Intramolecular Photoaddition of Terminal Allenes to Conjugated Cyclohexenones

Dan Becker,* Zvi Harel, Meshulam Nagler, and Arie Gillon

Department of Chemistry, Technion, Israel Institute of Technology, Haifa 32000, Israel

Received December 29, 1981

Terminal allenes linked to cyclohexenones by hydrocarbon chains were synthesized and irradiated with UV light. It was found that [2 + 2] cycloaddition occurs regiospecifically in high yield. The adducts were oxidized by ozone to 1,3-diketones which underwent cleavage to the corresponding keto acids.

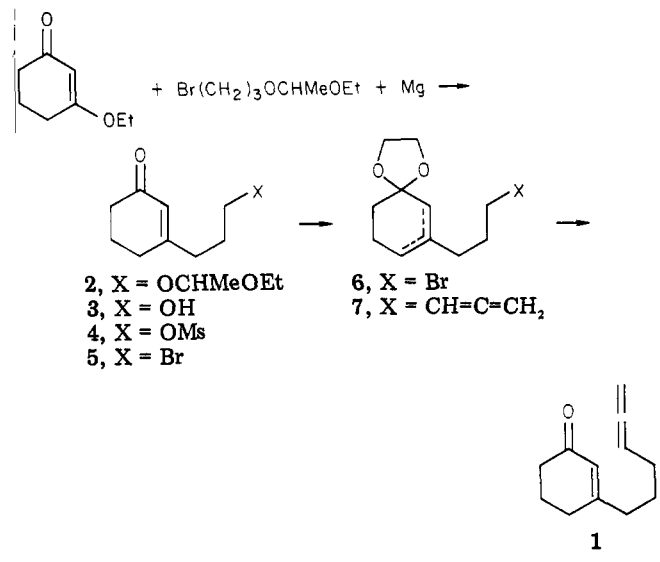
Photochemical intramolecular addition of 1,2-propadiene (allene) to cycloalkenones has been studied[1] and has been shown to be an effective tool in organic synthesis.[2] Its advantages are high yields and readily available starting materials, while its degree of regioselectivity is dependent upon the structure of the starting material[3]. Recently, Wiesner[4] suggested a rule whereby the stereochemistry of the adduct may be predicted through comparison with the reduction product by lithium in liquid ammonia, but to the best of our knowledge this empirical rule has failed to find adequate theoretical explanation. The exocyclic methylene in the adduct can be reduced to methyl,[5] cleaved to yield a ketone,[6] or oxidized to the corresponding epoxide, from which the desired system is obtained through rearrangement.[7]

The present paper reports a study on intramolecular photocycloaddition of terminal allenes to conjugated double bonds in cyclohexenones. When we began our work, a single publication was available dealing with application of this reaction in the synthesis of the alkaloid epilyiodine.[8] In the course of the study, we developed procedures for preparation of a variety of molecules containing these functional groups. Results described in later publications enabled us to improve the preparation of new systems. The decisive development was Linstrumelle's report[9] on a direct alkylation of allenyllithium. We found that the yield was improved in the presence of hexamethylphosphoramide as noted later by Gorē;[10] formation of alkynes is completely avoided. The structures of the photoproducts were determined in order to understand the factors controlling regiospecificity and the reaction potentials in the synthesis of spiro systems and substituted propellanes.

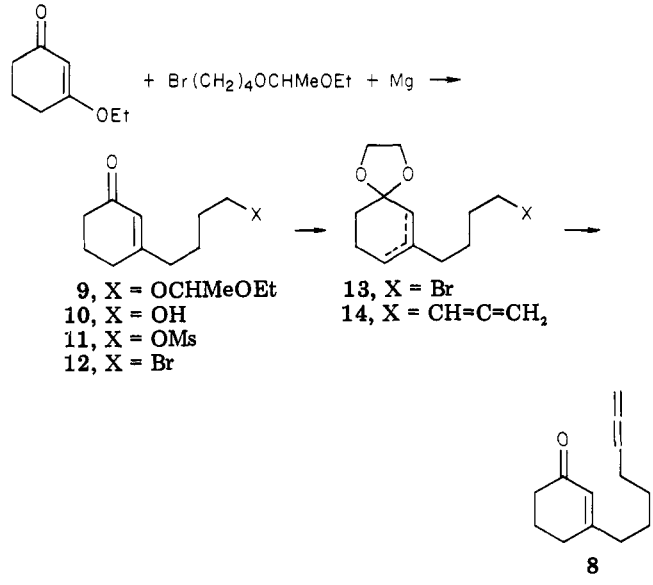
Results and Discussion

Syntheses. System 1 was prepared according to Scheme I, through alkylation of allenyllithium with a protected cyclohexenone derivative. The corresponding cyclohexenone was prepared from 3-ethoxy-2-cyclohexen-1-one and the appropriate Grignard reagent. This reaction is by no means trivial since this Grignard reagent tends to rearrange, and only strict observation of the experimental conditions[11] (excess of magnesium, temperature below 25 °C, and recourse to a less polar solvent) permitted obtention of a satisfactory yield of **2**. We tried an alternative approach based on Eaton's[12] report which describes

Scheme I



Scheme II



(1) (a) E. J. Corey, J. D. Bass, R. Le Mathieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964); (b) P. E. Eaton, *Tetrahedron Lett.*, 3695 (1964).

(2) (a) R. B. Kelly, J. Zamecnik, and B. A. Beckett, *Can. J. Chem.*, **50**, 3455 (1972); (b) F. E. Ziegler and J. A. Klock, *Tetrahedron Lett.* 315 (1974).

(3) (a) P. Crabbe, G. A. Garcia, and C. Rius, *J. Chem. Soc., Perkin Trans. 1* 810 (1973); (b) E. H. Bohme, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 2441 (1965); (c) J. F. Blount, G. D. Gray, K. S. Atwal, T. Y. R. Tsai, and K. Wiesner, *ibid.*, **21**, 4413 (1980).

(4) G. Marini-Bettolo, S. P. Sahoo, G. A. Poulton, T. Y. R. Tsai, and K. Wiesner, *Tetrahedron*, **36**, 719 (1980).

(5) K. Wiesner, L. Poon, I. Jirkovsky, and M. Fishman, *Can. J. Chem.* **47**, 433 (1969).

(6) R. B. Kelly, J. Eber, and H. K. Hung, *Can. J. Chem.* **51**, 2534 (1973).

(7) R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4645 (1966).

(8) K. Wiesner, V. Musil and K. J. Wiesner, *Tetrahedron Lett.*, 5643 (1968).

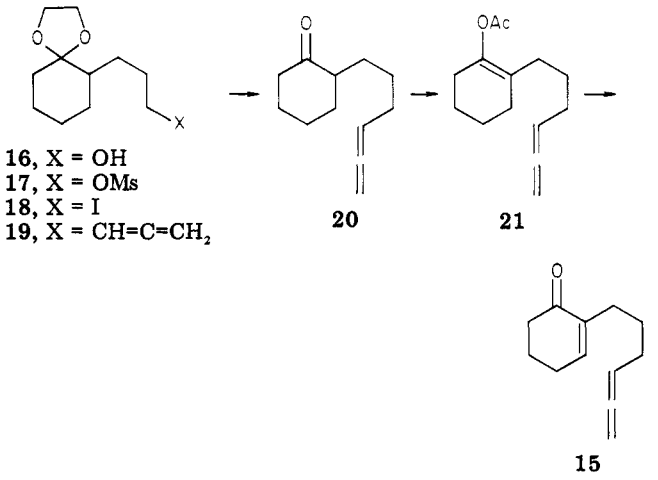
(9) G. Linstrumelle and D. Michelot, *J. Chem. Soc., Chem. Commun.*, 561 (1975).

(10) R. Baudowy, F. Delbeckq, and J. Gorē, *Tetrahedron Lett.*, 937 (1979).

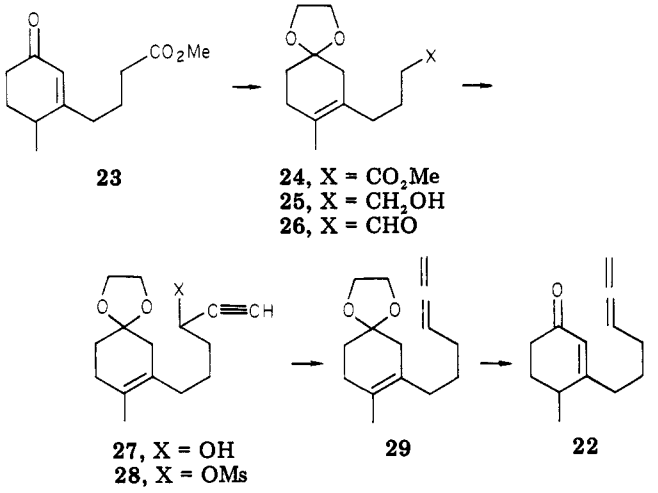
(11) A. A. Ponaras, *Tetrahedron Lett.*, 3105 (1976).

0022-3263/82/1947-3297$01.25/0

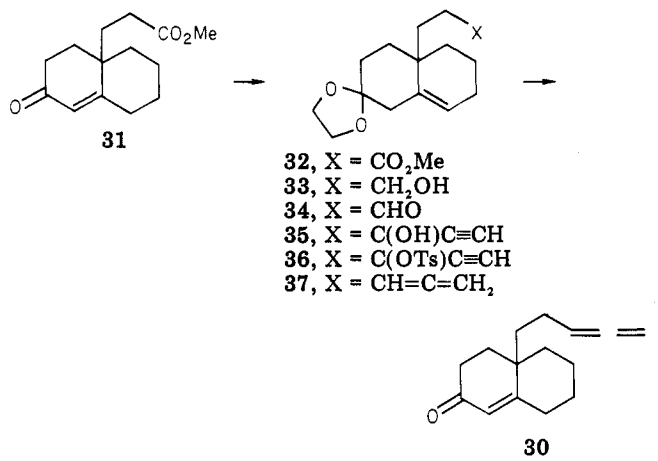
Scheme III



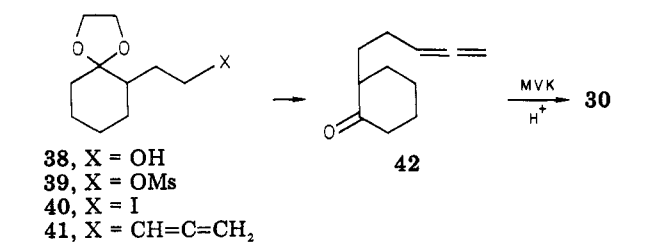
Scheme IV



Scheme V



Scheme VI



the preparation of $Li(CH_2)_3OCH(Me)OEt$. The desired product may be isolated by reaction with 3-ethoxy-2-cyclohexen-1-one, but the yield is unsatisfactory, and the process itself is awkward. In order to prevent spiroannulation, one must remove the protecting group under carefully controlled acidic conditions.[13] In these circumstances, we had first of all to effect transformation of the alcohol **3** to the bromide **5** via the mesylate **4** and only then to protect the ketone by conventional ketalization. Alkylation of allenyllithium with the bromide **6** in HMPA solution permitted, after acid hydrolysis, isolation of the keto allene **1** from the bromide **5** in 54% yield. The keto allene **8** was prepared as described for **1**. It was found that at −78 °C alkylation fails to occur, but if a large excess of allene is used, serving also as the solvent, at its boiling point (−35 °C) and the amounts of hexane and tetrahydrofuran are decreased to a minimum, the corresponding ketal allene **14** (Scheme II) can be isolated in over 90% yield (the overall yield for the seven-step process is 57%).

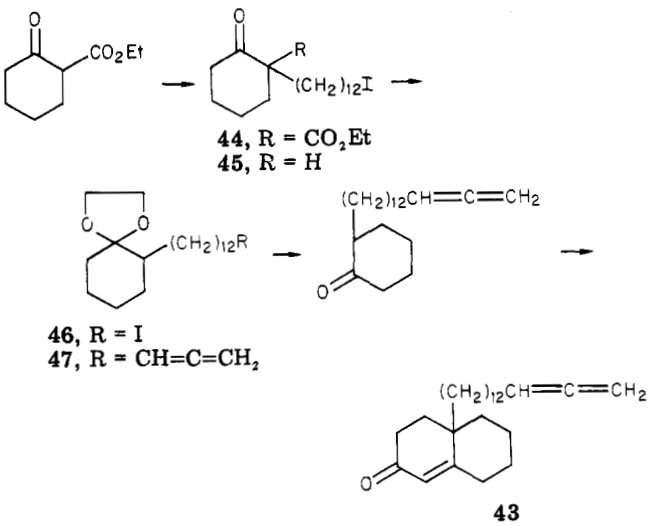
The keto allene **15**, in which the substituent is in the α-position, was prepared by electrochemical oxidation, as conventional methods for introducing a conjugated double bound (such a chlorination with sulfuryl chloride[14] and dehydrochlorination) led to decomposition of the allenic system. The ketal alcohol **16**[15] gave the corresponding alkyl halide, which was in turn reacted with allenyllithium to yield the keto allene **20** after hydrolysis (Scheme III). The acetate **21** was prepared according to House.[16] From **21** we prepared **15** in 26% yield by electrochemical oxidation in acetic acid on a carbon electrode according to Shano[17] using tetraethylammonium *p*-toluenesulfonate as the electrolyte. It is essential to have a ceramic separation between the electrodes.

For **22**, an alternative synthetic approach was developed (Scheme IV), the starting material being a keto ester; the intermediate **28** was also used for the synthesis of substituted allenes.[18] The keto ester **23** is obtainable from simple starting materials according to Newman.[19]

Protection of the ketone was effected according to Raphael[20] since conventional ketalization led to transesterification with ethylene glycol. Shifting of the double bond during ketalization can be unambiguously established by NMR.[21] Conversion of the ketal ester **24** into the aldehyde **26** was effected via the alcohol **25**, prepared by reduction with LAH followed by oxidation according to Corey.[22] It was also obtained by direct reduction with diisobutylaluminum hydride (in 65% yield) but proved difficult to purify. Condensation of **26** with lithium acetylide was effected according to Midland[23] at −78 °C with tetrahydrofuran as solvent; this solvent was used in preference to liquid ammonia because of higher yields and greater simplicity. The mesylate was prepared conven-

(12) P. E. Eaton G. F. Cooper, R. C. Johnson, and R. H. Muller, *J. Org. Chem.*, **37**, 1947 (1972).
(13) J. M. Conia and F. Rouessac, *Tetrahedron*, **16**, 45 (1961).
(14) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 162.
(15) K. B. Becker, *Helv. Chem. Acta*, **60**, 68 (1977).
(16) H. O. House, M. Gall, and H. O. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).
(17) T. Shono, M. Okawa, and I. Nishiguchi, *J. Am. Chem. Soc.*, **97**, 6144 (1975).
(18) To be submitted for publication.
(19) M. S. Newman and A. B. Mekler, *J. Org. Chem.*, **26**, 336 (1961).
(20) P. Doyle, I. R. Maclean, R. D. A. Murray, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 1344 (1965).
(21) D. Becker, N. C. Brodsky, and J. Kalo, *J. Org. Chem.*, **43**, 2557 (1978).
(22) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(23) M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975).

Scheme VII



tionally and reduced with LAH, the allene being obtained in 25% yield along with saturated and acetylenic byproducts.

Allene **30** was similarly obtained from the keto ester **31**.[24] Here we were able to slightly improve the yield to 33% by reducing the tosylate **36** with a zinc–copper couple in boiling methanol.[25]

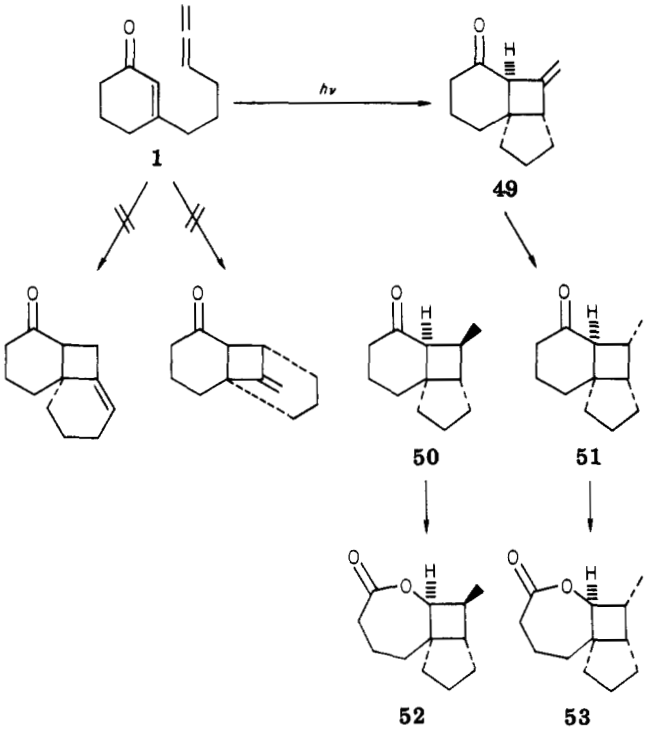
Since it turned out that direct alkylation with allenyllithium is feasible, we applied it in an alternative synthesis of **30**, with **38** as the starting material, conducting the annelation as the final step. In order to preserve the allene system, we preferred acidic annelation according to Heatcock[26] (realized in 29% yield with 65% of starting material recovered). In view of this result and of the fact that **42** can be prepared in high yield in a few steps, the process described in Scheme VI was a convenient preparation of **30**.

System **43** is similarly obtainable from 2-carboethoxycyclohexanone as shown in Scheme VII.

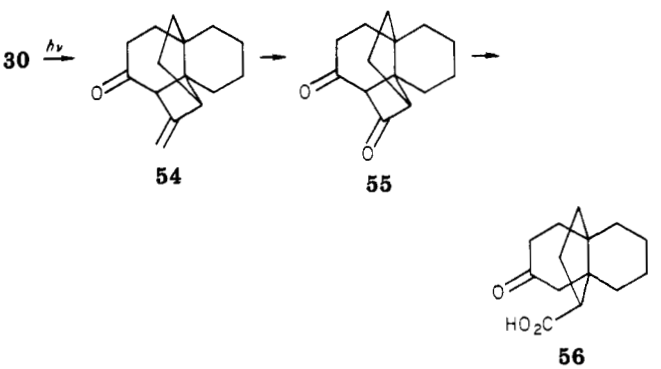
Photochemistry. In intermolecular [2 + 2] photochemical cycloaddition of ethylene[27a] or 1,2-propadiene[27b] the degree of the regioselectivity and the stereoselectivity are dependent on the structure of the enone. A recent publication by Coates[28] reports another example of intramolecular addition of an allenic side chain to an unsaturated five-membered lactone with low regioselectivity, in contrast to the corresponding olefin, which underwent regiospecific addition. We present here results on systems particularly designed to gain knowledge concerning regioselectivity of intramolecular photocycloadditions. Irradiations were carried out in cyclohexane, the concentration of the enone was <0.05 M, using a 450-W Hanovia lamp and a Pyrex filter ($\lambda > 295$ nm). In certain cases uranium glass ($\lambda > 330$ nm) is preferred.

Irradiation of **1** resulted in a single product, **49** (Scheme VIII) in quantitative yield. Since the adduct was stable in 2 N sodium methoxide *cis* addition is probable. The possibility of addition to the terminal bond of the allene can be rejected on the basis of the NMR spectrum (two vinylic hydrogens) and the fact that a methyl group is

Scheme VIII



Scheme IX



formed on catalytic reduction. In order to decide between parallel or cross addition, we oxidozed **50** and **51** to the corresponding lactones **52** and **53**. The structure of each isomer could be established conclusively on basis of the coupling constants of the hydrogen adjacent to the oxygen and the chemical shift of the methyl group in NMR spectrum (see Experimental Section). The addition is regiospecific and affords the parallel product.

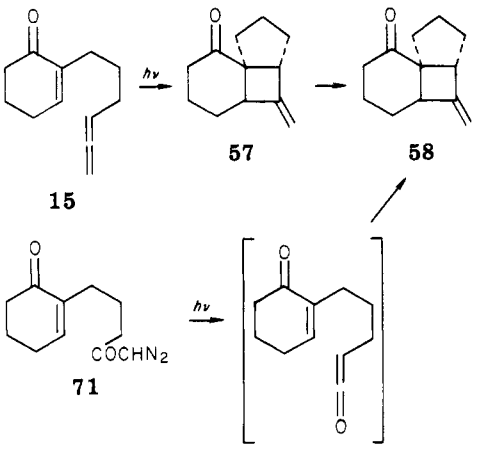
The synthetic potential of the reaction was shown in the synthesis of [4.4.3]propellane. Irradiation of **30** yielded a single adduct, **54**, in excellent yield. Ozonolysis of **54** yielded the 1,3-diketone **55**, which was unstable and decomposed under mild acidic conditions to give the keto acid **56**, thereby completing the synthesis of the propellane (Scheme IX).

It can be concluded that both **1** and **30**, in which the allene is three carbons away from the β-position of the double bond, add in parallel fashion. The mode of cycloaddition of the allene in these two models is the reverse of that found in the analogous ketenes.[29]

System **15** was irradiated in order to determine the factor responsible for the regiospecificity: the charge distribution in the allene or the chain length. Were it the

(24) D. Becker, D.S.c. Thesis, Israel Institute of Technology, 1968.
(25) E. Lee-Ruff and P. Khazanie, *Can. J. Chem.*, **53**, 1708 (1975).
(26) C. H. Heathcock, J. E. Ellis, J. E. McMurry, and A. Coppolino, *Tetrahedron Lett.*, 4995 (1971).
(27) (a) R. L. Cargill, G. H. Morton, and J. Bordner, *J. Org. Chem.*, **45**, 3929 (1980); (b) D. K. Mank Duc, M. Fetizon, I. Hanna, and A. Olesker, *J. Chem. Soc., Chem. Commun.*, 1209 (1980).
(28) W. R. Baker, P. D. Senter, and R. M. Coates, *J. Chem. Soc., Chem. Commun.*, 1011 (1980).
(29) D. Becker and D. Birnbaum, *J. Org. Chem.*, **45**, 570 (1980).

Scheme X



former, shifting of the chain from the β- to the α-position could dictate cross addition as was found in the ketene systems. Irradiation of **15** resulted in a single product **57** in high yield (Scheme X). The mode of addition was determined unambiguously through ozonolysis.

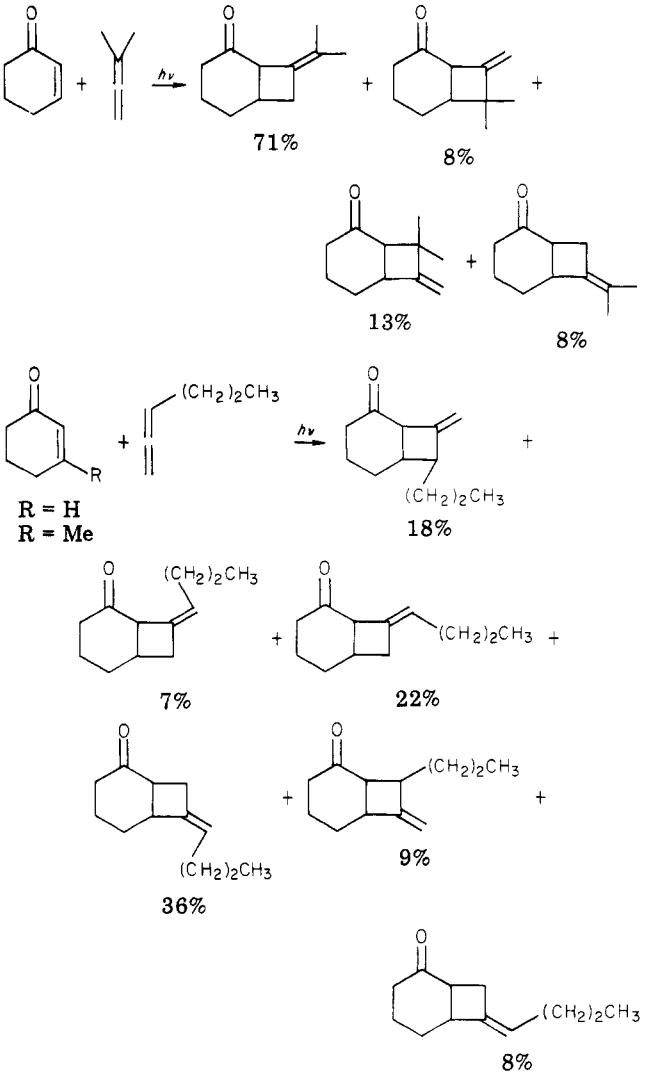
Diketone **58** was found to be identical with the adduct obtained upon irradiation of the diazo ketone **71**,[29] indicating that the addition was again in the parallel mode. Accordingly, it can be conclusively stated that in cycloaddition of allenes there is no preorientation step due to charge distribution, as has been suggested.[30] This finding is in agreement with recent calculations, which confirm the absence of negative charge on the central carbon of the allene system[31] so that allenes maybe expected to behave like 1,6-dienes, in which parallel addition is favored.[31]

It is likely that the regiospecificity observed in the systems studied so far is due to the fact that the allenes are substituted? As of now we have been unable to find any information about the intermolecular [2 + 2] photoaddition of substituted allenes.

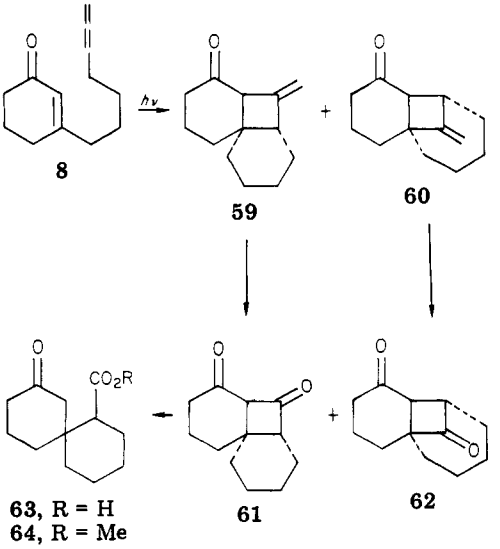
In order to verify this point, we irradiated the allenes 3-methyl-1,2-butadiene (commercially available) and 1,2-hexadiene (prepared by direct alkylation of allenyllithium with 1-iodopropane[9]) in the presence of 2-cyclohexenone or 3-methyl-2-cyclohexenone the results are described in Scheme XI.

Gas chromatography and NMR analyses[33] indicated that on irradiation of 3-methyl-1,2-butadiene with cyclohexenone yields at least four compounds; the head-to-head products account for 79% of the mixture, but the other isomers are also identifiable; we believe that selectivity is dictated by steric factors. On the other hand, when 1,2-hexadiene is added to cyclohexenone, at least six isomers in similar amounts can be isolated, indicating loss of orientation; similar results were obtained in the case of 3-methyl-2-cyclohexenone. It does not appear that intermolecular addition of substituted allenes cannot become an attractive synthetic process. Mechanistically, it is clear that the length of the chain is responsible for the regiospecificity found in intramolecular additions. In order to examine the effect of chain length, we prepared the system **8** in which the chain contains an extra carbon atom as

Scheme XI



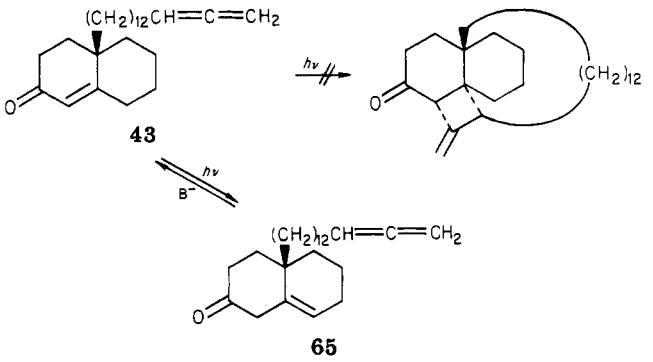
Scheme XII



compared to **1**. (Attempts to prepare a system with one carbon atom less have so far failed.) Irradiation of **8** yielded two adducts, **59** and **60** (Scheme XII) in 85:15 ratio, which were isolated and structurall defined through spectral data and ozonolysis to the corresponding keto ester **64** and diketon **62**. It can be stated that lengthening of the chain causes loss in regioselectivity; this also sup-

(30) D. Becker, Z. Harel, and D. Birnbaum, *J. Chem. Soc., Chem. Commun.*, 377 (1975).
(31) (a) W. Runge, W. Kosbahn, and J. Korner, *Ber. Bunsenges. Phys. Chem.*, **79**, 371 (1975); (b) L. Radom, W. A. Lathan, W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, **93**, 5339 (1971).
(32) (a) R. L. Cargill, J. R. Dalton, S. O'Connor, and D. G. Michels, *Tetrahedron Lett.*, 4465 (1978); (b) J. R. Scheffer and R. A. Wastradowski, *J. Org. Chem.*, **37**, 4317 (1972).
(33) A. Gillon, Thesis, Israel Institute of Technology, 1981.

Scheme XIII



ports our assumption that steric factors affect the structure of the adduct.

In view of the high yields obtained in the systems studied so far, we examined the possibility of preparing the unknown *trans*-propellane. On the basis of a model, it seemed likely that a 12-carbon-atom chain would enable the allene to access the double bond of the bicyclic system from the α-side. We prepared **43** and irradiated it as usual. As it turned out, however, the new product **65** (at 17% yield) did not contain a conjugated ketone (Scheme XIII). It preserved the allenic system and could be converted quantitatively into the starting material **43** under mild alkaline catalysis. We assume that in this system the photochemical reaction consists of shifting the double bond to the β,γ-position[34] rather than to cause [2 + 2] photocycloaddition. Perhaps the *trans*-propellane can be prepared with a longer allenic side chain.

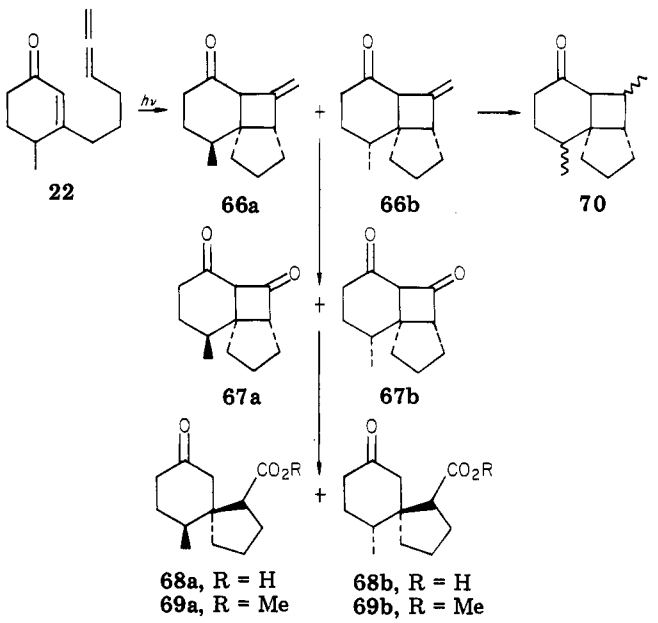
Several papers have been published in recent years on the sometimes high stereoselectivity of intermolecular addition of 1,2-propadiene to substituted cyclohexenones[4] on one hand and on intramolecular addition of olefins in substituted systems[35,36] on the other. We examined the stereoselectivity of intramolecular addition of an allene to a 4-substituted cyclohexenone. On irradiating **22**, we could isolate in 95% yield a mixture of **66a** and **66b** (Scheme XIV), and their structures were established through ozonolysis and reduction.

The diketones **67a,b** were unstable and rearranged immediately to yield the keto acids **68a,b** which were converted with an excess of diazomethane into the corresponding esters **69a,b**. The ratio of the isomers was found to be 1:1.6 through GLC and NMR. In order to exclude the possibility of epimerization of the carboxyl group during cleavage of the cyclobutanone, we treated the ester mixture with 2 N sodium methoxide, affording four compounds. Thus, **69a** and **69b** differ only in the configuration of the 4-methyl group. The *cis* structure was confirmed through catalytic reduction of **66**, yielding the products **70**, which were stable upon treatment with activated basic alumina. It can be concluded that the orientational effect of the methyl on the approach of the allene is limited. This is in complete agreement with intermolecular addition of 1,2-propadiene to substituted cyclohexenones.[27]

Conclusion

We described synthetic methods for preparation of systems containing an allene and a conjugated unsaturated ketone in a six-membered ring. Upon irradiation of those

Scheme XIV



systems containing these functional groups separated by three carbon atoms, regiospecific addition took place in the parallel mode and in excellent yield. The degree of regiospecificity decreases as the chain length increases; presumably the determining factor is steric. The adducts are starting materials for substituted spiro compounds and propellanes, which can be readily prepared in high yield through oznolysis and cleaveage of the 1,3-diketone to give the corresponding keto acid.

Experimental Section

The instruments used were as follows: ^{1}H NMR, Varian T-60; ^{13}C NMR, Bruker WP-60; MS, Varian MAT-711; GLC, F&M-810; IR, Perkin-Elmer 257; UV, Cary 15. Woelm silica gel (100–200 mesh, activity I, no. 02747) was used.

The commercial cyclohexane used as the solvent for irradiation was purified by shaking with concentrated sulfuric acid and 10% sodium carbonate, irradiation with a quartz 450-W Hanovia lamp for 4 h, and distillation.

3-[3-(1-Ethoxyethoxy)propyl]-2-cyclohexen-1-one (2). From acetaldehyde ethyl 3-bromopropyl acetal[12] (1.7 g, 8 mmol) and magnesium (0.58g, 24 mmol) in 10 mL of dry tetrahydrofuran was prepared the Grignard reagent according to the Ponaras[11] procedure. To the reagent was added dropwise, below 10 °C, 3-ethoxy-2-cyclohexen-1-one (1.12 g, 8 mmol) dissolved in 4 mL of 1:2 benzene/tetrahydrofuran, and then stirred for 3 h at room temperature. The reaction mixture was poured onto ice, and the solution was acidified with 5% hydrochloric acid to pH 5, extracted with ether (3 × 30 mL), and dried. The solvents were then removed to yield 2.65 g of crude oily keto acetal **2**: IR ($CHCl_3$) 1670 cm^{-1} (C=O, conj); NMR (CCl_4) δ 5.8 (s, 1 H), 4.6 (q, 1 H) 3.4 (m, 4 H), 1.2–2.4 (m, 10 H), 1.19 (d, 3 H), 1.18 (t, 3 H).

3-(3-Bromopropyl)-2-cyclohexen-1-one (5). Crude acetal **2** (11.2 g) was dissolved in 100 mL of methanol, 2 g of oxalic acid was added, and the solution was stirred for 1.5 h at room temperature. Anhydrous sodium bicarbonate (10 g) was added, the methanol was removed, and 25 mL of water was added. The mixture was then extracted with chloroform (3 × 50 mL) and dried, and the solvent was removed to yield 4.8 g of the crude keto **3**: IR ($CHCl_3$) 1660 cm^{-1}; NMR(CCl_4) δ 5.8 (br s, 1 H), 3.55 (t, 2 H), 3.05 (br s, 1 H), 1.2–2.5 (m, 10 H).

The crude ketol **3** was dissolved in 30 mL of dry tetrahydrofuran and 7 mL of triethylamine and cooled to 0 °C. Methanesulfonyl chloride (1 mL) was added dropwise and stirred for 2 h. Water (50 mL) was added, and the solvent was removed and extracted with methylene chloride (3 × 25 mL) and ether (2 × 25 mL). The organic layers were combined, washed with 25 mL of cooled 5% hydrochloric acid followed by sodium bicarbonate, and dried, and

(34) H. Wehrli, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chem. Acta*, **46**, 678 (1963).
(35) M. C. Pirrung, *J. Am. Chem. Soc.*, **103**, 82 (1981).
(36) (a) M. Fetizon, S. Lazar, C. Pascard, and J. Prange, *J. Chem. Soc., Perkin Trans. 1* 1407 (1979); (b) A. M. Birch and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1195 (1980).

the solvents were removed to yield 5.3 g of crude keto mesylate 4: IR ($CHCl_3$) 1660 (C=C—C=O), 1360 cm^{-1} (OSO_2); NMR (CCl_4) δ 5.83 (br s, 1 H), 4.22 (t, 2 H), 2.99 (s, 3 H), 1.4–2.6 (m, 10 H).

The crude keto mesylate 4 was dissolved in 60 mL of dry tetrahydrofuran, anhydrous lithium bromide (2.8 g, 32.2 mmol) was added, and the mixture was stirred overnight at room temperature. The solids were filtered and washed with ether, and the solvent was dried and removed. The crude keto bromide 5 was chromatographed on 80 g of Florisil and eluted with 1:2 ether/hexane to yield 5: 2.7 g (35% overall from acetal 2); IR ($CHCl_3$) 1660 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.8 (br s, 1 H), 3.4 (t, 2 H), 1.5–2.60 (m, 10 H); MS, found for $C_9H_{13}Br^{81}O$ m/e 218.0085 (theory m/e 218.0149).

7-(3-Bromopropyl)-1,4-dioxaspiro[4.5]dec-7-ene (6). Keto bromide 5 (0.48 g, 2.2 mmol), 3 mL of ethylene glycol and *p*-toluene sulfonic acid were dissolved in 30 mL of benzene in a system including a Dean–Stark trap for removal of water and refluxed for 24 h. To the cooled solution was added 25 mL of 5% aqueous sodium bicarbonate, it was extracted with benzene (3 × 25 mL) and dried, and the solvent was removed to yield 0.54 g (95%) of crude ketal bromide 6: NMR (CCl_4) δ 5.47 (m, 1 H), 3.87 (s, 4 H) 3.35 (t, 2 H) 1.2–2.4 (m, 10 H); MS, found for $C_{11}H_{17}Br^{81}O_2$ m/e 262.0392 (theory m/e 262.0410).

3-(4,5-Hexadienyl)-2-cyclohexen-1-one (1). 1,2-Propadiene (0.5 mL) was liquified into 10 mL of dry tetrahydrofuran at −78 °C, *n*-butyllithium (2.8 mL, 3.64 mmol, in hexane) was added dropwise to the solution under an argon atmosphere, and the mixture was stirred for 0.5 h. The ketal bromide 6 (0.5 g, 1.9 mmol), dissolved in 1 mL of hexamethylphosphoramide, was then added dropwise, and the solution was stirred for 0.5 h at −78 °C and then warmed to room temperature. Water was added, the solvents were removed, the ketal allene was extracted with ether (3 × 25 mL) and dried, and the solvent was removed to yield 0.4 g of crude ketal allene 7.

The latter was dissolved in 40 mL of methylene chloride, 20 mL of ethanol, 0.9 mL of water, and 2 mL of 32% hydrochloric acid, and the mixture was stirred overnight at room temperature. The solvents were then removed, 5 mL of water was added, the mixture was extracted ether (4 × 10 mL) and dried, and the solvent was removed. The residue was 0.3 g of crude oil, which was purified by TLC on silica gel to yield (54%) of keto allene 1: IR ($CHCl_3$) 1960 (C=C=CH_2), 1660 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.85 (s, 1 H), 5.10 (m, 1 H), 4.70 (m, 2 H) 1.2–2.4 (m, 12 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.35; H, 9.14.

3-[4-(1-Ethoxyethoxy)butyl]-2-cyclohexen-1-one (9). A Grignard reagent was prepared from 3.24 g (14.4 mmol) of acetaldehyde ethyl 4-bromobutyl acetal and 1.05 g (43 mmol) of magnesium in dry tetrahydrofuran below 25 °C. After 0.5 h at room temperature the solution was cooled to 0 °C, 3-ethoxy-2-cyclohexenone (1.9 g, 13.7 mmol) was added in 8 mL of 1:3 benzene/tetrahydrofuran below 10 °C, and the mixture was stirred for 3 h at room temperature. The reaction mixture was worked up as described for 2 to yield 2.83 g (88%) of crude cyclohexenone acetal 9: IR ($CHCl_3$) 1660 cm^{-1} (C=O); NMR (CCl_4) δ 5.8 (s, 1 H), 4.6 (q, 1 H), 3.47 (q, 4 H), 1.2–2.4 (m, 14 H), 1.19 (d, 3 H), 1.18 (t, 3 H).

3-(4-Hydroxybutyl)-2-cyclohexen-1-one (10). Acetal 9 (2.83 g, 11.8 mmol) was dissolved in 10 mL of ethanol and 6.5 mL of 2% aqueous hydrochloric acid and stirred for 0.5 h at room temperature. Sodium bicarbonate and 10 mL of water were added, and the reaction mixture was extracted with chloroform (3 × 25 mL) and dried. The solvent was then removed to yield 2.75 g of crude ketol 10: IR ($CHCl_3$) 3400–3600 (OH), 1665 cm^{-1} (C=O); NMR (CCl_4) δ 5.83 (s, 1 H), 3.57 (t, 2 H) 3.5 (br s, 1 H) 1.2–2.5 (m, 12 H).

3-(4-Bromobutyl)-2-cyclohexen-1-one (12). The crude ketol 10 (2.75 g) was converted to the keto mesylate as described for 4 to yield 3.48 g of crude 11: IR ($CHCl_3$) 1670 cm^{-1} (C=O); NMR (CCl_4) δ 5.90 (s, 1 H), 4.25 (t, 2 H), 3.0 (s, 3 H), 1.4–2.6 (m, 12 H).

The crude keto mesylate 11 (3.4 g) was converted to the crude keto bromide 12 as described for 5, and elution from a short silica gel column with benzene/methylene chloride (1:1) yielded pure product: 2.04 g (75%); IR ($CHCl_3$) 1665 cm^{-1}; NMR (CCl_4) δ 5.77 (s, 1 H), 3.42 (t, 2 H), 1.50–2.60 (m, 12 H); MS, found for $C_{10}H_{15}BrO$ m/e 230.0309, 232.0289 (theory m/e 230.0307, 232.0286). Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54; Br, 34.75. Found: C, 51.88; H, 6.69; Br, 34.58.

7-(4-Bromobutyl)-1,4-dioxaspiro[4.5]dec-7-ene (13). The keto bromide 12 (1.05 g, 4.5 mmol), with 5 mL of ethylene glycol and *p*-toluenesulfonic acid (80 mg, 0.46 mmol), was dissolved in 60 mL of dry benzene and converted to the ketal bromide as described for 6 to yield 1.14 g (91%) of ketal bromide 13: NMR (CCl_4) δ 5.77, 5.37 (s, 1 H), 3.87 (s, 4 H), 3.37 (t, 2 H), 1.2–2.4 (m, 12 H): MS, found for $C_{12}H_{19}BrO_2$ m/e 274.0566, 276.0545 (theory m/e 274.0568, 276.0548).

3-(5,6-Heptadienyl)-2-cyclohexen-1-one (8). 1,2-propanediene (3 mL) was liquified into a 50-mL two-neck flask equipped with a dry ice condenser, *n*-Butyllithium (9 mL, 1.4 M solution, 12.6 mmol) was added at −35 °C, and the reaction mixture was stirred for 0.5 h under a nitrogen atmosphere. The crude ketal bromide 14 (1.47 g, 5.4 mmol) was dissolved in 3 mL of hexamethylphosphoramide, 9 mL tetrahydrofuran was added dropwise, and the mixture was stirred for 1 h at −35 °C (reflux of allene). The reaction mixture was worked up as described for 7, and the ketal was removed as described for 1 to yield 0.79 g (95%) of keto allene 8: IR ($CHCl_3$) 1960 (C=C=C), 1665 cm^{-1} (C=O); NMR (CCl_4) δ 5.43 (s, 1 H), 5.07 (m, 1 H), 4.67 (m, 2 H), 1.2–2.4 (m, 14 H); MS, found for $C_{13}H_{18}O$ m/e 190.1364 (theory m/e 190.1357). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.88; H, 9.40.

2-(1,4-Dioxaspiro[4.5]decan-6-yl)propyl Methanesulfonate (17). Ketol 16[15] (12.2 g, 61 mmol) was converted to the ketal mesylate 17 as described for 4 to give 17.3 g (100%) of yellow liquid: NMR (CCl_4) δ 4.20 (t, 2 H, J = 2 Hz), 3.87 (s, 4 H), 2.90 (s, 3 H).

6-(3-Iodopropyl)-1,4-dioxaspiro[4.5]decane (18). A solution of 17 (14.1 g, 51 mmol) and sodium iodide (11.3 g, 75 mmol) in dry tetrahydrofuran (55 mL) was stirred overnight at room temperature. Ether was added, and the precipitate was filtered and washed with ether. The filtrate was concentrated, and the residue was dissolved in ether. The solution was washed with water, 10% sodium bisulfite solution, and saturated sodium chloride solution, dried over anhydrous sodium carbonate, filtered, and concentrated to yield 13.7 g (87%) of yellow liquid: NMR (CCl_4) δ 3.88 (s, 4 H), 3.16 (t, 2 H, J = 6 Hz); MS, found for $C_{11}H_{19}O_2I$ m/e 310.0437 (theory m/e 310.0429).

2-(4,5-Hexadienyl)cyclohexanone (20). Preparation of 20 from 18 (13.4 g, 43 mmol) as described for conversion of 6 into 7 was carried out in quantitative yield: IR (CCl_4) 1960 (C=C=CH_2), 1710 cm^{-1} (C=O); NMR (CCl_4) δ 5.1 (m, 1 H), 4.6 (m, 2 H), 1.3–2.4 (m, 15 H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 9.94.

2-(4,5-Hexadienyl)cyclohex-1-en-1-yl Acetate (21). Acetic anhydride (13.5 mL, 0.14 mol) and the keto allene 20 (5.2 g; 29 mmol) were dissolved in dry carbon tetrachloride (35 mL).[16] To this solution was added 70% aqueous perchloric acid (0.4 mL) in aliquots of 50–150 μL at time intervals of 1 h according to the progress of the reaction as monitored by TLC. The dark reaction mixture was poured into a cold mixture of pentane (90 mL) and sodium bicarbonate, and 5% aqueous sodium carbonate was added to the stirred mixture until the acid was neutralized. The organic layer was separated and the aqueous layer extracted with pentane (50 mL). The organic solutions were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The dark residue was dissolved in pentane and filtered through a short column of neutral alumina. The solvent was then removed to yield 5.2 g of yellow liquid, a mixture of the allene 21 and its acetylenic isomer. The product was purified by dissolution in ether (26 mL) and shaking for 30 min with 20% aqueous silver nitrate (20 mL). The organic layer was separated and filtered through celite. The ethereal solution was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to yield 4.1 g (51%) of the enol acetate allene 21: IR (CCl_4) 1960 (C=C=CH_2), 1750 cm^{-1} (C=O); NMR (CCl_4) δ 5.1 (m, 1 H), 4.63 (m, 2 H), 2.05 (s, 3 H); MS, found for $C_{14}H_{20}O_2$ m/e 220.1473 (theory m/e 220.1403). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.25; H, 9.20.

2-(4,5-Hexadienyl)-2-cyclohexen-1-one (15). The electrochemical oxidation reaction was carried out in a divided cell

comprised of a 500-mL stainless-steel beaker (the cathode) and inside it, cushioned in a layer of glass wool, a 100-mL ceramic beaker, with the anode being a carbon cylinder of 30-cm^2 area connected to a mechanical stirrer. The outer cell was charged with a solution of tetraethylammonium tosylate[17] (6 g) in glacial acetic acid (150 mL) and the inner cell with a solution of tetraethylammonium tosylate (2 g) and crude enolacetate allene **21** (3.8 g, 14 mmol) in glacial acetic acid (50 mL). A constant current (20 mA) was passed through the system with stirring, and the progress of the reaction was monitored by TLC. After 30 h, the solution in the outer cell was poured into water (300 mL) and extracted with ether (3 × 100 mL). The ethereal solution was washed with aqueous sodium bicarbonate, water, and saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was removed. The dark residue was dissolved in pentane and filtered through neutral alumina. Purification by a preparative TLC (silica; acetone–hexane, 1:6) yielded 0.65 g (26%) of keto allene **15**: IR(CCl_4) 1960 (C=C=CH_2), 1680 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 6.64 (m, 1 H), 5.07 (m, 1 H), 4.6 (m, 2 H), 1.3–2.5 (m, 12 H); UV (hexane) λ_{max} 230 nm (ϵ 8900). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.74; H, 9.20.

Methyl 4-(8-Methyl-1,4-dioxaspiro[4.5]dec-7-en-7-yl)-butyrate (24). The keto ester **23**[19] (5.0 g, 24 mmol), ethylene glycol (7.8 mL, 140 mmol), triethyl orthoformate (15.6 mL, 94 mmol), and *p*-toluenesulfonic acid (50 mg) were refluxed at 165 °C for 2 h. The solution was cooled to room temperature, and a small amount of powdered anhydrous bicarbonate was added. The mixture was diluted with petroleum ether and washed with saturated sodium chloride solution. The solution was dried over anhydrous sodium carbonate, filtered and concentrated. On removal of the triethyl orthoformate, 6.0 g (100%) of the ketal ester **24** was obtained: IR ($CHCl_3$) 1740 cm^{-1} (COMe); NMR ($CDCl_3$) δ 4.00 (s, 4 H), 3.66 (s, 3 H) 1.2–2.3 (m, 12 H); MS, found for $C_{14}H_{22}O_4$ m/e 254.1501 (theory m/e 254.1518). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.43; H, 8.62.

4-(8-Methyl-1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanol (25). A solution of ketal ester **24** (25.7 g, 100 mmol) in dry ether (150 mL) was added dropwise to a stirred slurry of lithium aluminum hydride (10.7 g, 280 mmol) in ether (250 mL). The reaction mixture was refluxed for 1.5 h and worked up as usual to yield 23.1 g (100%) of the ketal alcohol **25**: NMR ($CDCl_3$) δ 4.00 (s, 4 H), 3.60 (m, 2 H); MS, found for $C_{13}H_{22}O_3$ m/e 226.1557 (theory m/e 226.1568). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.92, H, 9.80.

4-(8-Methyl-1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanal (26). Chromium trioxide (2.52 g, 25.2 mmol) was added to a stirred solution of pyridine (3.98 g, 50.4 mmol) in methylene chloride (63 mL).[37] After the mixture was stirred 15 min at room temperature, a solution of the ketal alcohol **25** (1.0 g, 4.2 mmol) in 5 mL of methylene chloride was added in a single portion. The reaction mixture was worked up as usual to yield 0.8 g (80%) of the ketal aldehyde **26**: IR ($CHCl_3$), 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.78 (t, 1 H, J = 1.7 Hz), 3.95 (s, 4 H); MS, found for $C_{13}H_{20}O_3$ m/e 224.1387 (theory m/e 224.1412).

6-(8-Methyl-1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1-hexyn-3-ol (27). Dry acetylene was bubbled into dry tetrahydrofuran (25 mL) at −78 °C. A solution of *n*-butyllithium in hexane (15 mL, 18 mmol) was added dropwise into the reaction flask over 15 min in a nitrogen atmosphere. The solution was stirred for 10 min, after which a solution of the ketal aldehyde **26** (1.6 g, 6.4 mmol) in 5 mL of dry tetrahydrofuran was added, and the mixture was stirred further for 20 min and then warmed to room temperature. Water (5 mL) was then added, followed by anhydrous potassium carbonate until the aqueous phase became pasty. The organic phase was decanted and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic phase was dried over anhydrous sodium carbonate, filtered, and concentrated to yield 2.0 g of the crude ketal acetylene **27**: NMR ($CDCl_3$) δ 4.40 (m, 1 H), 4.00 (s, 4 H); MS, found for $C_{15}H_{22}O_3$ m/e 250.1546 (theory m/e 250.1568).

6-(8-Methyl-1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1-hexyn-3-yl Methanesulfonate (28). Methanesulfonyl chloride (1.43 g, 12.5 mmol) was added over 15 min in a nitrogen atmosphere to a cooled (−5 °C) stirred solution of **28** (2.85 g, 11.4 mmol) and triethylamine (1.73 g, 17.1 mmol) in dry ether (35 mL). After the mixture was stirred for 60 min at −5 °C, the precipitated triethylamine hydrochloride was removed by filtration. The supernatant was washed with ice–water, cold 5% hydrochloric acid, and 5% aqueous sodium bicarbonate. The solution was dried over anhydrous sodium carbonate, filtered, and concentrated to yield 3.2 g (86%) of the mesylate **28**: NMR ($CDCl_3$) δ 4.00 (s, 4 H) 3.14 (s, 3 H).

3-(4,5-Hexadienyl)-4-methyl-2-cyclohexen-1-one (22). A solution of **28** (3.5 g, 10.7 mmol) in dry ether (50 mL) was added dropwise to a stirred slurry of lithium aluminum hydride (2.0 g, 52.5 mmol) in ether (200 mL). After being refluxed for 2.5 h, the reaction mixture was cooled in an ice–water bath, and saturated aqueous sodium sulfate was carefully added until the precipitated salts turned white. The solution was decanted, and the precipitate was washed with ether. The combined organic solutions were concentrated to give 2.35 g of the crude ketal **29**. Methylene chloride (4 × 400 mL), ethanol (240 mL), water (9.6 mL), and concentrated hydrochloric acid (19.2 mL) were then added, and the solution was stirred overnight in a nitrogen atmosphere, diluted with water (1.4 L), and extracted with methylene chloride (480 mL). The combined organic extracts were washed with aqueous sodium bicarbonate, dried over anhydrous sodium carbonate, filtered, and concentrated to yield 2.0 g of yellow liquid, which was in turn chromatographed on a column of 200 g of silica gel 60 (0.063–0.200 nm) with hexane–methyl acetate (1:20) to yield 0.52 g (25%) of the keto allene **22**: IR ($CHCl_3$) 1960, 1660 cm^{-1}; NMR ($CDCl_3$) δ 5.86 (s, 1 H), 5.12 (m, 1 H), 4.7 (m, 2 H), 1.21 (s, 3 H, J = 5 Hz); MS, found for $C_{13}H_{18}O$ m/e 190.1348 (theory m/e 190.1358); UV (methanol) λ_{max} 238 nm (ϵ 11900). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.52; H, 9.77.

Methyl 3,4,5,6,7,8-Hexahydro-7,7-(ethylenedioxy)-4a-(2*H*)-naphthalenepropionate (32). The keto ester **31** (4.0 g, 17 mmol), ethylene glycol (20 mL, 0.36 mol), and *p*-toluenesulfonic acid (0.25 g) were refluxed in benzene (175 mL) for 18 h under continuous azeotropic removal of the water. The reaction mixture was neutralized with a small amount of sodium bicarbonate, washed with saturated aqueous sodium chloride, dried over anhydrous sodium carbonate, and filtered, and the solvent was removed to yield 4.6 g (97%) of the crude ketal ester **32**: IR ($CHCl_3$) 1740 cm^{-1} (CO_2Me); NMR ($CDCl_3$) δ 5.48 (m, 1 H), 3.97 (s, 4 H), 3.68 (s, 3 H).

3,4,5,6,7,8-Hexahydro-7,7-(ethylenedioxy)-4a(2*H*)-naphthalenepropanol (33). Reduction of **32** (8.2 g, 29.3 mmol) as described for conversion of **24** into **25** yielded ketal alcohol **33**: 92% yield; NMR ($CDCl_3$) δ 5.45 (m, 1 H), 3.93 (s, 4 H), 3.65 (m, 2 H).

3,4,5,6,7,8-Hexahydro-7,7-(ethylenedioxy)-4a(2*H*)-naphthalenepropanal (34). A mixture of **33** (3.5 g, 13.9 mmol), dry benzene (31 mL), dry dimethyl sulfoxide (31 mL), dry pyridine (1.12 mL), trifluoroacetic acid (0.56 mL), and dicyclohexylcarbodiimide (0.52 g, 46 mmol) was stirred at room temperature for 18 h. The reaction mixture was poured into ethyl acetate (250 mL), and a solution of oxalic acid (4.05 g, 51.5 mmol) in methanol (45 mL) was added. The mixture was stirred, and the white precipitate formed was removed by filtration. The filtrate was washed with water, 5% aqueous sodium bicarbonate, and saturated sodium chloride solution and dried over anhydrous carbonate. On removal of the solvent, a yellow liquid residue containing crystalline byproducts was obtained. Successive triturations with ethyl acetate yielded 3.5 g (100%) of ketal aldehyde **34**: IR ($CHCl_3$) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.85 (t, 1 H, J = 1.5 Hz), 5.52 (m, 1 H), 3.97 (s, 4 H).

α-Ethynyl-3,4,5,6,7,8-hexahydro-7,7-(ethylenedioxy)-4a-(2*H*)-naphthalanepropanol (35). Preparation of **35** as described above for the conversion of **26** into **27** yielded **35**: 97% yield; NMR ($CDCl_3$) δ 5.47 (m, 1 H), 4.35 (m, 1 H), 3.95 (s, 4 H); MS, calcd for $C_{17}H_{24}O_3$ m/e 276.1718, found m/e 276.1725.

2-Ethynyl-2-[3,4,5,6,7,8-hexahydro-7,7-(ethylenedioxy)-4a(2*H*)-naphthalenyl]propyl *p*-Toluenesulfonate (36). A solution of **35** (1.4 g, 5.1 mmol) in dry pyridine (12 mL) was cooled to 0 °C. *p*-Toluenesulfonyl chloride (1.9 g, 10 mmol) was added, and the solution was stored overnight in a refrigerator. The reaction mixture was then poured into ice–water (75 mL) and

(37) R. Ratcliffe and R. Rodeharst, *J. Org. Chem.* **35**, 4000 (1970).

extracted with ether (2 × 75 mL). The ethereal solution was washed successively with cold 5% aqueous hydrochloric acid, saturated aqueous bicarbonate, and water. The organic solution was dried over anhydrous sodium sulfate and filtered, and the solvent was removed to yield 1.7 g (87%) of the ketal tosylate **36**: NMR (CCl_4) δ 7.83 (d, 2 H, J = 8.5 Hz), 7.33 (d, 2 H, J = 8.5 Hz), 5.37 (m, 1 H), 5.03 (m, 1 H), 3.87 (s, 4 H), 2.47 (s, 3 H).

4a-(3,4-Pentadienyl)-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (30). A solution of **36** (4.1 g, 9.5 mmol) in dry methanol was added to a slurry of Zn–Cu couple prepared from 50 g of zinc in dry methanol (250 mL). The reaction mixture was stirred for 45 min at 65 °C, filtered through Celite, and concentrated. The residue was taken up with ether and washed with water. The solution was dried over anhydrous sodium carbonate, filtered, and concentrated. The residue was dissolved in a mixture of methylene chloride (500 mL), ethanol (250 mL), water (10 mL), and concentrated hydrochloric acid (20 mL). The solution was stirred overnight in a nitrogen atmosphere, diluted with water (1.5 L), and extracted with methylene chloride (4 × 400 mL). The extracts were combined and washed with 5% aqueous sodium bicarbonate. The solution was dried over anhydrous sodium carbonate, filtered, and concentrated. The residue was chromatographed on a column of 120 g of Florisil with hexane–methylene chloride (1:1) to yield 0.68 g (33%) of **30**.

2-(1,4-Dioxaspiro[4.5]decan-6-yl)ethyl Methanesulfonate (39). Methanesulfonyl chloride (6.05 mL, 78 mmol) was added dropwise over 30 min to a stirred cooled (0 °C) solution of the ketal alcohol **38**[25] (9.7 g, 52 mmol) and triethylamine (17.4 mL, 0.126 mol) in dry tetrahydrofuran (54 mL) in a nitrogen atmosphere. The reaction mixture was stirred for a further hour, diluted with water, and extracted with ether. The solution was washed with water, dried, and filtered, and the solvent was removed to yield 13.5 g (98%) of ketal mesylate **39**: NMR (CCl_4) δ 4.23 (t, 2 H, J = 6 Hz), 3.95 (s, 4 H), 2.94 (s, 3 H).

6-(2-Iodoethyl)-1,4-dioxaspiro[4.5]decane (40). A solution of **39** (13.4 g, 50 mmol) and sodium iodide (11.3 g, 75 mmol) in dry tetrahydrofuran (55 mL) was stirred overnight at room temperature. Ether was added, and the precipitate was filtered and washed with ether. The solvent was removed, and the residue was dissolved in ether and washed with water, 10% aqueous sodium bisulfite, and saturated aqueous sodium chloride. The solution was dried over anhydrous sodium carbonate and filtered, and the solvent was removed to yield 11.7 g (79%) of the ketal iodide **40**: NMR (CCl_4) δ 3.9 (s, 4 H), 3.2 (m, 2 H); MS, found for $C_{10}H_{17}O_2I$ m/e 290.0271 (theory m/e 296.0303).

2-(3,4-Pentadienyl)cyclohexanone (41). 1,2-Propadiene (1 mL) was distilled into cooled (−78 °C) tetrahydrofuran (15 mL). The solution was stirred in a nitrogen atmosphere and a 1.3 N solution of *n*-butyllithium in hexane (10 mL, 13 mmol) was added dropwise, upon which a white precipitate formed. The mixture was then stirred for a further 30 min, and a solution of **40** (3.0 g, 10 mmol) in dry tetrahydrofuran (5 mL) was added. The reaction mixture was stirred for 30 min, after which the cooling bath was removed. Having reached room temperature, the mixture was poured into water and extracted with ether. The organic solution was washed with water, dried over anhydrous sodium carbonate, filtered, and concentrated to yield 2.1 g of the crude ketal allene **41**. The latter was dissolved in acetone (100 mL) together with *p*-toluenesulfonic acid (0.56 g) and refluxed overnight. The solution was cooled to room temperature and neutralized with a small amount of powdered sodium bicarbonate. The acetone was removed, and the residue was dissolved in chloroform. The solution was washed with water, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed to yield 1.8 g of brown liquid which was in turn dissolved in pentane and filtered through a short column of neutral alumina to yield 1.0 g (60%) of the keto allene **42**: IR (CCl_4) 1965 (C=C=CH_2), 1710 cm^{-1} (C=O); NMR (CCl_4) δ 5.0 (m, 1 H), 4.63 (m, 2 H). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.28; H, 9.73.

4a-(3,4-Pentadienyl)-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (30). A mixture of **42** (1.2 g, 7.3 mmol), methyl vinyl ketone (0.60 g, 9.4 mmol), concentrated sulfuric acid (5.5 mL), and dry benzene (2.5 mL) was refluxed for 16 h. The reaction mixture was cooled to room temperature, poured into 10% aqueous sodium bicarbonate, and extracted with ether. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated, and the crude product was purified by preparative TLC (silica; acetone–hexane, 1:3) to yield 0.3 g (17%) of the ketal allene **30**: IR ($CHCl_3$) 1970 (C=C=CH_2), 1680 cm^{-1} (C=C—C=O); NMR ($CDCl_3$) δ 5.77 (s, 1 H), 5.10 (m, 1 H), 4.70 (m, 2 H); MS, calcd for $C_{15}H_{20}O$ m/e 216.1508, found m/e 216.1514; UV (methanol) λ_{max} 242 nm (ϵ 9980). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.07; H, 9.03.

Ethyl 1-(12-Iododecanyl)-2-oxocyclohexanecarboxylate (44). Ethyl 2-oxocyclohexanecarboxylate (8.4 g, 49.5 mmol) in dry tetrahydrofuran (20 mL) was added dropwise into a solution of sodium hydride (2.3 g, 77 mmol) in dry tetrahydrofuran (200 mL). The solution was refluxed for 30 min and cooled to room temperature. A solution of 1,12-diiodododecane (22 g, 52 mmol) in dry tetrahydrofuran (20 mL) was added, and the mixture was refluxed overnight. The mixture was cooled and filtered, the filtrate was concentrated, and the residue was treated with 5% aqueous hydrochloric acid and extracted with chloroform. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was column, chromatographed on 200 g of Florisil eluted with hexane–methylene chloride to give 7.1 g (31%) of iodo keto ester **44**: IR (CCl_4) 1715 cm^{-1} (C=O); NMR (CCl_4) δ 4.2 (q, 2 H, J = 7 Hz), 3.2 (t, 2 H, J = 6.5 Hz).

2-(12-Iodododecyl)cyclohexanone (45). Iodo keto ester **44** (5.9 g, 12.7 mmol), fine clay powder (0.7 g), 48% aqueous hydrobromic acid (12 mL), and glacial acetic acid (12 mL) were stirred and refluxed overnight in a nitrogen atmosphere. The mixture was cooled, poured into saturated sodium chloride solution, and extracted with ether. The organic solution was washed with sodium carbonate and water, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was chromatographed in a silica (150 g) column to yield 1.6 g of mixed bromo ketone and iodo ketone. This mixture was stirred in 2-butanone (10 mL) with sodium iodide (0.8 g, 5.3 mmol) and a trace amount of magnesium oxide at 80 °C for 40 min in a nitrogen atmosphere. The solvent was then removed, and the residue was extracted with pentane. The solvent was again removed to yield 1.6 g (32%) of iodo ketone **45**: IR (CCl_4) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 3.17 (t, 2 H, J = 7 Hz).

6-(12-Iodododecyl)-1,4-dioxaspiro[4.5]decane (46). Iodo ketone **45** (1.6 g, 4.1 mmol), ethylene glycol (1.0 g, 16 mmol), and *p*-toluenesulfonic acid were refluxed in benzene (50 mL) for 4 h with continuous removal of the water. A small amount of powdered sodium bicarbonate was added, and the solution was washed with 5% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride and dried over anhydrous sodium carbonate. The solution was filtered, and the solvent was removed to give 1.7 g (95%) of the iodo ketal **46**: NMR (CCl_4) δ 3.85 (s, 4 H), 3.15 (t, 2 H, J = 7 Hz).

2-(13,14-Pentadecadienyl)cyclohexanone (48). Preparation of **48** from **46** as described for the conversion of **40** to **42** was carried out in 63% yield. The acetylenic isomer was removed from the product with methanolic silver nitrate: IR ($CDCl_3$) 1950 (C=C=CH_2), 1710 cm^{-1} (C=O); NMR (CCl_4) δ 5.1 (m, 1 H), 4.65 (m, 2 H).

4a-(13,14-Pentadecadienyl)-4,4a,5,6,7,8-hexahydro-2-(3*H*)-naphthalenone (43). Preparation of **43** from **48** as described for the conversion of **42** into **30** was carried out in 27% yield: IR ($CDCl_3$) 1950 (C=C=CH_2), 1660 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.65 (s, 1 H), 5.07 (m, 1 H), 4.6 (m, 2 H); UV (hexane) λ_{max} 229 nm (ϵ 15 100); MS, found for $C_{25}H_{40}O$ m/e 356.3078 (theory m/e 356.3098).

Irradiation of Keto Allene 1. The keto allene **1** (0.120 g, 0.68 mmol) was dissolved in 150 mL of cyclohexane, and the mixture was irradiated through Pyrex ($\lambda > 295$) for 45 min with a 450-W Hanovia immersion lamp and stirred under nitrogen atmosphere at room temperature. The reaction was monitored by GLC and TLC; only one product could be detected, and on removal of the solvent the ketone **49** (0.115 g, 95%) was isolated: IR ($CHCl_3$) 1690 (C=O), 895 cm^{-1} (C=CH_2); NMR (CCl_4) δ 4.93 (m, 2 H), 3.0 (m, 2 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.20.

Reduction of 49. Ketone **49** (0.05 g, 0.28 mmol) in 5 mL of hexane was stirred with 10 mg of 10% palladium on charcoal in a hydrogen atmosphere at atmospheric pressure. After 3 h, no further consumption of hydrogen was detected, the solution was

filtered, and the solvent was removed to yield 0.045 g (95%) of a 1:1.9 mixture of **50** and **51**, GLC 4.5 and 4.87 min, respectively [15% Carbowax 20M on Chrom Q (85–100-mesh) 0.25 × 4 m column, oven temperature 210 °C, helium flow 40 mL/min]. **50**: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR (C_6D_6) δ 0.916 (d, J = 6 Hz, 3 H); MS, found for $C_{12}H_{18}O$ m/e 178.1369 (theory m/e 178.1358). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.59; H, 10.24 **51**: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR (C_6D_6) δ 0.87 (d, J = 6 Hz, 3 H); MS, found for $C_{12}H_{18}O$ m/e 178.1364 (theory m/e 178.1358). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.18; H, 9.96.

Oxidation of 50. The ketone **50** (10 mg, 0.056 mmol) was dissolved in 0.5 mL of chloroform, added to a solution of 3-chloroperbenzoic acid (18 mg, 0.1 mmol) in 0.3 mL of chloroform, and stirred overnight at room temperature under nitrogen. To the reaction mixture was added 5% sodium hydrogen carbonate, the organic layer was separated, washed with water, and dried, and the solvent was removed to give a crude oil which was purified by GLC to yield 7 mg (70%) of the lactone **52**: IR ($CHCl_3$) 1715 cm^{-1} (CO_2); NMR (C_6D_6) δ 3.6 (d, J = 7 Hz, 1 H), 1.1 (d, J = 6 Hz, 3 H); MS, found for $C_{12}H_{18}O_2$ m/e 194.1297 (theory m/e 194.1307).

Oxidation of 51. As described for **50** ketone **51** (10 mg, 0.056 mmol) gave a 70% yield of the lactone **53**: IR ($CHCl_3$) 1715 cm^{-1}; NMR (C_6D_6) δ 3.2 (d, J = 5 Hz, 1 H), 0.7 (d, J = 6 Hz, 3 H); MS, found for $C_{12}H_{18}O_2$ m/e 194.1294 (theory m/e 194.1307).

Irradiation of Keto Allene 30. The keto allene **30** (0.175 g, 0.81 mmol) in 150 mL of cyclohexane was irradiated for 1 h as described for 1 to yield the single product, **54**, in quantitative yield: IR ($CHCl_3$) 1690 (C=O), 890 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 4.95 (m, 2 H), 2.90 (m, 2 H). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.27; H, 8.92.

Ozonolysis of Photoproduct 54. A solution of **54** (0.155 g, 0.72 mmol) in 70 mL of methylene chloride (passed through basic alumina) was cooled to −78 °C. Ozone was then bubbled through until the solution turned bluish, and the excess was driven off by a stream of nitrogen. Dimethyl sulfide (0.35 mL) was added and the solution allowed to warm to −25 °C. After 30 min dimethylsulfide (0.35 mL) was added, and the cooling bath was removed. The solution was washed with water (3 × 100 mL) and dried over anhydrous sodium sulfate, and the solvent was removed to yield 0.135 (87%) of the crude diketone **55**: IR ($CHCl_3$) 1785 (cyclobutanone), 1695 cm^{-1} (C=O).

9-Carboxy[4.4.3]propellan-2-one (56). The crude mixture (0.135 g) obtained from ozonolysis of **54** was dissolved in a solution of 5 mL of tetrahydrofuran, 2 mL of water, and 3 drops of concentrated hydrochloric acid and stirred for 30 min at room temperature. The solvents were removed under reduced pressure, and the residue was taken up in 20 mL of ether and washed with water (3 × 20 mL). The solution was dried, and the solvent was removed to yield 90 mg (59%) of the keto acid **56** which was crystallized from isopropyl ether–methylene chloride: mp 209–210 °C; IR ($CHCl_3$) 1720–1710 cm^{-1} (CO_2H C=O); NMR (CCl_4) δ 6.27 (br s, 1 H); MS, found for $C_{14}H_{20}O_3$ m/e 236.1423 (theory m/e 236.1412). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.17; H, 8.37.

Irradiation of Keto Allene 15. The keto allene **15** (110 mg, 0.62 mmol) in cyclohexane (150 mL) was irradiated for 1 h. GLC monitoring showed complete conversion into a single product, **57**: IR (CCl_4) 1700 (C=O), 885 cm^{-1} (C=CH_2); NMR (CCl_4) δ 4.86 (t, 2 H, J = 2 Hz), 3.2 (m, 1 H), 2.8 (m, 1 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.59; H, 9.08.

Ozonolysis of Irradiation Product 57. Ozonolysis of **57** was carried out as described for **54**. A single product, **58**, was obtained, identical by TLC, GLC, melting point, and spectral data with the diketone obtained on irradiation of the diazo ketone **71**.[29]

Attempted Cleavage of 58. The diketone **58** (10 mg, 0.056 mmol) was dissolved in methanol–water (1:1, 2 mL) containing 10% potassium hydroxide. The solution was refluxed overnight in a nitrogen atmosphere. The methanol was removed, and the solution was acidified and extracted with chloroform (2 × 10 mL). When the mixture was dried and the solvent removed, the initial product was recovered unchanged.

Irradiation of Keto Allene 8. The keto allene **8** (213 mg, 1.12 mmol) in 150 mL of cyclohexane was irradiated as described for **1**, with cycloaddition taking place in quantitative yield. Two adducts (**59** and **60**) were formed in a 85:15 ratio according to GLC analysis [15% XE-60/Gaschrom Q (80–100 mesh), 0.25 in. × 4m, column He flow 70 mL/min, oven temperature 210 °C]: 7 and 8 min, respectively. Isomer **59**: IR ($CHCl_3$) 1690 cm^{-1} (C=O). NMR ($CDCl_3$) δ 4.95 (m, 2 H), 3.19 (s, 1 H); MS, bound for $C_{13}H_{18}O$ m/e 190.1316 (theory m/e 190.1357). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.51; H, 8.96. Isomer **60**: IR ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.90 (m, 2 H), 3.19 (m, 1 H); MS, found for $C_{13}H_{18}O$ m/e 190.1371 (theory m/e 190.1357). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.58; H, 9.54.

Ozonolysis of Photoproducts 59 and 60. The products (50 mg) were ozonoized as described for **54** to yield a crude oil which was dissolved in 5 mL of tetrahydrofuran and 1 mL of 5% hydrochloric acid and stirred at room temperature for 1 h. Sodium hydroxide (10%) was then added up to pH 12, the mixture was extracted with ether (3 × 25 mL) and dried, and the solvent was removed to yield 4.8 mg of the diketone **62**: IR ($CHCl_3$) 1785 (cyclobutanone), 1715 cm^{-1} (C=O). The water layer was acidified to pH 1 with 10% hydrochloric acid, extracted with ether (3 × 20 mL), and dried, and the solvent was removed to yield 40 mg of the keto acid **63**. The latter was in turn dissolved in an excess of diazomethane in ether to yield 45 mg of the crude keto ester **64**, which was purified by PLC on silica gel to yield 23.5 mg of the keto ester **64**: IR ($CHCl_3$) 1725 (CO_2Me), 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.68 (s, 3 H); MS, found for $C_{13}H_{20}O_3$ m/e 224.1412 (theory m/e 224.1407). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; 8.99. Found: C, 69.50; H, 9.01.

Irradiation of Keto Allene 43. The keto allene **43** (66 mg, 0.19 mmol) in cyclohexane (150 mL) was irradiated for 48 h. The solvent was removed, and the residue, which consisted of a single main product plus uncoverted starting material, was chromatographed by preparative TLC (silica; acetone–hexane, 1:3). The yield was 11 mg (17%) of product **65** and 26 mg of the starting material: IR ($CHCl_3$) 1900 (C=C=C) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 5.47 (m, 1 H), 5.07 (m, 1 H), 4.63 (m, 2 H); MS, found for $C_{25}H_{40}O$ m/e 356.2987 (theory m/e 356.3078).

Basic Isomerization of 65. The irradiation product **65** (11 mg) was dissolved in a saturated methanol solution of potassium carbonate (5 mL). The solution was refluxed for 1 h, poured into water, extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated to yield a reddish oil which was found to contain **43** as the main product.

Irradiation of 3-(4,5-Hexadienyl)-4-methyl-2-cyclohexen-1-one (22). The keto allene **22** (0.220 g, 1.16 mmol) in 150 mL of cyclohexane was irradiated for 45 min. TLC and GLC monitoring showed complete conversion into product **66**. The solvent was removed to yield 0.21 g (95%) of a yellowish liquid: IR ($CHCl_3$) 1690 (C=O), 895 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.95 (m, 2 H), 3.12 (m, 2 H), 0.95 (d, 3 H, J = 7 Hz); UV (hexane) λ_{max} 295 nm (ϵ 58), 305 (58). MS, found for $C_{13}H_{18}O$ m/e 190.1365 (theory m/e 190.1358). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.72; H, 9.75.

Reduction of Photoproduct 66. A solution of the irradiation product **66** (69 mg, 0.35 mmol) in methanol (5 mL) was stirred with 10% palladium on charcoal (10 mg) in a hydrogen atmosphere. After 2 h, with no further consumption of hydrogen, the solution was filtered and concentrated to give 61 mg (88%) of the product **70**: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR (CCl_4) δ 0.7–1.2 (m, 6 H); MS, found for $C_{13}H_{20}O$ m/e 192.1515 (theory m/e 192.1514).

Attempted Equilibration of 70. A solution of **70** (30 mg, 0.14 mmol) in ether (30 mL) was stirred with basic alumina (activity I, 20 g) at room temperature for 3.5 h, filtered, and concentrated to yield the original amount of unchanged **70**.

Ozonolysis of Photoproduct 66. A solution of **66** (0.208 g, 1.1 mmol) in 70 mL of methylene chloride was ozonized as described for **54** to yield 0.2 g of crude diketone **67** with 96% conversion: IR ($CHCl_3$) 1785 (cyclobutanone), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.6 (m, 1 H), 3.5 (m, 1 H).

Methyl 10-Methyl-7-oxospiro[4.5]decane-1-carboxylate (69). The crude diketone **67** (0.2 g, 10 mmol) was cleaved with acid as described for **56** to yield 0.21 g of the crude keto acid **68** which was purified on a short silica gel column and eluted with 1:1 ether/hexane: 0.14 g (63%); IR ($CHCl_3$) 1720–1710 cm^{-1} (CO_2H, C=O); NMR ($CDCl_3$) δ 8.4 (s, 1 H), 1.12 (d) and 1.02 (d)

(3 H). Treatment of **68** with an ethereal solution of diazomethane yielded the keto ester **69** which consisted, according to GLC, of two isomers in 1.6:1 ratio: IR ($CHCl_3$) 1735 (CO_2Me), 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.69 (s) and 3.60 (s) (3 H), 1.12 (d, J = 8 Hz) and 1.02 (d, J = 7 Hz) (3 H). Anal. Calcd $C_{13}H_{20}O_3$: C, 69.61; H, 8.89. Found: C, 69.66; H, 8.81.

Equilibrium of Keto Ester 69. A solution of the keto ester **69** (13 mg) in a 2 N methanolic solution of sodium methoxide (2 mL) was stirred overnight at room temperature under a nitrogen atmosphere. A saturated solution of sodium chloride (4 mL) was added, and the methanol was removed under reduced pressure. The mixture was acidified with 2 N hydrochloric acid and extracted with dichloromethane (5 × 10 mL). The extract was dried over anhydrous sodium sulfate, filtered, and concentrated to yield a dark residue which was in turn dissolved in ether and treated with an ethereal solution of diazomethane. The solvent was removed, and the residue was purified by preparative TLC to yield 7.4 mg of **69**. An NMR ($CDCl_3$) spectrum of the mixture included absorptions at δ 3.60, 3.62, 3.65, and 3.69, in the region of the carbomethoxyl group.

Acknowledgment. Eliezer Goldberg, Head, Scientific Editing Office of the Technion.

Registry No. **1**, 82026-08-2; **2**, 82026-09-3; **3**, 61589-86-4; **4**, 61563-72-2; **5**, 74056-07-8; **6**, 82026-10-6; **7**, 82026-11-7; **8**, 82026-12-8; **9**, 82026-13-9; **10**, 78877-14-2; **11**, 82026-14-0; **12**, 74056-08-9; **13**, 82026-15-1; **14**, 82026-16-2; **15**, 82026-17-3; **16**, 62547-87-9; **17**, 82026-18-4; **18**, 82026-19-5; **19**, 82026-20-8; **20**, 82026-21-9; **21**, 82026-22-0; **22**, 57234-60-3; **23**, 57234-61-4; **24**, 82026-23-1; **25**, 82026-24-2; **26**, 82026-25-3; **27**, 82026-26-4; **28**, 57234-62-5; **29**, 82026-27-5; **30**, 57234-68-1; **31**, 15070-50-5; **32**, 82026-28-6; **33**, 71280-40-5; **34**, 82026-29-7; **35**, 82026-30-0; **36**, 82043-89-8; **37**, 82026-31-1; **38**, 57133-56-9; **39**, 82026-32-2; **40**, 82026-33-3; **41**, 82026-34-4; **42**, 82026-35-5; **43**, 82026-36-6; **44**, 82026-37-7; **45**, 82026-38-8; **46**, 82026-39-9; **47**, 82043-90-1; **48**, 82026-40-2; **49**, 82026-41-3; **50**, 82026-42-4; **51**, 82078-85-1; **52**, 82026-43-5; **53**, 82079-43-4; **54**, 57234-65-8; **55**, 82026-44-6; **56**, 82026-45-7; **57**, 82026-46-8; **58**, 82078-86-2; **59**, 82026-47-9; **60**, 82026-48-0; **61**, 82026-49-1; **62**, 82026-50-4; **63**, 82026-51-5; **64**, 82026-52-6; **65**, 82026-53-7; **66a**, 82078-87-3; **66b**, 82078-88-4; **67a**, 82078-89-5; **67b**, 82078-90-8; **68a**, 82078-91-9; **68b**, 82078-92-0; **69a**, 82026-54-8; **69b**, 82078-93-1; **70**, 82026-55-9; acetaldehyde ethyl 3-bromopropyl acetal, 34399-67-2; 3-ethoxy-2-cyclohexen-1-one, 5323-87-5; acetaldehyde ethyl 4-bromobutyl acetal, 56904-94-0; 1,2-propadiene, 463-49-0; 1-acetyloxy-2-(5-hexyn-1-yl)cyclohexane, 82026-56-0; methyl vinyl ketone, 78-94-4; ethyl 2-oxocyclohexanecarboxylate, 1655-07-8; 1,12-diiodododecane, 24772-65-4; 2-(14-pentadecyn-1-yl)cyclohexanone, 82026-57-1; 3-methyl-1,2-butadiene, 598-25-4; 1,2-hexadiene, 592-44-9; 2-cyclohexenone, 930-68-7; 3-methyl-2-cyclohexenone, 1193-18-6.

Regiospecific Synthesis of Sarkomycin and Some Analogues

John N. Marx* and Gevork Minaskanian

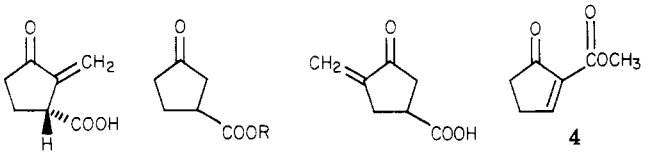
Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Received January 13, 1982

The first regiospecific total synthesis of the anticancer compound sarkomycin (1) is described. The starting material is 2-(carbomethoxy)cyclopent-2-enone (4), a useful precursor for cyclopentanoid natural products. The cyano derivative **5**, the amide derivative **6**, and the keto lactone **9** were also synthesized. The latter may be considered as a "cyclized" form of sarkomycin and was shown to open slowly to the natural product upon treatment with dilute acid.

Sarkomycin (1), a compound produced by a strain of the soil microorganism *Streptomyces erythrochromegenes*,[1] exhibits weak antibacterial activity and strong activity against the ascites type of tumor.[2] After its initial isolation and structure determination,[3] it attracted considerable attention[4] and was used in clinical trials in Japan[5] and the U.S.A.[6] In spite of initial reports of positive action, it was concluded that the compound is not active against solid tumors.[6]

The structure of sarkomycin (1) is deceptively simple, yet the early synthetic work was far from satisfactory. The initial report by Toki[7] of its synthesis via a Mannich condensation route from 3-carbethoxycyclopentanone (**2a**)



1 **2a**, R = Et; **b**, R = H **3** **4**

contrasted with the reported[8] synthesis of isosarkomycin (**3**) from 3-carboxycyclopentanone (**2b**) under similar Mannich conditions. In fact, Hill[9] has shown that Mannich condensation on either the acid or the ester gives a 2:1 mixture, respectively, of 5- to 2-substitution products. Thus, the originally reported[7,8] products were highly impure.[9] The early work[10,11] had also resulted in an incorrect

(1) Yamamoto, T.; Yamaoka, S. *J. Antibiot., Ser. A.* **1954**, *7*, 7. Umezawa, H.; Takeuchi, T.; Nitta, K. *Ibid.* **1953**, *6*, 101. Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Yamaoka, S.; Nitta, K.; Okami, Y. *Ibid.* **1953**, *6*, 147.

(2) Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Osato, T.; Okami, Y.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother. (Washington, DC)* **1954**, *4*, 514.

(3) Hooper, I. R.; Cheney, L. C.; Cron, M. J.; ,Fardig, O. B.; Johnson, D. A.; Johnson, D. L.; Patermiti, F. M.; Schmitz, H.; Wheatley, W. B. *Antibiot. Chemother. (Washington, DC)* **1955**, *5*, 585.

(4) For reviews see: (a) Sung, S.-C. *Antibiotics (NY)* **1967**, *1*, 156. (b) Kondo, S. *J. Antibiot., Ser. B* **1963**, *16*, 210. (c) Umezawa, S.; Suami, T.; Kinoshita, M. *Keio Univ. Centenary Mem. Publ.* **1958**, 722. Goto, S.; Amano, H. *Chiryo* **1956**, *38*, 72.

(5) Ishiyama, S. *J. Antibiot. Ser. A* **1954**, *7*, 82.

(6) Magill, G. B.; Golbey, R. B.; Karnofsky, D. A.; Burchenal, J. H.; Stock, C. C.; Rhodes, C. P.; Crandall, C. E.; Yorukoglu, S. N.; Gellhorn, A. *Cancer Res.* **1956**, *16*, 960.

(7) Toki, K. *Bull. Chem. Soc. Jpn* **1957**, *30*, 450.

(8) Umezawa, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 267.

(9) Hill, R. H.; Foley, P. J.; Gardella, L. A. *J. Org. Chem.* **1967**, *32*, 2330.

0022-3263/82/1947-3306$01.25/0