# Oxycyclopropanes in Organochemical Synthesis

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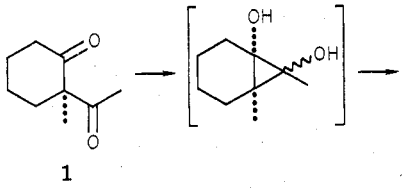
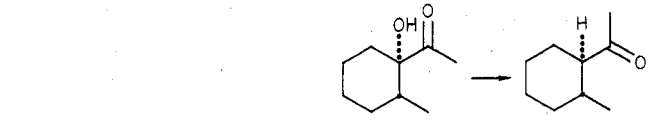
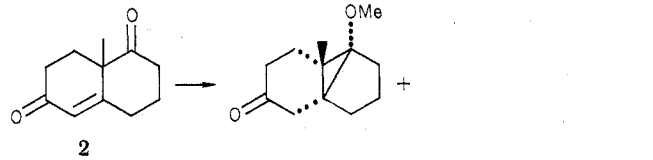
In a study designed to broaden the scope of carbon–carbon bond-forming reactions by way of reduction of two electropositive carbon sites, the β-diketone **1** and the β-diketone vinylogue **2** were submitted to reduction with zinc in aqueous, methanolic hydrochloric acid (the Clemmensen reduction).[1] The formation of the skeletally rearranged products (vide infra) was explained on the basis of the intermediacy of cyclopropanols and their acid-catalyzed ring opening. In the case of the reduction of enedione **2** two cyclopropyl ethers represented isolable products.[1b,c] Hydrolysis of the deoxo form (**3**) of one of them in acid led by unidirectional ring scission to ketone **4**.[1c] This overall experience and especially the last observation led to the realization of oxygenated cyclopropanes having great potential as building blocks in general organochemical synthesis and particularly in the construction of complex, natural substances.

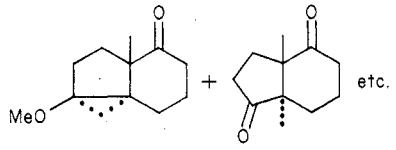


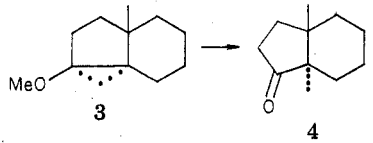
**1**





**2**

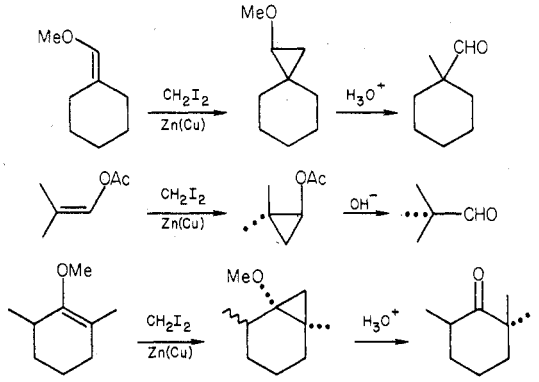


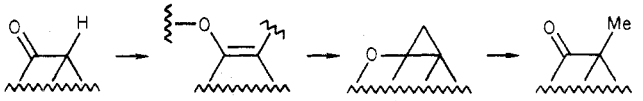


**3** **4**

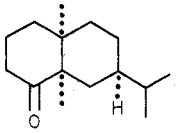
**α-Methylations.** The interaction of carbenoid species with oxy olefins constitutes one of the simplest procedures for the preparation of oxycyclopropanes. In view of the oxy olefins, i.e., enol derivatives, being masked keto systems, the combination of oxycyclopropane synthesis and acid-induced unravelling represents an interesting three-step equivalent of the α-alkylation of carbonyl compounds (vide infra), especially of relevance to the formation of α-keto quaternary centers and to angular methylation of terpenes and steroids.

Scheme I

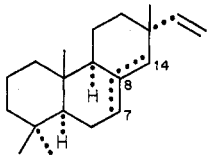




This concept formed the basis of an early study of oxycyclopropane models,[2] the total synthesis of (–)-valeranone (**5**) and partial syntheses of isopimaradiene (**6a**) and sandaracopimaradiene (**6b**).



**5**



**6a**, $\Delta^{7(8)}$
**b**, $\Delta^{8(14)}$

Scheme I, examples of conversion of an aldehyde enol ether,[3] an aldehyde enol ester,[4] and a ketone enol ether[3] into cyclopropanol derivatives by way of the Simmons–Smith reaction and unidirectional ring cleavage of the products, illustrates two of the three facile steps of the α-methylation and quaternization of carbonyl compounds.

A seven-step, total synthesis of the sesquiterpenic ketone (–)-valeranone (**5**) featured as two main reactions the stereospecific introduction of an oxycyclopropane moiety and its fully regioselective protolysis with con-

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(1) (a) E. Wenkert and K. Kariv, *Chem. Commun.*, 570 (1965); (b) E. Wenkert and J. Zylber, unpublished observations; (c) E. Wenkert, K. Kavkova, and J. S. Bindra, *Nouv. J. Chim.*, 1, 431 (1977).

(2) For a description of some of the chemistry of alkyl- and aryl-substituted cyclopropanols, see C. H. DePuy, *Acc. Chem. Res.*, 1, 33 (1968).

(3) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Am. Chem. Soc.*, **92**, 7428 (1970).

(4) E. Wenkert and D. P. Svedberg, unpublished observations; D. P. Svedberg, M.S. dissertation, Indiana University, 1974.

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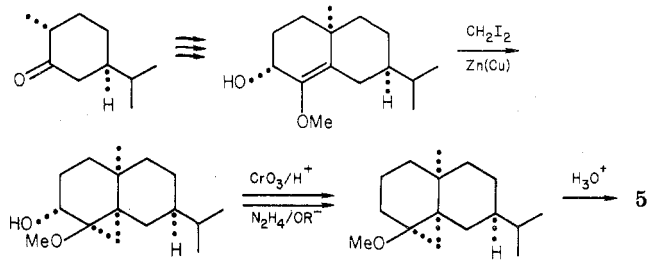
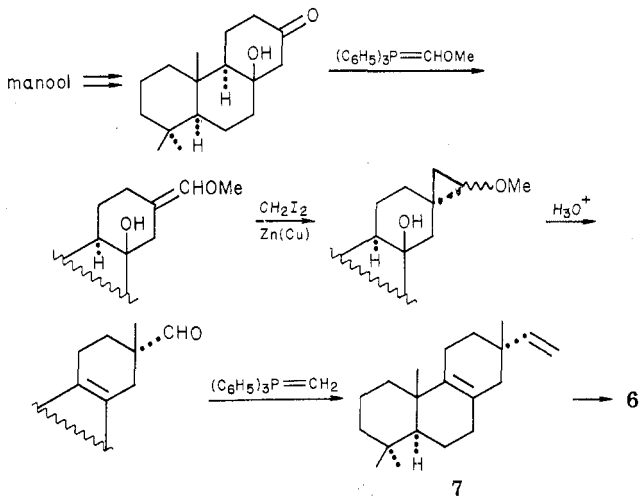
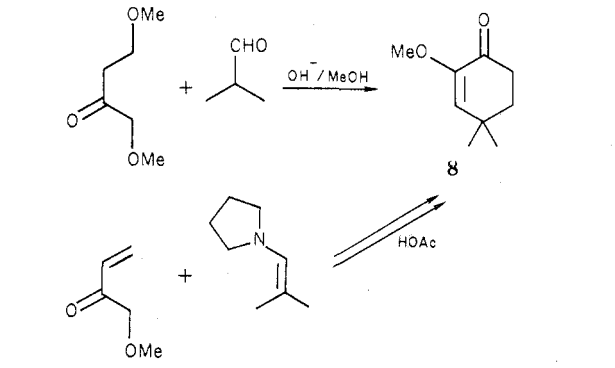
comitant formation of a requisite angular methyl function (vide infra).[5]




The stereoselectivity of the cyclopropanation step in the valeranone synthesis was the consequence of the enol ether unit being also an allyl alcohol moiety and the propensity of the latter for orienting the incoming methylene group cis to the hydroxy function in a Simmons–Smith reaction. A related cyclopropanation of an enol ether–homoallyl alcohol system was the basis for a stereoselective transformation of manool into $\Delta^{8(9),15(16)}$-pimaradiene (**7**)[6] and thence into isopimaradiene (**6a**) and sandaracopimaradiene (**6b**).[7]




**Cyclobutanones.** The first step in the valeranone synthesis involved a Robinson annelation leading to an $\alpha$-oxy-$\alpha,\beta$-unsaturated carbonyl system. This new dimension of a well-known process required the development of 1,4-dimethoxy-2-butanone and methoxymethyl vinyl ketone as annelating agents. The following syntheses of 2-methoxy-4,4-dimethyl-2-cyclohexenone (**8**) illustrate simple uses of these agents.[8]

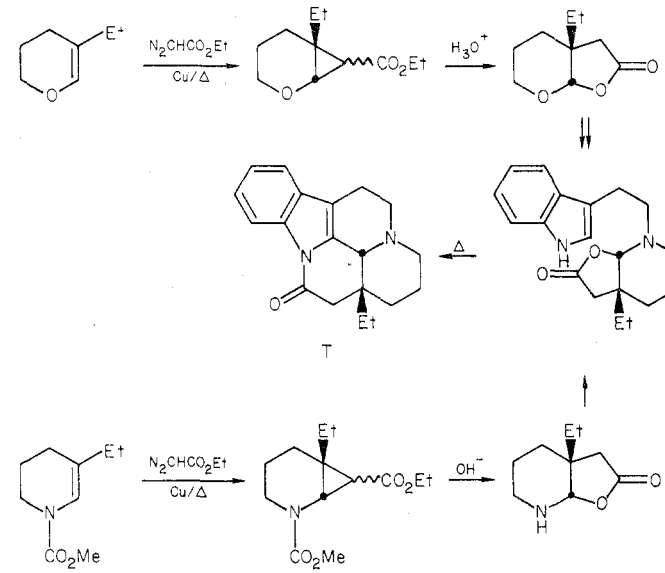



(5) (a) E. Wenkert and D. A. Berges, *J. Am. Chem. Soc.*, **89**, 2507 (1967); (b) E. Wenkert, D. A. Berges, and N. F. Golob, *ibid.*, **100**, 1263 (1978).

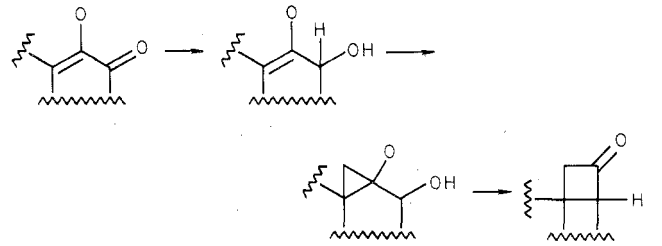
(6) D. K. M. Duc, M. Fêtizon, and E. Wenkert, *Synth. Commun.*, **3**, 277, 482 (1973).

(7) E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968).

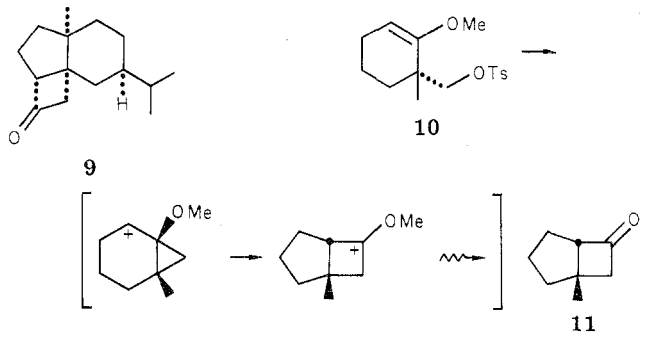
Scheme II




The ease of preparation of $\alpha$-oxy-$\alpha,\beta$-unsaturated carbonyl compounds (vide supra) and the expected facility of solvolytic rearrangement of $\alpha$-oxycyclopropylcarbinols into cyclobutanones led to the development of a three-step scheme of cyclobutanone synthesis.



The acid-induced conversion of the $\alpha$-oxycyclopropylcarbinol intermediate of the valeranone synthesis into tricycle **9**,[5b] the **10** → **11** solvolysis presumably via




an $\alpha$-oxycyclopropylcarbinyl cation intermediate,[9] and related homo-Favorskii rearrangements[9] represented early indications of the potential efficacy of this scheme.

The ease of construction of bicyclo[3.2.0]heptanones from 2-methoxy-2-cyclohexenones (vide infra)[3,10,11] suggested a route of synthesis for the structurally unusual, monoterpenic alcohol grandisol (**12**).

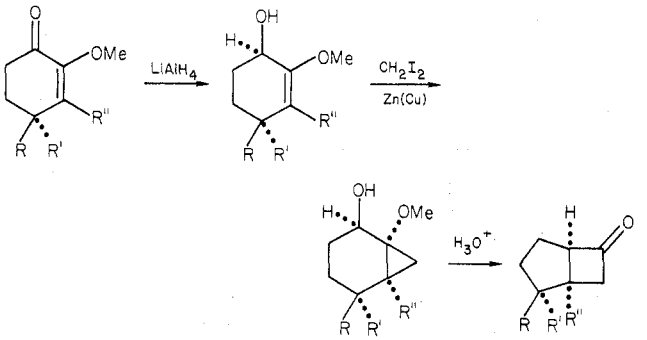
As the following reaction scheme indicates, the syn-

(8) E. Wenkert, N. F. Golob, S. S. Sathe, and R. A. J. Smith, *Synth. Commun.*, **3**, 205 (1973).

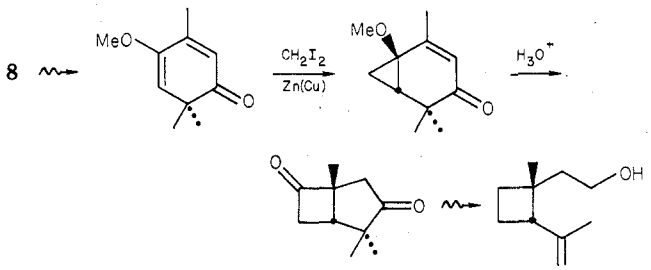
(9) E. Wenkert, P. Bakuzis, R. J. Baumgarten, C. L. Leicht, and H. P. Schenk, *J. Am. Chem. Soc.*, **93**, 3208 (1971).

(10) E. Wenkert, N. F. Golob, R. P. Hatch, D. Wenkert, and R. Pellicciari, *Helv. Chim. Acta*, **60**, 1 (1977).

(11) P. Ceccherelli, R. Pellicciari, N. F. Golob, R. A. J. Smith, and E. Wenkert, *Gazz. Chim. Ital.*, **103**, 599 (1973).

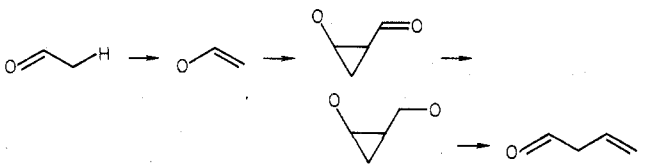


thesis of the cyclobutane-containing terpene involved the vinylogue of an α-oxycyclopropylcarbonyl system in the cyclobutane-forming step and utilized the cis configuration of the intermediate bicyclo[3.2.0]heptanes for the introduction of the proper stereochemistry of the side chains of the natural product.[5b]

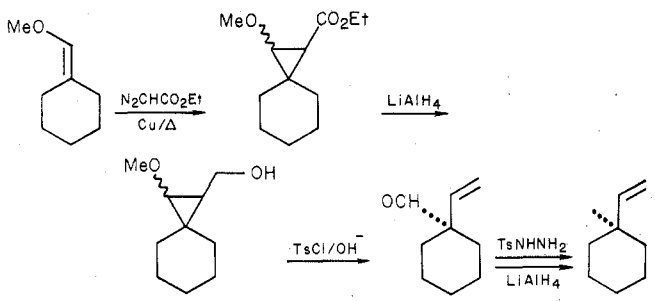


12

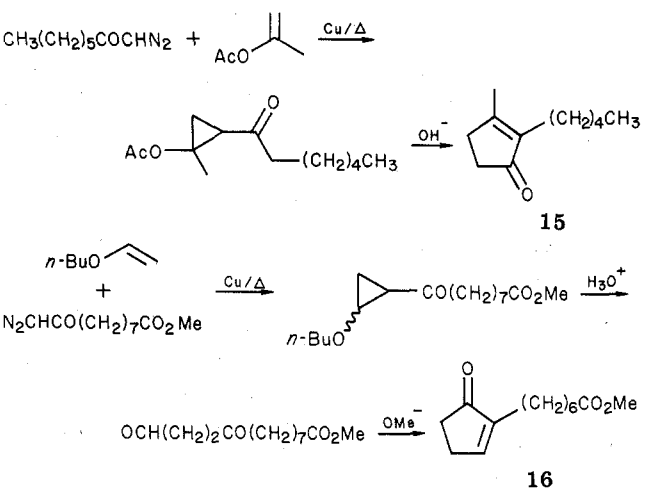
**β,γ-Unsaturated Keto Compounds, β-Methylfurans, α- or β-Methylene γ-Lactones.** A simple transformation of enol derivatives into oxycyclopropanes consists of the copper-assisted interaction of the former with α-diazocarbonyl compounds. Whereas this procedure is as facile as the Simmons–Smith reaction, it leads to cyclopropanes with two vicinal functional groups, one an electron donor and the other an electron acceptor, whose complementarity of reactivity enhances the ease of cyclopropane fission in ionic reactions. The following illustration of the formation of β-oxycyclopropylcarbonyl compounds and the cleavage of β-oxycyclopropyl carbinols derived therefrom shows the application of the reaction scheme to the synthesis of β,γ-unsaturated keto substances.



The conversion of cyclohexanecarboxaldehyde into 1-methyl-1-vinylcyclohexane (vide infra), representing the structure pattern of several resin acids (e.g., **6**) and related diterpenes, portrays in model form the α-vinylation of a carbonyl system.[3,12,13]



**Scheme III**



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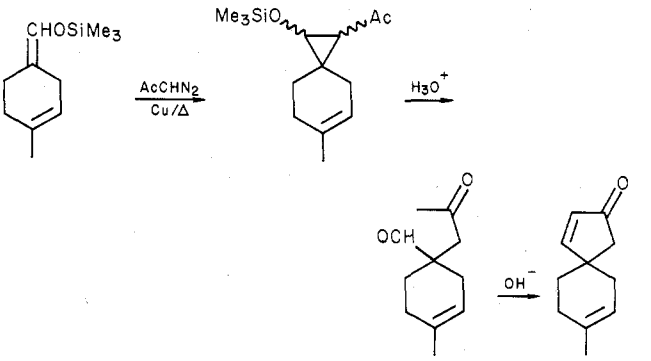

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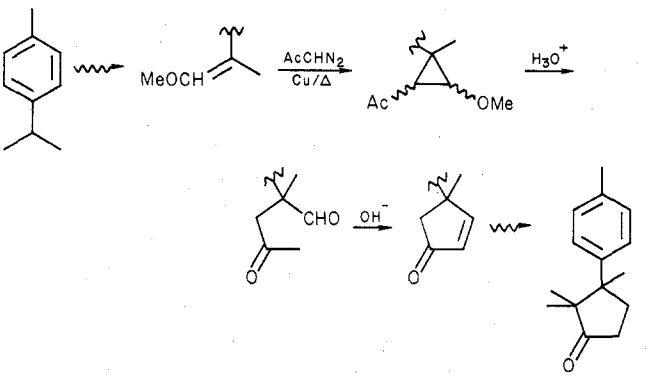

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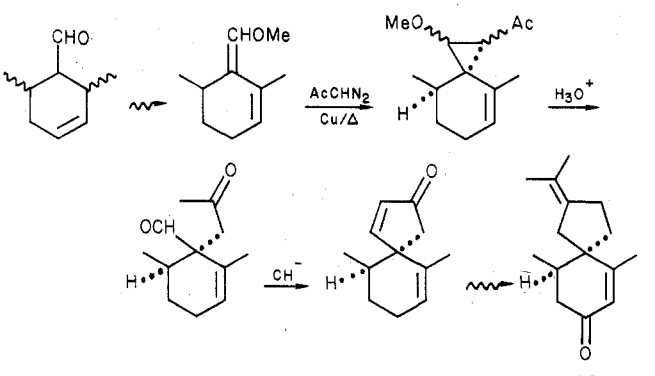


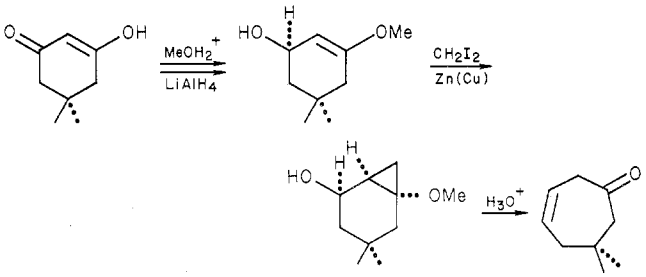
19

The following transformation of a β-oxycyclopropyl carbinol into a β,γ-unsaturated ketone represents an

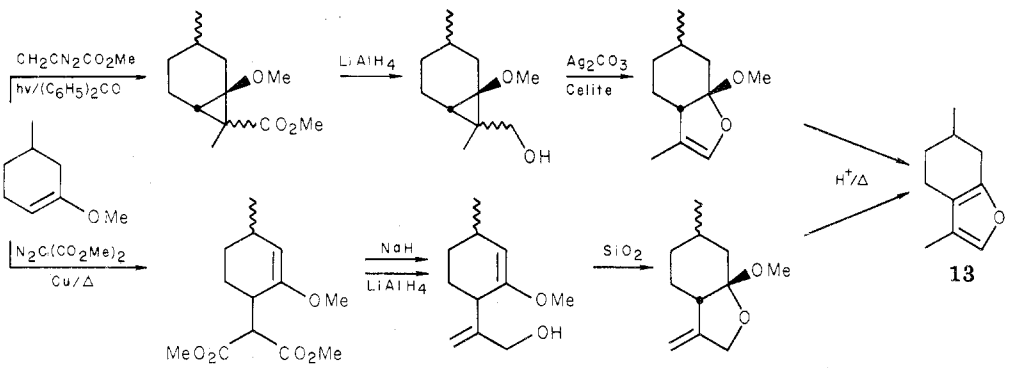
(12) E. Wenkert, B. L. Buckwalter, and S. S. Sathe, *Synth. Commun.*, **3**, 261 (1973).

(13) E. Wenkert, M. E. Alonso, H. E. Gottlieb, E. L. Sanchez, R. Pellicciari, and P. Cogolli, *J. Org. Chem.*, **42**, 3945 (1977).

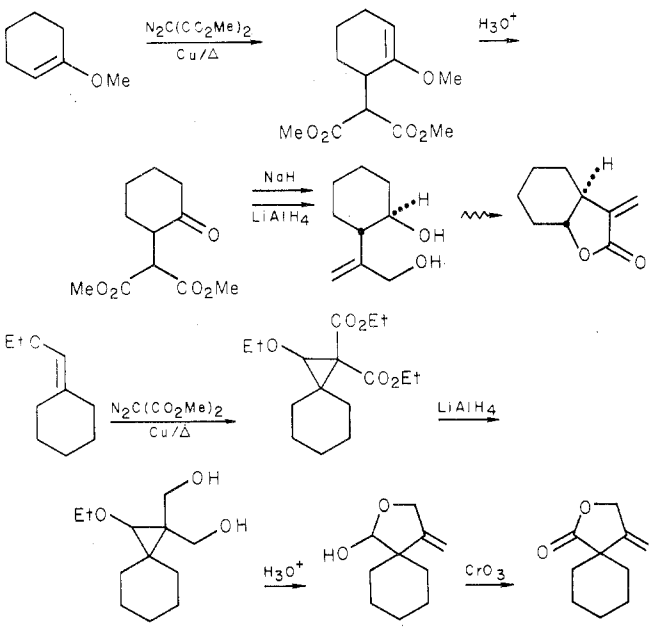
interesting application of the reaction scheme in the area of ring expansion.[12]



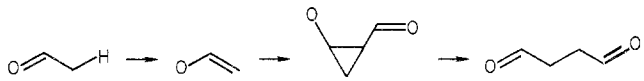
Slight variations of the theme (vide infra) resulted in two syntheses of the monoterpene menthofuran (**13**).[14]



The β-methylfuran unit, e.g., in **13**, is widespread among terpene structures but frequently in oxidized form, thus, for instance, as α- and β-methylene γ-lactones. The synthesis of such moieties also is feasible with the present chemistry (vide infra).[14]



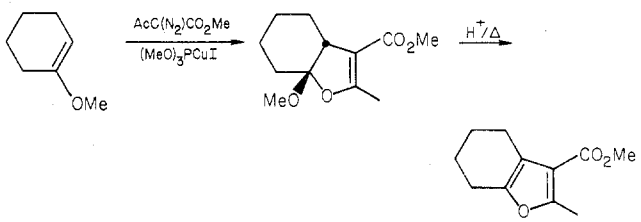
**γ-Dicarbonyl Substances.** In analogy with the cleavage of β-oxycyclopropylcarbinols, treatment of β-oxycyclopropylcarbonyl systems with acid leads to regioselective cyclopropane scission and the formation of γ-dicarbonyl compounds.[3,13,15,16,17] This tendency forms the basis of a simple route of conversion of monoketo systems into 1,4-dicarbonyl substances or their equivalents (vide infra).



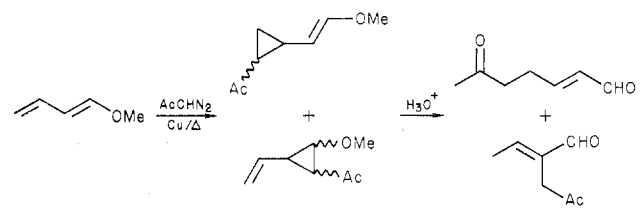
A simple application of the reaction scheme to the synthesis of the alkaloid eburnamonine (**14**) is illustrated in Scheme II.[18]

Replacement of the starting enol derivative by an enamide modifies the reaction scheme from a synthesis of γ-diketo systems to one of γ-imino keto units. The alternate eburnamonine (**14**) synthesis reflects this point.

Substitution of α-diazo ketones by α-diazo-β-dicarbonyl compounds in the cyclopropanation process constitutes a route to furans (vide infra).[19]



Replacement of enol ethers or esters by conjugated dienol derivatives leads mainly to olefinic 1,6-diketo systems (vide infra).[19]

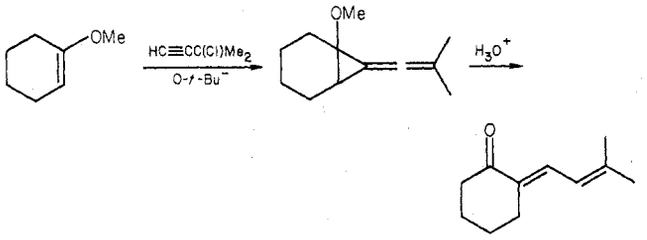


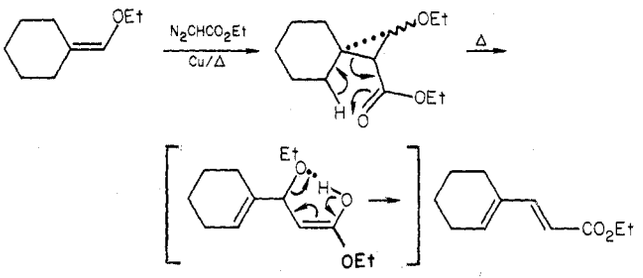
**Cyclopentenones.** In view of the ease of transformation of γ-diketones into cyclopentenones by base-catalyzed, intramolecular aldolization and subsequent dehydration, the route of 1,4-diketone synthesis functions also as a mode of approach to cyclopentanoid compounds. The reaction sequences in Scheme III indicate the utility of the method for the synthesis of naturally occurring substances or equivalents and precursors thereof, dihydrojasmone (**15**),[3,20] a prostaglandin

(14) E. Wenkert, M. E. Alonso, B. L. Buckwalter, and K. J. Chou, *J. Am. Chem. Soc.*, **99**, 4778 (1977).
(15) E. Wenkert, C. A. McPherson, E. L. Sanchez, and R. L. Webb, *Synth. Commun.*, **3**, 255 (1973).
(16) E. Wenkert, A. A. Craveiro and E. L. Sanchez, *Synth. Commun.*, **7**, 85 (1977).
(17) E. Wenkert, K. J. Chou, and R. F. Hatch, *Synth. Commun.*, **7**, 375 (1977).
(18) E. Wenkert, T. Hudlický, and H. D. H. Showalter, *J. Am. Chem. Soc.*, **100**, 4893 (1978).
(19) E. Wenkert, T. E. Goodwin, and B. C. Ranu, *J. Org. Chem.*, **42**, 2137 (1977).
(20) Cf. J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2575 (1971), for a synthesis of jasmone by the same scheme.

intermediate (**16**),[21] an acoranic sesquiterpene precursor (**17**),[21] $\alpha$-cuparenone (**18**),[21] and $\beta$-vetivone (**19**).[21]

**Miscellaneous Transformations.** Oxycyclopropanes with vicinal functional groups can undergo a wide variety of yet other transfigurations. Two of these, both syntheses of conjugated dienic carbonyl systems but derived by distinctly different routes, are illustrated in the following equations.[17,22]




It can be seen from the above discussion that oxycyclopropanes are highly versatile building blocks whose further use in organochemical synthesis, particularly in the realm of naturally occurring substances, should prove of immense value.

*I express herewith my deep gratitude to the predoctoral and postdoctoral associates, cited in the references, whose steadfast research efforts made the above advances in oxycyclopropane chemistry possible. My research group is indebted to the National Science Foundation for support of part of the work during the 1965–1973 period.*

(21) E. Wenkert, B. L. Buckwalter, A. A. Craveiro, E. L. Sanchez, and S. S. Sathe, *J. Am. Chem. Soc.*, **100**, 1267 (1978).

(22) E. Wenkert and J. R. de Sousa, *Synth. Commun.*, **7**, 457 (1977).