Propensity of 4-Methoxy-4-vinyl-2-cyclopentenones Housed in Tri- and Tetracyclic Frameworks for Deep-Seated Photochemical Rearrangement

Leo A. Paquette,* Fabrice Gallou, Zhong Zhao, David G. Young, Jian Liu, Jiong Yang, and Dirk Friedrich†

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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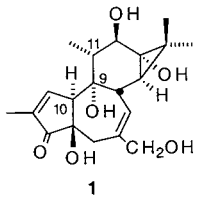
Abstract: The excited-state behavior of a select group of highly enantioenriched tri- and tetracyclic 2-cyclopentenones has been examined in two solvents. Prepared by a convergent pathway involving the coupling of cyclopentenyl bromide **12** to several chiral ketones followed by desilylation, perruthenate oxidation, and ring-closing metathesis, the reactants were conveniently irradiated through quartz. Following promotion to the triplet level, a cyclopropylcarbinyl biradical intermediate is presumably generated provided that the double bond linked to C4 is not saturated. Four pathways have been observed to operate, only one of which has been observed previously under rather different conditions. The new photorearrangements include non-Norrish fragmentation to a ketene, generation of a spirocyclic intermediate, and ring expansion to a cyclobutyl radical in advance of intramolecular fragmentation of the four-membered ring. In the latter instance, a hydroazulenone derivative is formed. In the majority of the examples, product structure and absolute stereochemistry were corroborated by means of X-ray diffraction analysis.

In view of the co-occurrence of phorbol (**1**) and ingenol (**2**) as their fatty acid esters in a wide variety of *Euphorbia* species[1,2]and the impressive tumor-promoting properties of these substances,[3] we thought it of considerable interest to determine if **2** could be synthesized in possible biomimetic fashion from a precursor structurally related to **1**.[4] Despite the efforts of



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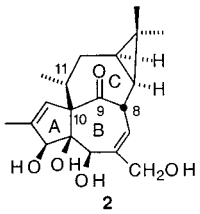

2

several research groups, **2** has not yet yielded to synthesis.[5] The chief obstacle to this challenge appears to be the highly strained nature of the bridge that spans C8 and C10 in an "inside−outside" manner. Accordingly, any plan that entails the potential migration of C11 away from C9 (as found in phorbol) to C10 as in ingenol is certain to be endothermic in nature.[6] Thus, a photoisomerization was viewed to be an attractive option that might surmount this hurdle. Described herein is a remarkable array of deep-seated photorearrangements uncovered for the substrates selected for study.[7] While none has advanced a successful approach to **2**, the several excited-state pathways defined during this investigation significantly embellish our appreciation of the boundary limits of cyclopentenone photochemistry.

Strain Energy and Stereoalignment Considerations. The relative stereochemistry at C8 and C10 in ingenol is primarily responsible for locking **2** into near rigidity. The C-ring is notably twisted. Consequently, closure of the B−C substructure has proven to be difficult.[8−12] Although molecular mechanics (MM3) calculations of the heat of formation of various phorbol/ingenol prototypes are likely to be only approximate because of the divergent functionality involved, they establish that

† Present address: Aventis Pharmaceuticals, Inc., 1041 U.S. Route 202/206, P.O. Box 6800, Bridgewater, NJ 08807-0800.

(1) Hecker, E. *Carcinogenesis, Vol. 2. Mechanisms of Tumor Promotion and Cocarcinogenesis*; Slaga, T. J., Sivak, A., Boutwell, R. K., Eds.; Raven Press: New York, 1978.

(2) Hecker, E.; Adolf, W.; Hergenhahn, M.; Schmidt, R.; Sorg, B. *Cellular Interactions by Environmental Tumor Promoters*; Fujuki, H., et al., Eds.; Japan Sci. Soc. Press, Tokyo/VNU Science Press: Utrecht, 1984; pp 3−36.

(3) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193.

(4) (a) Rigby, J. H. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publ., Amsterdam, 1993; Vol. 12, p 233. (b) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387.

(5) For the earlier efforts of this group, consult: (a) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (b) Ross, R. J.; Paquette, L. A. *J. Org. Chem.* **1987**, *52*, 5497. (c) Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192. (d) Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589. (e) Paquette, L. A.; Sauer, D. R.; Edmondson, S. D.; Friedrich, D. *Tetrahedron* **1994**, *50*, 4071.

(6) Appendino, G.; Tron, G. C.; Cravotto, G.; Palmisano, G.; Annunziata, R.; Baj, G.; Surico, N. *Eur. J. Org. Chem.* **1999**, 3413.

(7) Preliminary communication: Paquette, L. A.; Zhao, Z.; Gallou, F.; Liu, J. *J. Am. Chem. Soc.* **2000**, *122*, 1540.

(8) (a) Winkler J. D.; Henegar K. E.; Williard, P. G. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (b) Winkler J. D.; Hong B.-C.; Hey J. P.; Williard, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 8839. (c) Winkler, J. D.; Henegar, K. E.; Hong, B.-C.; Williard, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 4183. (d) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296.

(9) (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (b) Funk, R. L.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Org. Chem.* **1993**, *58*, 5873.

(10) Rigby, J. H.; de Claire, V.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992.

(11) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032.

(12) Molander, G. A.; Bessieres, B.; Eastwood, P. R.; Noll, B. C. *J. Org. Chem.* **1999**, *64*, 4124.

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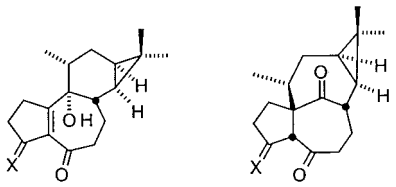
ingenanes are the more strained isomers by a significant margin. The model structures **3** and **4** constitute an exemplary pair.

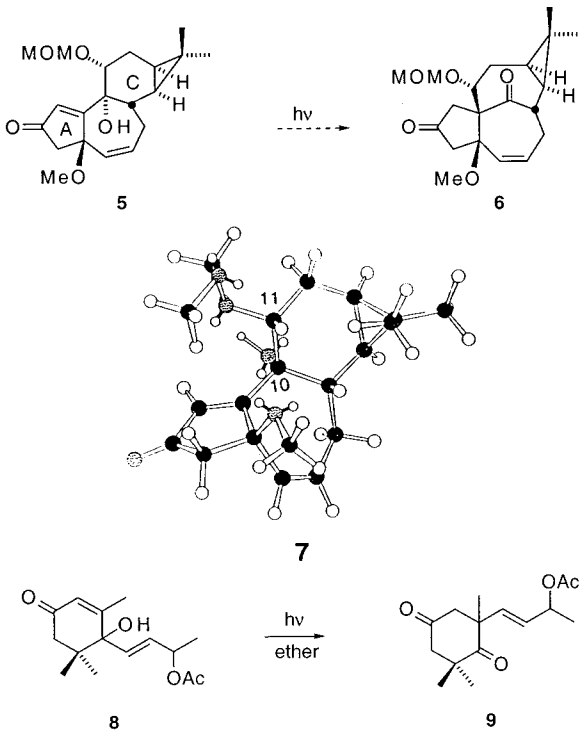


3a, X=H_2
b, X=O

4a, X=H_2
b, X=O

Despite the fact that **4** contains an additional carbonyl group, the thermodynamic benefits of this linkage (179 kcal/mol) relative to the energy of a C═C bond (146 kcal/mol) are inadequate to render **4** more stable overall. Thus, **3a** in its lowest energy conformation is approximately 15.8 kcal/mol less strained than **4a**. For the **3b**/**4b** pair, the ingenane is assessed to possess 13.2 kcal/mol of additional energy.

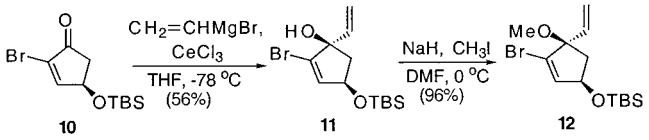
Entirely comparable computational analysis of **5** reveals that



its C9−C11 bond is particularly well stereoaligned with the π-bond of the neighboring cyclopentenone moiety (see **7**). A conformation can be attained in which there is also good stereoalignment of the p orbitals at C5 and C10. On the basis of the reported ease with which vomifoliol acetate (**8**) and related compounds undergo photoisomerization to 1,4-cyclohexanediones exemplified by **9**,[13] we were prompted to select **5** as a prototypical substrate. At issue was the feasibility of effecting its excited-state conversion into the ingenane **6** by virtue of a 1,2-shift from its photoexcited state. This process requires the breaking of a σ bond at some stage (a "σ-route migration"). Alternatively, a "π-route migration" involving a cyclopropylcarbinyl biradical is also possible. This investigation was undertaken to make suitable distinction between these options.

Synthesis of the Reactants Leading to 5. The preparative route to the target was designed to be enantioselective. Thus,

Scheme 1



the synthetic pathway began with the readily available (4*R*)-(+)-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one (>95% ee),[14] bromination−dehydrobromination of which gave rise to **10**[15] (Scheme 1). Exposure of **10** to vinylmagnesium bromide in the presence of anhydrous cerium trichloride to deter unwanted enolization[16] resulted in preferred nucleophilic attack from the face anti to the siloxy substituent with predominant generation of **11**. Subsequent O-methylation gave rise smoothly to **12** as planned.

The electrophilic partner was obtained by the sequence of transformations outlined in Scheme 2. Following the efficient conversion of commercially available (+)-2-carene into (1*R*,3*R*,6*S*)-4-methylene-7,7-dimethylbicyclo[4.1.0]heptan-3-ol,[6d,17] the allylic hydroxyl was protected as the MOM ether. Deprotonation of the resulting norcaranone **13** was seen to favor the cyclopropylcarbinyl center. Although the direction of enolization of α-alkoxy ketones is sometimes difficult to predict,[18] the situation in **13** is one in which the fused dimethylcyclopropane ring blocks the top face from approach by the base. Enolization toward the OMOM group is accordingly deterred for steric reasons. Attempts to bring about the C-allylation of this reactive intermediate gave **14** in a maximum yield of 28%. Not only did it prove difficult to separate **14** from O-allylated, bisallylated, and cyclopropane-cleaved byproducts, the allyl side chain was projected in undesired β fashion (NOE analysis).

To circumvent this complication, the potassium enolate of **13** was O-acylated with allyl chloroformate to deliver **15** quantitatively. This intermediate served well as a precursor to **16** into which it was transformed stereo- and regiospecifically with reasonable efficiency when exposed to 5 mol % of the tris(dibenzylideneacetone)dipalladium·chloroform complex[19] in 1,2-dimethoxyethane containing 10 mol % Diphos.[20] Advantage was then taken of the ease with which bromide **12** undergoes halogen−metal exchange in the presence of 2 equiv of *tert*-butyllithium.[21,22] Admixture of the resulting cycloalkenyl organometallic with **16** in the presence of anhydrous $CeCl_3$ at low temperature resulted in the formation of **17** in 95% yield. In a two-step sequence involving fluoride ion-promoted desilylation and perruthenate oxidation,[23] **17** was transformed via **18** into **19**, thereby setting the stage for ring-closing metathesis in the presence of Grubbs' ruthenium-based catalyst.[24] The

(13) Katsumura, S.; Isoe, S. *Helv. Chim. Acta* **1982**, *65*, 1927.

(14) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1996**, *73*, 36.

(15) Nakazawa, M.; Sakamoto, Y.; Takahashi, T.; Tomooka, K.; Ishikawa, K.; Nakai, T. *Tetrahedron Lett*. **1993**, *34*, 5923.

(16) Imamato, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392.

(17) (a) Gollnick, K.; Schroeter, S.; Ohloff, G.; Schade, G.; Schenck, G. O. *Liebigs Ann.* **1965**, *687*, 14. (b) Gollnick, K.; Schade, G. *Tetrahedron* **1966**, *22*, 133.

(18) Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857.

(19) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. J. *Organomet. Chem*. **1974**, *65*, 253.

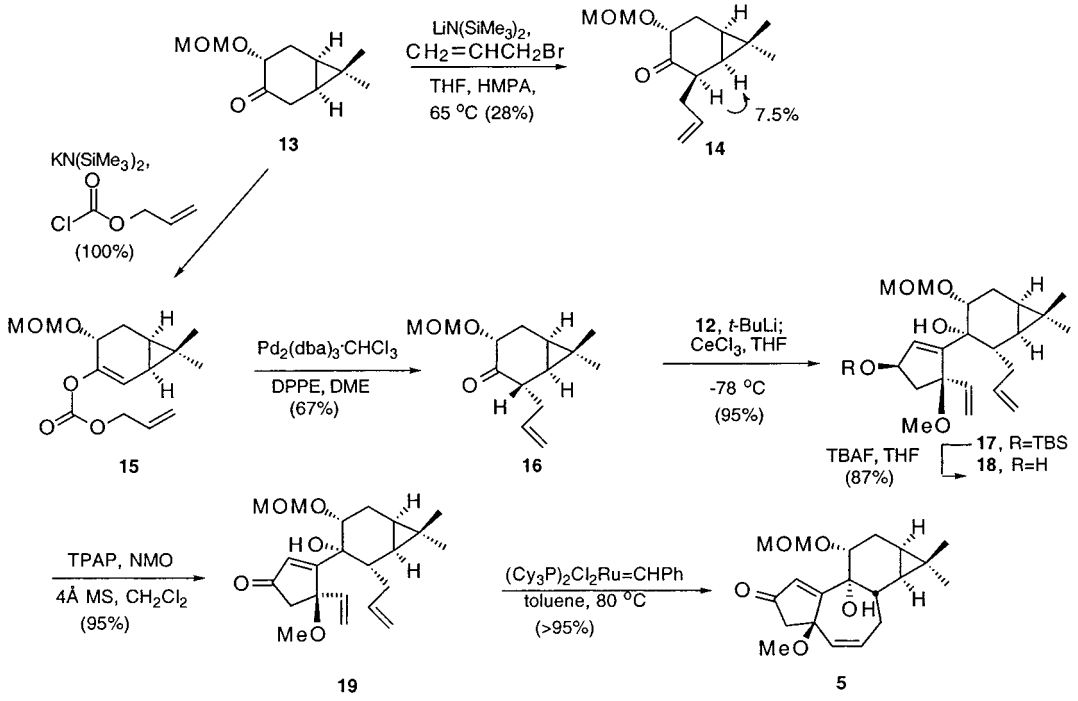
(20) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (b) Tsuji, J.; Ohashi, Y.; Minami, I. *Tetrahedron Lett*. **1987**, *28*, 2397.

(21) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(22) (a) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. (b) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(23) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Scheme 2

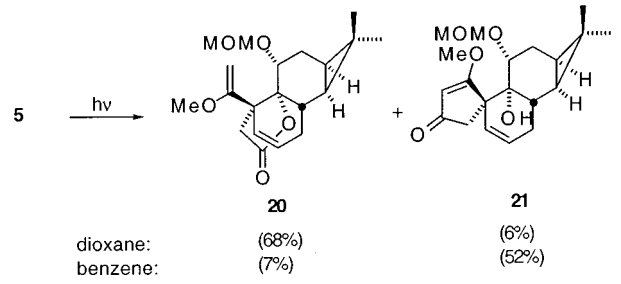


cyclization leading to generation of the cycloheptene ring was notably efficient. No involvement of the double bond within the cyclopentenone ring could be detected. Beyond this, chiral HPLC analysis indicated **5** to be enantiomerically pure.

Exploratory Photochemistry and Product Structure Elucidation. While four examples of the conversion of ingenane congeners into tigliane systems (i.e., formally **2** → **1**) have been reported,[6,25,26] bond migration in the reverse direction has not been observed for reasons of strain buildup as outlined above. The projected conversion of **5** to **6** was founded not only on stereoelectronic grounds but as well on the realization that the isomerization takes the form of an excited-state vinylogous α-ketol rearrangement. Examples of the susceptibility of α-hydroxy ketones to base-promoted equilibration are many.[27] The most important consideration derived from the fact that ultraviolet light has long been recognized[28] to transform 2-cyclopentenones readily into their corresponding triplet excited states.[29] The efficiency of this step was expected to contribute heavily to initiation of the photochemical events in the A-ring of **5**.

Irradiation of **5** with a 450 W Hanovia lamp through quartz in either dioxane or benzene solution led predominantly to the two solid products **20** and **21** (Scheme 3), neither of which exhibited any spectral evidence (viz., C/H correlation analysis) that the integrity of ring C had been altered as required of **6**. Interestingly, the production of **20** was significantly favored (>10:1) over **21** in the more polar reaction medium. The reverse was true of the product distribution in benzene (1:7.5). The infrared spectrum of **20** was characterized by an intense carbonyl absorption at 1775 cm^{-1} suggesting that the ketone carbonyl of the starting material had been transformed into an ester or a lactone. This finding was corroborated by the appearance of a carbon signal at δ 175.9. The ^1H NMR spectrum also revealed the presence of a terminal vinyl group (=CH_2), an isolated methylene group α to the carbonyl (as a widely separated AB pair at δ 3.40 and 2.22), and a residual intracyclic double bond. Firm evidence confirming the detailed structure and absolute configuration of **20** was derived from an X-ray crystallographic analysis (Figure 1).

Scheme 3



The spectral features of **21** proved to be entirely different, except for the identical way in which the B/C substructure could be mapped. In the infrared, strong bands are seen at 3400 and 1684 cm^{-1} thereby signaling the unchanged nature of the tertiary hydroxyl but significant electronic perturbation of the ketone carbonyl relative to **5** (1714 cm^{-1}). Although three olefinic protons were noted, one of these had migrated significantly upfield (to δ 5.32) relative to its position in the spectrum of **5** (δ 6.17). This proton was clearly no longer serving as the β-H of an α,β-unsaturated carbonyl fragment. In addition, the quaternary methoxyl-substituted carbon displayed by **5** (δ 82.9) was replaced by a very different fully substituted carbon (δ 72.4) that caused us to entertain a spirocyclic structure. This proposal received ultimate corroboration following X-ray diffraction measurements (Figure 2). The absolute configuration of the newly generated stereogenic center holds particular mechanistic significance.

(24) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
(25) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423.
(26) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265.
(27) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772 and relevant references therein.
(28) Eaton, P. E. *J. Am. Chem. Soc.* **1962**, *84*, 2344.
(29) Eaton, P. E.; Hurt, W. S. *J. Am. Chem. Soc.* **1966**, *88*, 5038. (b) For a recent review, consult: Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

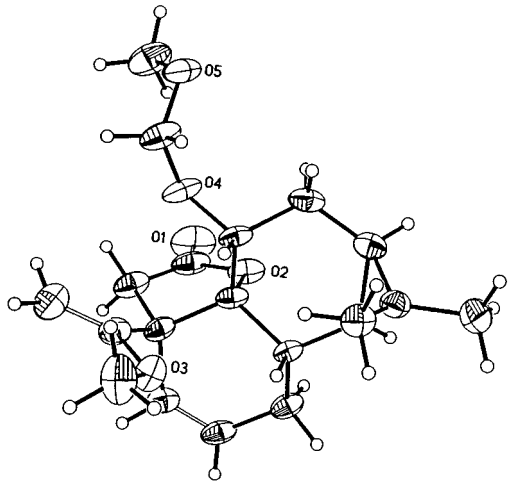


Figure 1. Computer-generated perspective drawing of **20** as determined by X-ray crystallography.

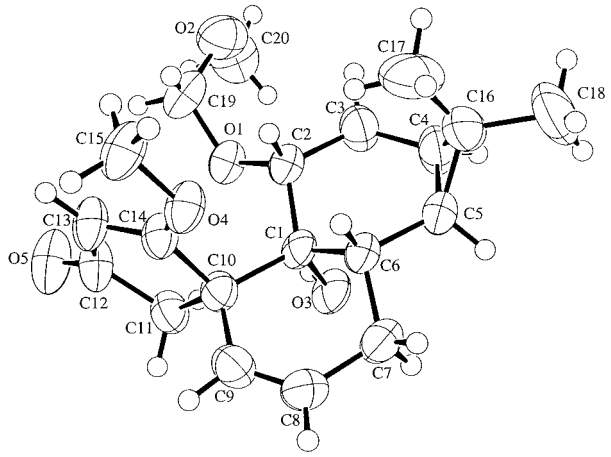


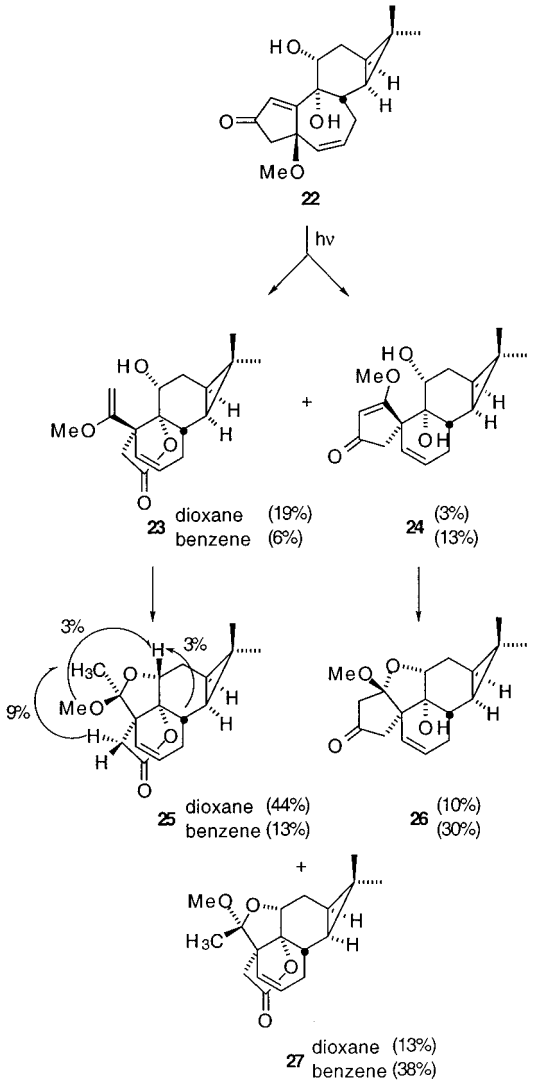
Figure 2. Computer-generated perspective drawing of **21** as determined by X-ray crystallography.

Consequences of MOM Deprotection. A less than obvious property of **20** and **21** is the close proximity of the MOM-protected oxygen atom to the vinyl ether functionality in both structures. Consequently, in an effort to ascertain whether a comparable pattern of photoisomerization would be followed and if further interaction of these functional groups would be observed, **5** was selectively hydrolyzed to **22** with chlorotrimethylsilane and tetra-*n*-butylammonium bromide[30] (efficiency of 66%). In photochemical experiments that were performed identically at room temperature in dioxane and benzene as the solvents of choice, **22** gave evidence of being transformed as before into a pair of isomeric products. However, as the reaction mixtures were allowed to stand longer and longer, additional compounds made their appearance (Scheme 4). Direct evidence that only **23** and **24** represent primary photoproducts was easily gained by appropriate studies that monitored product appearance versus time. The close similarities of the ^{1}H and ^{13}C NMR spectra of **23** and **24** to those of **20** and **21** served to define their structures to be as shown.

It could be directly surmised from COSY analyses of **25**−**27** that the norcarane part structure had not been chemically altered. Also firmly established by this technique was the presence of two α-keto methylene groups in **26**, but only one in both **25** and **27**. In all three photoisomers a double bond had been lost, although the degree of unsaturation remained the same. Consequently, an additional ring had necessarily been generated in all three structures. The presence of a lactone carbonyl in **25** and **27** was deduced from an intense infrared band at 1774−1772 cm^{-1}. In **26**, the carbonyl absorption was shifted to lower wavenumber (1748 cm^{-1}), in a region characteristic of a cyclopentanone ring. Another major distinguishing feature was the appearance of an added methyl singlet in the ^{1}H NMR spectrum of **25** and **27**, but not in **26**. Although the NOE analysis of **27** was somewhat complicated by the fortuitous overlap of several signals, the stereochemistry of **25** was revealed on this basis (see formula). The distinction between these two epimers proved to be fully consistent with all the available spectral parameters.

(30) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213.

Scheme 4



When similar attempts to deduce the absolute configuration of **26** did not lead to unequivocal stereochemical assignments, alternative recourse was made to X-ray diffraction analysis. The ORTEP diagram depicted in Figure 3 reveals that **26** forms as a consequence of the stereodirected intramolecular Michael addition of the hydroxyl in **24** to the neighboring 3-methoxycyclopentenone to afford a stable, stereoisomerically pure acetal subunit.

Saturation of the Cycloheptene Double Bond. As it was becoming increasingly apparent that the mechanistic features of the above photoisomerizations involved the cycloheptene double bond, corresponding interest in the response of the

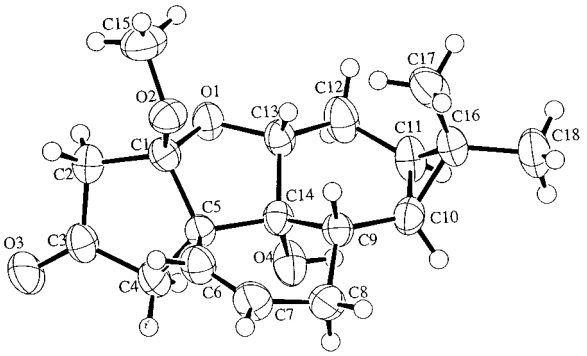
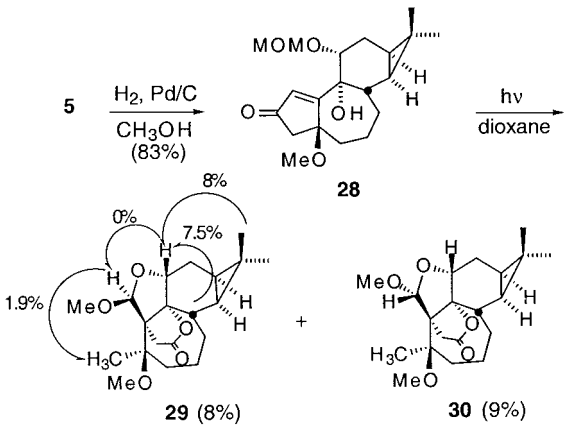


Figure 3. Computer-generated perspective drawing of **26** as determined by X-ray crystallography.

Scheme 5

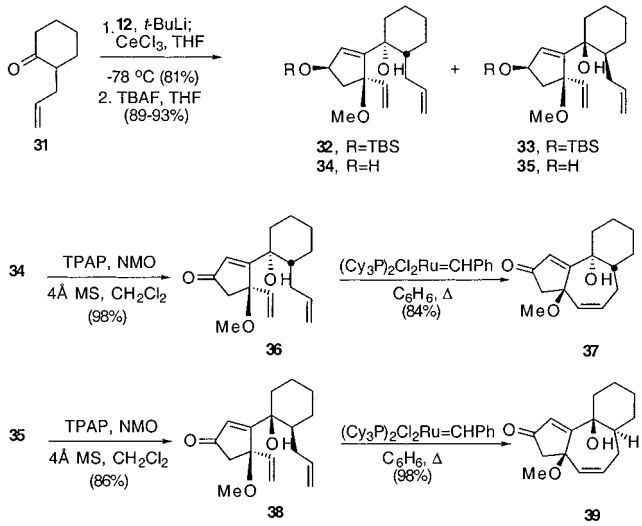


dihydro derivative to photoexcitation grew. Experimentation with **28**, obtained by the controlled hydrogenation of **5**, was expected to help narrow the mechanistic possibilities in a meaningful way. Similar exploratory irradiation of **28** led in low yield to **29** (8%), **30** (9%), and a third photoisomer (<1%) (Scheme 5). In the latter instance, the amount of material was too small for rigorous identification.

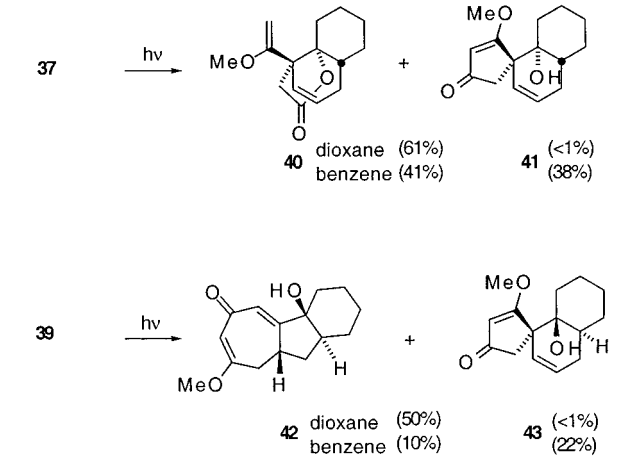
The lactonic nature of both **29** and **30** was readily inferred from their intense infrared bands at 1769 and 1776 cm^{-1}, respectively. These data, combined with the observations of a newly introduced methyl singlet at high field and a reduction in the relative area of the $-OCH_2O-$ signal attributable to the MOM group from two to one, suggested that these photoproducts were pentacyclic. Additional COSY, HMQC, and HMBC experiments confirmed further that this pair of lactones shares a common framework and differs uniquely in the configuration of one center. The final necessary distinction was achieved by NOE methods (see **29**). The presence of two β-oriented methoxyl groups made identification of this epimer fairly straightforward. This comprehensive spectral analysis allowed for unambiguous recognition of the fact that ring B in **28** had not undergone ring contraction in a manner so characteristically adopted by **5** and **22**. These results point to the influential role of B-ring unsaturation on product formation in the earlier studied examples.

Examination of a Diastereomeric Structural Alternative. The convergent assembly process for accessing **5** and its congeners **22** and **28** relied entirely on the coupling of two highly enantioenriched building blocks. As a consequence, we became increasingly intrigued with the prospect of learning whether the photochemical reactivity of a different diastereomer would be matched or mismatched. To this end, we sought to prepare **37** and **39** in order to gain added mechanistic enlightenment. The synthetic route outlined in Scheme 6 began with commercially available 2-allylcyclohexanone (**31**). Reaction of this racemic ketone with the enantiopure lithiated form of **12** in the presence of cerium trichloride gave rise to a mixture of allylic carbinols **32** and **33**, which could be separated by careful chromatography on silica gel. Although the individual desilylation and oxidation of these intermediates gave rise quite efficiently to **36** and **38**, a distinction between their absolute stereostructures was not possible until arrival at a crystalline photoproduct (see below).

Scheme 6



Scheme 7



Ring-closing metathesis of **36** and **38** led conveniently to **37** and **39**, respectively. While the stereodisposition of the three stereogenic centers across rings B and C in **37** parallels that in hand earlier, the situation in **39** is reversed. Included in the resultant modification of conformational features is inter alia the absence of a feasible lactonization pathway. These changes are nicely reflected in the photoconversion of **37** to **40** and **41**, and of **39** to **42** and **43** (Scheme 7). Both product mixtures were readily separated into their pure components via chromatography. Although the high-field ^1H and ^{13}C NMR spectra of **40** and **41** unmistakably identified them to directly parallel **23** and **24** in structure, specific knowledge of their absolute configuration was still lacking. For this reason, the three-dimensional structure of **40** was deduced by crystallographic methods (Figure 4). Definition of the absolute configuration of **40** in this manner permitted reliable definition of the stereochemistry of all eight

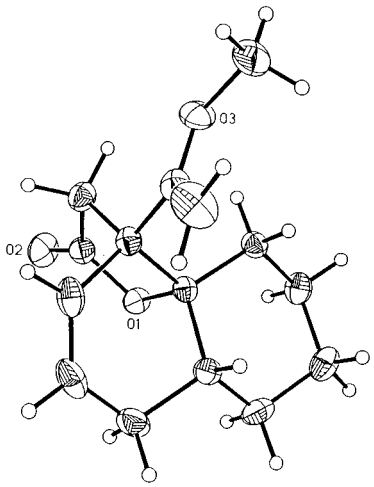


Figure 4. Computer-generated perspective drawing of **40** as determined by X-ray crystallography.

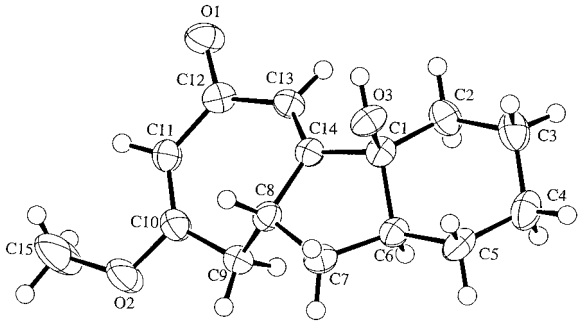


Figure 5. Computer-generated perspective drawing of **42** as determined by X-ray crystallography.

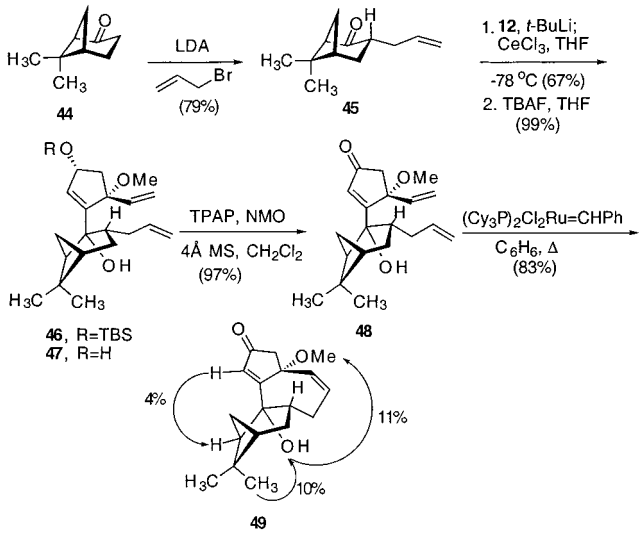
precursors in Scheme 6 as well as the three companion photoproducts.

The spectral features displayed by **42** are entirely different than those of any photoproduct previously encountered in this study. This photoisomer showed infrared bands at 3376, 1666, and 1599 cm^{-1} consistent with retention of the hydroxyl and of the conjugated enone chromophore. However, its ^1H NMR spectrum is characterized by only two olefinic proton signals, the more deshielded appearing as a triplet at δ 5.97 and the second as a doublet at higher field (δ 5.51). The presence of a carbonyl ^{13}C absorption at δ 190.9 and *four* olefinic carbon peaks (δ 173.9, 165.1, 122.1, and 105.2) indicated that the original cycloheptene double bond had become part of a cross-conjugated dienone network. Final definition of its structure as **42** was achieved by means of X-ray crystallographic analysis (Figure 5). The necessary diastereomeric relationship between **41** and **43** requires that the absolute configuration of the B/C-ring junctures be as shown. This conclusion is further supported by the data recorded for **42**.

Not surprisingly, therefore, the stereochemical features that distinguish **37** from **39** exert a primary effect on the excited-state mechanistic pathways. While one eventuates in *B-ring contraction* to the cyclohexene level with tandem lactonization, the second culminates in *twofold ring-A expansion* with generation of a hydroazulenone part structure. Full explication of these phenomena is provided in the sequel.

Probe of a Pinanyl-Fused System. In an effort to change the structural motif of ring C, we have also investigated the consequences of the presence of a bicyclo[3.1.1]heptane subunit in a photochemical precursor. The requisite cyclopentenone **49** was obtained in a comparable manner from (1*R*)-(+)-nopinone

Scheme 8



(**44**, Scheme 8).[31] The stereochemical outcomes of the C-allylation leading to **45** and the subsequent coupling with **12** to generate **46** were controlled by equatorial approach to the enolate anion such that the more stable chair develops, and by the steric contributions of the endo methyl substituent on the substituted methano bridge, respectively. These considerations hold importance because the vinyl and allyl substituents become proximally juxtaposed in trans fashion during the prelude to the ring-closing metathesis that gives rise to **49**. The identification of **49** was made straightforward by the well-separated nature of many key proton signals. Following their proper assignment by making recourse to COSY and HMBC experiments, the NOE correlations depicted on the illustrated structure were arrived at quickly.

Whereas the photolysis of **49** in dioxane did not lead to the formation of characterizable products, comparable treatment of benzene solutions proved conducive to photodimerization. Chromatography on silica gel led to the isolation of **50a** (48%) and **50b** (3%), in addition to a third primary photoproduct (**51**) formed to the extent of 15%. The closely related NMR and mass spectral evidence recorded for **50a** and **50b** suggested that a dimerization reaction course not previously encountered was operational presently.

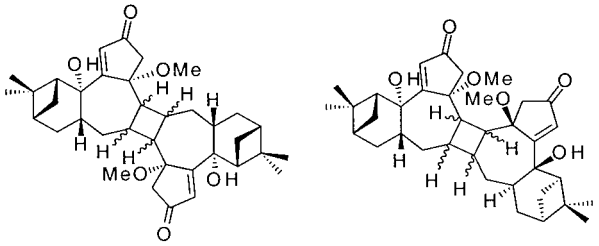
Like the starting material, products **50a** and **50b** also displayed an intense infrared absorption at ca. 1724 cm^{-1} suggesting that the cyclopentenone had been minimally perturbed. Furthermore, their high-field ^1H and ^{13}C NMR spectra revealed that whereas the number of CH_2 and CH_3 groups had also not changed (DEPT analysis), only the conjugated enone double bond remained. Consequently, the π-bond contained within the cycloheptene ring of **49** had to have become involved in the photoinduced bonding process. The full spectral analysis of **50a** and **50b** is given in Supporting Information. The eight formal possibilities given in Scheme 9 (presented in full in the Supporting Information) remain after exclusion of less symmetric alternatives. Photodimers **50a** and **50b** constitute two members of that group. The structural features of **51** continue to elude us.

Mechanistic Discussion

Known Photochemical Reactions of 2-Cyclopentenones. The ability of 2-cyclopentenones to undergo efficient inter- and

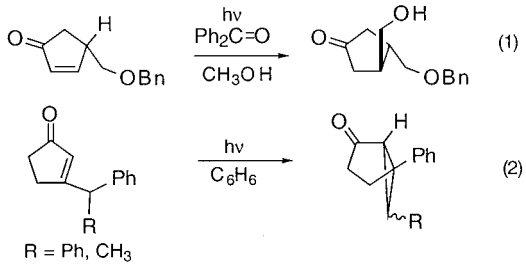
(31) $[\alpha]_D^{20}$ +14.6 (neat).

Scheme 9

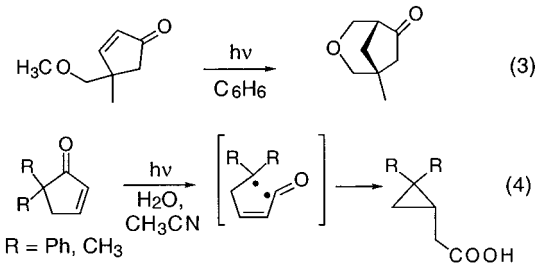


intramolecular photochemical [2 + 2] cycloadditions to alkenes has long been recognized to hold substantial synthetic potential.[32] Cyclobutane ring formation occurs from the triplet excited state of the enone and passes through one or more triplet 1,4-biradical intermediates.[29b,33] The major attractions of this chemistry have been the ease of implementation, frequent high-level regioselectivity, and capacity for delivering complex ring systems.

In addition to the above, the sensitized addition of methanol across the double bond (eq 1)[34] and the photoisomerization of

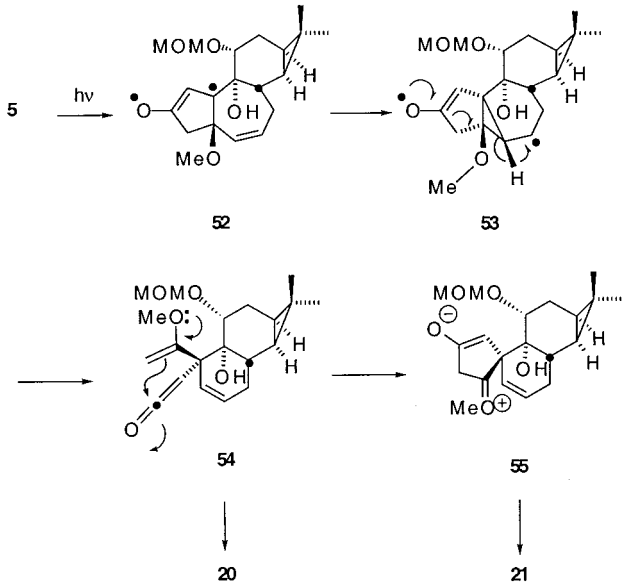


3-substituted derivatives as typified by eq 2[35] have also received significant attention. Furthermore, rearrangements akin to eq 2 are known in which an aryl group at C4 migrates to C3.[36] These processes, as well as intramolecular hydrogen abstraction phenomena (eq 3),[37] are clearly also triggered by activation of



the conjugated double bond.

Scheme 10



On the other hand, the documented examples of Norrish type 1 cleavage as exemplified by eq 4 are few in number.[38] Here, the high level of α-substitution effectively redirects reaction such that generation of the 1,5-biradical operates.

The 2-cyclopentenone systems studied earlier were, however, not designed to elicit and elucidate the quite different processes uncovered in the present investigation. Consequently, the ensuing interpretative discussion is intended to rationalize at the mechanistic level the course of these new and largely unprecedented photoisomerization reactions.

Excited-State Behavior of 5. The first point to be noted is that the original cyclopentenone A-ring in **5** is transformed into either a fused lactone ring or a spirocyclic 3-methoxy-substituted five-membered enone. Concurrently, the cycloheptene B-ring has undergone one-carbon ring contraction in both examples. We consider the most economical pathway to originate with excitation of **5** to its $\pi \rightarrow \pi^*$ state,[29] this initial event being followed by 3-exo cyclization to lead from **52** to **53** (Scheme 10). The occurrence of this bonding into the cycloheptene π-linkage nicely sets the stage for concurrent A-ring fragmentation, rupture of the cyclopropane ring just formed, and evolution of a ketene unit as depicted in **54**. Not only are the stereoelectronics of this process well aligned for stepwise fragmentation, but prevailing stereochemistry also positions the ketene residue syn to the hydroxyl. Intramolecular cyclization within **54** to give **20** presumably operates smoothly. Also, it seems likely that the proximity of the ketene and vinyl ether functionalities in **54** is notably conducive to thermal cyclization as in **55**. Subsequent prototropic shift within this dipolar species would result in charge annihilation and the formation of **21**.

The photochemistry of **22** and **37** can be rationalized in identical terms. The product distribution where **22** is concerned is made more complicated because of postphotochemical events. These involve acid-promoted intramolecular acetalization processes that bring the free hydroxyl group into heterocyclization events (see **25**−**27**).

Contrasting Biradical Reactivity in the Diastereomeric Series. Although the distribution of products from **39** indicates the ultimate operation of a diverted mechanistic pathway, the

(32) Crimmins, M. T. *Chem. Rev*. **1988**, *88*, 1453. (b) Crimmins, M. T.; Reinhold, R. L. *Org. React. (NY)* **1993**, *44*, 297. (c) Crimmins, M. T. *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Paquette, L. A., Eds.: Pergamon: Oxford: 1991; Vol. 5, pp 123−150. (d) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev*. **1995**, *95*, 2003.

(33) For recent developments, see: (a) Andrew, D.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5647. (b) Maradyn, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5359. (c) Andrew, D.; Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc*. **1994**, *116*, 10870. (d) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc*. **1991**, *113*, 8525.

(34) (a) Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3978. (b) Parry, R. J.; Haridas, K.; De Jong, R.; Johnson, C. R. *Tetrahedron Lett*. **1990**, *31*, 7549. (c) Buenger, G. S.; Marquez, V. E. *Tetrahedron Lett*. **1992**, *33*, 3707.

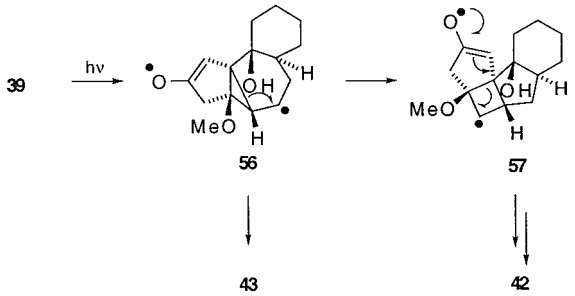
(35) Zimmerman, H. E.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 5245.

(36) Zimmerman, H. E.; Little, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 4623.

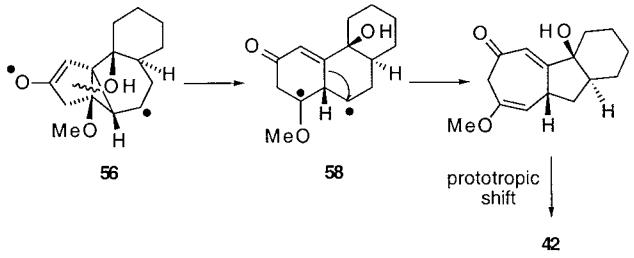
(37) (a) Schreiber, W. L.; Agosta, W. C. *J. Am. Chem. Soc.* **1971**, *93*, 3814. (b) Wolff, S.; Schreiber, W. L.; Smith, A. B., III; Agosta, W. C. *J. Am. Chem. Soc*. **1972**, *94*, 7797.

(38) (a) Agosta, W. C.; Smith, A. B., III; Kende, A. S.; Eilerman, R. G.; Benham, J. *Tetrahedron Lett.* **1969**, 4517. (b) Agosta, W. C.; Smith, A. B., III; *J. Am. Chem. Soc.* **1971**, *93*, 5513.

Scheme 11



Scheme 12



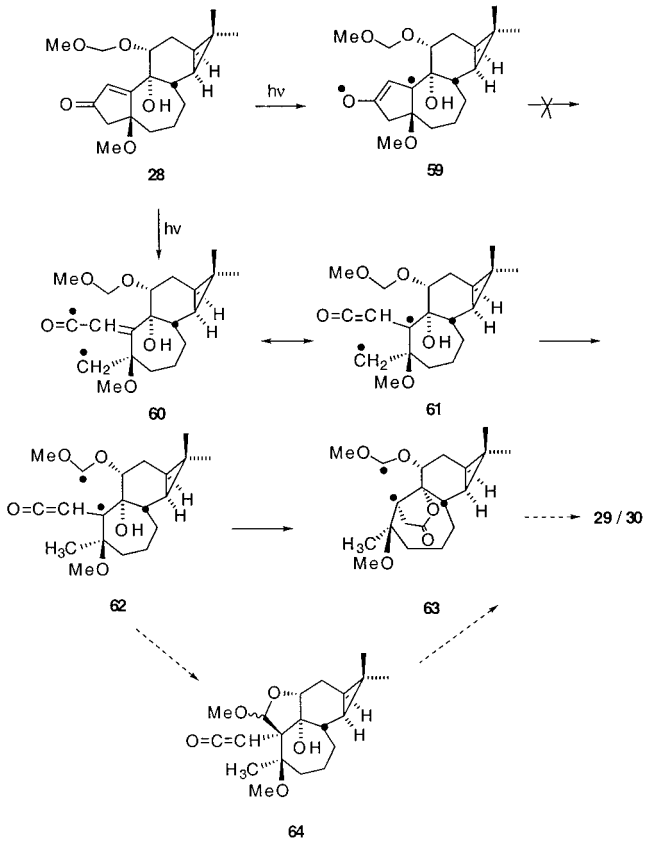
excited-state events can again be accounted for in terms of $\pi \rightarrow \pi^*$ initiation and conversion to the cyclopropylcarbinyl biradical **56** (Scheme 11).[39] As in the earlier example, the formation of this highly reactive species can be anticipated since 3-exo cyclizations have rate constants approximating 1000 s^{-1}.[40,41] The isolation of **42** leads to the conjecture that **56** is capable of expansion to the cyclobutyl radical **57** en route to **42**.

An additional consideration is relevant here. If one considers the five-ring internal bond breaking in **56** to leave an odd-electron center at the methoxyl-bearing carbon, one obtains the stabilized 1,3-biradical **58** with the β-carbon of the cyclohexenone bonded to the middle carbon of this subunit (Scheme 12). 1,2-Shifts of π groups substituted at the central carbon of a 1,3-biradical are known.[42] Should **58** intervene and be subject to such a migration, smooth conversion to **42** would occur. At present, we cannot distinguish between the pair of mechanistic options that result in hydroazulenone formation. It is clear, however, that the stereochemical nature of the B/C-ring fusion exerts a high level of control on the fate of intermediates such as **53** and **56**.

Fate of the Dihydro Derivative 28. Mechanistic Substantiation. The mechanisms advanced above are certain to be viewed by some as highly speculative with no substantiating data. It is for this very reason that **28** was included in this investigation. The expectation was that experiments involving a substrate having a saturated seven-membered ring would go far in narrowing the possibilities by eliminating the 3-exo cyclization alternative for the $\pi \rightarrow \pi^*$ biradical. In fact, **28** responds marginally well to photoactivation and leads with low efficiency to products possessing structural features quite divergent from those encountered heretofore.

One of the several noteworthy structural features of **29** and **30** is the presence of a newly generated methyl group in a position geminal to the methoxy substituent. The evolution of

Scheme 13



this part structure is consistent with the notion that the $\pi \rightarrow \pi^*$ biradical **59** now has no productive outlet (Scheme 13). As a consequence, α cleavage to deliver **60** becomes kinetically significant. Resonance theory predicts that radical character will also be manifested at the α-ketenyl carbon as in **61**. The stabilized intermediate must undergo several additional steps prior to arrival at the products. The timing that we prefer involves hydrogen atom transfer from the MOM substituent to $\cdot CH_2^-$, a process that is advantaged because of the close proximity of these two groups and the obvious gain in stability. It is imperative that the conversion to **62** occur prior to lactonization. Molecular models provide clear indication that ring closure in this fashion has the net consequence of distancing these reaction centers. These divergent steps could be competitive and account for the low efficiency with which **29** and **30** are formed.

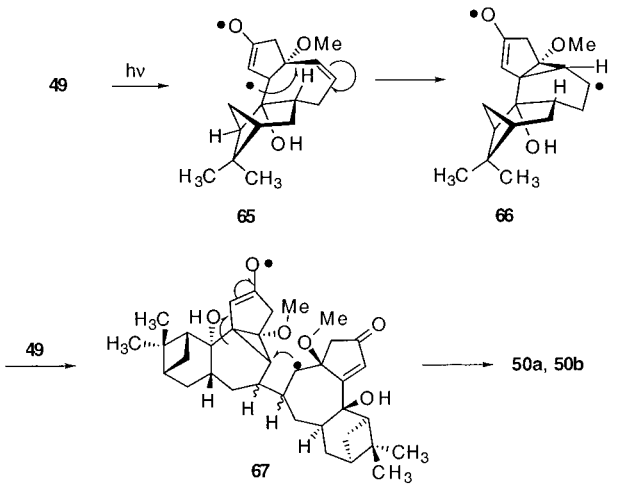
Two ring closures lead from **62** to the observed products. Should lactonization occur in advance of biradical coupling, viz. **62** → **63** → **29/30**, the stereoselective course of the tetrahydrofuran ring-forming step is guaranteed. This reaction pathway may therefore be favored. Since **62** is a conformationally flexible entity, this penultimate intermediate has the potential for C−C bond formation from either surface of the cycloheptane ring. Further, it appears possible that closure from the α face could occur reversibly since the ketene moiety then would be unable to pursue any further facile intramolecular processes.

Whatever the actual timing of the individual steps, the data reveal how critical the cycloheptene double bond is to the unprecedented photochemical behavior of **5**, **22**, **37**, and **39**.

Triplet Fate of Pinanyl Dienone 49. The triplet 1,4-biradical **65**, which is in principle formed upon photoexcitation of **49**, is not observed to participate in reactions comparable to those previously encountered with closely related cyclopentenones

(39) Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065.
(40) Furxhi, E.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 4064.
(41) Another important point is that a methoxy group only slightly accelerates the opening of a cyclopropylcarbinyl radical: Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 3618.
(42) Zimmerman, H. E.; Heydinger, J. A. *J. Org. Chem.* **1991**, *56*, 1747.

Scheme 14



(Scheme 14). In this instance, the fate of **65** could be formation of a cyclopropylcarbinyl biradical, i.e., **66**, as usual. This is followed by regioselective attack on a second (ground-state) molecule of **49** to generate **67**, collapse of which leads to cyclobutane ring formation. The stereochemical course of this pathway would implicate the head-to-head dimers as the major products. However, as discussed above, proof of this particular point has eluded us to the present time.

Summary. The experiments detailed here demonstrate that the positioning of a 4-vinyl substituent on a cyclopentenone ring results in adoption of the "π-route migration" option when such unsaturation is present. The range of photoisomerizations available to these unsaturated ketones is thereby expanded significantly. In the absence of this added unsaturation, the same transformations are not possible. There exists no reason to expect these phenomena to be limited to these systems. The involvement of cyclopropylcarbinyl biradicals such as **53**, **56**, and **66** gives evidence of being easily accessible by a reaction mode that holds considerable mechanistic diversity. In addition to their intrinsic novelty, the observed photochemical isomerizations constitute new, synthetically attractive methods for gaining entry into polycyclic structures difficult to access by other methods. It is important to recognize that while cyclopropylcarbinyl biradicals themselves are not novel species, the structural environments in which they are generated in this work gives rise to much of the observed phenomena.

Experimental Section

(1*R*,4*R*)-2-Bromo-4-(*tert*-butyldimethylsiloxy)-1-vinyl-2-cyclopenten-1-ol (11). To freshly dried cerium trichloride[43] (46.4 g, 124.7 mmol) under N_2 was added 125 mL of 1.0 M vinylmagnesium bromide in THF (125 mmol). The mixture was stirred at room temperature for 1 h and an additional hour at −78 °C. At this point, a solution of **10**[15] (36.22 g, 124.4 mmol) in dry THF (125 mL) was introduced dropwise, and the mixture was allowed to warm to room temperature overnight prior to quenching at 0 °C with saturated NH_4Cl solution (300 mL) and extraction with ether (3×). The combined organic layers were washed with brine, dried, and concentrated to leave a residue that was chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give 22.37 g (56%) of **11** as a colorless oil. IR (neat, cm^{-1}) 3444, 1493, 1372, 1181; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 2.0 Hz, 1 H), 5.73 (dd, J = 17.2, 9.6 Hz,1 H), 5.31 (dd, J = 17.2, 0.9 Hz,1 H), 5.15 (dd, J = 10.6, 0.9 Hz, 1 H), 4.64−4.60 (m, 1 H), 2.69 (s, 1 H), 2.62 (dd, J = 13.3, 6.8 Hz, 1 H), 1.98 (dd, J = 13.3, 4.8 Hz, 1 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 136.2, 132.1, 114.1, 83.3, 73.0, 49.0, 25.7 (3C), 18.0, −4.8 (2C); HRMS (EI) m/z (M^+) calcd 319.0579, obsd 319.0565; $[\alpha]_D^{22}$ +131.2 (c 1.05, $CHCl_3$).

Anal. Calcd for $C_{13}H_{23}BrO_2Si$: C, 48.90; H, 7.26. Found: C, 49.01; H, 7.31.

[[(1*R*,4*R*)-3-Bromo-4-methoxy-4-vinyl-2-cyclopenten-1-yl]oxy]-*tert*-butyldimethylsilane (12). To a solution of **11** (1.90 g, 6.0 mmol) in DMF (100 mL) cooled to 0 °C was added sodium hydride (230 mg, 7.5 mmol). The resulting mixture was stirred for 1 h, treated with freshly distilled methyl iodide (0.60 mL, 9.0 mmol) at 0 °C, allowed to warm slowly to room temperature overnight, quenched with water (100 mL), and extracted with ether (3×). The combined organic phases were dried and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 5% ethyl acetate in hexanes) to provide **12** (1.90 g, 96%) as a colorless oil. IR (neat, cm^{-1}) 1618; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, J = 2.3 Hz, 1 H), 5.74 (dd, J = 17.3,-10.7 Hz, 1 H), 5.31 (dd, J = 17.2, 1.1 Hz, 1 H), 5.17 (dd, J = 10.7, 1.2 Hz, 1 H), 4.63 (ddd, J = 3.1, 4.3, 7.1 Hz, 1 H), 3.28 (s, 3 H), 2.47 (dd, J = 7.3, 14.0 Hz, 1 H), 2.04 (dd, J = 14.0, 4.2 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 138.1, 129.6, 114.5, 88.3, 72.8, 50.8, 42.4, 25.8 (3C), 18.1, −4.7, −4.8; HRMS (EI) m/z (M^+) calcd 333.0675, obsd 333.0710; $[\alpha]_D^{25}$ +102.8 (c 1.01, $CHCl_3$).

Anal. Calcd for $C_{14}H_{25}BrO_2Si$: C, 50.45; H, 7.56. Found: C, 50.59; H, 7.58.

(1*S*,4*R*,6*R*)-4-(Methoxymethoxy)-7,7-dimethylbicyclo[4.1.0]heptan-3-one (13). To a cold (0 °C) magnetically stirred solution of (−)-(1*R*,3*R*,6*S*)-4-methylene-7,7-dimethylbicyclo[4.1.0]heptan-3-ol[6d,17] (11.40 g, 75.0 mmol) in CH_2Cl_2 (0 °C) was added chloromethyl methyl ether (6.60 g, 82.5 mmol) followed by diisopropylethylamine (10.7 g, 82.5 mmol). After reaction had been allowed to proceed for 3 h at room temperature, CH_2Cl_2 (250 mL) was introduced prior to washing with water (2×). The aqueous washes were back-extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 2% ethyl acetate in hexanes) afforded the MOM ether as a colorless oil (9.70 g, 87%). IR (neat, cm^{-1}) 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88−4.83 (m, 2 H), 4.60 (d, J = 6.7 Hz, 1 H), 4.56 (d, J = 6.7 Hz, 1 H), 3.98 (t, J = 3.1 Hz, 1 H), 3.37 (s, 3 H), 2.58 (ddt, J = 16.2, 8.3, 2.7 Hz, 1 H), 2.35−2.25 (m, 2 H), 1.52 (dt, J = 15.4, 3.2 Hz, 1 H), 0.98 (s, 3 H), 0.88 (s, 3 H), 0.77 (dd, J = 16.9, 8.9 Hz, 1 H), 0.72 (ddd, J = 12.8, 9.1, 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 111.9, 92.9, 73.9, 55.2, 28.7, 27.2, 25.1, 20.7, 18.1, 15.8, 14.3; HRMS (EI) m/z (M^+) calcd 196.1463, obsd 196.1463; $[\alpha]_D^{20}$ +23.3 (c 2.15, $CHCl_3$).

Ozone was bubbled through a cold (−78 °C) solution of the above acetal (11.0 g, 56.1 mmol) in 4:1 methanol-CH_2Cl_2 (150 mL) until a blue color persisted (6 h). Dimethyl sulfide (100 mL) was added, and the resulting mixture was stirred overnight, concentrated under reduced pressure, and chromatographed over silica gel (elution with 15% ethyl acetate in hexanes) to give **13** as a colorless oil (11.03 g, 99%). IR (neat, cm^{-1}) 1720, 1451, 1407; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J = 6.8 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 3.61 (t, J = 3.6 Hz, 1 H), 3.35 (s, 3 H), 2.79 (dd, J = 17.5, 8.5 Hz, 1 H), 2.47 (ddd, J = 15.7, 9.2, 3.7 Hz, 1 H), 2.23 (d, J = 17.6 Hz, 1 H), 1.75 (dt, J = 15.9, 5.4 Hz, 1 H), 1.15 (dt, J = 0.6, 3.0 Hz, 1 H), 1.01 (s, 3 H), 0.91−0.74 (m, 1 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 95.7, 76.8, 55.7, 34.2, 28.1, 27.9, 23.6, 19.2, 16.0, 14.7; HRMS (EI) m/z (M^+) calcd 198.1247, obsd 198.1251; $[\alpha]_D^{20}$ 40.4 (c 0.835, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.72; H, 9.21.

(1*R*,2*R*,4*R*,6*R*)-2-Allyl-4-(methoxymethoxy)-7,7-dimethylbicyclo-[4.1.0]-heptan-3-one (14). Ketone **13** (198 mg, 1.00 mmol) dissolved in THF (4 mL) was added to a cold (−78 °C), magnetically stirred solution of lithium hexamethyldisilazide in THF (11 mL of 1 M, 11 mmol). The reaction mixture was stirred for 45 min at this temperature, maintained at 0 °C for 1 h, and heated at reflux for 30 min. To the hot enolate solution was added allyl bromide (156 mg, 1.3 mmol) as a solution in THF (2 mL) and HMPA (1 mL). After 8 h of heating and subsequent cooling to room temperature, saturated NH_4Cl solution (10 mL) was introduced and the aqueous phase was extracted with ether

(43) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*, Wiley: Chichester, UK, 1995; pp 1031−1034.

(3×). The combined organic layers were dried and concentrated to leave a residue that was purified by gradient elution chromatography on silica gel (elution with 2−9% ethyl acetate in hexanes) to separate cyclopropyl-cleaved, polyallylated, and O-allylated products. There was isolated 67 mg (28%) of **14**. IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (dddd, J = 17.2, 10.6, 9.4, 5.8 Hz, 1 H) 5.00 (m, 2 H), 4.65 (d, J = 5.8 Hz, 1 H), 4.60 (d, J = 5.8 Hz, 1 H), 3.68 (t, J = 2.9 Hz, 1 H), 3.65 (s, 3 H), 3.19 (ddd, J = 14.0, 8.6, 5.5 Hz, 1 H), 2.60 (ddd, J = 12.9, 7.1, 5.8 Hz, 1 H), 2.52 (ddd, J = 15.8, 9.3, 2.1 Hz, 1 H), 2.01 (dt, J = 14.0, 8.6 Hz, 1 H), 1.90 (dt, J = 16.1, 3.4 Hz, 1 H), 1.40 (t, J = 8.6 Hz, 1 H), 1.01 (s, 3 H), 0.85 (s, 3 H), 0.80−0.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 136.8, 116.1, 95.8, 78.7, 55.9, 43.5, 32.3, 31.1, 29.2, 28.8, 20.0, 16.8, 16.0; HRMS (EI) *m*/*z* (M^+) calcd 238.1563, obsd 238.1566; $[\alpha]_D^{22}$ +63.0 (*c* 0.90, $CHCl_3$).

Allyl (1*R*,4*R*,6*R*)-4-(Methoxymethoxy)-7,7-dimethylbicyclo[4.1.0]-hept-2-en-3-yl Carbonate (15). To a cold (−78 °C), magnetically stirred solution of lithium hexamethyldisilazide (6.34 mL of 1.0 M, 6.34 mmol) in THF (30 mL) was added dropwise a solution of **13** (966 mg, 4.88 mmol) in THF (6 mL). After 1 h, neat allyl chloroformate (0.67 mL, 6.34 mmol) was introduced dropwise at the same temperature and allowed to react for another 30 min. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), diluted with ether (30 mL), and extracted with ether (3×). The combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded **15** (1.35 g, quantitative) as a colorless oil. IR (neat, cm^{-1}) 1628; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99−5.90 (m,1 H), 5.75 (d, J = 3.9 Hz, 1 H), 5.42 (dd, J = 17.2, 1.4 Hz, 1 H), 5.30 (dd, J = 10.4, 1.2 Hz, 1 H), 4.70 (s, 2 H), 4.67 (dd, J = 5.7, 0.8 Hz, 2 H), 3.98 (dd, J = 5.3, 3.6 Hz, 1 H), 3.40 (s, 3 H), 2.26 (ddd, J = 15.2, 8.8, 5.2 Hz, 1 H), 2.02 (dt, J = 15.1, 1.9 Hz, 1 H), 1.15 (dd, J = 8.4, 3.9 Hz, 1 H), 1.01 (s, 3 H), 1.03−0.90 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 149.4, 131.2, 119.1, 117.4, 95.3, 68.8 (2C), 55.3, 27.6, 27.1, 24.2, 22.9, 17.6, 14.9; HRMS (EI) *m*/*z* (M^+ - OCH_2OCH_3) calcd 221.1083, obsd 221.1130; $[\alpha]_D^{25}$ +133.0 (*c* 0.91, $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.87; H, 7.89.

(1*R*,2*S*,4*R*,6*R*)-2-Allyl-4-(methoxymethoxy)-7,7-dimethylbicyclo-[4.1.0]-heptan-3-one (16). To a solution of **15** (976 mg, 3.46 mmol) and freshly prepared $Pd_2(dba)_3{\cdot}CHCl_3$[19] (120 mg, 3 mol %) in dry dimethoxyethane (8 mL) was added Diphos (276 mg, 20 mol %) in a single portion. The reaction mixture was stirred overnight, concentrated, and subjected directly to gradient elution chromatography on silica gel containing 5% silver nitrate (3−50% ethyl acetate in hexanes) to furnish 563 mg (67%) of **16** and 32% of **13**.

For **16**: colorless oil. IR (neat, cm^{-1}) 1724, 1442, 1377; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (dddd, J = 17.0, 10.1, 6.9, 6.9 Hz, 1 H), 5.08−5.00 (m, 2 H), 4.74 (d, J = 6.7 Hz, 1 H), 4.67 (d, J = 6.7 Hz, 1 H), 3.85 (dd, J = 4.9, 4.9 Hz, 1 H), 3.38 (s, 3 H), 2.56 (ddt, J = 12.9, 6.4, 5.1 Hz, 1 H), 2.33 (ddd, J = 15.5, 8.2, 4.2 Hz, 1 H), 2.26−2.15 (m, 1 H), 2.04 (dt, J = 14.1, 5.2 Hz, 1 H), 1.88 (dt, J = 15.9, 5.8 Hz, 1 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.88 (dd, J = 8.8, 6.4 Hz, 1 H), 0.66 (dd, J = 9.0, 5.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 136.0, 116.3, 95.6, 74.9, 55.6, 44.1, 34.7, 27.9, 27.8 (2C), 19.7, 18.4, 15.1; HRMS (EI) *m*/*z* (M^+) calcd 238.1551, obsd 238.1560; $[\alpha]_D^{25}$ +121.2 (*c* 1.17, $CHCl_3$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.62; H, 9.27.

(1*R*,2*S*,3*R*,4*R*,6*R*)-2-Allyl-3-[(3*R*,5*R*)-3-(*tert*-butyldimethylsiloxy)-5-methoxy-5-vinyl-1-cyclopenten-1-yl]-4-(methoxymethoxy)-7,7-dimethylbicyclo[4.1.0]heptan-3-ol (17). Anhydrous cerium trichloride was generated from 39.65 g (106.4 mmol) of the heptahydrate by an accepted method.[43] To this white powder was added ketone **16** (20.61 g, 86.6 mmol) dissolved in 335 mL of dry THF. Stirring was continued at room temperature under N_2 for 4 h. To a separate flask containing bromide **12** (34.50 g, 103.9 mmol) dissolved in dry THF (265 mL) cooled to −78 °C was introduced *tert*-butyllithium in pentane dropwise. When the addition was completed, the mixture was stirred at −78 °C for 1 h and transferred dropwise via cannula to the ketone·$CeCl_3$ complex in THF at −78 °C. After 5 h of agitation at this temperature, saturated NH_4Cl solution (100 mL) was slowly introduced and the mixture was allowed to warm to room temperature overnight before being extracted with ether (5×). The combined organic layers were washed with brine, dried, and chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to afford **17** as a colorless oil (40.43 g, 95%). IR (neat, cm^{-1}) 3480 (br); ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, J = 17.6, 6.8 Hz, 1 H), 5.76−5.63 (m, 1 H), 5.36 (d, J = 1.0 Hz, 1 H), 5.15−4.97 (m, 4 H), 4.58−4.53 (m, 2 H), 4.49 (d, J = 6.9 Hz, 1 H), 4.37 (d, J = 6.9 Hz, 1 H), 3.36−3.08 (m, 1 H), 3.24 (s, 3 H), 3.17 (s, 3 H), 2.75 (dd, J = 11.9, 6.7 Hz, 1 H), 2.52 (br m, 1 H), 2.09−1.80 (m, 3 H), 1.80 (dd, J = 11.6, 6.2 Hz, 1 H), 0.98 (s, 3 H), 0.94 (s, 3 H), 0.91 (s, 9 H), 0.82−0.77 (m, 1 H), 0.48 (dd, J = 9.4, 4.6 Hz, 1 H), 0.06 (s, 6 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCL_3$) δ 151.6, 138.5, 137.9, 129.6, 115.2, 113.2, 96.1, 89.4, 81.5, 77.6, 73.1, 55.4, 51.0, 44.4, 43.6, 35.5, 28.4, 25.8 (3C), 24.8, 23.9, 22.2, 18.1, 17.6, 16.2, −4.6 (2C); HRMS (EI) *m*/*z* (M^+) calcd 429.3361, obsd 429.3316; $[\alpha]_D^{25}$ +65.6 (*C* 1.65, $CHCl_3$).

Anal. Calcd for $C_{28}H_{48}O_5Si$: C, 68.25; H, 9.82. Found: C, 68.27; H, 9.74.

(1*R*,2*S*,3*R*,4*R*,6*R*)-2-Allyl-3-[(3*R*,5*R*)-3-hydroxy-5-methoxy-5-vinyl-1-cyclop enten-1-yl]-4-(methoxymethoxy)-7,7-dimethylbicyclo[4.1.0]-heptan-3-ol (18). A solution of **17** (15.53 g, 31.52 mmol) in dry THF (200 mL) was cooled to 0 °C, treated with tetrabutylammonium fluoride (63.0 mL of 1.0 M in THF, 63.0 mmol), stirred at 0 °C, and extracted with ether. The combined ether layers were dried and concentrated, and the crude product was redissolved in 2 L of CH_2Cl_2, redried, and freed of solvent. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes) afforded **18** as a colorless oil (10.39 g, 87%). This compound proved not to be stable and was directly carried into the next step. IR (neat, cm^{-1}) 3447, 1634, 1443; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, J = 17.6, 10.9 Hz, 1 H), 5.78−5.71 (m, 1 H), 5.50 (d, J = 1.5 Hz, 1 H), 5.17−5.00 (m, 4 H), 4.64−4.62 (m, 1 H), 4.51 (d, J = 6.9 Hz, 1 H), 4.44 (s, 1 H), 4.39 (d, J = 6.9 Hz, 1 H), 3.42−3.22 (m, 1 H), 3.26 (s, 3H), 3.20 (s, 3 H), 2.93 (dd, J = 12.2, 6.4 Hz, 1 H), 2.50−2.45 (m, 1 H), 2.17−1.97 (series of m, 3 H), 1.79 (dd, J = 12.2, 7.1 Hz, 1 H), 1.63 (br s, 1 H), 1.36−1.26 (m, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.92−0.86 (m, 1 H), 0.38 (dd, J = 9.4, 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 138.0, 137.5, 128.9, 115.2, 113.5, 96.0, 89.6, 81.4, 77.5, 72.4, 55.3, 51.0, 44.1, 43.0, 35.3, 28.3, 24.7, 24.0, 22.0, 17.4, 16.0; HRMS (EI) *m*/*z* (M^+ − H_2O) calcd 360.2302, obsd 360.2317.

(5*S*)-5-Allyl-3-[(1*R*,2*S*,3*R*,4*R*,6*R*)-2-allyl-3-hydroxy-4-(methoxymethoxy)-7, 7-dimethylbicyclo[4.1.0]hept-3-yl]-5-methoxy-2-cyclopenten-1-one (19). A solution of **18** (9.87 g, 26.01 mmol) in dry CH_2Cl_2 (1 L) was treated with powdered 4 Å molecular sieves (8.02 g), *N*-methylmorpholine *N*-oxide (4.57 g, 39.0 mmol), and tetra-*n*-propylammonium perruthenate (459 mg, 5 mol %) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 5 h, concentrated, and directly chromatographed on silica gel. Elution with 15% ethyl acetate in hexanes provided **19** as a faint yellow oil (9.29 g, 95%). IR (neat, cm^{-1}) 3479, 1722, 1698, 1631, 1595; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, J = 17.6, 10.9 Hz, 1 H), 5.86 (s, 1 H), 5.80−5.65 (m, 1 H), 5.31 (d, J = 10.9 Hz, 1 H), 5.26 (d, J = 17.6 Hz, 1 H), 5.04−4.98 (m, 2 H), 4.51 (d, J = 7.0 Hz, 1 H), 4.34 (d, J = 7.0 Hz, 1 H), 4.24 (s, 1 H), 3.51 (t, J = 8.3 Hz, 1 H), 3.30 (s, 3 H), 3.21 (s, 3 H), 2.92 (d, J = 17.1 Hz, 1 H), 2.66 (d, J = 17.1 Hz, 1 H), 2.30−2.23 (br s, 1 H), 2.12−2.02 (m, 3 H), 1.41−1.34 (m, 1 H), 1.01 (s, 3 H), 0.98−0.92 (m, 1 H), 0.95 (s, 3 H), 0.40 (dd, J = 9.4, 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 184.1, 136.6, 136.3, 127.1, 115.9, 115.3, 95.2, 86.5, 80.5, 79.1, 55.1, 51.9, 44.7, 43.6, 35.1, 27.9, 24.0, 23.5, 21.9, 17.4, 15.7; HRMS (EI) *m*/*z* (M^+) calcd 376.2251, obsd 376.2218; $[\alpha]_D^{22}$ +43.3 (*c* 1.07, $CHCl_3$).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.19; H, 8.57. Found: C, 69.96; H, 8.59.

(1a*R*,1b*S*,4a*R*,7b*R*,8*R*,9a*R*)-1,1a,1b,2,4a,5,7b,8,9,9a-Decahydro-7b-hydroxy-4a-methoxy-8-(methoxymethoxy)-1,1-dimethyl-6*H*-cyclopropa[3.4]-benz[1.2*e*]azulen-6-one (5). A 2 L round-bottomed flask containing freshly distilled benzene (900 mL) was fitted by way of a high-dilution trap to a reflux condenser. The benzene was heated at reflux for 15 min, and a solution of phenylmethylene bis(tricyclohexylphosphino)ruthenium dichloride (434 mg, 15 mol %) in freshly distilled benzene (30 mL) was introduced via cannula. Subsequently,

a solution of **19** (1.32 g, 3.51 mmol) in the same medium (100 mL) was added slowly overnight under argon via the high-dilution adapter as a vigorous reflux rate was maintained. After 24 h of heating, an additional 434 mg (15 mol %) of the ruthenium catalyst in benzene (30 mL) was delivered via cannula, and the reflux period was extended for an additional 24 h. Throughout the entire reaction period, the solution maintained an orange-brown color. After being left open to the air for 5 h, a black color was pervasive. The mixture was concentrated and chromatographed on silica gel (elution with 4 → 10% ethyl acetate in hexanes) to afford **5** as a colorless oil (1.19 g, 97%). IR (neat, cm^{-1}) 3496, 1714, 1608, 1455; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 1 H), 5.99 (ddd, J = 11.2, 7.3, 2.0 Hz, 1 H), 5.73 (dd J = 11.3, 2.6 Hz, 1 H), 4.43 (d, J = 6.7 Hz, 1 H), 4.41 (d, J = 6.7 Hz, 1 H), 3.69 (t, J = 8.1 Hz, 1 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.63 (s, 2 H), 2.61−2.53 (m, 1 H), 2.18 (dd, J = 11.2, 5.8 Hz, 1 H), 2.09 (dd, J = 18.8, 7.7 Hz, 1 H), 2.02−1.81 (m, 2 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.92−0.86 (m, 1 H), 0.25 (dd, J = 9.1, 5.9 Hz, 1 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 181.0, 138.8, 132.2, 130.2, 96.3, 82.9, 79.2, 77.4, 55.5, 51.8, 51.7, 37.2, 32.8, 28.4, 24.3, 23.7, 21.4, 18.7, 15.8; HRMS (EI) m/z (M^+) calcd 348.1937, obsd 348.1940; λ_{max}^{CHCl3} 232 (ϵ 2200), 250 (2525), 282 (310), 334 (80); $[\alpha]_D^{25}$ +221 (c 0.70, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.66; H, 8.13.

Photoisomerization of 5. Prototypical Procedure. Into a quartz test tube containing the enone sample (20−60 mg) was introduced the proper solvent (1−3 mL), and the solution was deoxygenated by bubbling dry N_2 through a serum cap seal for 5 min. The needle serving as a gas outlet was capped, and the tube was positioned on the outside wall of a quartz condenser fitted internally with a 450 W Hanovia lamp. The irradiation was performed with careful monitoring of the reaction progress by TLC. When Pyrex test tubes were used, only very little reaction was observed in the same time frame. At the end of the process, the solution was transferred into a round-bottomed flask and evaporated under reduced pressure without warming. The residue was chromatographed on silica gel (elution with ether−hexane mixtures) in order to separate the isomeric photoproducts.

For **20**: (68% with dioxane as solvent; 7% with benzene as solvent); white solid, mp 136.0−137.0 °C. IR (neat, cm^{-1}) 1775, 1626, 1477, 1293; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89−5.83 (m, 1 H), 5.18−5.14 (m, 1 H), 4.48 (d, J = 7.0 Hz, 1 H), 4.43 (d, J = 7.0 Hz, 1 H), 4.05 (d, J = 3.2 Hz, 1 H), 4.01 (d, J = 3.2 Hz, 1 H), 3.51 (s, 3 H), 3.53−3.31 (m, 1 H), 3.40 (d, J = 16.4 Hz, 1 H) 3.31 (s, 3 H), 2.34−1.98 (series of m, 5 H), 2.22 (d, J = 16.5 Hz, 1 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.87 (t, J = 8.5 Hz, 1 H), 0.30 (dd, J = 9.8, 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 163.5, 132.6, 127.1, 98.1, 87.7, 82.4, 80.3, 56.2, 55.3, 51.6, 41.4, 32.4, 29.3, 29.2, 26.1, 24.6, 22.1, 17.5, 16.1; FAB MS m/z (M^+ + H) calcd 349.20, obsd 349.23; $[\alpha]_D^{25}$ −77.6 (c 0.41, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.80; H, 8.37.

For **21**: (6% with dioxane as solvent; 52% with benzene as solvent); white solid, mp 146−149 °C. IR ($CHCl_3$, cm^{-1}) 3400, 1684; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddd, J = 2.2, 5.1, 9.9 Hz, 1 H), 5.32 (s, 1 H), 5.25−5.17 (m, 1 H), 4.68 (d, J = 7.0 Hz, 1 H), 4.53 (d, J = 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.45 (dd, J = 4.8, 5.4 Hz, 1 H), 3.37 (s, 3 H), 3.12 (d, J = 18.6 Hz, 1 H), 2.35−2.15 (m, 3 H), 2.22 (d, J = 18.5 Hz, 1 H), 2.09−2.00 (m, 1 H), 1.91 (dt, J = 6.1, 10.6 Hz, 1 H), 1.39 (dt, J = 5.2, 15.2 Hz, 1 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.81 (ddd, J = 5.8, 7.4, 9.0 Hz, 1 H), 0.34 (dd, J = 6.6, 9.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 190.3, 130.3, 129.0, 105.6, 96.7, 72.4, 59.0, 56.2, 55.1, 46.2, 32.9, 29.8, 29.7, 28.6, 24.5, 23.6, 19.3, 17.8, 15,2; HRMS (EI) m/z (M^+) calcd 348.1937, obsd 348.1956; $[\alpha]_D^{20}$ +5.1 (c 0.70, $CHCl_3$).

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Supporting Information Available: Spectroscopic details for **50a** and **50b**, experimental details for compounds **22** −**51**, and tables giving the crystal data and structure refinement information, bond lengths and bond angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **20**, **21**, **26**, **40**, and **42** (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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