Photochemical Cycloaddition Reactions of Enones to Alkenes; Synthetic Applications

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This review discusses the structural variations in the products of photochemical cycloadditions of olefins to enones, and cites the various ways in which the reaction may be synthetically useful.

Die photochemische Cycloaddition von konjugierten Enonen an Alkene stellt in vielen Fällen eine präparativ brauchbare Methode zur Herstellung von sonst nur schwer zugänglichen Cyclobutan-Derivaten und ihren Folgeprodukten dar. In dieser Übersicht werden nach einer allgemeinen Besprechung der Reaktion die Strukturmöglichkeiten der Cycloadditionsprodukte und die synthetische Anwendbarkeit dieser Additionsreaktion anhand von Beispielen aufgezeigt.

Dimerisations of α,β-unsaturated carbonyl compounds have been studied for some time. They were the subject of an extensive review by Mustafa[1] in 1951. Partly because of the potential importance of the dimerisations of the nucleic acid bases, they have continued to be a topic of interest[2]. The synthetic applications of dimerisation reactions are necessarily limited, however, due to the symmetrical nature of the product.

Relatively recently it was realized that cyclobutanes could be formed by the addition of α,β-unsaturated ketones to alkenes. A number of interesting synthetic procedures have emerged from the study of this reaction. They, as well as some generalizations about the factors controlling the structure of the products, are the subject of this review.

Büchi[3] (reinvestigating earlier work by Ciamician) reported the first cycloaddition of an α,β-unsaturated ketone to a double bond, the intramolecular cyclisation of carvone. In 1962, de Mayo and Takeshita[4] described the addition of the enolic double bond in a β-diketone to cyclohexene, and soon after, Eaton[5] published his first work on the addition of 2-cyclopentenone to cyclopentene. In 1963, Corey[6] submitted a preliminary report of his extensive investigations on the cycloadditions of 2-cyclohexenone. Results have now progressed to the point where the synthetic potential and versatility of the reaction have become evident.

1. Mechanism of the Reaction

In the last few years, extensive mechanistic studies have been carried out on the cycloaddition reactions of enones. One is on firm ground, however, only when one states that the additions to cyclohexenone[7] and cyclopentenone[8] proceed through triplet states of the ketones.

There have been various suggestions in the literature concerning the possible participation of species other than the lowest triplet state. Chapman[9] proposed that the singlet state of 4,4-dimethylcyclohexenone was responsible for the cycloaddition to diphenylethylene, a view that must be regarded with skepticism in the light of his later publications concerning the triplet addition of the same ketone to other olefins[10]. Arguments for the participation of the second triplet state in cyclopentenone cycloadditions[11] are now also considered suspect[12].

The necessity of invoking a diradical intermediate in the reaction would seem to follow from the triplet nature of the reacting ketone, although a conceivable alternative has been suggested[8]. The simultaneous formation of both cyclobutane bonds could occur with the storage of the triplet excitation energy in the ketone part of the molecule. Other evidence, however, makes the existence of the diradical highly probable. The cycloaddition of cyclohexenone with *cis*- and *trans*-2-butene gave an almost identical mixture of adducts[13], strongly supporting a diradical intermediate. With cyclopentenone[8], the mixtures of products were similar for the 2-butenes and 3-hexenes, but somewhat different for *cis*- and *trans*-dichloroethylene. This could reflect an intermediate which has a rate of ring closing approaching the rate of bond rotation.

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[1] A. Mustafa, Chem. Rev. **51**, 1 (1952).

[2] For example: P. Yates, D. J. MacGregor, Tetrahedron Letters **1969**, 453.

[3] G. Büchi, I. M. Goldman, J. Amer. Chem. Soc. **79**, 4741 (1957).

[4] P. de Mayo, H. Takeshita, A. B. M. A. Sattar, Proc. Chem. Soc. **1962**, 119.

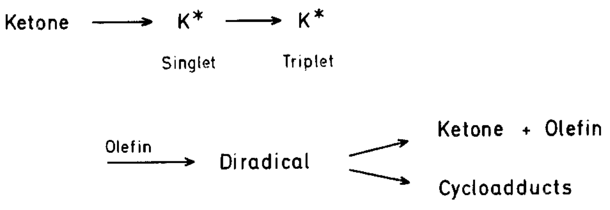
[5] P. E. Eaton, J. Amer. Chem. Soc. **84**, 2454 (1962).

[6] E. J. Corey, R. B. Mitra, H. Uda, J. Amer. Chem. Soc. **85**, 362 (1963).

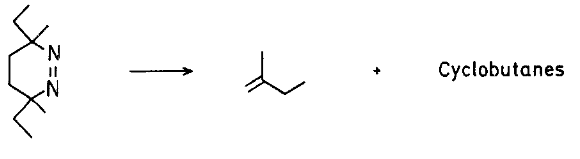
[7] E. Y. Y. Lam, D. Valentine, G. S. Hammond, J. Amer. Chem. Soc. **89**, 3482 (1967).

[8] P. de Mayo, J. P. Pete, M. F. Tchir, Canad. J. Chem. **46**, 2535 (1968).

It has been shown by both de Mayo[14] and Wagner[15] that, in cycloadditions of cyclopentenone, some species exists along the reaction coordinate which can revert to the ground-state starting molecules. The species could be the diradical intermediate, or it could be a complex formed before the diradical. Although neither has yet been established, a choice of the former is not entirely without justification.



It is well known that diradicals of this type can lead to olefin formation as well as intramolecular bond formation[16,17,18]. Recently, for example, Bartlett[17] studied the decomposition of the cyclic azo compound **1** under varying conditions. Olefin yields from 49 to 77% were obtained:



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The diradical formed in the cycloaddition reaction is confronted by the same two choices: there is no obvious and compelling reason why it should not avail itself of them both.

2. Structures of the Primary Photoproducts

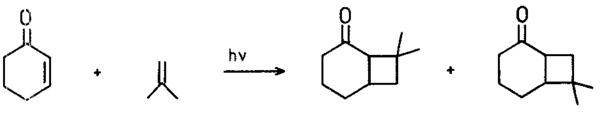
The known cycloaddition reactions of α,β-unsaturated ketones are covered in this review, either in the text or in Table 1. Intramolecular cycloadditions[3,19,20,21] are not included. The stereochemistry of the products has been shown where possible. There are three ways in which isomeric products may be obtained:

head-to-head and *head-to-tail* isomers,
cis and *trans* isomers,
syn and *anti* isomers.

These are discussed in detail below.

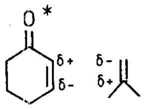
2.1. Head-to-head and Head-to-tail Adducts

When the unsaturated ketone is being added to an unsymmetrical olefin, two basic types of products are possible. If the larger end of the olefin comes closer to the ketone, the product is called the *head-to-head* adduct (**2**), and the opposite orientation (**3**) is the *head-to-tail* adduct:



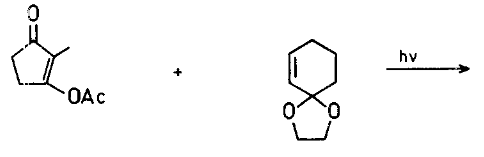
2 **3**

Because the orientation in several of his cycloadducts could not be explained by the stablest diradical approach, Corey[13] formulated a hypothesis in 1964 to explain his results. He suggested that an initial complex is formed between an excited state of the ketone and the olefin, and that the preferred orientation of the complex occurred when the oppositely charged ends of the double bonds were closest to each other:



The orientation observed in the major photoadduct of cyclohexenone with isobutylene could be adequately explained by this picture, as could that of other cyclohexenone adducts. The orientation effect, however, was rather less marked when cyclopentenone was added to propylene[22].

Recently, de Mayo and Challand[23] demonstrated that another orientation-controlling factor exists. Studying the addition of **4** to **5**, they suggested that the solvent-dependent ratio of *head-to-head* and *head-to-tail* adducts was due to an interaction of the overall dipoles of the reacting molecules. A similar explanation has been used for the solvent effects observed in cyclopentenone dimerisations[8,24]. The proportion of compound **6**, in which the dipoles are juxtaposed, increased markedly with the dielectric constant of the solvent, thereby showing the insulating effect of the solvent on the dipole interactions:



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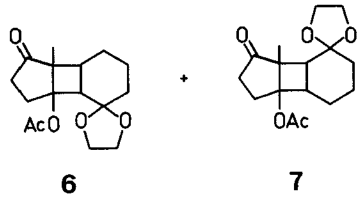

6 **7**

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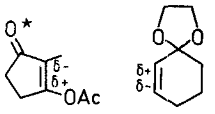
[9] O. L. Chapman, G. Lenz, *Organic Photochemistry*, Marcel Dekker, Inc., New York, 1967, p. 304.

[10] O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson, E. L. Brown, J. Amer. Chem. Soc. **90**, 1657 (1968).

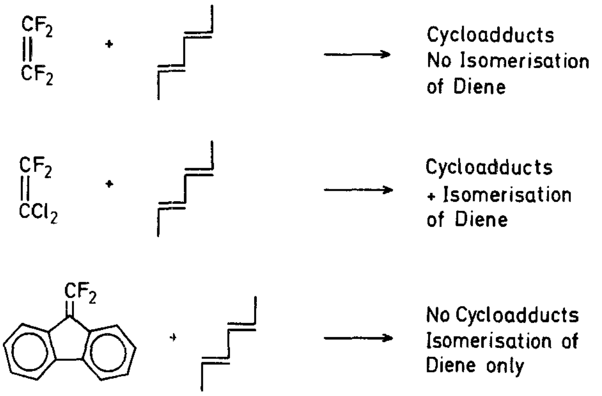
[11] P. de Mayo, J. P. Pete, M. Tchir, J. Amer. Chem. Soc. **89**, 5712 (1967).

What is lacking in this picture, however, is a driving force for the formation of the *head-to-tail* adduct **6**. The interaction of the dipoles can be reduced by the use of a polar solvent, but that interaction will still exist, and will still be unfavourable. One could also expect the Corey effect to lead to predominantly *head-to-head* isomers, although the assignments of the charges here are open to some question.

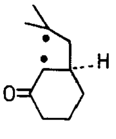


With 40% of adduct **6** formed in acetonitrile and in methanol, the combined strengths of the Corey and the de Mayo (albeit insulated by the polar solvents) effects seem puny indeed.

An alternate approach, using the diradical reversion theory, circumvents this and other difficulties. As suggested earlier in this review, the diradical reversion concept in cycloadditions is not incompatible with the behavior of known diradicals. The behavior of some halogenated olefins in cycloaddition reactions is particularly instructive[18]:



Bartlett[18] attributes this behavior to diradical reversion. It is interesting, and vital to subsequent arguments, to notice that isomerisation of the diene increases as the stability of the resultant diradical increases. In other words, contrary to the case of oxetane formation where stabler diradicals often lead to more product, here stabler diradicals lead to less product. The stabler diradicals must return at a faster rate to the ground-state starting molecules. Assuming that reversion can occur, and that stabler diradicals can give a greater degree of return to the ground state, Corey's results can be rationalized. Of the four possible diradicals (**8**, **9**, **10**, and **11**) from the addition of cyclohexenone to isobutylene, the rate of formation of **8** would probably be the greatest, of **11** the least. One can easily imagine very little of **11** being formed in competition with the other possibilities. Compound **8**, being the stablest and fastest formed, may show the most reversion to ground states. The predominant product then could arise from either **9** or **10**, or both. If the k_1' value is greater than k_1, but k_2'/k_3' is greater than k_2/k_3, then, if the latter factor wins out, the *head-to-tail* isomer would predominate:



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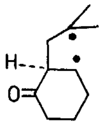

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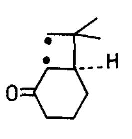

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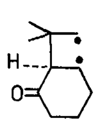

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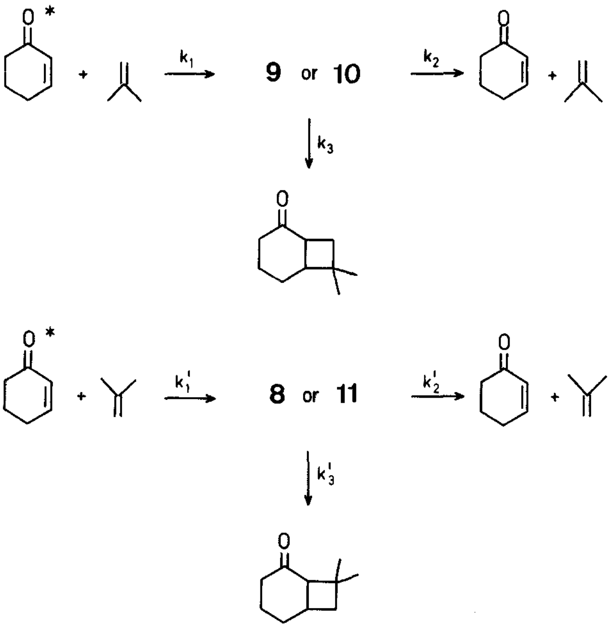

In additions to cyclopentenone, the k_2 route back to starting materials could be less favored because of the difficulty of putting the double bond back into the five-membered ring. Consequently the k_2 route may be less important in this reaction, and more product might be expected from the stablest diradical, as is observed[22].

Compounds with polar groups on one end of the double bond place an additional restraint on the conformational freedom of the diradical. The diradical which leads to *head-to-head* adducts from the dimethoxyethylene addition requires superimposing of the polar groups before ring closure can be achieved. This would surely inhibit *head-to-head* adduct formation by increasing the relative importance of the k_2 path. In fact, no *head-to-head* isomers have been found in such cycloadditions.

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[12] P. DE MAYO, M. F. TCHIR, A. A. NICHOLSON, unpublished results.

[13] E. J. COREY, J. D. BASS, R. LE MATHIEU, R. B. MITRA, J. Amer. Chem. Soc. **86**, 5570 (1964).

[14] P. DE MAYO, A. A. NICHOLSON, M. F. TCHIR, Canad. J. Chem. **47**, 711 (1969)

[15] P. J. WAGNER, D. J. BUCHECK, Canad. J. Chem. **47**, 713 (1969).

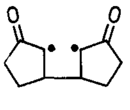
[16] S. G. COHEN, S. HSIAO, E. SAKLAD, C. H. WANG, J. Amer. Chem. Soc. **79**, 4400 (1957).

[17] P. D. BARTLETT, N. A. PORTER, J. Amer. Chem. Soc. **90**, 5317 (1968).

[18] P. D. BARTLETT, Science **159**, 833 (1968).

The polar effects observed by de Mayo and Challand[23], and also in the dimerization of cyclopentenone[8,24,25,26], are readily explainable by the diradical reversion theory. In both cases, various diradicals of slightly different energy are formed. The proportion of *head-to-head* adduct increases as the interaction of the polar ends of the diradical molecule is insulated by polar solvents.

For the dimerization, the *head-to-head* diradical **12** may be the stablest and fastest formed. However, it may also revert to ground state at a faster rate, particularly when the interaction of the carbonyl groups is not insulated by polar solvents. More product then could arise from **13**:



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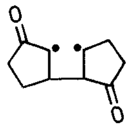

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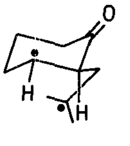
In the case of de Mayo and Challand's reaction, the various diradicals may be formed at approximately equal rates. The diradical leading to **6**, however, would have a more difficult time closing due to the interaction of the acetate and ketal, and give more reversion. As the polarity of the solvent increases, this effect disappears, resulting in more **6**.

2.2. *cis* and *trans* Isomers

Cyclopentenone yields photoadducts in which the 5-4 ring junction is always *cis*. Cyclohexenone gives both *cis* and *trans* ring junctions even though the *trans* adducts are somewhat more strained than the *cis*[13]. It has not yet been established why the *trans* adducts should occur.

For additions to 4,4-dimethycyclohexenone, Chapman[10] favors an explanation involving the participation of two excited states, one leading to the *cis* adduct and one to the *trans*. His conclusion is based on the results of differential quenching experiments, which must remain suspect because of the nature of the quencher, di-*t*-butyl nitroxide. This has been shown to behave as a spin-relaxant[27] and could, therefore, assist in the conversion of the triplet diradical to the singlet. The result of such behavior is, at present, unknown. Regardless of the explanation, however, the quencher is useful for synthetic purposes, by increasing the amount of *trans* adduct formed. The *cis* adducts can always be formed from the *trans* by treatment with base.

Although a number of interpretations are possible for the formation of the *trans*-fused adducts, a simple steric argument appears to handle the data adequately. In order for *trans* adduct to be formed, there must be time for the first-formed bond to assume the *equatorial* position on the cyclohexane ring. Taking as an example the *head-to-tail* addition of isobutylene to cyclohexenone, there are three staggered conformations for the diradical (**14**, **15**, and **16**):



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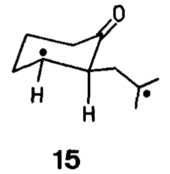

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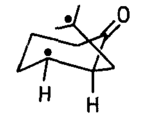

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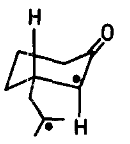
Conformer **14** would lead to *trans* adduct, **16** would give the *cis*, and **15** could give neither. The relative populations of **14** and **16**, along with the ease with which each of the two conformers can close to complete the cyclobutane bond, should control the amount of each type of product obtained.

Examination of models (using sp^2-hybridized carbons for the radicals) shows that **14** is more favored than **16**, and also that the steric problems become more severe when **16** tries to close to form the cyclobutane than when **14** does.

The *head-to-head* adduct formed from cyclohexenone and isobutylene would likely arise from the diradical shown in conformations **17**, **18**, and **19**:



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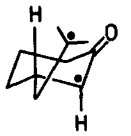

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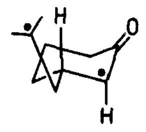

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In this case, no compelling preference can be found for conformer **17**, which leads to *trans* adduct, and neither do the strong steric inhibitions exist for closing the ring in a *cis* fashion. One might therefore expect the amount of *trans* isomer to diminish. Corey[13] reports only a single *head-to-head* adduct, to which he assigns the *cis* configuration. Furthermore, his additions to allene and acrylonitrile, which gave mostly *head-to-head* adducts, gave only *cis* adducts.

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[19] R. C. Cookson, J. Hudec, R. O. Williams, Tetrahedron Letters **1960**, 29.

[20] P. Yates, P. Eaton, Tetrahedron **12**, 13 (1961).

[21] W. Herz, M. G. Nair, J. Amer. Chem. Soc. **89**, 5474 (1967).

[22] P. E. Eaton, Accounts Chem. Res. **1**, 50 (1968).

[23] B. D. Challand, P. de Mayo, Chem. Commun. **1968**, 982.

[24] G. Mark, F. Mark, O. E. Polansky, Liebigs Ann. Chem. **719**, 151 (1969).

[25] P. E. Eaton, W. S. Hurt, J. Amer. Chem. Soc. **88**, 5038 (1966).

[26] J. L. Ruhler, P. A. Leermakers, J. Amer. Chem. Soc. **89**, 4944 (1967).

[27] R. W. Kreilick, J. Amer. Chem. Soc. **90**, 2711 (1968).

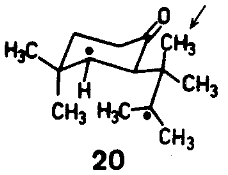
[28] P. J. Nelson, D. Ostrem, J. D. Lassila, O. L. Chapman, J. Org. Chem. **34**, 811 (1969).

[29] P. de Mayo, G. Bauslaugh, unpublished results.

[30] H. Nozaki, M. Kurita, T. Mori, R. Noyori, Tetrahedron **24**, 1821 (1968).

Chapman's results with 4,4-dimethylcyclohexenone can be explained in a similar fashion. The addition to 1,1-dimethoxyethylene[10] gives *cis* and *trans* adducts, the ratio of which varies with the solvent. Solvent variations would influence the polar interactions in the molecule and affect the population of conformers, thereby affecting the *cis-trans* ratio. The addition of the 4,4-dimethylcyclohexenone to 2,3-dimethyl-2-butene[28] leads to only a *trans* adduct. Upon examination of models, it becomes clear that the conformation which would lead to *cis* adduct is the least favored, and that for it to close would require serious interactions of the methyl groups. The interaction in the conformer leading to the *trans* adduct is not so bad, and the *trans* adduct becomes the only alternative to reversion to ground state. The relatively large amount of oxetane formed in Chapman's reactions is testimony to the reluctance of these diradicals to close to form cyclobutanes. Oxetane formation normally does not compete favorably with enone cycloaddition, and does here presumably because of a high degree of reversion of the diradicals to the starting materials.

One might argue that the same steric effects should be operative for both 1,1-dimethoxyethylene and for 2,3-dimethyl-2-butene. However, as well as the likelihood that the methyl groups are bulkier than the methoxy groups, the two methyl groups on the first-attached carbon could play a key role in the steric effects. In diradical **20**, the marked methyl group is moved closer to groups on the cyclohexane ring as the *cis* ring juncture is formed:



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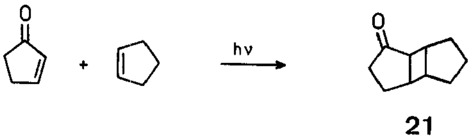
On the other hand, interactions of that methyl group are relieved as the *trans* ring is formed. This additional steric factor, on top of those existing with methyl groups on the other end of the double bond, appears to inhibit *cis* ring formation completely.

2.3. *syn* and *anti* Isomers

Published data on enone cycloadditions shows a marked propensity of the adducts for the *anti* configuration. For example, cyclopentenone adds to cyclopentene to give almost exclusively **21**, with a *cis,anti,cis* configuration[5]. In all of the reported reactions, only small amounts of *syn* adducts could be detected.



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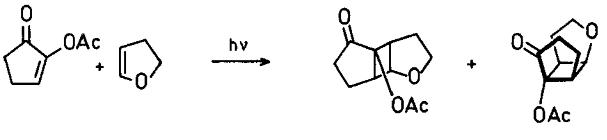
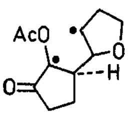
Perhaps the key to finding a general method of producing *syn* adducts from cycloalkenones was found[29] in the addition of 2-acetoxy-3-oxocyclopentene (**22**) to 4,5-dihydrofuran (**23**); in this reaction, the *syn* adduct (**24**) was obtained in yields almost as high as the *anti* (**25**) (Only *head-to-tail* adducts were found):



22 **23** **25** **24**

The proportion of *syn* adduct decreased from ~40% in cyclohexane to ~20% in acetonitrile, demonstrating the occurrence of a polar interaction of the substituents. Irradiation of 2-acetoxy-3-oxocyclopentene (**22**) with cyclopentene instead of 4,5-dihydrofuran yielded only the *anti* adduct, with no more than 2% of the *syn*.

Again, a number of interpretations of these results are possible, this author favoring application of the diradical reversion theory. The candidates for diradicals leading to *anti* adduct are **26** and **27**. The *syn* adduct could arise from **28** or **29**:



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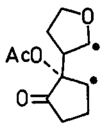

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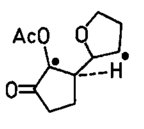

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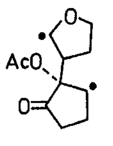

29

In each of the *anti* adduct diradicals, the dipoles of the two halves of the molecule must be rotated towards each other in order for cycloaddition to occur. The polar groups in each half of the molecule would therefore inhibit ring closure in **26** and **27**, and assist their reversion to ground state compounds. Diradicals **28** and **29** possess exactly the opposite kind of polar interaction, with the preferred orientation of the dipoles almost the same as the orientation necessary for cycloaddition. A favorable dipole effect then assists in overcoming the normal steric abhorrence for *syn* adducts.

2.4. Other Factors Affecting the Cycloaddition Reaction

Competing reactions sometimes interfere with the cycloaddition reactions of alkenones. The problem can sometimes be avoided by using a higher con-

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[31] P. DE MAYO, M. F. TCHIR, unpublished results.

[32] A. COX, P. DE MAYO, R. W. YIP, J. Amer. Chem. Soc. **88**, 1043 (1966).

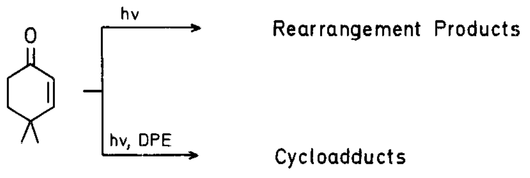
[33] M. KASHA, J. Amer. Opt. Soc. **38**, 929 (1948).

[34] P. DE MAYO, M. USSELMAN, unpublished results.

[35] E. J. COREY, R. B. MITRA, H. UDA, J. Amer. Chem. Soc. **86**, 485 (1964).

[36] J. D. WHITE, D. N. GUPTA, J. Amer. Chem. Soc. **88**, 5364 (1966).

centration of the olefin. Chapman[9] found that in the reaction of 4,4-dimethylcyclohexenone with diphenylethylene,



rearrangement could be avoided by using a 5-fold excess of the olefin.

The triplet energy of the olefin must be higher than that of the enone, to avoid quenching of the cycloaddition by energy transfer. Nozaki et al.[30] failed to get cycloadducts with styrene and with 1,3-cyclohexadiene, because of low triplet energies.

Oxetane formation apparently becomes important when cyclobutane formation is sterically hindered[10,28]. In his addition of 1,1-dimethoxyethylene to 4,4-dimethylcyclohexenone, Chapman [10] found the formation of oxetane to be highly solvent dependent. In *t*-butanol, no oxetane was formed; in *n*-hexane it was the major product (42%).

No detailed studies have been published showing the effect of temperature on product distribution. Tchir[31], however, has noted some change in the ratio of products obtained after the irradiation of cyclohexenone in cyclohexene over a range of −80° to +80°. Temperature effects have been noted for other cycloaddition reactions[32], but as yet no generalizations can be made about the alkenone cycloadditions.

It may be important to use light of wavelengths as long as possible, to avoid photodecomposition of the products. The n-π^* band of the enones will absorb well over 3000 Å, but it is possible for significant ketone n-π^* absorption to occur around 3000 Å. The pyrex and vycor filters normally used, then, may not efficiently prevent irradiation of the products. A desirable procedure may well be to use a copper sulfate filter[33] which cuts off light below 3300 Å.

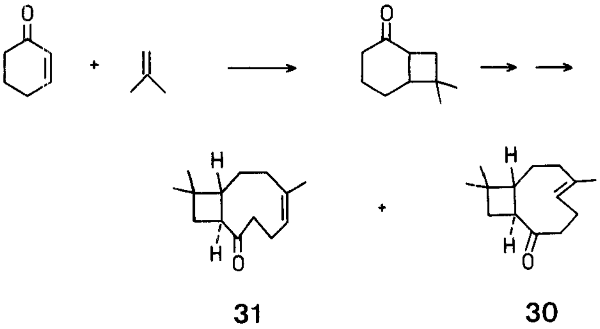
Photodecomposition could lead to aldehydes, as reported by Corey[13], or could lead to rearrangement. Usselman[34] found that the cycloadduct from cyclopentenone and 3-hexyne absorbed more strongly than cyclopentenone itself at 3130 Å, and that photorearrangement could only be prevented by using irradiation at 3660 Å.

3. The Syntheses of Cyclobutane Systems

The cycloaddition reaction with enones has been used in the syntheses of a number of natural products containing the cyclobutane ring.

3.1. Caryophyllenes

The first application of enone cycloaddition to synthesis led Corey[35] to *d,l*-caryophyllene (**30**) and *d,l*-isocaryophyllene (**31**). The key step in the sequence was the addition of isobutylene to cyclohexenone. The desired products were obtained several steps later:



Cycloaddition of Isobutylene to Cyclohexenone[13]: The cycloaddition is carried out in an irradiation vessel fitted with a Hanovia quartz immersion well, a dry-ice condenser leading to a three-way stopcock, and a third outlet fitted with a serum stopper. The immersion well is cooled by rapidly running water and the apparatus is immersed in a dry-ice/ethanol bath. A Type L, 450-W Hanovia mercury arc with a ®Corex filter is used as light source. A solution of cyclohexenone (11.51 g, 0.12 mol), isobutylene (170 ml, 1.82 mol), and pentane (150 ml) is added to the vessel which is then six times evacuated and filled with argon. The solution is irradiated for 8.5 hr, at which time syringe aliquots show that the unsaturated carbonyl peak of cyclohexenone has been replaced by a saturated carbonyl peak. Distillation yields 13 g (71%) of photoproduct mixture; b.p.$_{0.45}$: 53–57°. Careful refractionation on a 46 cm spinning-band column separates the six photoadducts. In other reactions, chromatographs on silica gel and preparative GLC are also used to separate the photoproducts.

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[37] J. D. White, D. N. Gupta, J. Amer. Chem. Soc. **90**, 6171 (1968).

[38] K. Wiesner, L. Poon, I. Jirkovsky, M. Fishman, Canad. J. Chem. **47**, 433 (1969).

[39] Z. Koblicova, K. Wiesner, Tetrahedron Letters **1967**, 2563.

[40] P. Sunder-Plassman, J. Zderic, J. H. Fried, Tetrahedron Letters **1966**, 3451.

[41] P. Sunder-Plassman, P. H. Nelson, L. Durham, J. A. Edwards, J. H. Fried, Tetrahedron Letters **1967**, 653.

[42] P. H. Nelson, J. W. Murphy, J. A. Edwards, J. H. Fried, J. Amer. Chem. Soc. **90**, 1307 (1968).

[43] E. J. Corey, S. Nozoe, J. Amer. Chem. Soc. **86**, 1652 (1964).

[44] P. de Mayo, H. Takeshita, Canad. J. Chem. **41**, 440 (1963).

[45] P. de Mayo, Pure Appl. Chem. **9**, 597 (1964).

[46] B. D. Challand, H. Hikino, G. Kornis, G. Lange, P. de Mayo, J. Org. Chem. **34**, 794 (1969).

[47] H. Hikino, P. de Mayo, J. Amer. Chem. Soc. **86**, 3582 (1964).

[48] G. L. Lange, P. de Mayo, Chem. Commun. **1967**, 704.

[49] B. D. Challand, G. Kornis, G. L. Lange, P. de Mayo, Chem. Commun. **1967**, 704.

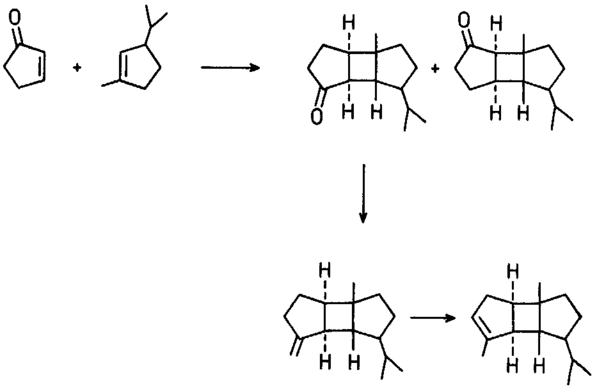
[50] L. Westfelt, P. Yates, M. Nye, D. Helmlinger, P. de Mayo, unpublished results.

[51] M. Nye, P. de Mayo, unpublished results.

[52] P. Laszlo, P. von R. Schleyer, J. Amer. Chem. Soc. **86**, 1171 (1964).

3.2. Bourbonenes

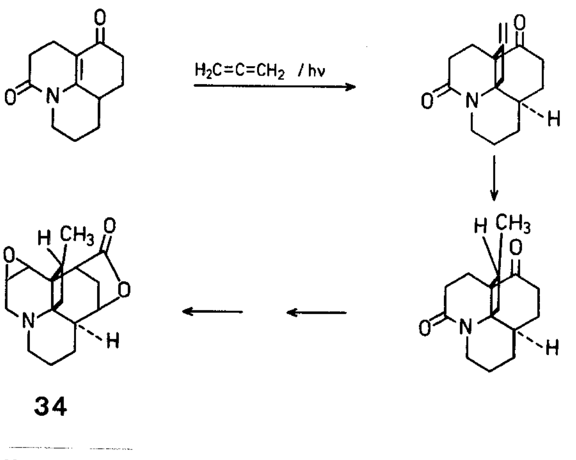
In a simple synthesis of α- and β-bourbonene (**32** and **33**), a cyclopentenone cycloaddition was used[36,37]:



33 **32**

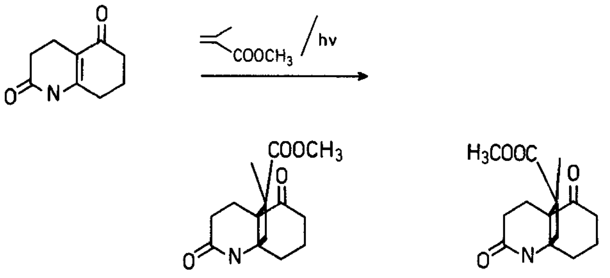
3.3. Annontinine

The Lycopodium alkaloid annotinine (**34**) has been synthesized using an enone cycloaddition to allene[38] and stereospecific hydrogenation of the resultant exomethylene double bond by blocking the ketone side by conversion to the ketal:



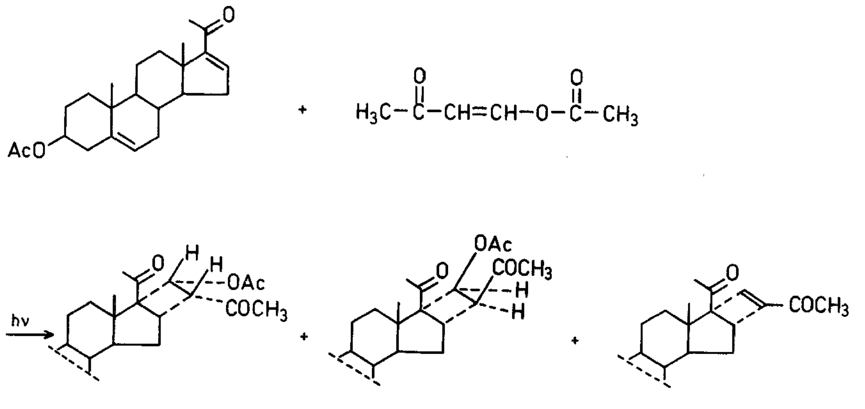
34

An addition leading to several potentially useful alkaloid precursors has been reported[39] in work on Lycopodium alkaloid syntheses:



3.4. Additions to Steroids

A number of additions to steroid enones have been reported[40,41,42]. The reaction shown below[41] was the first example of the cycloaddition of two different enones:

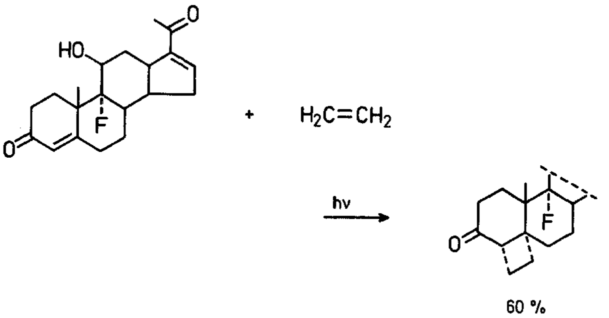


$$H_3C-\overset{O}{\overset{\|}{C}}-CH=CH-O-\overset{O}{\overset{\|}{C}}-CH_3$$

43 % 18 % 8 %

The second such example was used in a prostaglandin synthesis (see Section 4.8.).

Ethylene and tetrafluoroethylene were also added to ring D of steroids[40]. A steroid with enones in both ring A and ring D was irradiated with ethylene, the predominant product being the ring A adduct[40]:



60 %

An α,β,γ,δ-unsaturated ketone with a double bond between C-4 and C-6 of the steroid skeleton was irradiated with ethylene and with maleic anhydride[42]. Small yields of mainly ring A adduct were obtained with ethylene, good yields of ring B adduct with maleic anhydride.

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[53] P. E. Eaton, Tetrahedron Letters **1964**, 3695.

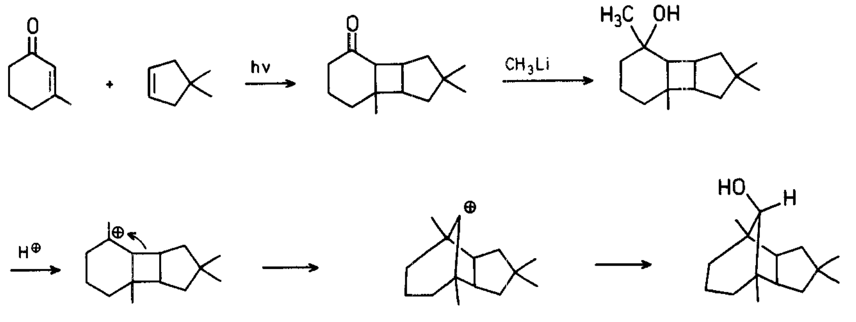
[54] R. Criegee, H. Furrer, Chem. Ber. **97**, 2949 (1964).

4. Cleavage and Rearrangement Reactions of the Photoadducts

The synthetic usefulness of the enone cycloaddition reaction is greatly increased by a number of rearrangement reactions that can be carried out on the cycloadducts.

4.1. Carbonium Ion Rearrangements

Simple alkenone adducts, by virtue of having the cyclobutane ring formed next to a potential carbonium ion site, can be made to undergo Wagner-Meerwein type reargements. This reaction has been used to advantage in the synthesis of α-caryophyllene alcohol[43] (**35**):



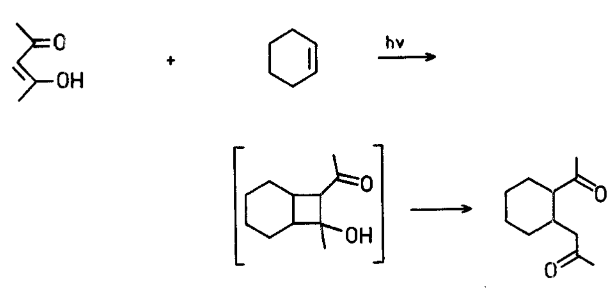
35

4.2. Rearrangement of β-Diketone Adducts

The discovery[44,45,46] that the enolic bond in β-diketones adds to a variety of olefins has led to new synthetic methods for a number of types of compounds.

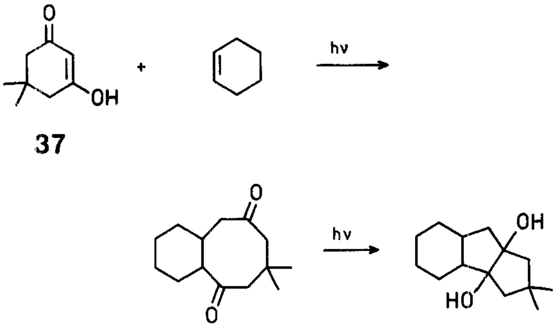
4.2.1. 1,5-Diketones

The initially formed adducts from β-diketones and olefins spontaneously rearrange to 1,5-diketones in high yield. Acetylacetone was the first β-diketone studied[44] and when added to cyclohexene gave the diketone **36**.



36

The reaction also worked well with cyclopentene, 1-methylcyclohexene, and 2-acetoxypropene[44]. Cyclic β-diketones undergo the same reaction sequence[47], thus permitting synthesis of cycloalkane-1,5-diones. The cyclooctane-1,5-dione **38** was converted to the diol **39** upon irradiation:

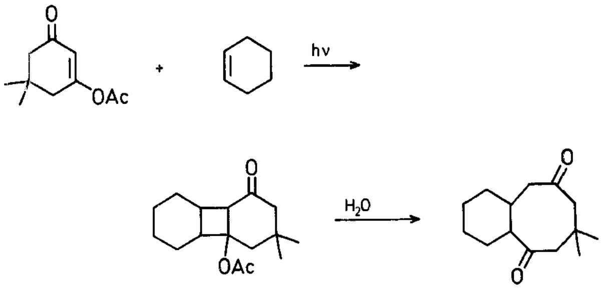


37

38 **39**

Addition of Dimedone (37) to Cyclohexene[46]: A solution of dimedone (15.0 g, 0.107 mol) and cyclohexene (1.25 l, 12.3 mol) in ether (4 l) is placed in an irradiation apparatus fitted with a water-cooled immersion well, and the system is flushed with and kept under nitrogen. After 28 hr irradiation, the solvent is evaporated, the resultant oil dissolved in ether, washed with 5% aqueous sodium hydroxide, and water, and then dried. The residue upon evaporation (29.8 g) is distilled and chromatographed on alumina. The major product is eluted first (with benzene) and upon crystallization from light petroleum ether yields dione **38**; m.p. 92–94°; I.R. (CCl_4): $\nu_{max} = 5.86\ \mu$. Further elution (benzene/ether) gives diol **39** in ~15% yield; crystallized from light petroleum ether, m.p. 79–81°.

The rearrangement could be prevented by using the acetylated enol, allowing isolation of the simple cycloadducts. The rearrangement then could be induced by hydrolyzing the acetate:



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[55] W. Hartmann, R. Steinmetz, Chem. Ber. **100**, 217 (1967).

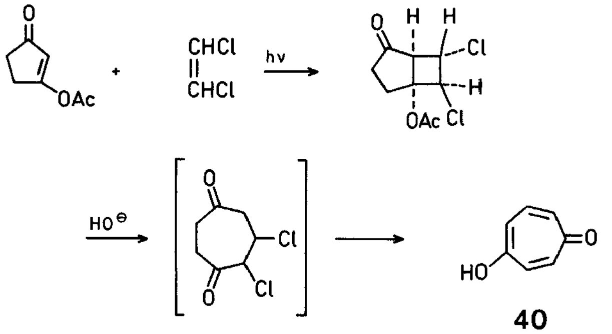
[56] R. W. Guthrie, Z. Valenta, K. Wiesner, Tetrahedron Letters **1966**, 4645.

[57] H. Dugas, M. E. Hazenberg, Z. Valenta, K. Wiesner, Tetrahedron Letters **1967**, 4931.

[58] K. Wiesner, V. Musil, K. J. Wiesner, Tetrahedron Letters **1968**, 5643.

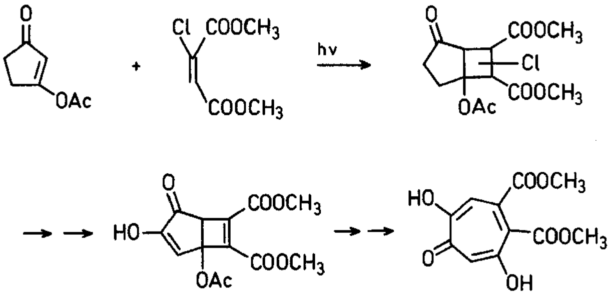
[59] K. Wiesner, S. Uyeo, A. Philipp, Z. Valenta, Tetrahedron Letters **1968**, 6279.

The formation of cyclic 1,5-diketones lead to a simple synthesis of γ-tropolone[47] (**40**):



40

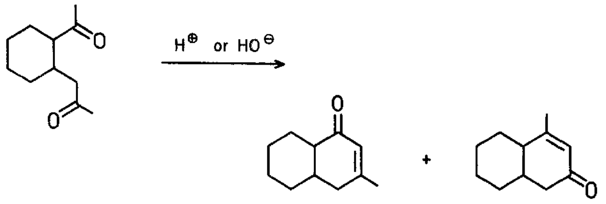
The same kind of rearrangement was used in a stipitatonic acid (**41**) synthesis[48]:



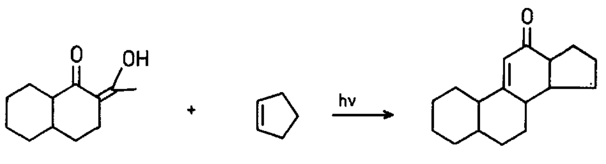
41

4.2.2. Fused Ring Systems containing an α,β-Unsaturated Ketone Group

The 1,5-diketones formed in the above reactions could readily be cyclized to α,β-unsaturated ketones by the addition of acid or base[44]:

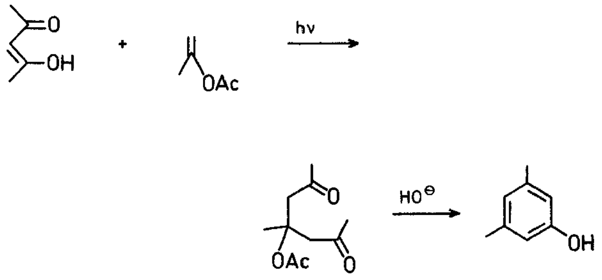


The potential value of this reaction was shown in a simple synthesis of the steroid skeleton[30]:



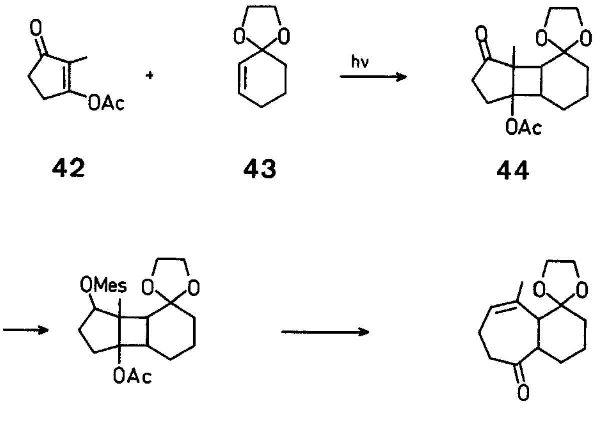
4.2.3. Substituted Phenols

The inclusion of a leaving group in the alkene leads to cyclization to a phenol, rather than to an α,β-unsaturated ketone. The adduct of 2-acetoxypropene and acetylacetone yielded 3,5-dimethylphenol[44]:



4.2.4. Formation of Cyclic γ,δ-Enones

In the synthesis of β-himachalene[49], the enol acetate **42** was added to the olefin **43**. Instead of rearrangement of the adduct **44** to the diketone, the keto group was reduced, a leaving group put on, and then the acetate hydrolyzed. Rearrangement then led to the desired γ,δ-enone **45**, from which the remainder of the synthesis could be completed:

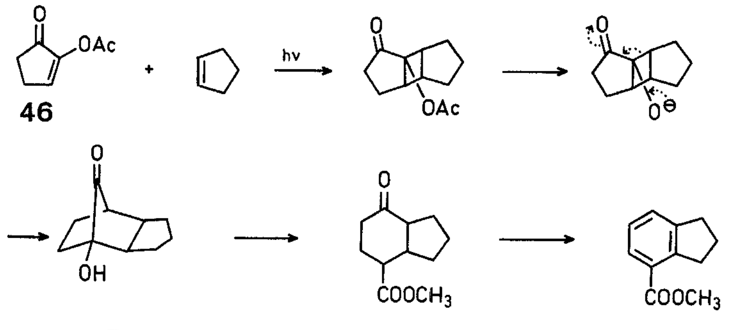


42 **43** **44**

45

4.3. Rearrangements of α-Diketone Adducts

The enol acetate of cyclopentane-1,2-dione (**46**) has been added to a number of different olefins. When the acetate in the adducts is hydrolyzed, rearrangement to a 1-hydroxy-7-oxobicyclo[2.2.1]heptane system (**47**) occurs[50]:

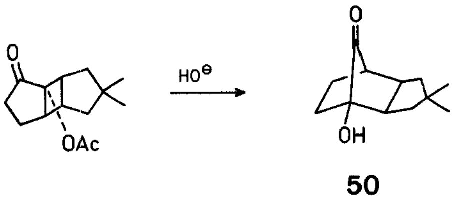


46

47 **48** **49**

Compound **47** was cleaved by lead tetraacetate to **48** which then could be converted to the benzoic acid derivative[51] **49**.

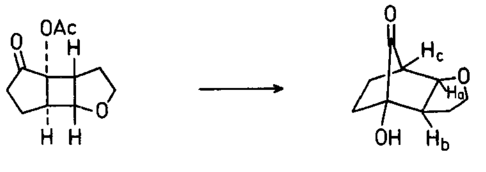
The rearrangement was used during work on synthesis of methyl isomarasmate[50] to form the compound **50**:



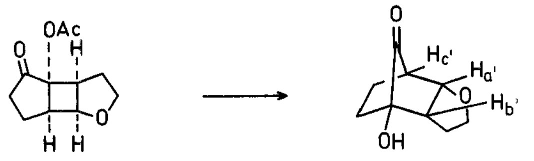
50

The rearrangement can be effected merely by dissolving the adduct in methanolic sodium hydroxide; after 5–10 minutes, the product is extracted with ether.

The *syn* and *anti* adducts lead to different rearrangement products. This provided a useful way of identifying the 4,5-dihydrofuran adducts[29]:



51

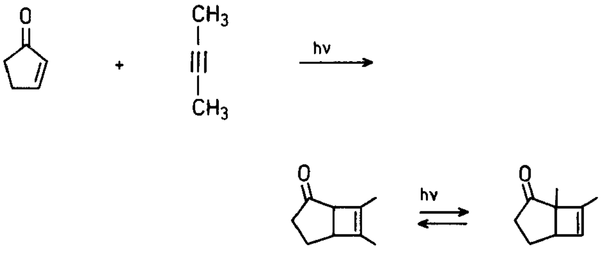


52

In the N.M.R. spectrum of compound **51**, hydrogen H_a showed up as a doublet (J = 8 cps), coupling with H_b but not H_c. The coupling of *endo* hydrogen H_a with the bridgehead hydrogen (H_c) in such compounds has been reported to be close to zero[52]. Hydrogen H'_a, on the other hand, appears as quartet (J = 8 and 4 cps), consistent with the coupling of an *exo* hydrogen with both H'_b and H'_c[52]. Accordingly, the second adduct, leading to rearranged compound **52**, was assigned the *syn* structure.

4.4. Photoisomerisations of Cyclobutenes

The cyclobutene **53** was obtained by the addition of cyclopentenone to 2-butyne[53,54]:

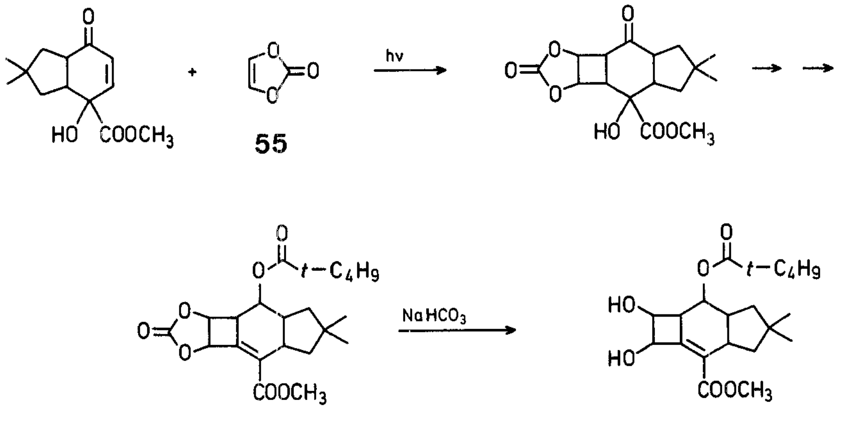


53 **54**

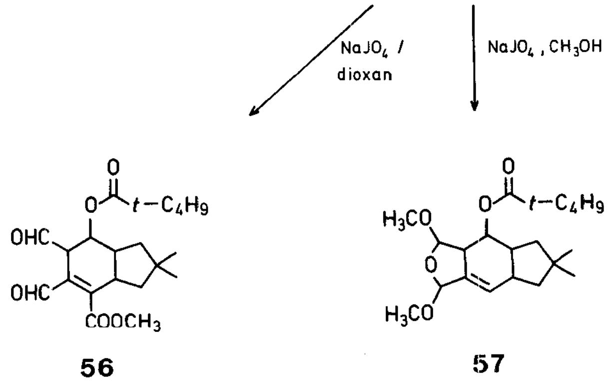
The initial adduct photoisomerises to **54**. A similar rearrangement has been observed for the 3-hexyne adduct of cyclopentenone, although not for the 3-hexyne adduct of cyclohexenone[34].

4.5. Vinylene Carbonate Adducts

The dimerization and addition to maleic anhydride of vinylene carbonate (**55**) has been reported[55]. The addition of **55** to alkenones was used during work on the synthesis of isomarasmic acid[50]. The adduct was retained for a number of steps in the synthesis, and then cleaved at the appropriate time to the dialdehyde **56**. Cleavage to the dialdehyde was accomplished by sodium periodate in aqueous dioxane; periodate in methanol led to compound **57**:



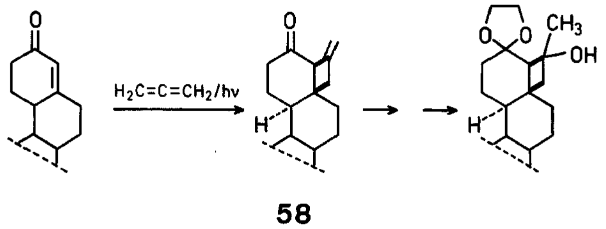
55



56 **57**

4.6. Allene Cycloadducts

The products of allene cycloadditions to enones[13,53] offer interesting possibilities for further reactions. Cyclobutanones and primary and secondary cyclobutanols can readily be formed. Cleavage to dicarbonyl compounds occurs upon treatment with aqueous hydrochloric acid in tetrahydrofuran. Diketones and ketoaldehydes so formed cyclize spontaneously to bicyclic compounds. This reaction has been used enroute to the synthesis of atisine[56]:



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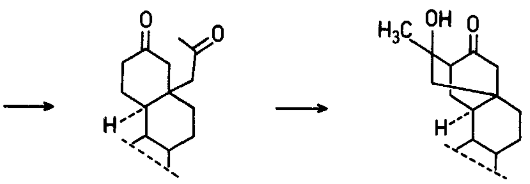
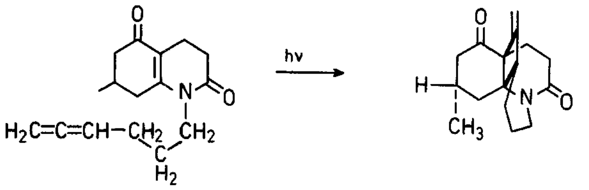
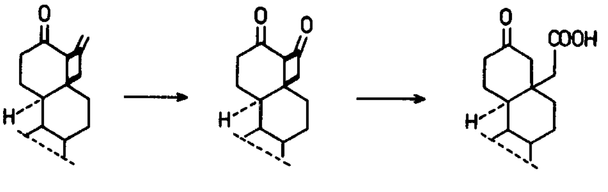


A similar sequence, using addition to allene, was used in the first syntheses of 12-*epi*-lycopine[57]. An improved method[58] involved an intramolecular addition to a 1,2-diene. The diketone rearrangement was again used in the subsequent steps:



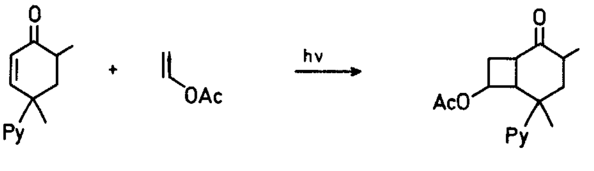
Conversion of the atisine adduct (**58**) to the cyclobutanone **59** was accomplished via the use of osmium tetroxide. Cleavage with acid yielded the keto acid **60**, an intermediate in the synthesis of the diterpene alkaloid veatchine[59]:



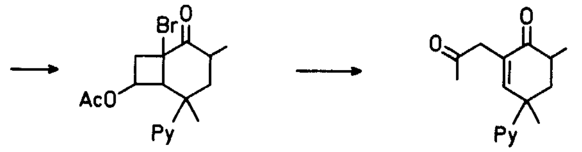
58 **59** **60**

4.7. Vinyl Acetate Adducts

During work on the Ormosia alkaloid skeleton, a new type of rearrangement involving an enone cycloadduct was found[60]. The product **62** from the irradiation of enone **61** with vinyl acetate was brominated with pyridine bromide perbromide to give **63**, which was cleaved to compound **64** upon treatment with base:



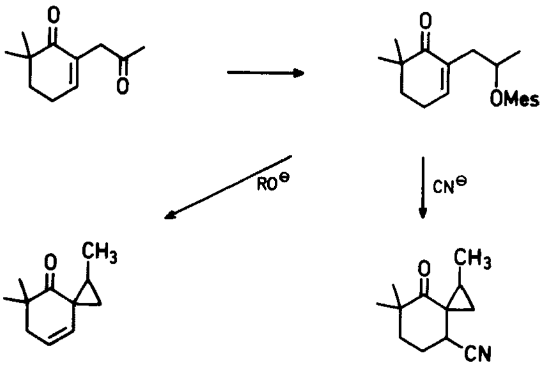
61 **62**



63 **64**

This rearrangement should be of general use since the *head-to-tail* adducts normally are obtained. If convenient, the bromo group α to the carbonyl group could possibly be introduced before the cycloaddition. Further work has shown[61] that the cyclohexenone cycloaddition generally proceeds in yields of 50–78%, and that substitution at C-2 lowers the yields only slightly. A more general cleavage method has also been found[61] involving treatment of the initial adduct with cerium(IV) ammonium nitrate[62]; yields of 60–80% of the diketone are obtained. The reaction represents a new method of introducing a carbon chain of any length into the α-position of conjugated cycloalkenones. The 1,4-dicarbonyl nature of the product suggests attractive new syntheses of furans, pyrroles, and thiophenes.

It has also been found[61] that the diketone cleavage product is a surprisingly efficient source of cyclopropyl ketones:



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[61] Z. Valenta, private communication.

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Table 1. Cycloaddition Reactions of Simple Alkenones[a]

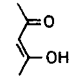
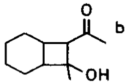
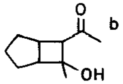
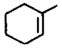
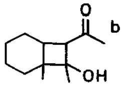
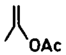
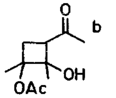
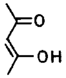
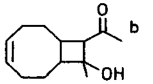
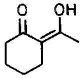
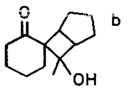
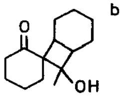
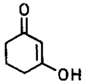
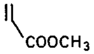
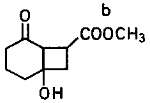
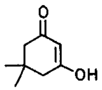
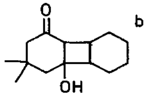
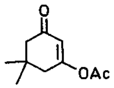
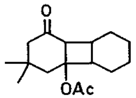
Alkenone	Alkene	Cycloadducts	Reference
		 [b]	44
		 [b]	44
		 [b]	44
		 [b]	44
		 [b]	30
		 [b]	30
		 [b]	30
		 [b]	47
		 [b]	47
			47

Table 1, continued

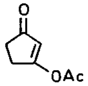
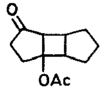
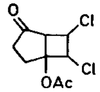
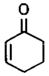
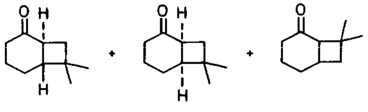
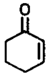
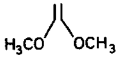
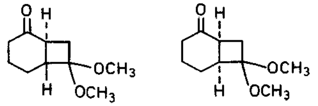
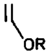
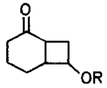
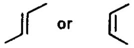
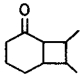
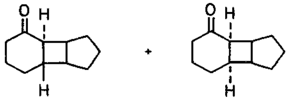
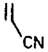
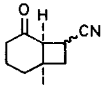
Alkenone	Alkene	Cycloadducts	Reference
			47
	$\mathrm{CHCl{=}CHCl}$		47
		3 Stereoisomers  26.5 % 6.5 % 6 %	13
		 49 % 21 %	13
	 R = Benzyl, Methyl, or Acetyl	 (2 or 3 Stereoisomers)	13
		 (3 Stereoisomers)	13
		 29 % (of Adduct) 71 %	13
		 + other Isomers	13

Table 1, continued

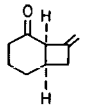
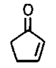
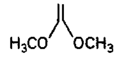
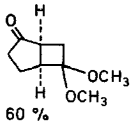
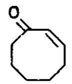
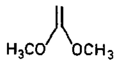
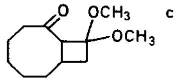
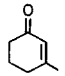
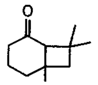
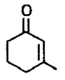
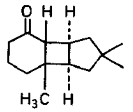
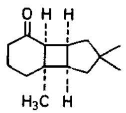
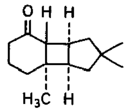
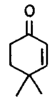
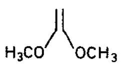
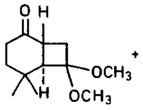
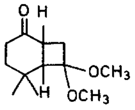
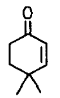
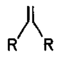
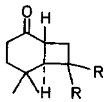
Alkenone	Alkene	Cycloadducts	Reference
	$H_2C{=}C{=}CH_2$	 55 %	13
		 60 %	13
		 c 37 %	13
		 + other products	13
		 74 % +  12 % +  14 %	43
		 + 	10
	 R = C_6H_5		9

Table 1, continued

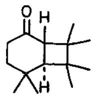
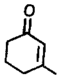
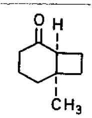
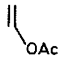
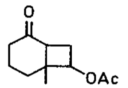
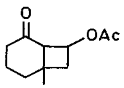
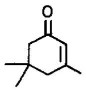
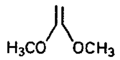
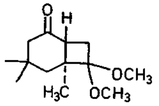
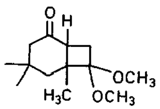
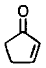
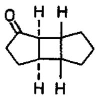
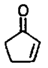
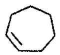
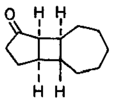
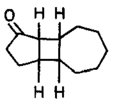
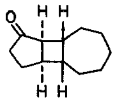
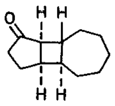
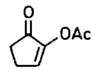
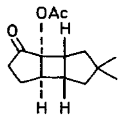
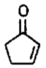
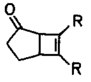
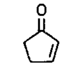
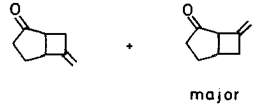
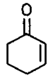
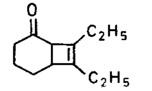
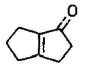
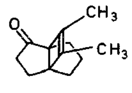
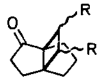
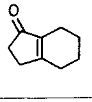
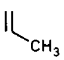
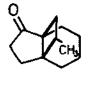
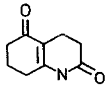
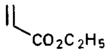
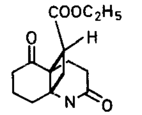
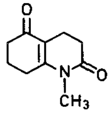
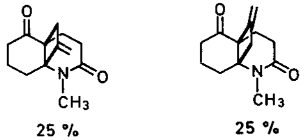
Alkenone	Alkene	Cycloadducts	Reference
			28
	CH_2 ‖ CH_2	 40 %	65
		 +  68 %	65
		 + 	10
			5
		 major  minor  	64
			50
	R I ‖‖‖ I R R = CH_3 or C_2H_5		34, 53

Table 1, continued

Alkenone	Alkene	Cycloadducts	Reference
	$H_2C=C=CH_2$		53
	$C_2H_5-C\equiv C-C_2H_5$		34
	$CH_3-C\equiv C-CH_3$		67
	$CHR=CHR$ R = H or Cl		68
			66
			66
	$H_2C=C=CH_2$		66

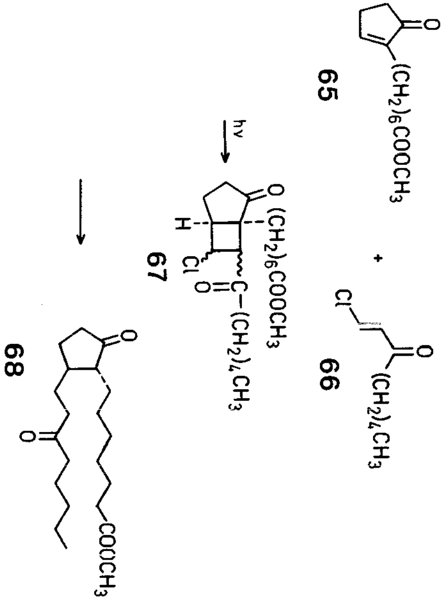
[a] Other examples in text.

[b] Not isolated, rearranges to diketone.

[c] Product of dark reaction of dimethoxyethylene with photochemically produced *trans* isomer of cyclooctenone.

4.8. Reductive Cleavage of Cyclobutane

An example of a cycloaddition of two different α,β-unsaturated ketones is the addition reaction[41] of the ketones **65** and **66**, used in a synthesis of the prostanoic acid skeleton[63]. The adduct **67** found in 35% yield was cleaved to compound **68** (possessing the desired skeleton) by treatment with zinc and acetic acid:



65 66 67 68

Received: January 2, 1970

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[67] R. L. Cargill, J. Dorn, A. E. Siebert, Abstract of Papers, Amer. Chem. Soc., Chicago, August 1964, 25 S.

[68] R. L. Cargill, J. R. Damewood, M. M. Cooper, J. Amer. Chem. Soc. **88**, 1330 (1966).