

New photochemistry of 2,5-cyclohexadien-1-ones and related compounds

Arthur G. Schultz

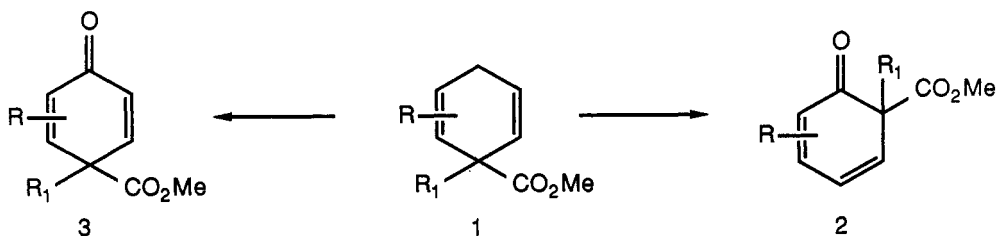
Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York
12180-3590 USA

Abstract - New procedures for photorearrangement of 2,5-cyclohexadien-1-ones to bicyclo[3.1.0]hexenones and substituted phenols have been developed. The intermediate oxyallyl zwitterions undergo intramolecular cycloaddition to furan, the alkyl azide group, and a variety of olefins. Intramolecular 2+2 photocycloadditions of 4-(3'-alkenyl)-2,5-cyclohexadien-1-ones also are described.

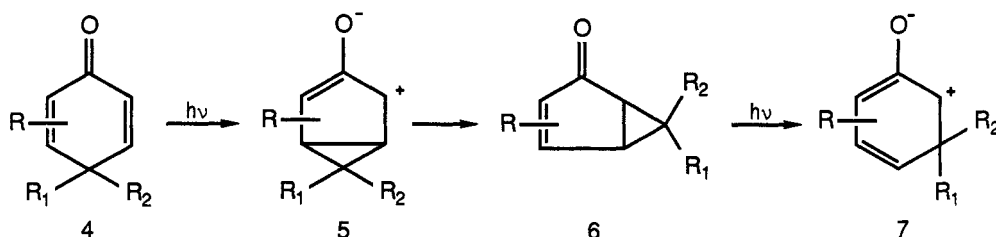
INTRODUCTION

The photorearrangements of 2,4- and 2,5-cyclohexadien-1-ones have been of interest to organic chemists for many years. Cyclohexadienone photochemistry has been used in multistep organic synthesis, but the full synthetic potential remains to be exploited. A recent development of methods for the conversion of 1,4-cyclohexadienes **1** into 2,4-cyclohexadien-1-ones **2** (ref. 1) and 2,5-cyclohexadien-1-ones **3** (ref. 2) represents an important step towards this goal. Cyclohexadienes **1** are prepared by the alkali metal in ammonia-promoted reductive alkylation of benzoic acid derivatives. The methodology provides 2,4- and 2,5-cyclohexadien-1-ones with a wide range of substituents in both racemic and enantiomerically pure form.

This account will focus on the photochemistry of 2,5-cyclohexadien-1-ones **3** and related compounds. Particular emphasis will be directed at: 1) the intramolecular reactivity of oxyallyl zwitterions generated from photorearrangements of 2,5-cyclohexadien-1-ones and 2) the intramolecular 2+2 photocycloaddition of 2,5-cyclohexadien-1-ones.



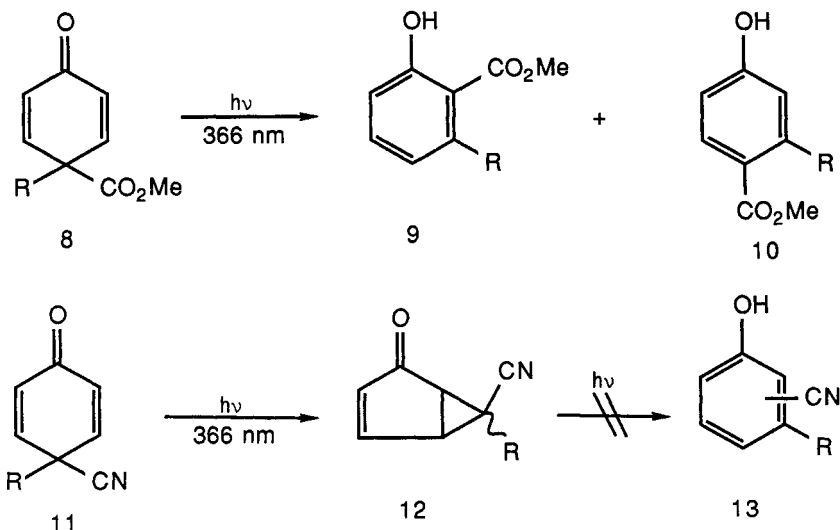
Although many research groups have contributed to the continually expanding body of dienone photochemistry, much of the current understanding of type A photoreactivity of 2,5-cyclohexadien-1-ones **4** is due to Zimmerman and Schuster (ref. 3). Convincing evidence has been gathered to support the existence of oxyallyl zwitterions **5** in the type A photorearrangement to bicyclo[3.1.0]hexenones **6**.



Chapman and co-workers have demonstrated the viability of intermolecular cycloaddition of furan and addition of methanol to oxyallyl zwitterions **7** generated from photorearrangement of bicyclo[3.1.0]hexenones (ref. 4). Subsequently, Williams and co-workers reported the first examples of intramolecular reactions of photochemically generated steroidal oxyallyl zwitterions related to **7** with proximate alcohol and ketone carbonyl groups (ref. 5).

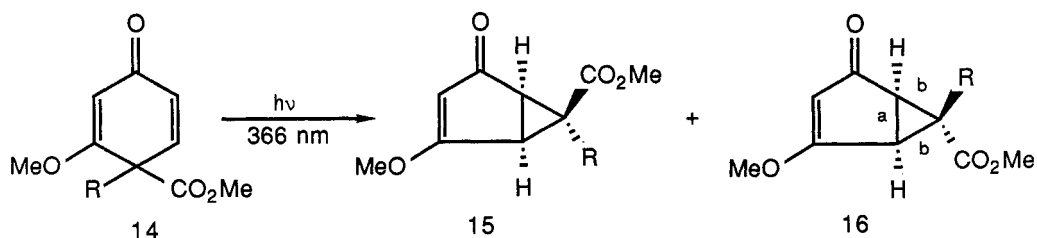
PHOTOREARRANGEMENTS OF 2,5-CYCLOHEXADIEN-1-ONES

It has been shown that irradiations of 4-alkyl-4-carbomethoxy-2,5-cyclohexadien-1-ones **8** at 366 nm give phenols **9** and **10**, presumably via photorearrangement of intermediate bicyclo[3.1.0]hexenones; e.g., **6** (ref. 2b). The exclusive migration of the carbomethoxy rather than the primary alkyl group in the intermediate zwitterion **7** is noteworthy. An analogous migration tendency has been determined for the carbomethoxy group in the acid-catalyzed dienone-phenol rearrangement (ref. 6).



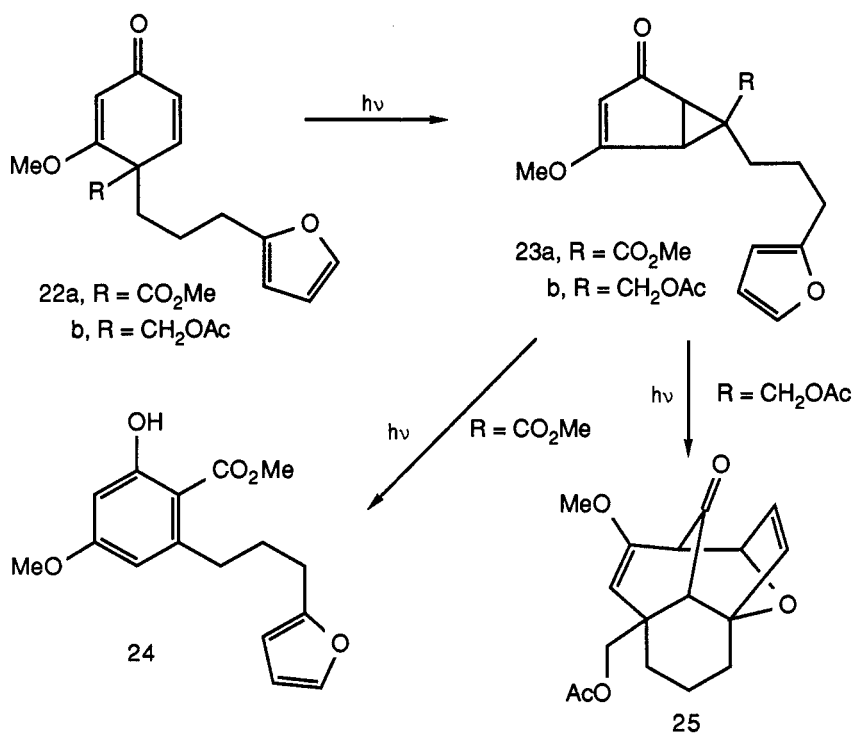
The corresponding photorearrangements of 4-alkyl-4-cyano-2,5-cyclohexadien-1-ones **11** provide ~9:1 diastereoisomeric mixtures of bicyclo[3.1.0]hexenones **12** with no traces of phenolic products; e.g., **13** (ref. 2b). In principle, the enhanced photostability of cyano-substituted bicyclohexenones, **12**, might be a result of a retardation in the rate of photoisomerization to the type **7** zwitterion. Alternatively, zwitterion **7** might be generated, but the failure to observe cyano group migration could be a result of a low "migration tendency" relative to the carbomethoxy group. Control experiments indicate that the first explanation probably is not correct. The photoisomerization of cyclohexadienones of type **11** may provide a unique opportunity to study the migration tendency of a cyano group to an electron deficient center in the absence of acidic catalysts.

In contrast to the photorearrangement of **8** to phenols **9** and **10**, 366 nm irradiation of a series of 3-methoxy-2,5-cyclohexadien-1-ones **14** gave bicyclo[3.1.0]hexenones **15** and **16** with complete regioselectivity in good to excellent yields (ref. 2b). Continued irradiation of

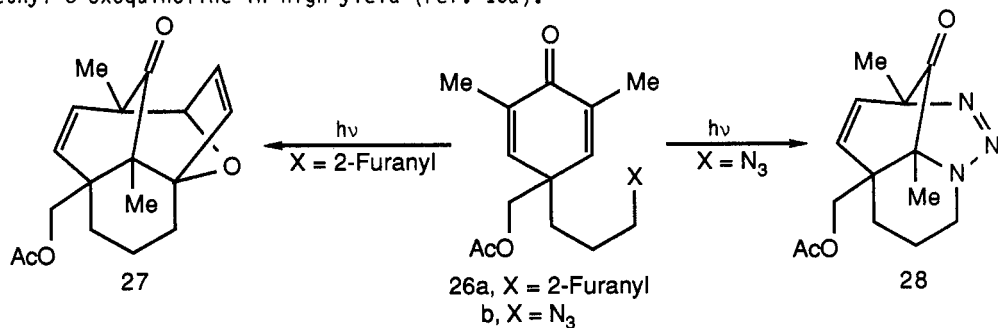


15 and **16** resulted in photoisomerization to predominately the diastereoisomeric series **15** with the carbomethoxy group endo to the 3-methoxyenone chromophore.

The stabilizing effect of the β -methoxy group in bicyclohexenones **15** and **16** is at least partially a result of the wavelength of light used in the photorearrangement of **14** to **15** and **16** (366 nm). Irradiation of **14** (or **15** and **16**) with light > 300 nm provided the anticipated phenols. It is suspected that the reluctance of **15** and **16** to undergo photorearrangement to phenols (but, interestingly, not photointerconversion) may be related to the anticipated (ref. 7) lowering of the $\pi \rightarrow \pi^*$ triplet state of the enone group by the 3-methoxy substituent. Indeed, the normal $n \rightarrow \pi^*$ initiated photorearrangement to a bicyclohexenone is completely suppressed in the case of the 3,5-dimethoxy-2,5-cyclohexadien-1-one **17**. This and other synthetically useful substituent effects are topics of current studies directed at an exploration of the excited state kinetics of **14**, **17**, and related substances.

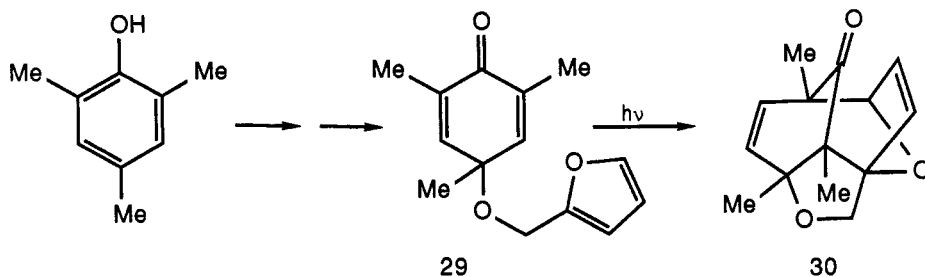


Triazenes such as **28** appear to be useful synthetic intermediates, but only limited chemical reactivity data are available at present. It is noteworthy that reaction of **28** with atmospheric moisture results in loss of molecular nitrogen and incorporation of one equivalent of H₂O to give 1,2,3,4,4a,7,8,8a-octahydro-4a-(acetoxymethyl)-7-hydroxy-7,8a-dimethyl-8-oxoquinoline in high yield (ref. 10a).



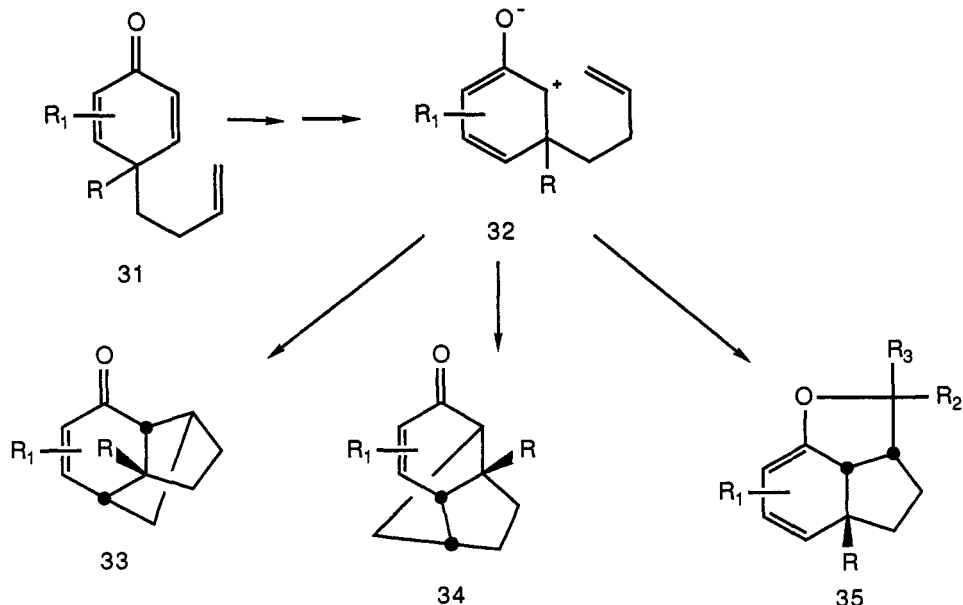
Symmetrically substituted phenols also are convenient sources of photoreactive 2,5-cyclohexadien-1-ones. For example, 2,4,6-trimethyl phenol provides 4-furfuryloxy-2,4,6-trimethyl-2,5-cyclohexadien-1-one (**29**), albeit in low overall yield. Brief irradiation of **29** in benzene solution at 366 nm gave the bridged furan adduct **30** in excellent yield (ref. 10b). The molecular structure of **30** was determined by X-ray crystallographic analysis, confirming that this and other adducts obtained by intramolecular oxyallyl zwitterion additions to the furan ring have the C(8)-C(9) double bond endo to the carbonyl group. endo-Orientation also has been reported for the intermolecular process (ref. 4).

While the available data do not elucidate the timing of adduct bond formations (stepwise or concerted), it is apparent that orientational preference in the intramolecular process



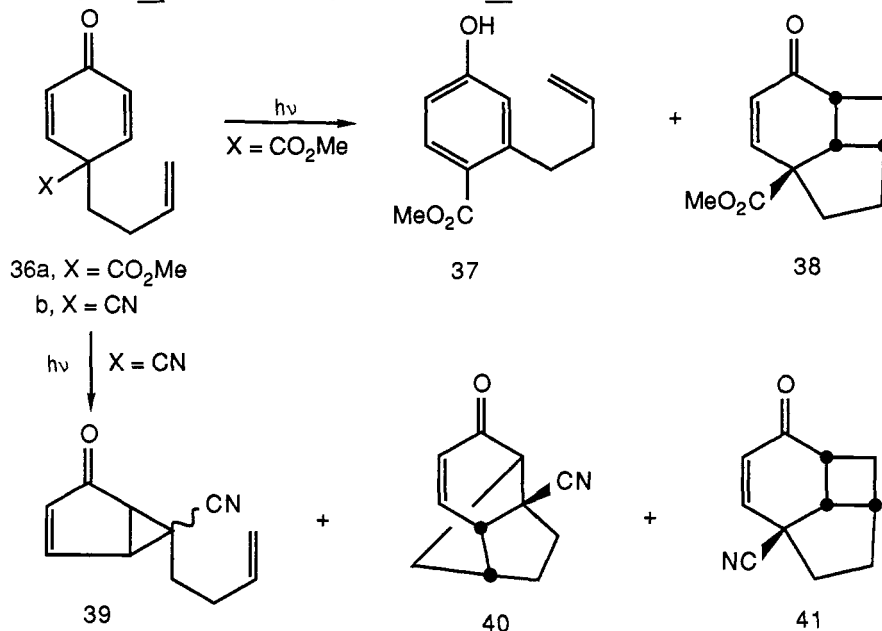
correlates with product stability. Molecular models show that endo-30 is considerably more stable than the exo-isomer. Molecular mechanics calculations support this hypothesis and suggest that the major source of instability is ring strain in the connecting tetrahydrofuran unit. This reasoning can be extended to an analogous consideration of 25 and 27.

The vinyl substituted oxyallyl zwitterion behaves as a two-electron component in cycloadditions to furan and the azide group to give adducts 25, 27, and 28. This zwitterion in 32 reacts as a four electron component with olefins to give bridged carbocycles 33 and 34; heterocycle 35 also has been obtained. Preliminary data indicate that the distribution of products strongly depends on the nature of the substituents attached to the olefin (ref. 11).



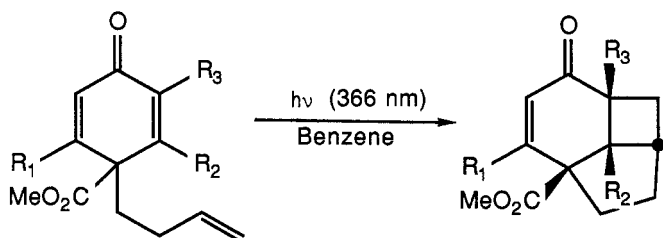
INTRAMOLECULAR 2+2 PHOTOCYCLOADDITIONS OF 4-(3'-ALKENYL)-2,5-CYCLOHEXADIEN-1-ONES

In the course of an investigation of the photoreactivity of 4-(3'-butenyl)-2,5-cyclohexadien-1-ones, we discovered an intramolecular 2+2 photocycloaddition (ref. 12). Thus, irradiation of 36a gave an approximately equivalent distribution of phenol 37, the product of carbomethoxy group rearrangement in zwitterion 32, and 1-carbomethoxy[4.3.1.0^{7,10}]-tricyclodec-2-en-4-one (38). The nitrile derivative 36b was prepared to suppress the migration tendency of the C(4) substituent (*vide supra*). Irradiation of 36b produced bicyclohexenone 39, 1-cyanotricyclodecenone 40 (derived from photorearrangement of 39; cf., photostability of 12) and the tricyclodecenone 41.



The inter- and intramolecular 2+2 photocycloaddition of an α,β -unsaturated carbonyl system to an alkene is an important process for the construction of acyl substituted cyclobutanes (ref. 13). However, photocycloadditions of olefins or acetylenes to 2,5-cyclohexadien-1-ones are unprecedented. This chemistry is of mechanistic significance because the 2+2 cycloaddition must be in competition with the normally efficient type A photorearrangement of 2,5-cyclohexadien-1-ones. The potential synthetic value of the formation of tricyclo-decenones of type 38 follows from: 1) the now general availability of 4,4-disubstituted-2,5-cyclohexadien-1-ones in racemic or enantiomerically pure form, 2) the diverse functionality in 38 and analogues that would be available for subsequent synthetic manipulation, and 3) the wide range of synthetic conversions of acyl substituted cyclobutanes already available (ref. 13).

The type A photorearrangement can be avoided completely with the 3-methoxy-2,5-cyclohexadien-1-ones 42a-e. For example, irradiation of 42a at 366 nm in deaerated benzene solution for 3 h gave 43a (>95% yield) along with less than 5% of the regioisomeric tricyclo-decenone 43b. Remarkably, 42b, the 4-(3'-butenyl) analogue of the unreactive 17, gave 43c in quantitative yield with about the same quantum efficiency as that for the conversion of 42a to 43a.



- 42a, $R_1 = \text{OMe}; R_2 = R_3 = \text{H}$
 b, $R_1 = R_2 = \text{OMe}; R_3 = \text{H}$
 c, $R_1 = \text{OMe}; R_2 = \text{Me}; R_3 = \text{H}$
 d, $R_1 = \text{OMe}; R_2 = \text{H}; R_3 = \text{Me}$
 e, $R_1 = R_3 = \text{OMe}; R_2 = \text{H}$

- 43a, $R_1 = \text{OMe}; R_2 = R_3 = \text{H}$
 b, $R_1 = R_3 = \text{H}; R_2 = \text{OMe}$
 c, $R_1 = R_2 = \text{OMe}; R_3 = \text{H}$
 d, $R_1 = \text{OMe}; R_2 = \text{Me}; R_3 = \text{H}$
 e, $R_1 = \text{Me}; R_2 = \text{OMe}; R_3 = \text{H}$
 f, $R_1 = \text{OMe}; R_2 = \text{H}; R_3 = \text{Me}$
 g, $R_1 = R_3 = \text{OMe}; R_2 = \text{H}$

Cyclohexadienone 42c provided an opportunity to examine the bifurcation of cycloaddition to β -methyl and β -methoxy substituted enone units. Irradiation of 42c in benzene gave an 87:13 mixture of 43d and 43e. However, increased quantities of 43e were obtained in solvents capable of hydrogen-bonding to the carbonyl group oxygen of 42c.

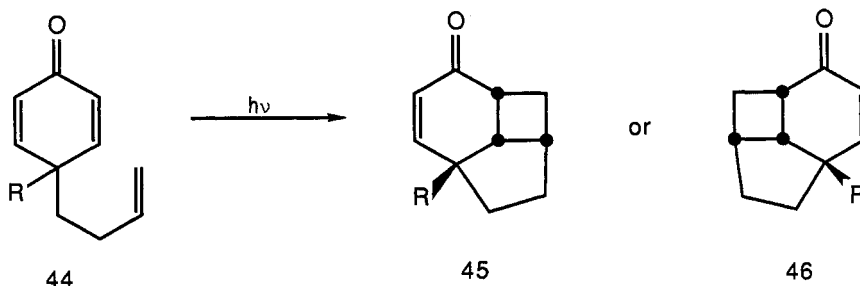
Intramolecular 2+2 photocycloaddition of 42d was completely regioselective to give methyl substituted cyclobutane 43f in 93% yield. A high degree of regioselectivity also was exhibited in the case of 42e which gave mainly 43g. Thus, there is little competition from cyclization to the vinylogous ester double bond when C(5) and C(6) are unsubstituted (case 42a) or when C(5) is unsubstituted and C(6) bears a methyl (case 42d) or methoxy (case 42e) substituent.

The diastereoselective reductive alkylation of the chiral benzamide 18 provided 19b, which was converted to enantiomerically pure 42a. This material underwent intramolecular 2+2 photocycloaddition without racemization. This result is striking in light of the photo-racemization encountered with 20.

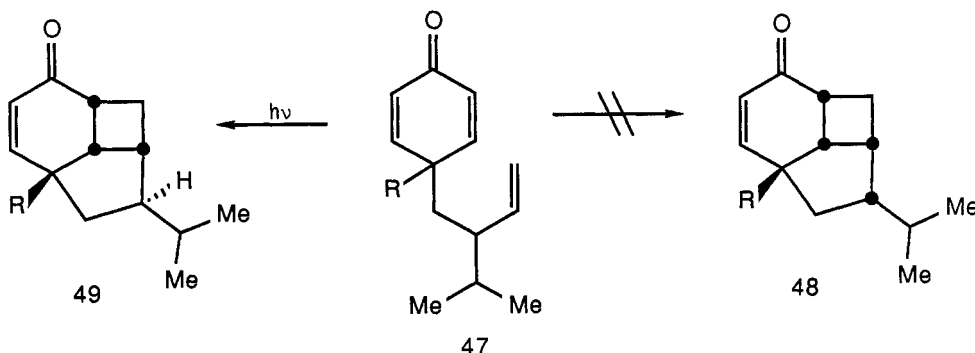
Additional studies (ref. 12) with a wide range of substituted 4-(3'-butenyl)-2,5-cyclohexadien-1-ones have demonstrated that: 1) Biradicals appear to be involved in the intramolecular 2+2 photocycloaddition. 2) Quaternary centers may be generated at each carbon atom of the cyclobutane ring. 3) The partitioning of pathways for type A photoreactivity vs 2+2 cycloaddition in 36a and other substrates lacking 3-methoxy substitution is sensitive to changes in solvent composition and temperature; cyclobutane formation is favored in hydrocarbon solvents at low temperature. 4) The 4-allyl- and 4-(4'-pentenyl)-2,5-cyclohexadien-1-ones do not undergo 2+2 photocycloadditions under conditions utilized for 42 and related derivatives. 5) 4-Carbomethoxy-3-methoxy-4-(3'-pentenyl)-2,5-cyclohexadien-1-one and related acetylenic substrates undergo efficient 2+2 cycloaddition to give the corresponding cyclobutene in excellent yields. Preliminary characterization of the excited-state

responsible for 2+2 cycloaddition suggests that significant mixing of the $\pi \rightarrow \pi^*$ triplet-state with the $n \rightarrow \pi^*$ triplet-state normally associated with type A photoreactivity is required for diversion of the photochemistry of 2,5-cyclohexadien-1-ones from the type A process to intramolecular 2+2 cycloaddition.

The diastereoselective Birch reductive alkylation of chiral benzamides provides enantiomerically pure 2,5-cyclohexadien-1-ones with a wide range of substitution. In certain cases, it would be desirable to prepare symmetrical 2,5-cyclohexadien-1-ones and induce asymmetry during subsequent cyclizations. This principle is illustrated for the intramolecular 2+2 photocycloaddition of 44 to give 45 or the enantiomer 46.



We have examined the concept of remote stereocontrol (ref. 14) via placement of a chiral center on the butenyl side chain; e.g. 47. Racemic 47 was prepared to serve both as a potential synthetic intermediate in the preparation of racemic 9-isocyanopupekeanane, a natural marine isocyanide (ref. 15) and as a probe of the mechanism of the intramolecular 2+2 photocycloaddition. If the transition state for formation of the cyclobutane ring resembles the starting 2,5-cyclohexadien-1-one, 47, then 48, in which the bulky carbomethoxy and isopropyl groups are anti disposed, ought to be the major product. If product development control operates, then 49 would be the expected product because the isopropyl group is away from the cup-shaped cavity defined by the tricyclo[4.3.1.0]decenone ring system. In fact, 47 gives only 49 as determined by X-ray crystallographic analysis of the derived 2,4-dinitrophenylhydrazone of 49 (ref. 16). This result and the discovery that 2+2 photocycloaddition probably involves reversible formation of 1,4-biradicals suggests that product development control may be a useful predictive model for photocyclization of 4-(3'-butenyl)-2,5-cyclohexadien-1-ones.



An alternative procedure for remote stereocontrol incorporates a chiral auxiliary at C(4) in 44. A small selectivity of 70:30 has been observed for the (2'S)-4-[(2'-methoxymethyl)pyrrolidinyl]carbonyl derivative. Separation of diastereoisomers and hydrolytic removal of the chiral auxiliary provides enantiomerically pure tricyclodecenone. Other potentially useful chiral auxiliaries are being examined (ref. 16).

Acknowledgement

This research was supported by the National Science Foundation (CHE83-19474) and the National Institutes of Health (GM26568). It is a pleasure to acknowledge the enthusiasm, careful observations, and dedicated efforts of my co-workers in this project; their names are found in the references.

REFERENCES

1. (a) A. G. Schultz, J. P. Dittami, F. P. Lavieri, C. Salowey, P. Sundararaman, and M. B. Szymula, J. Org. Chem. **49**, 4429 (1984). (b) A. G. Schultz and S. Puig, J. Org. Chem. **50**, 915 (1985). (c) A. G. Schultz, F. Lavieri, and T. E. Snead, J. Org. Chem. **50**, 3086 (1985). (d) A. G. Schultz, K. K. Eng, and R. K. Kullnig, Tetrahedron Lett. **27**, 2331 (1986). (e) A. G. Schultz, R. R. Staib, and K. K. Eng, J. Org. Chem. **52**, 2968 (1987).
2. (a) A. G. Schultz, F. P. Lavieri, and M. Macielag, Tetrahedron Lett. **27**, 1481 (1986). (b) A. G. Schultz, F. P. Lavieri, M. Macielag, and M. Plummer, J. Am. Chem. Soc. **109**, 3991 (1987).
3. Reviews of 2,5-cyclohexadienone photochemistry: (a) H. E. Zimmerman, Adv. Photochem. **1**, 183 (1963). (b) O. L. Chapman, Adv. Photochem. **1**, 323 (1963). (c) K. Schaffner Adv. Photochem. **4**, 81 (1966). (d) P. Kropp Org. Photochem. **1**, 1 (1967). (e) O. L. Chapman and D. S. Weiss Org. Photochem. **3**, 197 (1973). (f) D. I. Schuster Acc. Chem. Res. **11**, 65 (1978). (g) K. Schaffner and M. M. Demuth, Rearrangements in Ground and Excited States **3**, P. de Mayo, Ed., Academic Press, New York (1980).
4. (a) L. L. Barber, O. L. Chapman, and J. D. Lassila, J. Am. Chem. Soc. **91**, 3664 (1969). (b) O. L. Chapman, J. C. Clardy, T. L. McDowell, and H. E. Wright, J. Am. Chem. Soc. **95**, 5086 (1973).
5. (a) J. R. Williams, R. H. Moore, R. Li, and J. F. Blount, J. Am. Chem. Soc. **101**, 5019 (1979). (b) J. R. Williams and R. H. Moore, R. Li, and C. M. Weeks, J. Org. Chem. **45**, 2324 (1980).
6. J. N. Marx, J. C. Argyle, and L. R. Norman, J. Am. Chem. Soc. **96**, 2121 (1974).
7. H. E. Zimmerman and D. C. Lynch, J. Am. Chem. Soc. **107**, 7745 (1985).
8. A. G. Schultz, P. Sundararaman, M. Macielag, F. P. Lavieri, and M. Welch, Tetrahedron Lett. **26**, 4575 (1985).
9. C. J. Samuel, J. Chem. Soc., Perkin Trans II, 736 (1981).
10. (a) A. G. Schultz, M. Macielag, and M. Plummer, J. Org. Chem. **53**, 391 (1988). (b) A. G. Schultz, S. Puig, Y. Wang, J. Chem. Soc., Chem. Commun. 785 (1985).
11. A. G. Schultz and M. Plummer, manuscript in preparation.
12. A. G. Schultz, M. Plummer, A. G. Taveras, and R. K. Kullnig, J. Am. Chem. Soc. **110**, 0000 (1988).
13. (a) S. W. Baldwin, Org. Photochem. **5**, 123 (1982). (b) W. Oppolzer, Acc. Chem. Res. **15**, 135 (1982). (c) P. de Mayo, Acc. Chem. Res. **4**, 41 (1971). (d) P. A. Wender and J. C. Lechleiter, J. Am. Chem. Soc. **100**, 4321 (1978). (e) M. C. Pirrung, J. Am. Chem. Soc. **101**, 7130 (1979). (f) M. T. Crimmins and J. A. DeLoach, J. Org. Chem. **49**, 2076 (1984). (g) M. Demuth, Pure and Appl. Chem. **58**, 1233 (1986). (h) M. T. Crimmins and S. W. Mascarella, J. Am. Chem. Soc. **108**, 3435 (1986). (i) G. L. Lange and M. Lee, J. Org. Chem. **52**, 325 (1987).
14. Unpublished results of W. Geiss, RPI laboratories.
15. (a) B. J. Burreson, P. J. Scheuer, J. Finer, and J. Clardy, J. Am. Chem. Soc. **97**, 4763 (1975). (b) M. R. Hagadone, B. J. Burreson, P. J. Scheuer, J. S. Finer, and J. Clardy, Helv. Chim. Acta **62**, 2484 (1979).
16. Unpublished results of W. Geiss and A. G. Taveras, RPI laboratories.