealed in two ampoules as described above and was thermolyzed under the same conditions for 2 h. The solvent was carefully removed, and the residue was subjected to multiple shave-recycle HPLC separation (Partisil, 100% hexanes) to afford, in order of elution, (1*Z*,3*Z*)-**21c** (less polar, minor isomer A) and (1*Z*,3*E*)-**22c** (more polar, major isomer B) as volatile, colorless oils. Losses incurred during solvent removal and HPLC prevented accurate determination of yields. The crude yield is estimated to be essentially quantitative (^{1}H NMR).

(1*Z*,3*Z*)-4-(Cyclohepten-1′-yl)-1-(phenylsulfinyl)buta-1,3-diene (25a) and Its 1*E*,3*Z* Isomer 26a. A mixture of propargyl alcohol **19c** (123 mg, 0.748 mmol), anhydrous ether (11.2 mL), and triethylamine (0.21 mL, 1.5 mmol) under N_2 was cooled with stirring to −78 °C. A solution of PhSCl [0.548 mL, 0.822 mmol, prepared by adding a solution of Cl_2 (1.73 mL, 0.842 M in CCl_4, 1.46 mmol) to Ph_2S_2 (333 mg, 1.53 mmol) at 0 °C under N_2] was added to the propargyl alcohol solution dropwise by syringe, and the stirring was continued at −78 °C for 2 h and then at room temperature overnight (9 h). The reaction was quenched with water (3.3 mL), the resulting mixture was extracted with ether, and the organic solution was washed with 5% $NaHCO_3$ and then brine and dried. Solvent evaporation under reduced pressure afforded a residue, which was dissolved in ether and filtered through a short pad of silica gel. Concentration afforded a residue which was subjected to HPLC separation (Partisil, 40% EtOAc/hexanes) and vacuum drying to give two geometric isomers as viscous liquids in the following order of elution: 1*E*,3*Z*-triene **26a** (44.2 mg, 22%, less polar, minor isomer A) and 1*Z*,3*Z*-triene **25a** (121.0 mg, 59%, more polar, major isomer B). The ratio of (1*Z*,3*Z*)-**25a** to (1*E*,3*Z*)-**26a** was determined to be 73:27 in three ways: 73:27 (yield), 72:28 (^{1}H NMR), and 75:25 (HPLC).

(1*Z*,3*Z*)-1-((4″-Chlorophenyl)sulfinyl)-4-(cyclohepten-1′-yl)buta-1,3-diene (25b) and Its 1*E*,3*Z* Isomer 26b. To a solution of propargyl alcohol **19c** (103 mg, 0.627 mmol) and triethylamine (0.174 mL, 1.25 mmol) in anhydrous ether (9.4 mL) at −78 °C under N_2 was introduced neat *p*-chlorophenylsulfenyl chloride (0.079 mL, 0.66 mmol) dropwise with a syringe. The stirring was continued at −78 °C for 2 h and at room temperature overnight (12 h). The reaction was quenched with water (3.1 mL), and then the mixture was extracted with ether. The organic solution was washed with 5% $NaHCO_3$ and brine and then dried. Solvent evaporation afforded a residue, which was dissolved in ether and then filtered through silica gel. Concentration afforded a residue, which was subjected to HPLC separation (Partisil, 40% EtOAc/hexanes) and vacuum drying to give two geometric isomers as viscous liquids in the following order of elution: (1*E*,3*Z*)-**26b** (36.0 mg, 19%, less polar, minor isomer A) and (1*Z*,3*Z*)-**25b** (103.3 mg, 54%, more polar, major isomer B). The ratio of 1*Z*,3*Z* to 1*E*,3*Z* isomers was 74:26 (determined in three ways: by weight, 74:26; by ^{1}H NMR, 76:24; and by HPLC, 71:29).

(1*Z*,3*Z*)-4-(Cyclohepten-1′-yl)-1-((4″-methylphenyl)-sulfinyl)buta-1,3-diene (25c) and Its 1*E*,3*Z* Isomer 26c. A solution of propargyl alcohol **19c** (188 mg, 1.14 mmol) and triethylamine (0.32 mL, 2.3 mmol) in anhydrous ether (17.1 mL) was reacted with *p*-toluylsulfenyl chloride [prepared from di-*p*-toluyl disulfide (188 mg, 0.749 mmol) and a solution of Cl_2 in CCl_4 (1.08 mL, 0.656 M, 0.708 mmol)] as described above at −78 °C under N_2 for 2 h and then at room temperature overnight (15 h). The reaction was quenched with water (5.7 mL), the mixture was extracted with ether, and the organic solution was washed with 5% $NaHCO_3$ and brine and dried. Solvent evaporation afforded a residue, which was dissolved in ether and passed through a short silica gel column. Concentration of the eluate afforded a residue which by HPLC separation (Partisil, 40% EtOAc/hexanes) and vacuum drying gave two geometric isomers as viscous liquids in the following order of elution: (1*E*,3*Z*)-**26c** (62.0 mg, 19%, less polar, minor isomer A) and (1*Z*,3*Z*)-**25c** (172.0 mg, 53%, more polar, major isomer B). The ratio of 1*Z*,3*Z* to 1*E*,3*Z* was 76:24 (determined in three ways: by yield, 75:25; by ^{1}H NMR, 77:23; by HPLC, 74:26).

1-((*tert*-Butyldimethylsilyl)oxy)but-3-yne (28). This material (prepared from **27**) has been previously reported.[27]

1-((*tert*-Butyldimethylsilyl)oxy)-6-cycloheptylidenehex-3-yn-5-ol (29a). To a solution of protected alcohol **28** (1.225 g, 6.64 mmol) in dry THF (13 mL) at −78 °C was added *n*-BuLi (4.02 mL, 1.58 M in hexanes, 6.35 mmol) dropwise under N_2. The resulting mixture was stirred for 10 min, a solution of aldehyde **18c** (799 mg, 5.78 mmol) in THF (6 mL) was transferred slowly into the mixture via cannula, and then THF (2 × 1 mL) was used to rinse the aldehyde residue to the resulting mixture. The stirring was continued for 20 min, the reaction mixture was warmed to room temperature, and saturated $NaHCO_3$ (10 mL) was added. The organic layer was separated from the aqueous layer, the latter was extracted with ether (3 × 10 mL), and the combined organic solution was then dried. Solvent evaporation followed by flash column purification (silica gel, 15% Et_2O/hexanes) gave the desired propargyl alcohol **29a** (1.321 g, 71%) as a pale yellow oil.

(3*Z*,5*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(cyclohepten-1′-yl)-3-(phenylsulfinyl)hexa-3,5-diene (31a) and Its 3*E*,5*Z* Isomer 32a. To a solution of propargyl alcohol **29a** (232 mg, 0.720 mmol) and dry Et_3N (0.20 mL, freshly distilled from CaH_2) in anhydrous ether (8.8 mL) was introduced a solution of PhSCl in CCl_4 [freshly prepared from Ph_2S_2 (92.1 mg, 0.418 mmol) and Cl_2 (0.411 mL, 0.964 M in CCl_4, 0.396 mmol)] slowly via cannula at −78 °C under N_2. Additional ether (1 × 2 mL) was used to rinse the PhSCl residue into the mixture. The stirring was continued for 2 h at −78 °C, and then water (7 mL) was added to the resulting white suspension after being warmed to room temperature. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with ether (3 × 6 mL). The combined organic solution was washed with saturated $NaHCO_3$ and dried. Removal of solvent gave a yellow residue, which was subjected to ^{1}H NMR analysis to determine the product ratio [(3*E*,5*Z*)-**32a**/(3*Z*,5*Z*)-**31a** = 18/82)]. The yellow residue was then passed through a short column of silica gel with ether, and the solvent was removed. The resulting residue was subjected to HPLC separation (silica gel, 20% EtOAc/hexanes) and vacuum dried to give two geometric isomers in the following elution sequence: (3*E*,5*Z*)-**32a** contaminated with inseparable aromatic impurities (38.9 mg; less polar, minor isomer A) and (3*Z*,5*Z*)-**31a** (225.0 mg, 73%; more polar, major isomer B). Their double bond geometries were determined through their corresponding products from the desulfurization reactions described below.

(3*Z*,5*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(cyclohepten-1′-yl)hexa-3,5-diene (33). To a solution of **32a** (less polar, minor isomer A, 62.0 mg, 0.144 mmol; contaminated by a minor impurity as indicated above) in anhydrous ether was added MeOH (0.0146 mL, 0.360 mmol) under N_2, and the resulting mixture was cooled to −78 °C with stirring. A solution of *t*-BuLi (0.319 mL, 1.76 M in pentane, 0.561 mmol) was introduced in one portion by syringe, and stirring was continued for 10 min. Methanol (0.0146 mL) was added slowly followed by saturated $NaHCO_3$ (6 mL). The resulting mixture was allowed to warm to room temperature and extracted with ether (3 × 8 mL). The combined organic solution was dried, and then the solvent was removed to afford a yellow residue. The latter was purified by flash column chromatography (silica gel, 1% Et_2O/hexanes) to give a pale yellow liquid consisting of the unstable olefin **33** and a small amount of its rearranged products (16.1 mg, 36%). This material was characterized only by ^{1}H NMR, but its rearranged product was more fully characterized (see below).

(2*E*,4*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-cycloheptylidenehexa-2,4-diene (34). The flash column chromato-

(27) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093.

graphically purified mixture (preceding experiment) of endocyclic triene **33** and the rearranged exocyclic triene product **34** (20.9 mg, prepared by reduction of triene sulfoxide **32a**, the less polar, minor isomer A) was dissolved in $CDCl_3$ (0.5 mL), and its thermal rearrangement was monitored by ^1H NMR at room temperature. The ^1H NMR spectrum showed a decrease in the amount of starting endocyclic triene **33**, an increase in the rearranged exocyclic triene **34**, and the appearance of a new, minor product assigned as the Δ^2-geometric isomer of the latter [tentative assignment based on a ^1H NMR resonance at δ 4.38 ppm (dd, $J \sim$ 6.4, 1.7 Hz); the ratio of the exocyclic triene products, **34** and its presumed Δ^2-isomer **35**, remained constant at ca. ~20:1 during the course of the isomerization]. After 111 h, the solvent was removed, and the yellow residue was passed through a short column of silica gel with ether. The solvent was evaporated, and the resulting residue was subjected to HPLC purification (silica gel, 100% hexanes) to give the rearranged product **34** quantitatively (contaminated by ~4% of the minor compound **35** indicated above and ~5% of the starting endocyclic triene **33**). The half-life at ~23 °C for disappearance of starting endocyclic triene was ~15 h.

(3*E*,5*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(cyclohepten-1′-yl)hexa-3,5-diene (36). A solution of *t*-BuLi in pentane (0.266 mL, 1.76 M, 0.468 mmol) was introduced in one portion by syringe to a well-stirred solution of sulfoxide **31a** (more polar, major isomer B, 51.9 mg, 0.120 mmol) and dry MeOH (12.2 mL) in anhydrous ether (2.4 mL) at −78 °C under N_2. After 10 min, water (4 mL) was added dropwise, and the mixture was then warmed to room temperature. Ether (3 × 6 mL) was used to extract the resulting mixture, and the combined organic layer was washed with saturated $NaHCO_3$ and dried. The solvent was removed, and then the resulting residue was subjected to flash column chromatographic purification (silica gel, 1% Et_2O/hexanes) to give a single compound **36** (26.3 mg, 71%) as a colorless liquid.

[(1*Z*,3*Z*)-4-(Cyclohepten-1′-yl)buta-1,3-dien-1-yl]diphenylphosphine Oxide (39a) and Its 1*E*,3*Z* Isomer 40a. To a solution of propargyl alcohol **19c** (203 mg, 1.24 mmol) and triethylamine (0.340 mL, 2.44 mmol) in anhydrous ether (18.6 mL) was introduced at −78 °C under N_2 chlorodiphenylphosphine (0.244 mL, 1.36 mmol) dropwise with a syringe, and the resulting mixture was stirred for 2 h and then at room temperature overnight. The reaction was quenched with water (6.2 mL), and the resulting mixture was extracted with ether. The organic solution was washed with 5% $NaHCO_3$ and saturated NH_4Cl and dried. Solvent evaporation followed by passage of an ether solution of the residue and concentration of the eluate afforded a viscous residue. The latter was subjected to HPLC separation (reverse-phase Partisil, 40% CH_3CN/acetone) and vacuum drying to give two geometric isomers, each as white solids, in the following order of elution: (1*Z*,3*Z*)-**39a** (180.1 mg, 42%, isomer A, mp 119–122 °C) and (1*E*,3*Z*)-**40a** (201.4 mg, 47%, isomer B, mp 103–104 °C). The ratio of 1*Z*,3*Z* to 1*E*,3*Z* isomers was 47:53 (by weight, 47:53; by ^1H NMR, 48:52; by HPLC, 46:54).

(1*Z*,3*Z*)-Diethyl (4-(Cyclohepten-1′-yl)buta-1,3-dien-1-yl)phosphonate (39b) and Its 1*E*,3*Z* Isomer 40b. To a solution of propargyl alcohol **19c** (306 mg, 1.86 mmol) and triethylamine (0.517 mL, 3.72 mmol) in anhydrous ether (37.2 mL) was added diethyl chlorophosphite (0.330 mL, 2.24 mmol) dropwise at 0 °C under N_2 and, after 5 min, the mixture was allowed to warm to room temperature, and stirring was continued for 12 h. Water (10 mL) was added, and the resulting mixture was extracted with ether. The organic solution was washed with saturated NH_4Cl and dried. Solvent evaporation afforded a viscous residue. Passage of the residue through a short silica gel column with ether followed by concentration of the eluate afforded a residue, which upon HPLC separation (Partisil, 60% EtOAc/hexanes) gave two main components in the following order of elution: (1*Z*,3*Z*)-**39b** (156.4 mg, 30%, less polar, minor isomer A) and (1*E*,3*Z*)-**40b** (250.1 mg, 47%, more polar, major isomer B). The ratio of *Z*,*Z* to *E*,*Z* isomers was 40/60 [38:62 (by yield); 42:58 (by ^1H NMR); 40:60 (by HPLC)].

2-((*tert*-Butyldimethylsilyl)oxy)but-3-yne (42). To a stirred solution of *tert*-butyldimethylchlorosilane (17.15 g, 113.8 mmol), imidazole (15.49 g, 227.5 mmol), and ether (76 mL) at room temperature under N_2 was added but-3-yn-2-ol (**41**, 6.00 mL, 75.8 mmol) by means of a syringe. The stirring was continued for 1 h, and then the reaction was quenched with saturated NH_4Cl (40 mL). The resulting mixture was extracted three times with ether, the organic solution was dried, and then the solvent was removed. Flash column purification (silica gel, 3% Et_2O/hexanes) gave the desired ether **42** (10.08 g, 72%) as a colorless liquid, sufficiently pure for use in the next step.

2-((*tert*-Butyldimethylsilyl)oxy)-6-cycloheptylidenehex-3-yn-5-ol (43). Propargyl alcohol **43** (diastereomeric mixture) was obtained from alkyne **42** and aldehyde **18c** in 86% yield as a viscous liquid after flash column chromatographic purification (silica gel, 25% Et_2O/hexanes) as for preparation of **29a**.

2-((*tert*-Butyldimethylsilyl)oxy)-6-cycloheptylidenehex-3-yn-5-yl Benzoate (44). Propargyl alcohol **43** was reacted with benzoyl chloride as described for preparation of **20a** to yield an oil after solvent evaporation. Chromatotron purification (silica gel, 2% Et_2O and 2% pyridine/hexanes) gave a fraction which was washed with 10% aqueous solution of $CuSO_4$ and then dried. The solvent was evaporated to give the desired diastereomeric mixture of propargyl benzoate **44** (5.241 g, 92%) as a viscous liquid.

3-*tert*-Butyl-2-((*tert*-butyldimethylsilyl)oxy)-6-cycloheptylidenehexa-3,4-diene (45). The desired vinylallene **45** (diastereomeric mixture) was synthesized from **44** in 84% yield as a pale yellow liquid as described above for preparation of **13a**.

3-*tert*-Butyl-6-cycloheptylidenehexa-3,4-dien-2-ol (46). A mixture of vinylallene **45** (1.359 g, 3.75 mmol), ether (7.5 mL), and *n*-Bu_4NF (1 M in THF, 15.0 mL) was stirred at room temperature for 9 h under N_2. The reaction was quenched with saturated aqueous NH_4Cl, the resulting mixture was extracted with ether, and the combined organic solution was dried. The solvent was removed, and then a solution of the residue in ether was passed through a short silica gel column. The eluate was concentrated, and then the residue was subjected to HPLC separation (Partisil, 20% EtOAc/hexanes) to afford the desired diastereomeric vinylallenols **46** (after vacuum drying) in the following order of elution: diastereomer A (less polar, 452.6 mg, 48%); diastereomer B (more polar, 543.9 mg, contaminated by minor impurities by ^1H NMR).

3-*tert*-Butyl-6-cycloheptylidenehexa-3,4-dien-2-one (47). To a stirred, cooled (−60 °C) solution of oxalyl chloride (0.175 mL, 2.01 mmol) in CH_2Cl_2 (distilled over CaH_2, 4.6 mL) was added dropwise by syringe dimethyl sulfoxide (0.311 mL, 4.36 mmol), and then the stirring was continued for 10 min. A solution of vinylallenol **46** (diastereomer A, 452.6 mg, 1.82 mmol) in CH_2Cl_2 (1.8 mL) was added to the Swern reagent by cannula. Methylene chloride (2 × 1 mL) was used for further rinsing the alcohol into the oxidizing solution. After 15 min, Et_3N (1.26 mL) was added dropwise, the mixture was allowed to warm up to room temperature and then water (9.2 mL) was added. The resulting mixture was extracted with CH_2Cl_2, and the combined organic solution was dried. Solvent evaporation followed by Chromatotron purification (silica gel, 5% Et_2O/hexanes) gave the desired ketone **47** (325.5 mg, 73%; 35% from the corresponding TBDMS protected vinylallenyl alcohol **45**) as a pale yellow liquid. Diastereomer B of vinylallenol **46**, which was contaminated with an unidentified impurity (vide supra), was oxidized similarily to afford the same ketone **47** in 26% yield from the TBDMS protected vinylallenyl alcohol **45**. The overall yield of pure ketone **47** was thus 61% for the two steps, deprotection followed by Swern oxidation.

Thermolysis of 3-*tert*-Butyl-6-cycloheptylidenehexa-3,4-dien-2-one (47). A solution of **47** (276 mg, 1.12 mmol) in methylene chloride (22 mL) was refluxed for 12 h under N_2. After the reaction mixture was cooled to room temperature, the solvent was evaporated to give a pale yellow residue. The ^1H NMR spectrum of the crude product revealed a **48**/**49** ratio of 63/37 [similar ratios were obtained by reducing the trienone mixture with $NaBH_4/CeCl_3$/MeOH followed by HPLC separation: 64/36 (by HPLC), 68/32 (by weight)]. The residue was then subjected to Chromatotron purification (silica gel, 10% Et_2O/hexanes) to give the mixture of triene geometric isomers (274 mg, 99%). All attempts to separate the trienes were unsuccessful. Accordingly, the following reduction–oxidation reactions were perfomed in order to separate and characterize the two trienones.

(3*Z*,5*Z*)-3-*tert*-Butyl-6-(cyclohepten-1′-yl)hexa-3,5-dien-2-one (48). Manganese dioxide (315 mg, 3.62 mmol) was added

to a well-stirred solution of trienol **50** (more polar, major isomer B: 36.0 mg, 0.145 mmol) in pentanes (2.9 mL), and the reaction was monitored by TLC. After 2 and 10 h, additional MnO_2 (315 mg and 157 mg, respectively) was added to the reaction mixture. The stirring was continued for another 5 h, at which time TLC showed the reaction to be complete. The mixture was filtered with CH_2Cl_2, and then the filtrate was dried. Solvent evaporation followed by flash column purification (silica gel, 2.5% EtOAc/hexanes) gave the ketone **48** (27.7 mg, 77%) as a pale yellow liquid.

(3*E*,5*Z*)-3-*tert*-Butyl-6-(cyclohepten-1′-yl)hexa-3,5-dien-2-one (49). Manganese dioxide (1.794 g, 20.6 mmol) was added to a well stirred solution of trienol **51** (less polar, minor isomer A: 128.2 mg, 0.516 mmol) in pentanes (10.3 mL). After 3 h, TLC showed that the reaction was not complete, and additional MnO_2 (1.70 g) and pentanes (10 mL) were added. Further portions of MnO_2 (1.80 g and 1.82 g) were again added after 7 and 10 h, respectively. The stirring was continued for another 5 h, at which point TLC showed the reaction to be complete. The mixture was filtered with ether and dried. Solvent evaporation followed by HPLC purification (Partisil, 2.5% EtOAc/hexanes) gave the pure ketone **49** (15.0 mg, 12%) as a pale yellow liquid. This reaction was run only once, and no further attempts were made to improve this procedure.

(3*Z*,5*Z*)-3-*tert*-Butyl-6-(cyclohepten-1′-yl)hexa-3,5-dien-2-ol (50) and Its 3*E*,5*Z* Isomer 51. A mixture of isomeric trienones **48** and **49** (from the above thermal rearrangement of **47**; 452.5 mg, 1.84 mmol), MeOH (distilled over Mg, 5.5 mL), and $CeCl_3$ (726 mg) was stirred at 0 °C under N_2. Sodium borohydride (107 mg, 2.8 mmol) was added in one portion. The stirring was continued for 5 min, and the reaction was quenched with water (22.4 mL). The resulting mixture was extracted with ether, and the organic solution was dried. Solvent evaporation afforded a residue, which was passed through a short silica gel column with ether, and the resulting eluate was then concentrated. The residue was subjected to HPLC separation (Partisil, 20% EtOAc/hexanes) and vacuum drying to give two alcohols as viscous liquids in the following order of elution: **51** (less polar, minor isomer A, 130.7 mg, 28%) and **50** (more polar, major isomer B, 273.8 mg, 60%).

4-((*tert*-Butyldimethylsilyl)oxy)-1-(2′,6′,6′-trimethylcyclohexen-1′-yl)pent-2-yn-1-ol (53). Propargyl alcohol **53** was prepared from alkyne **42** and β-cyclocitral (**52**) in 94% yield as a colorless viscous liquid after flash column purification (silica gel, 20% Et_2O/hexanes) as described above for preparation of **29a**.

4-((*tert*-Butyldimethylsilyl)oxy)-1-(2′,6′,6′-trimethylcyclohexen-1′-yl)pent-2-yn-1-yl Benzoate (54). To a well-stirred solution of a diastereomeric mixture of propargyl alcohol **53** (3.424 g, 10.17 mmol) in pyridine (10.2 mL) at 0 °C was added benzoyl chloride (1.24 mL, 10.7 mmol) dropwise using a syringe. The stirring was continued at 0 °C for 5 min and at room temperature for 10 min. The reaction was then quenched with 5% $NaHCO_3$ (40.7 mL), and the resulting mixture was extracted three times with ether. The combined organic solution was washed with saturated $CuSO_4$ and dried. Solvent evaporation on a rotary evaporator and vacuum drying gave the desired propargyl benzoate **54** (diastereomeric mixture; 9.875 g, 97%) as a viscous liquid.

4-Hydroxy-1-(2′,6′,6′-trimethylcyclohexen-1′-yl)pent-2-yn-1-yl Benzoate (55). To a well-stirred solution of a diastereomeric mixture of propargyl benzoate **54** (4.352 g, 9.88 mmol) in THF (19.8 mL) was added a solution of *n*-Bu_4NF (39.5 mL, 1.00 M in THF, 39.5 mmol) in one portion by means of a syringe. The stirring was continued for 1 h, and then the reaction was quenched with saturated NH_4Cl (158 mL). The resulting mixture was extracted three times with ether, and the organic solution was dried. The solvent was removed on a rotatory evaporatory under reduced pressure, and the residue was subjected to flash column purification (silica gel, 30% Et_2O and 2% pyridine/hexanes). The major fraction was then washed with saturated $CuSO_4$ and dried. Solvent evaporation followed by vacuum drying gave the desired alcohol **55** (diastereomeric mixture; 2.969 g, 92%) as a white solid.

1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)penta-1,2-dien-4-ol (56). A mixture of 1,2-diiodoethane (224 mg, 0.795 mmol), samarium metal powder (131 mg, 0.871 mmol), and THF (4.0 mL) were stirred for 1 h at room temperature under N_2. The deep blue SmI_2 solution was added to a well-stirred mixture of a diastereomeric mixture of propargyl benzoate **55** (118.1 mg, 0.362 mmol), *s*-BuOH (0.036 mL, 0.39 mmol), $Pd(PPh_3)_4$ (0.9 mg), and THF (1.8 mL) under N_2 by cannula, and the resulting mixture was stirred for 10 min. The reaction was quenched with saturated NH_4Cl, and the organic layer was separated from the aqueous layer. The aqueous solution was extracted with ether, and the combined organic solution was dried. Solvent evaporation followed by Chromatotron purification (silica gel, 35% Et_2O/hexanes) and vacuum drying gave a mixture of allenol diastereomers **56** (60.8 mg, 81%) as a viscous iquid. The diastereomeric mixture was carried onto the next step without separation. For characterization purposes, a small portion of the mixture was subjected to HPLC separation (Partisil, 30% EtOAc/hexanes) to afford in order of elution diastereomer A (less polar) and diastereomer B (more polar) in a ~1:1 ratio.

1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)penta-1,2-dien-4-one (57). Periodinane (the Dess–Martin reagent, 409 mg, 0.935 mmol) was added in one portion to a well-stirred solution of a diastereomeric mixture of vinylallenol **56** (175.4 mg, 0.850 mmol) in CH_2Cl_2 (1.7 mL) under N_2 at 0 °C. The stirring was continued at 0 °C for 10 min and at room temperature for 5 min and then the mixture was diluted with ether (17 mL), and a solution of $Na_2S_2O_3 \cdot 5H_2O$ (1.624 g, 6.54 mmol) in saturated aqueous $NaHCO_3$ was added. The mixture was vigorously stirred for another 5 min, and the organic layer was separated from the aqueous layer. The organic extract was washed with water and dried. Gravity filtration followed by solvent evaporation gave a residue which was filtered with ether through a short silica gel column. The eluate after concentration afforded a residue which was subjected to HPLC purification (Partisil, 15% EtOAc/hexanes) to give the desired vinylallenone **57** contaminated by a small amount of an inseparable impurity. The presence of small amounts of rearranged products was also detectable. For the thermal rearrangement study, the residue after workup was subjected to Chromatotron purification (silica gel, 15% Et_2O/hexanes) and used directly since it was prone to ready isomerization.

(1(1′)*Z*,2*Z*)-1-(6′,6′-Dimethyl-2′-methylenecyclohexylidene)pent-2-en-4-one (58) and Its 1(1′)*Z*,2*E* Isomer 59. The Chromatotron-purified (silica gel, 15% Et_2O/hexanes) vinylallenone **57** (prepared from oxidation of 100 mg of vinylallenol **56** using the Dess–Martin reagent as described in the preceding experiment) was dissolved in C_6D_6 (0.5 mL) in an NMR tube. The tube was flushed with N_2, cooled to dry ice temperature, evacuated, and sealed. The NMR tube containing the vinylallenone was thermolyzed in an oil bath at 68.5 °C for 0.5 h and cooled, and then an ^1H NMR spectrum was taken. After the solvent was evaporated, the residue was subjected to HPLC purification (Partisil, 10% EtOAc/hexanes) to give in order of elution two geometric isomers: (1(1′)*Z*,2*Z*)-**58** (19.0 mg, 19% from the vinylallenol; less polar isomer A) and (1(1′)*Z*,2*E*)-**59** (16.7 mg, 17% from the vinylallenol; more polar isomer B). The A/B ratio was 50/50 (53/47 by weight, 47/53 by HPLC, and 50/50 by NMR). In control experiments, the individual geometric isomers were dissolved in C_6D_6, sealed in two separate NMR tubes, and thermolyzed at 68.5 °C as described above. The isomers were stable for at least 1 h at this temperature.

3-*tert*-Butyl-1-(2′,6′,6′-trimethylcyclohexen-1′-yl)penta-1,2-dien-4-ol (60). The desired diastereomeric mixture of the vinylallenol **60** was prepared from **55** as a colorless oil in 52% yield after chromatotron purification (silica gel, 30% Et_2O/hexanes) according to the procedure for synthesis of **13a**.

3-*tert*-Butyl-1-(2′,6′,6′-trimethylcyclohexen-1′-yl)penta-1,2-dien-4-one (61). To a solution of oxalyl chloride (0.150 mL, 1.72 mmol) in CH_2Cl_2 under N_2 at −60 °C was added dropwise dimethyl sulfoxide (0.058 mL, 0.82 mmol, dried over type 4A molecular sieve) by syringe, and then the mixture was stirred for 10 min. A solution of a diastereomeric mixture of vinylallenol **60** (376.6 mg, 1.43 mmol) in CH_2Cl_2 (1.4 mL) was added via cannula. Methylene chloride (2 × 1 mL) was used to rinse the remaining vinylallenol into the reaction mixture. After 30 min, Et_3N (1.03 mL) was added, and the mixture was warmed to room temperature. Stirring was continued for 10 min, and then water (9.3 mL) was added. The organic layer was separated from the aqueous layer, and the latter was extracted with CH_2Cl_2. The combined organic solution was dried, and the solvent was removed. HPLC purification (Partisil, 2% EtOAc/hexanes) gave the desired

vinylallenone 61 as a colorless liquid (229.4 mg, 62%).

(1(1′)*Z*,2*Z*)-3-*tert*-Butyl-1-(6′,6′-dimethyl-2′-methylenecyclohexylidene)pent-2-en-4-one (62) and Its 1(1′)*Z*,2*E* Isomer 63. A solution of vinylallenone **61** (210 mg, 0.806 mmol) in benzene (1.5 mL) was added to an ampoule under a nitrogen atmosphere. The solution was cooled to dry ice temperature and evacuated, and then the ampoule was sealed. The ampoule containing the vinylallenone was heated in an oil bath at 68.5 °C for 17.5 h. The ampoule was cooled and then opened. Three drops of the solution was transferred to C_6D_6 in an NMR tube in order to determine the (1(1′)*Z*,2*Z*)-**62**/(1(1′)*Z*,2*E*)-**63** ratio (62:38 ratio by ^{1}H NMR). Finally, HPLC purification (Partisil, 2% EtOAc/hexanes) gave the trienones in the following order of elution: (1(1′)*Z*,2*Z*)-**62** (111.4 mg, 53%, major isomer A, less polar) and (1(1′)*Z*,2*E*)-**63** (77.2 mg, 37%, minor isomer B, more polar) as colorless liquids. The ratio of geometric isomers was 61/39: 62/38 (^{1}H NMR); 61/39 (HPLC); 59/41 (yield). In separate control experiments, the two geometric isomers were stable to the thermal conditions described above.

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Supplementary Material Available: Spectral data for all new compounds and general experimental details (80 pages). Ordering information is given on any current masthead page.

Stereo- and Enantiospecific Syntheses of (−)-Reiswigins A and B. Assignment of Absolute and Relative Configuration

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The first synthesis of reiswigin A (**20**) was accomplished in only eight steps providing optically pure material in 7% overall yield with control of the relative and absolute stereochemistry at carbons 1, 7, and 8. The synthesis was designed to provide a mixture of isomers at carbon 13 since the stereochemistry at this center was not assigned in the structure determination. Sakurai reaction of allylic silane **12** with enone **13** affords ketone **5** as a mixture of diastereomers. Protection of the ketone, cleavage of the double bond, and intramolecular aldol reaction gives cyclopentenecarboxaldehyde **4**. Addition of 3-methyl-3-butenylmagnesium bromide to imine **17** by Koga's procedure followed by alkylation of the enamide with methyl iodide gives **3**. This crucial step not only controls the relative stereochemistry at carbons 1, 7, and 8 but also effects a kinetic resolution, permitting assignment of absolute stereochemistry to reiswigin A as shown in **20**. Me_2AlCl-catalyzed ene reaction of **3** gives alcohol **19**. Oxidation of the alcohol and acid-catalyzed conjugation of the double bond and hydrolysis of the ketal gives a mixture of reiswigin A (**20**) and **21**. The stereochemistry at carbon 13 is assigned based on NMR shifts. Addition of cyclohexenylpotassium to crotonaldehyde gives dienol **26b**. Anionic oxy-Cope rearrangement gives aldehyde **28**, which was used for stereo- and enantiospecific syntheses of both reiswigins A (**20**) (11 steps, 12%) and B (**36**) (11 steps, 6%).

Diterpenes reiswigins A (**1**) and B (**2**) were recently isolated by Koehn and co-workers from a deepwater marine organism *Epipolasis reiswigi* collected by submersible at 330 m.[1] These compounds show potent in vitro activity against Herpes simplex type I virus and murine A59 hepatitis virus. The structure and relative stereochemistry at three of the four chiral centers (carbons 1, 7, and 8) were determined by a combination of one- and two- dimensional NMR spectroscopy and mass spectroscopy. The relative configuration at carbon 13 and the absolute stereochemistry could not be assigned from the available data. The structural novelty and potentially useful biological activity of these unusual hydroazulenoid diterpenes encouraged us to develop a practical synthesis of these compounds which would permit complete structure assignment and allow the preparation of analogues for biological testing.

Initially, we chose to develop a synthesis of **1** which would control the relative and absolute stereochemistry at carbons 1, 7, and 8 but would lead to a mixture of isomers at carbon 13 so that we would be assured of producing both reiswigin A and its epimer at carbon 13.[2] It was our expectation that, with both isomers in hand, we would be able to assign the stereochemistry of reiswigin A. It was therefore important that the synthesis be designed to permit modification of the stereochemistry at carbon 13 once we had assigned it.

Retrosynthetic analysis suggested that the cycloheptenone moiety of **1** could be most easily made by a type II intramolecular ene reaction of unsaturated aldehyde **3** as developed by Marshall and Andersen,[3] followed by oxidation of the alcohol and conjugation of the double bond. An intramolecular aldol condensation was a less attractive method for ring closure since two regioisomeric enones could be formed. Aldehyde **3** could be prepared by conjugate addition to enal **4** followed by methylation of the enolate. Conjugate addition to **4** should occur selectively from the β-face. Methylation of the enolate, however, would be expected to occur predominantly from the less hindered undesired α-face rather than the desired β-face. Enal **4** should be readily available by oxidative cleavage of cyclohexene **5** followed by intramolecular aldol

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