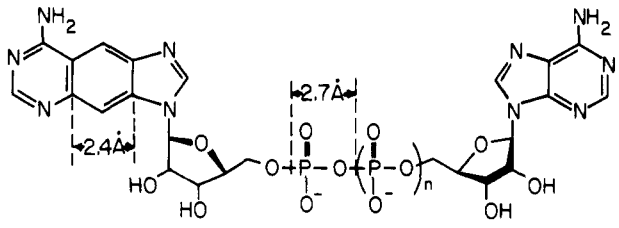

27a, n = 3
b, n = 4

experiments. These compounds (**27a,b**) are intramolecularly stacked when free in aqueous soluion, as judged by their low fluoresence quantum yield and short lifetime compared with *lin*-benzo-AMP. When adenylate kinase is present, the fluorescence quantum yields and lifetimes of **27a** and **27b** are increased. The reversal of quenching signifies that the intramolecular stacking has been broken and that these inhibitors are bound to the enzyme in an "open" or "extended" form of the oligophosphate chain. The difference in the extent of the reversal of fluorescence quenching for **27a** and **27b** by adenylate kinase is indicative of different modes of association at the enzyme active site for these two inhibitors.[65] *lin*-Benzo-A(5′)p_4(5′)A (**27a**) may derive its stronger association to adenylate kinase, compared with that of **27b**, from mimicking more closely the interactions of ATP with the enzyme, hence leading to stronger stacking interaction with Tyr-95, resulting in partial quenching of the *lin*-benzoadenine fluorescence not observed for **27b** with the enzyme. According to the X-ray structure of crystalline adenylate kinase, AMP and ATP bind at opposite ends of the cleft, with their phosphates extending toward each other and in the center of the cleft.[5] Recently, the complex between the inhibitor Ap_5A and human adenylate kinase has been crystallized,[45] and determination of this structure should be helpful in further definition of the geometry achieved during catalysis.

lin-Benzo-ATP (**2d**) has been shown to be an acceptable substrate for light production in the firefly luciferase system.[66] This ATP analogue displays strong enzyme binding and a reduced rate of enzyme catalysis compared with ATP. Variations in the color of the bioluminescence emission suggest that a lateral extension in the purine base induces an incremental change in the conformation of luciferase in the vicinity of the excited light emitter.

Enzyme Flexibility. The interaction of glucose and of ATP with yeast hexokinase mentioned at the outset[2,4,5,7] results in an "induced fit", as postulated originally by Koshland,[67] who also asked whether "changes of a few ångstroms in distance may be sufficient to prevent enzyme action."[68] We seek an answer in dimensionally quantitative terms with specific sets of enzymes and cofactors. We are encouraged in this enterprise by the demonstrated[69] conformational fluctuation and flexibility of proteins,[70] as opposed to mechanical rigidity, and by a dynamic description of enzyme action.[71]

Support for these endeavors has come from the National Institutes of Health under Research Grant GM-05829. I am indebted to my colleague Dr. Louisa Lee Melhado for valued editorial assistance.

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Intramolecular [2 + 2] Photoaddition/Cyclobutane-Fragmentation Sequence in Organic Synthesis†

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During the last decade, synthesis has advanced at an ever increasing pace toward the objective of constructing complex organic molecules in a minimum number of steps in high overall yield. There is no doubt that this progress is due largely to the challenge presented by the variety of fascinating structures found in nature. Moreover, this progress may be partially ascribed to the development and refinement of key reactions, which provide most of the required structural complexity efficiently with predictable and high regio- and stereochemical control.

At the outset of our work we felt that intramolecular [2 + 2] photoadditions of enones to olefins, combined with subsequent cyclobutane cleavage reactions, might

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† Dedicated to Professor Vladimir Prelog on the occasion of his 75th birthday.

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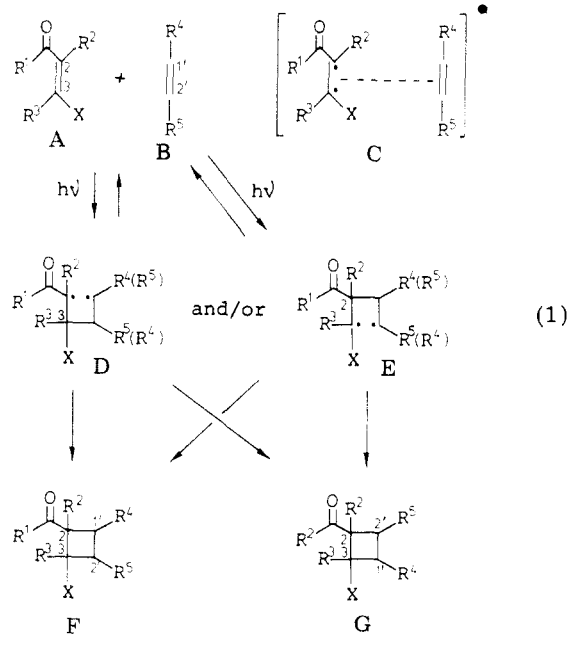
prove of value in the realm of natural product synthesis.

Although the intramolecular photoaddition of carvone leading to carvone–camphor was first described by Ciamician in 1908, virtually no attention was paid to this type of reaction until 1957–1958.[1] Subsequently, the reinvestigation of the carvone photoisomerization by Büchi[2] and exemplary irradiation of the cyclopentadiene–quinone Diels–Alder adduct by Cookson[3] led to the exploitation of intramolecular enone–olefin photoadditions as an efficient route to various cage compounds. This activity culminated in 1964 in Eaton's synthesis of cubane.[4] Since the early 1960s mechanistic and synthetic work, particularly in the laboratories of Corey,[5] Eaton,[6] and de Mayo,[7] focused on *inter*molecular photo[2 + 2] additions of cyclic conjugated enones to olefins.

Experimental evidence indicates an initial n,π^* excitation of the enone A which undergoes an intersystem crossing to an n,π^*- or π,π^*-triplet state T_1.[8] It was



(1)

proposed that a complex C between T_1 and the ground-state olefin is formed which determines the orientation in the final adduct.[5] This short-lived exciplex (C) collapses to 1,4-biradical(s) D and/or E which can then cyclize to give the products F and G or revert to the starting materials A and B. However, direct biradical formation without the intermediacy of a triplet exciplex C may be also operative in some cases. It is also still uncertain whether the first bond is formed at C(2) or C(3) of the enone or if there is any preference whatsoever. In agreement with such a mechanism, the stereochemical integrity of the ethylene fragment is lost during the cycloaddition. Furthermore, the biradical reversion process causes dissipation of energy. Detrimental energy loss by potential cis/trans isomerization of the excited enone limits this reaction to enones A when either R^1 and R^3 are part of a five- or six-membered ring or when R^2 and R^3 are incorporated in a five-membered ring. Another important problem deals with the regiochemistry of the cycloaddition; except with mono- or 1,1-disubstituted highly electron-rich ethylenes or allenes B unpredictable mixtures of the regioisomers F and G are obtained. Despite these difficulties, bimolecular enone–olefin photoadditions have been applied successfully to the syntheses of cyclobutane-containing natural products such as caryophyllene[9] and bourbonene.[10] More interesting applications involve subsequent transformations of the cyclobutane ring as demonstrated by the synthesis of caryophyllene alcohol,[11] γ-tropolone,[12] β-himachalene,[12] atisine,[13] loganin,[14] methyl isomarasmate,[15] prostanoides,[16] pseudoguaianolides,[17] germacrane and *trans*-decalin sesquiterpenes,[18] hirsutene,[19] and modhephene.[20] However, the main impediment for the extensive use of such photoannelations in synthesis remains the generally poor regiochemical control. In this respect, *intra*molecular versions starting from enones A bearing a simple olefin attached to R^1, R^2, R^3, or X by a chain of two to four atoms are usually regioselective. Thus, in the absence of special constraints, the favored ring system will be that derived from an initial 1,5-addition of the triplet T_1 to form a diradical possessing a five-membered ring (if five-membered ring formation is impossible, a six-membered ring is next favored). This empirical rule, known as "the rule of five", noted first by Srinivasan[21a] and Hammond[21b] and further established particularly by Wolff and Agosta,[21c] resides obviously on entropic factors. Furthermore, the biradical reversion process is disfavored entropically as compared to the bimolecular process, which decreases energy dissipation.

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(4) P. E. Eaton and T. W. Cole, Jr., *J. Am. Chem. Soc.*, **86**, 962, 3157 (1964).

(5) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).

(6) Review: P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968).

(7) Review: P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971); R. O. Loutfy and P. de Mayo, *J. Am. Chem. Soc.*, **99**, 3559 (1977).

(8) N. J. Turro, "Modern Molecular Photochemistry", Benjamin/Cummings, Menlo Park, CA, 1978, p 458.

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(10) J. D. White and D. N. Gupta, *J. Am. Chem. Soc.*, **90**, 6171 (1968).

(11) E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, **86**, 1652 (1964).

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(14) G. Büchi, J. A. Carlson, J. E. Powell, Jr., and L.-F. Tietze, *J. Am. Chem. Soc.*, **92**, 2165 (1970).

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(16) J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 1639 (1969).

(17) D. Termont, P. De Clerq, D. De Keukeleire, and M. Vandewalle, *Synthesis*, 46 (1977); M. Demuynck, P. De Clerq, and M. Vandewalle, *J. Org. Chem.*, **44**, 4863 (1979).

(18) P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.*, **99**, 267 (1977); **102**, 6340 (1980); G. L. Lange and F. C. McCarthy, *Tetrahedron Lett.*, 4749 (1978); J. R. Williams and J. F. Callahan, *J. Chem. Soc., Chem. Commun.*, 404, 405 (1979).

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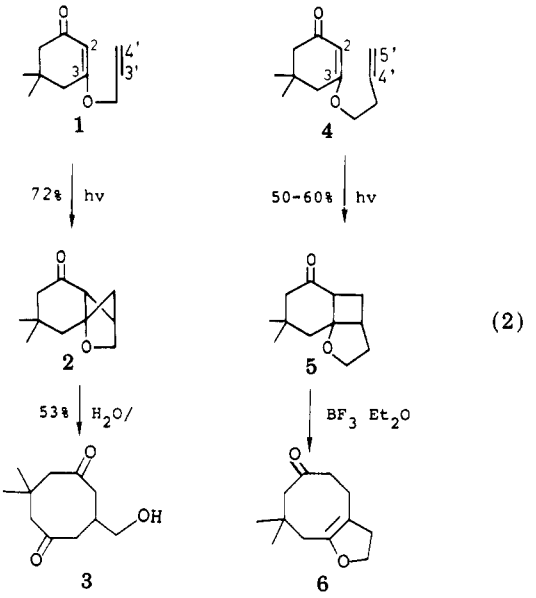
To our surprise the combination of regiocontrolled intramolecular enone–olefin additions with subsequent cyclobutane cleavage has not been widely recognized as a useful synthetic tool until recently. It is the purpose of this Account to illustrate these synthetic possibilities with the help of some pertinent examples and to rationalize the observed selectivities.

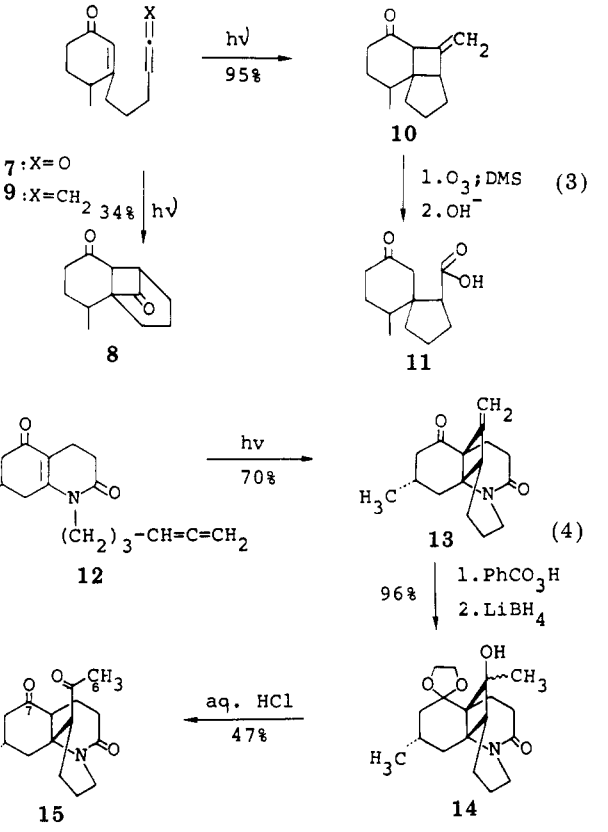
The operation of the "rule of five" is nicely illustrated by the intramolecular photoannelation of the allyl and 3-butenyl ethers derived from dimedone.[22] Thus, ir-



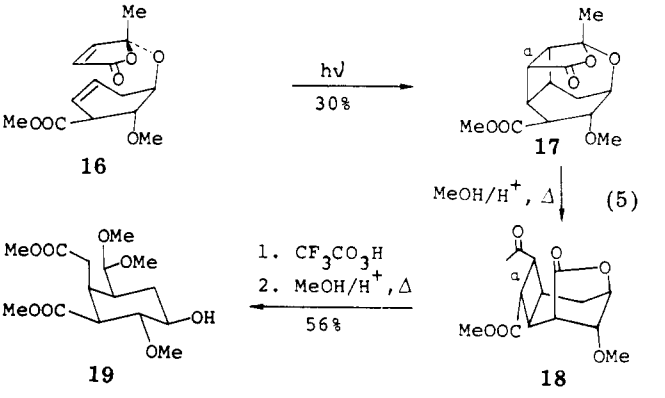
(2)

radiation of **1** (cyclohexane/Pyrex) furnished with high selectivity the bridged adduct **2**, isolated in over 72% yield. By contrast, under identical conditions the higher homologue **4** isomerized exclusively to the fused photoadduct **5**. The structures of **2** and **5** were confirmed by the hydrolytic or Lewis acid promoted cleavage reactions **2** → **3** and **5** → **6**. This striking bridge-length-dependent reversal of the regioselectivity agrees perfectly with the intermediacy of five-membered-ring diradicals. Thus, starting from **1**, initial bond formation occurs between C(2)/C(3′) or C(3)/C(4′), whereas on irradiation of **4**, C(3) and C(4′) are joined first. However, the "rule of five" can be overridden by the electronic nature of the olefinic unit as seen by the ketene photoaddition **7** → **8** (eq 3).[23] In contrast the intramolecular and electronically derived orientational effects cooperate in the efficient conversion **9** → **10**. The 1,3 relation of carbonyl and methylene groups in the photoadduct **10** permits a ready cyclobutane cleavage by successive ozonolysis and retro-Claisen reactions to give the spiroketone **11**.

The first intramolecular enone–allene photoaddition was achieved in the laboratories of Wiesner (eq 4).[24]



Regioselective photoaddition **12** → **13**, carbonyl ketalization, and hydration of the methylene group using an epoxidation/reduction sequence provided **14**, which on acidic hydrolysis underwent a retroaldolization, providing the 1,5-diketone **15**. Subsequent aldol ring closure joining the centers C(6) and C(7) led ultimately to the synthesis of 12-epilycopodine. A much more recent approach to reserpine exploits an internal photoaddition (**16** → **17**) for the selective placement of vicinal aldehyde and acetic ester appendages onto an endocyclic olefin (eq 5).[25] Methanolysis of **17** cleaved the



ketal bridge and epimerized the liberated methyl ketone. Baeyer–Villiger oxidation of the resulting methyl ketone **18** afforded an acetate, ready for the cleavage of bond a by methanol-promoted retroaldolization to give the pentasubstituted cyclohexane **19**.

A much more direct and elegant mode to combine photoannelation with a subsequent retroaldolization has been developed by de Mayo[7] (eq 6).

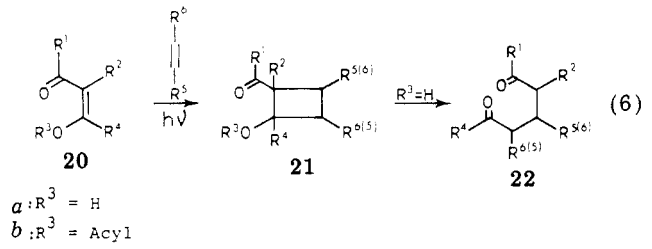
This valuable method to prepare 1,5-diketones from 1,3-diketones is well documented. One of the draw-

(22) Y. Tamura, Y. Kita, H. Ishibashi, and M. Ikeda, *Tetrahedron Lett.*, 1977 (1972); *J. Chem. Soc., Chem. Commun.*, 101 (1973); Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.*, **40**, 2702 (1975); see also F. M. Schell, P. M. Cook, S. W. Hawkinson, R. E. Cassady, and W. E. Thiessen, *ibid.*, **44**, 1380 (1979).

(23) D. Becker, Z. Harel, and D. Birnbaum, *J. Chem. Soc., Chem. Commun.*, 377 (1975); D. Becker and D. Birnbaum, *J. Org. Chem.*, **45**, 570 (1980).

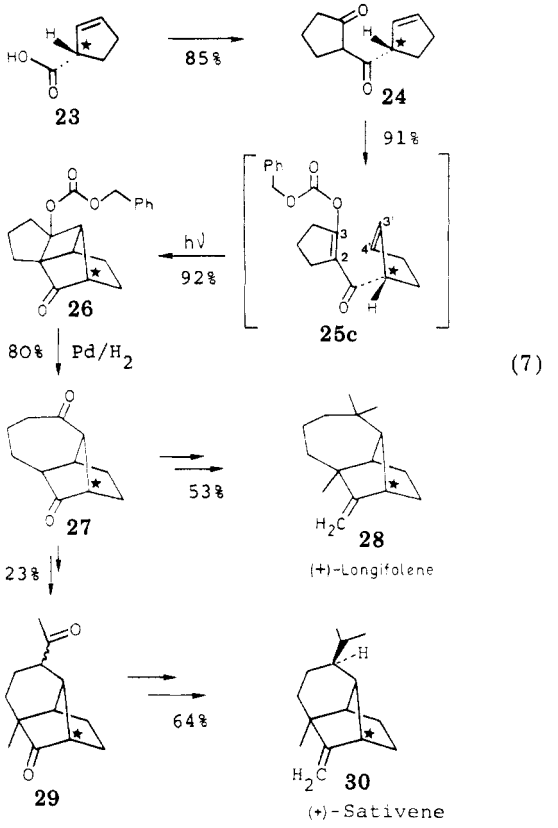
(24) K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Lett.*, 5643 (1968).

(25) B. A. Pearlman, *J. Am. Chem. Soc.*, **101**, 6404 (1979).



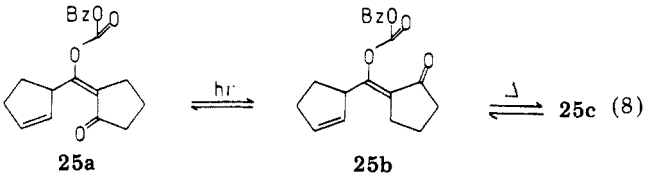
(6)

backs of the bimolecular reaction, however, is the poor predictability of its regiochemistry. On the other hand, the potential of a *regioselective annelative two-carbon ring expansion* provided by intramolecular variants starting from cyclic 1,3-diketones **20a** or their enol derivatives such as **20b** carrying alkenyl chains R^1, R^2, or R^4 has been surprisingly neglected until recently. In 1978 we reported the first example of one of these intramolecular versions (R^1 = 2-alkenyl) which constitutes the key reaction leading to a ready enantioselective synthesis of (+)-longifolene[26,27] and (+)-sativene[27] (eq 7). The crucial step of our approach (**25** → **26**) is in



(7)

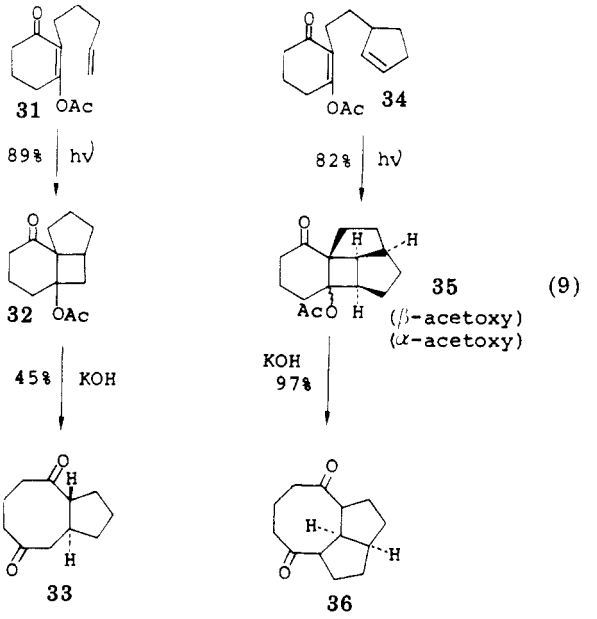
fact a highly efficient and regioselective photoaddition leading (in agreement with the "rule of five") to the exclusive joining of C(2) with C(4′). Subsequently hydrogenolysis of the protecting carbonate triggered off a spontaneous retroaldol cleavage **26** → **27** giving the skeleton of longifolene in high overall yield. Appropriate functionalization of the sterically differentiable carbonyl groups of **27** led to enantiomerically pure (+)-longifolene in over 25% overall yield starting from the (*S*)-carboxylic acid **23**. The crystalline, enantiomerically pure key intermediate (+)-**27** was also converted to (+)-sativene (**30**), by using a $Tl/(NO_3)_3$-mediated ring contraction leading to **29**.[27] It is worth mentioning that O-acylation of the asymmetric 1,3-diketone **24** seemed not to occur regioselectively; however, this point is of little relevance here since light–induced isomerization of the exocyclic (*E*)- and (*Z*)-enol carbonates **25a** and **25b**, followed by spontaneous 1,5-acyl migration of the latter permits readily equilibration (**25a** ⇄ **25b** ⇄ **25c**) (eq 8). **25c** should then be selectively trapped by the



(8)

photoaddition **25c** → **26** owing to the endocyclic nature of the conjugated olefinic bond and to its favorable position with respect to the isolated double bond.

Further work on intramolecular de Mayo reactions, carried out in our laboratory as well as in that of G. Pattenden, centers on derivatives of cyclohexane- and cyclopentane-1,3-diones. Thus **31** underwent readily a regio- and stereoselective photoaddition to give **32**, which on alkaline saponification furnished the retroaldol product **33**.[28,29] Similarly, irradiation of **34** afforded a mixture of the stereoisomers **35a** (β-acetoxy) and **35b** (α-acetoxy) where the cyclobutane is fused to the cyclohexanone ring cis in **35a** and trans in **35b**.[29] This stereochemistry was easily assigned by IR evidence; the carbonyl band of the minor trans-fused isomer **35b** appears at higher frequency (1730 cm^{-1}) than that of the major cis-fused adduct **35a** (1700 cm^{-1}). Both isomers gave on hydrolysis an identical mixture of the three possible tricyclodiones **36**.

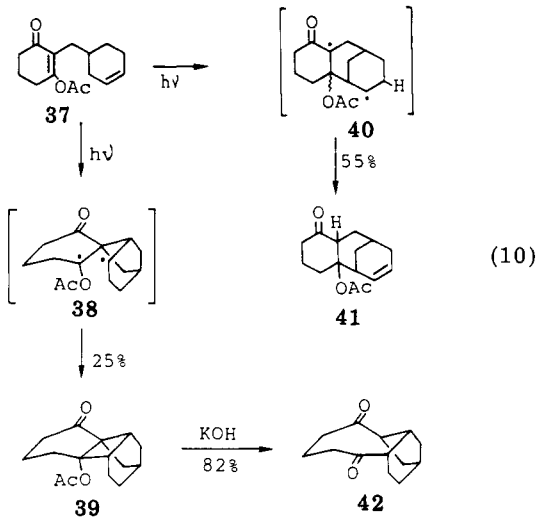


(9)

A limitation of the "rule of five" was demonstrated by the irradiation of **37** (eq 10). The expected adduct **39** was obtained in only 25% yield together with the major product **41** (55%), which probably arises from a H-shift in the diradical intermediate **40**.

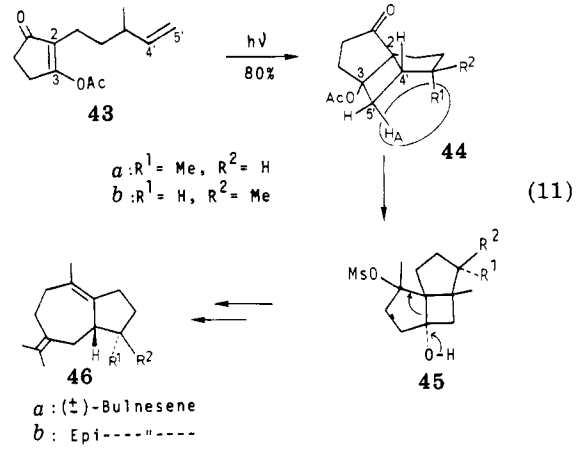
Further insight into intramolecular photoannelation/fragmentation sequences was provided by the in-

(26) W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, **100**, 2583 (1978).
(27) W. Oppolzer, *Pure Appl. Chem.*, **53**, 1181 (1981); T. Godel, Dissertation No. 1971, Université de Genève, 1980.
(28) M. J. Begley, M. Mellor, and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, **235** (1979).
(29) W. Oppolzer and T. G. C. Bird, *Helv. Chim. Acta*, **62**, 1199 (1979).



(10)

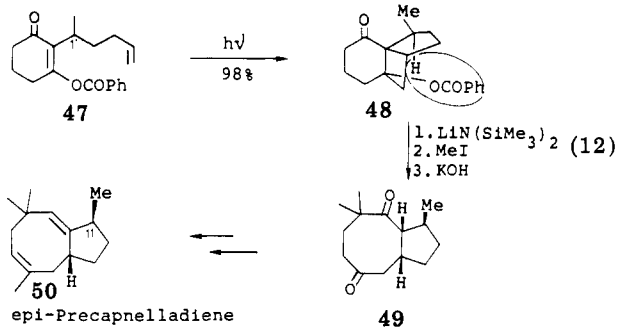
centive to use them for the synthesis of sesquiterpenes. Thus, during a new approach to bulnesene (**46a**)[30] (eq 11) the general question arose as to how far a chiral



(11)

center in the chain that links the reaction partners induces the configuration of the new centers which are formed in the addition process. In fact, irradiation of **43** gave in 80% yield a 1:3 mixture of the adducts **44a** and **44b**. This selectivity in favor of the least sterically crowded adduct (avoiding the nonbonding interaction between R^1 and H_A) may be kinetically controlled during the primary bond formation between C(2) and C(4′). However, it seems reasonable to assume that this substituent repulsion is "felt" more severely in the final ring closure joining C(3) and C(5′). Accordingly, biradical reversion to **43** could compete more efficiently with ring closure during the formation of **44a** than in the process leading to **44b**. Hence, the reversibility of the first bond formation may confer the ultimate steric outcome of the cycloaddition to the final joining of C(3) and C(5′). The configurational assignment of **44a** and **44b** was confirmed by transformation of **44a** to (±)-bulnesene (**46a**); fragmentation of the tricyclo-[5.3.0.0^{1,5}]decane skeleton was accomplished by base-promoted fragmentation of the (in situ prepared) mesylate **45a**.

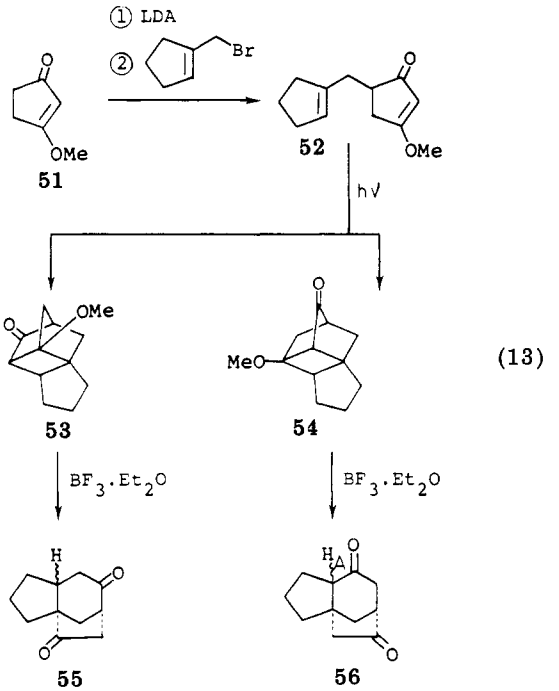
An even more pronounced stereoselection was experienced in the photoaddition of **47** containing a chiral center at C1′: **48** (eq 12), obtained as the sole product in 98% yield, shows the carbonyl group cis relative to the secondary methyl group, which thus avoids strong



(12)

interference with the benzoate group. α,α-Dimethylation of the photoadduct **48** followed by alkaline saponification gave the retroaldol product **49**, which was then converted to **50**. Due to the steric control in the photoaddition step, **50** proved to be the C(11) epimer of the sesquiterpene precapnelladiene.[31]

Although intramolecular [2 + 2] photoadditions offered a new and direct route to zizaene-type terpenes, regiochemical problems were encountered. Thus, irradiation of the readily accessible dienone **52** furnished a mixture of the regioisomers **53** and **54**, which with boron trifluoride etherate fragmented to the tricyclo-[6.2.1.0^{1,5}]undecadiones **55** (24% from **52**) and **56** (31% from **52**) (eq 13).[32] The lack of regioselectivity observed



(13)

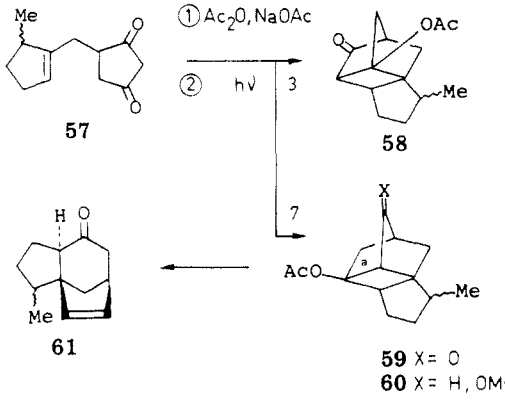
here does not violate the "rule of five": both processes **52** → **53** and **52** → **54** permit initial formation of a diradical intermediate possessing a five-membered ring. Since the ratio **53**/**54** does not depend on the bulkiness of the ether substituent in the starting enol ether, electronic rather than steric reasons seem to determine the orientation in this case.

Similarly photoaddition of the acetylated diones **57** gave a mixture of the regioisomers **58** and **59** (eq 14). The chromatographically separated adducts **59** were transformed to the mesylates **60**, which underwent an alkali-promoted fragmentation of the bond a to give the

(30) W. Oppolzer and R. D. Wylie, *Helv. Chim. Acta*, **63**, 1198 (1980).

(31) A. M. Birch and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1195 (1980).

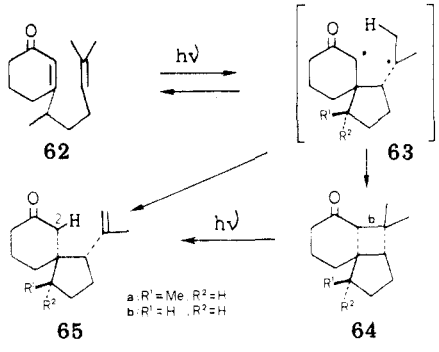
(32) W. Oppolzer and S. C. Burford, *Helv. Chim. Acta*, **63**, 788 (1980).



(14)

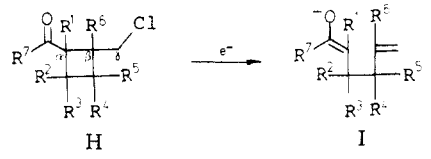
zizaene precursor **61** (α-methyl) together with the undesired major β-methyl epimer.[33]

With the aim of synthesis of acorane spiroterpenes, the photoannelation of **62** has been studied by several research groups including ours[34-36] (eq 15). In contrast



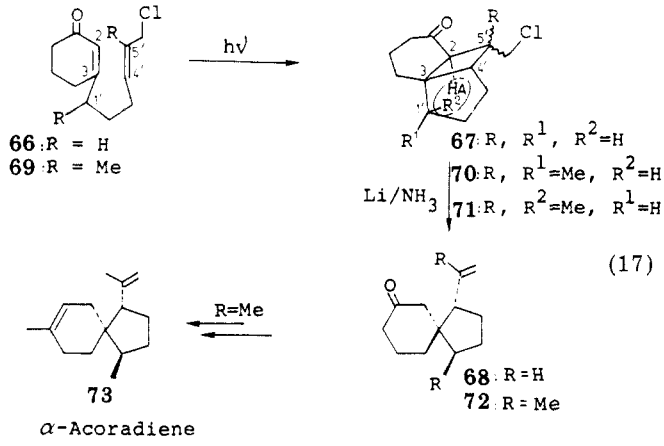
(15)

to certain claims,[34] irradiation of **62** (benzene/Pyrex) gave, with high regioselectivity,[35] the cyclobutanes **64a** and **64b** in 60% yield together with the spiro products **65a** and **65b** in a ratio of 10:3.5:3:1.[36] It appears that the spiro compounds **65** result from a hydrogen shift in the intermediate biradical **63**. We could also reconfirm that extensive photolysis of **64** (cyclohexane/Pyrex) leads to **65**, apparently by a Norrish type II cleavage of the bond b.[34b] Thus, irradiating **64** (2.9:1 mixture of **64a** and **64b**, 90 mg, 125-W medium-pressure Hg lamp) for 6 h furnished in 28% yield a 1:3.5 mixture of **64** and **65**, together with other products.[36] For preparative reasons we preferred a much more efficient and "cleaner" cyclobutane cleavage. We therefore envisaged the possibility of a reductive α,β fragmentation (H → I) of a γ-halocyclobutyl ketone (eq 16). To our



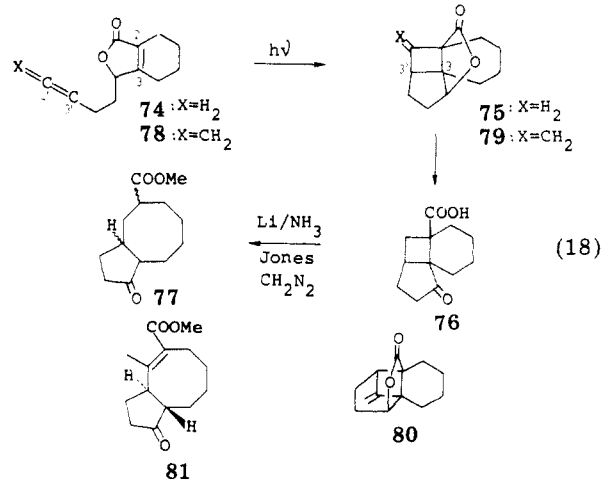
(16)

knowledge this reaction was, surprisingly new. [2 + 2] cycloaddition of **66** (benzene/Pyrex) proceeded again regioselectively to give in 95% yield a 4:1 mixture of C(5′) epimers **67** (eq 17).[37] In both isomers the cyclobutane is cis fused to the five- as well as to the six-membered ring. Hence, three out of four chiral centers were assembled in the addition with high steric control. The configuration at C(5′) in **67** was not assigned since reductive fragmentation (lithium in NH_3/THF, −78 °C) destroyed its chiral nature, leading to the spiro ketone **68** as a single isolable product (57%). This novel photoaddition–cleavage sequence was applied to the synthesis of acorances and **69** was irradiated to afford a 3.3:1 mixture of **70** and **71** in 76% yield.[38] The predominant formation of the sterically less crowded adduct **70** (avoiding repulsions between R^2 and H_A) may be rationalized by using the same arguments as for the photoannellations of **43** and **47**. Reductive fragmentation (Li/NH_3/THF/−78 °C) of the C(5′)-epimer mixture, as well as of the separated epimers of **70**, gave the spiro ketone **72** (59%). Conversion of **72** to **73** thus completed a new, stereoselective approach to α-acoradiene, thus illustrating the feasibility of the novel γ-halocyclobutyl ketone fragmentation.



(17)

Combination of regioselective photoannelation (**74** → **75**) with the reductive cleavage of the 1,4-keto acid **76**, derived from **75**, led to **77** (stereoisomer mixture) in 44% yield (eq 18).[39] [2 + 2] photoaddition of the allenylbutenolide **78** proceeded less selectively, giving the fused and bridged adducts **79** and **80** in a (2–3):1



(18)

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(38) W. Oppolzer and F. Zuttermann, unpublished work.
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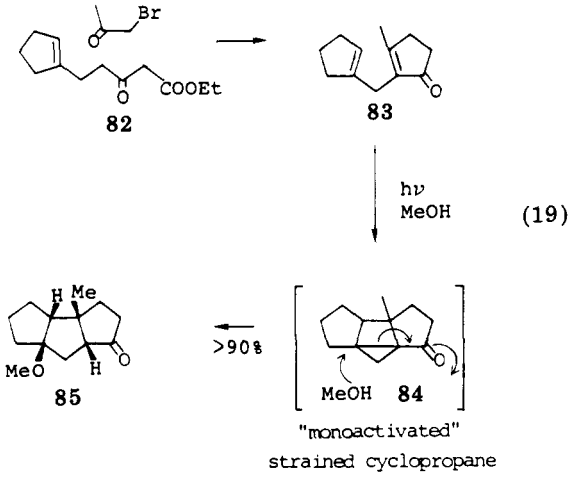
ratio. Analogous conversion of **79** to a single bicyclo[6.3.0]undecenone, **81**, illustrates a potential route to ophiobolin-type terpenes.

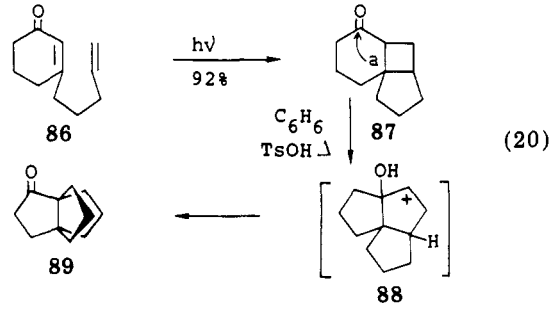
An easy entry to the hirsutane skeleton is offered by the photochemical intramolecular [2 + 2] addition of the easily accessible dicyclopentylmethane **83** in methanol (eq 19).[40] The cis–cisoid–cis product **85** thus



(19)

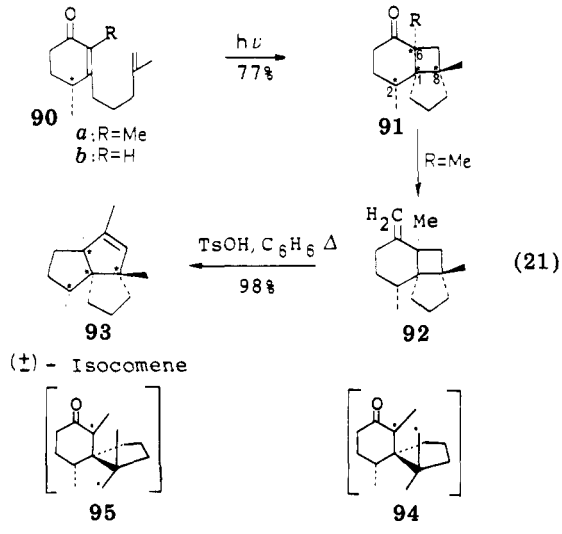
obtained in one operation (over 90% yield) appears to result from a spontaneous nucleophilic opening by the solvent of the presumed highly strained intermediate **84**.

Utilization of cyclobutane ring strain for regioselective cationic 1,2 shifts offers further interesting possibilities in conjunction with intramolecular photoadditions. Thus, treatment of the cyclobutyl ketone **87** with anhydrous acid afforded predominantly the propellane **89** by a series of rearrangements starting with the migration of bond a (eq 20).[41]



(20)

An even more spectacular example is the synthesis of the unusual, sterically congested polycyclopentanoid terpene isocomene (**93**) (eq 21).[42] Photoaddition of **90a** gave **91a** as the single adduct in 77% yield with stereochemical control over the formation of the three contiguous quaternary chiral centers. Wittig methylenation (**91** → **92**) and subsequent acid-mediated 1,2 migration of bond a afforded isocomene in high yield. The outstanding stereochemical control exerted by a nonconcerted cycloaddition (**90a** → **91a**) could be again attributed to the intramolecular and reversible nature of the first step. Hence, formation of the first bond seems to be directed by the C(2)-methyl group to the opposite face of the enone, thereby establishing the configuration at C(1). Subsequent cyclobutane formation from the diradical intermediate **94** should be straightforward, leading to cis fusion of the four- and five-membered rings. However, the epimeric diradical **95** might rather revert to **90a** than form the strained trans-annelated C(8) epimer of **91a**. The cis annelation of the four- and six-membered rings in **91a** (controlling C(6)) is less predictable but readily assignable (IR carbonyl band at 1705 cm^{-1}). In fact, irradiation of **90** furnished a 1:2 mixture of **91** and its trans-fused C(6) epimer, showing IR bands at 1700 and 1715 cm^{-1}, respectively.



(21)

Conclusion

It follows from the above discussion that intramolecular photoadditions combined with cyclobutane transformtions can proceed with high regio- and stereoselective formation and cleavage of C–C bonds. The aforementioned attempts to rationalize this control may be useful in further synthetic planning. Intentional applications of the reaction sequence for the expedient construction of several complex naturally occurring structures bearing multiple chiral centers demonstrate already its potential. Accordingly it is felt that such processes and related ones will play an increasing role in organic synthesis.

It is a pleasure to acknowledge the contributions of my very able collaborators. Their names are cited in the appropriate references. We thank the Swiss National Science Foundation, Sandoz Ltd., Basel, and Givaudan S.A., Vernier, for generous finanical support of our work.

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