New Alkylation Methods[1]

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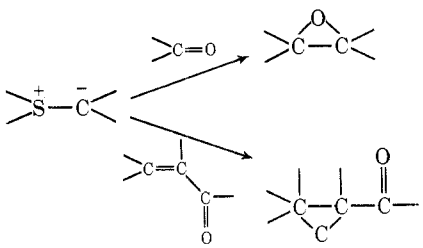
The construction of molecular architecture continues as one of the most exciting challenges to the practicing chemist. The problem involves creating both the proper framework and stereochemistry. Devising single steps to create many bonds can make the synthesis of complex molecules simple. To do so with stereochemical control makes such syntheses elegant and practical.

Real advances in establishing methodology for the development of the synthetic plan have been made. Most noteworthy is the systematization of transformations under the concept of functional group equivalents (synthons)[2] which forms the basis for computer-designed syntheses.[3] This approach is limited by the available synthetic reactions. Thus, real strides in synthesis require the discovery of new methodology. Of the various reaction types in organic synthesis, none is more basic than the formation of carbon–carbon bonds—*i.e.*, alkylation reactions.

The continuing evolution of new reagents has enhanced the ability of the bench chemist to carry out specific transformations. A powerful addition to this arsenal is sulfur ylides (π-sulfuranes). Although these species were known for over 40 years,[4] the work of mainly Corey[5] and Franzen[6] provided the basis for synthetic applications in terms of epoxide and cyclopropane formation. However, their work was for the



most part restricted to simple alkylides. Stabilized ylides (carbanion center conjugated with electron-withdrawing groups) have found limited use because of their unreactivity.[7]

Since few different structural types of sulfur ylides are known, this area offers a unique opportunity. The cycloalkylides hold special promise because, unlike the stabilized ylides, their reactivity should parallel that of the simple alkylides, and the condensation products can be converted into a diversity of structural units.

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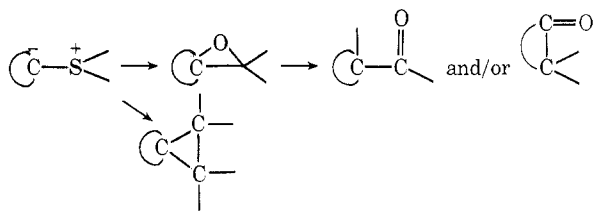
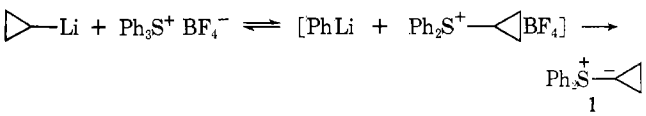


Generation of Cyclopropyl Ylides

The cyclopropylides, the smallest member of this new series of sulfonium ylides, captured our attention because of the anticipated inherent reactivity of the condensation products—oxaspiropentanes and spiropentanes. Initially, the parent cyclopropylide 1



was generated by the reaction of cyclopropyllithium with triphenylsulfonium fluoroborate.[8] The low yields of this process (~20%) suggested the desirability of generating the ylide directly from preformed cyclopropylsulfonium salt. The parent salt and its 2-methyl-substituted derivative are available as outlined in Scheme I.[9]

Alkylation of diphenyl sulfide with a 1-iodo-3-haloalkane in the presence of silver fluoroborate to enhance the reactivity of the alkylating agent[6,10] leads in excellent yields to the 3-halo-1-alkyldiphenyl sulfonium fluoroborates. Cyclization is accomplished with either sodium hydride in tetrahydrofuran or potassium *tert*-butoxide in dimethyl sulfoxide. The ylide may be generated irreversibly utilizing dimsylsodium[11] in 1,2-dimethoxyethane at −40°. The thermal instability of the ylide necessitates the use of

(1) This account formed a part of a lecture presented at the Twenty-Third National Organic Chemistry Symposium of the American Chemical Society, Tallahassee, Fla., June 17–21, 1973.

(2) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(3) E. J. Corey and W. T. Wipke, *Science*, **166**, 178 (1969); E. J. Corey, W. T. Wipke, R. D. Cramer III, and W. J. Howe, *J. Amer. Chem. Soc.*, **94**, 421, 431 (1972); E. J. Corey, R. D. Cramer III, and W. J. Howe, *ibid.*, **94**, 440 (1972).

(4) C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 713 (1930). For an early application see A. W. Johnson and R. B. LaCount, *J. Amer. Chem. Soc.*, **83**, 417 (1961).

(5) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(6) V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961); V. Franzen and H. E. Driesen, *ibid.*, **96**, 1881 (1963).

(7) For a few examples see K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966); G. B. Payne, *ibid.*, **32**, 3351 (1967); J. Adams, L. Hoffman, Jr., and B. M. Trost, *ibid.*, **35**, 1600 (1970); G. B. Payne, *ibid.*, **33**, 3517 (1968).

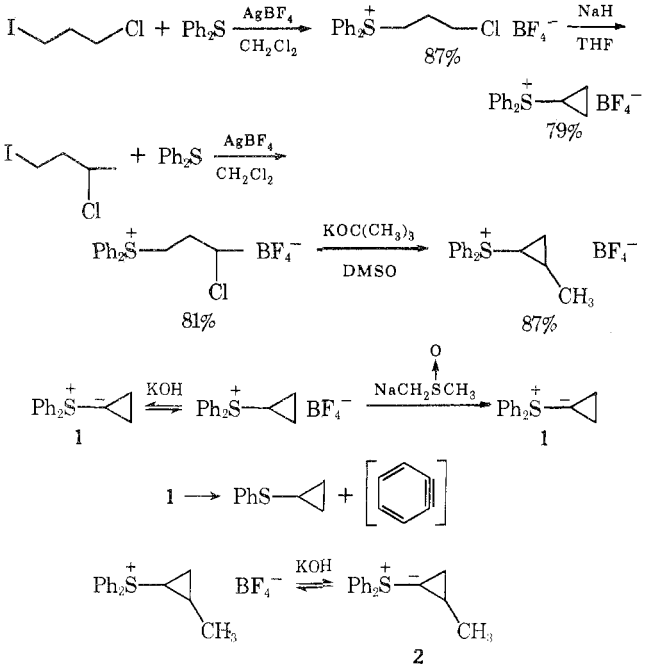
(8) B. M. Trost, R. W. LaRochelle, and M. J. Bogdanowicz, *Tetrahedron Lett.*, 3449 (1970).

(9) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **93**, 3773 (1971); **95**, 5298 (1973).

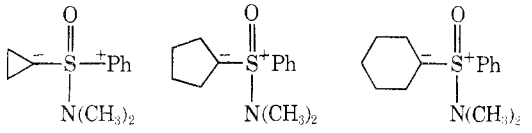
(10) For potential complications, see C. S. F. Tang and H. Rapoport, *J. Org. Chem.*, **38**, 2806 (1973).

(11) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

Scheme I
Preparation of Sulfonium Cyclopropylides



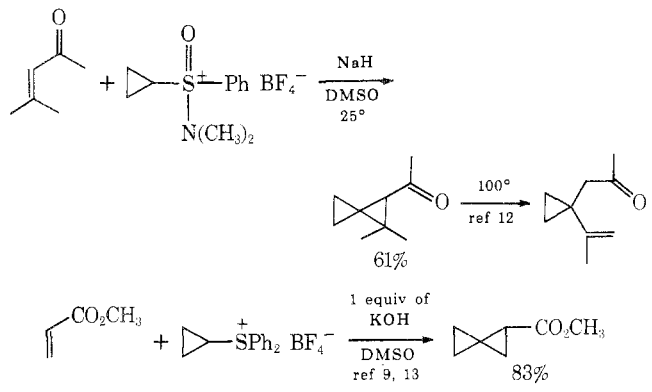
low temperatures. At room temperature **1** has a half-life of about 2.5 min and decomposes to phenyl cyclopropyl sulfide and presumably benzyne.[9] Synthetically it is more convenient to generate the ylide under reversible conditions. With a weak base, such as KOH, an equilibrium between the salt and its ylide which heavily favors the former is established. The rapid reprotonation of the ylide minimizes irreversible thermal decomposition at room temperature. Similar treatment of the methyl-substituted salt led to its corresponding ylide **2**. Johnson and coworkers described the preparation of the related dimethylaminooxosulfonium ylides (**3a–c**) along similar lines.[12]



3a **3b** **3c**

Spiropentane Formation

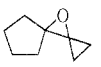
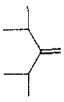
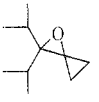
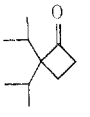
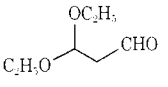
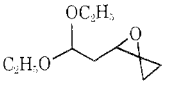
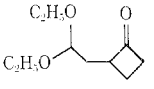
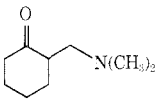
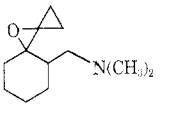
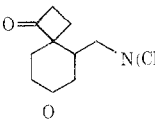
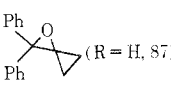
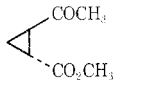
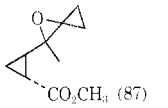
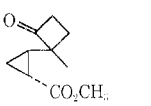
The addition of these intermediates to α,β-unsaturated ketones and esters proceeds smoothly to generate spiropentanes. Even under the reversible ylide generation conditions, cyclopropanation of methyl acrylate proceeds smoothly without concomitant ester hydrolysis. Besides providing the simplest and highest yield entry into these fascinating molecules,[13] this reaction allows entry into variously substituted cyclopropanes as the pyrolysis of the spiropentane from mesityl oxide illustrates.[12,14]



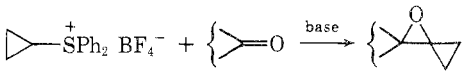
Oxaspiropentane and Cyclobutanone Synthesis

The condensation of **1** with aldehydes and ketones produces oxaspiropentanes in excellent isolated yields.[9,15] Table I presents some illustrative examples.

Table I
Formation of Selected Oxaspiropentanes and Cyclobutanones Utilizing 1

Entry	Aldehyde or ketone	Oxaspiropentanes	Cyclobutanones	Overall % yield
1		 (94)		(94)
2		 (59)		(59)
3				(59)
4				(44)
5		 (R = H, 87)		(R = H, 87) (R = Ph, 91)
6				(86)
7		 (87)		(71)

These reactive intermediates are also available by the epoxidation of alkylidene cyclopropanes.[16] The



presence of a heteroatom plus the high strain energy of the ring system makes these compounds highly reactive—a fact from which derives their synthetic usefulness. With cyclopropyl methyl ketone (Table I, entry 6) and benzophenone (Table I, entry 5) as sub-

(12) C. R. Johnson, G. F. Katekar, R. F. Huxol, and E. R. Janiga, *J. Amer. Chem. Soc.*, **93**, 3771 (1971); C. R. Johnson and E. R. Janiga, *ibid.*, **95**, 7692 (1973).

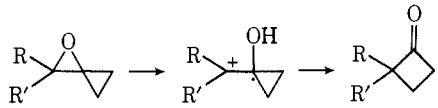
(13) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 5307 (1973).

(14) D. E. Applequist and G. F. Fanta, *J. Amer. Chem. Soc.*, **82**, 6393 (1960); L. M. Konzelman and R. T. Conley, *J. Org. Chem.*, **33**, 3828 (1968); H. E. Simmons, E. P. Blanchard, and H. D. Hartzler, *ibid.*, **31**, 295 (1966); J. J. Gajewsky and L. T. Burka, *ibid.*, **35**, 2190 (1970).

(15) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 5311 (1973); M. J. Bogdanowicz and B. M. Trost, *Tetrahedron Lett.*, 887 (1972).

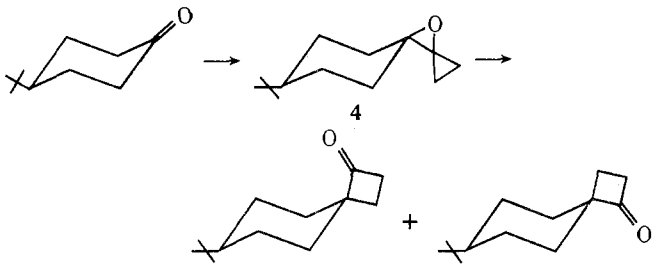
(16) J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, **33**, 991 (1968); J. K. Crandall and D. R. Paulson, *Tetrahedron Lett.*, 2751 (1969); J. R. Salaun and J. M. Conia, *Chem. Commun.*, 1579 (1971); J. R. Wiseman and H. F. Chan, *J. Amer. Chem. Soc.*, **92**, 4749 (1970).

strates, the oxaspiropentanes were not isolable. The corresponding cyclobutanones were the direct reaction products. Presumably, ring opening to the corresponding cation is unusually facilitated in these cases by the presence of excellent carbonium ion stabilizing groups (R = c-C_3H_5, R′ = CH_3, and R = R′ = Ph).

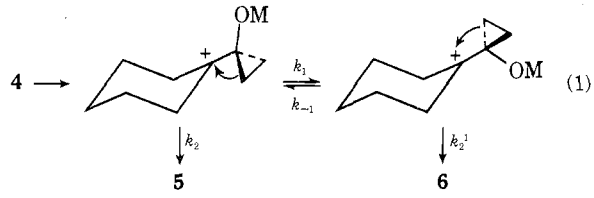


In fact, this rearrangement comprises one of the useful applications of the ylide.[17] Treatment of the oxaspiropentanes with aqueous tetrafluoroboric acid in a two-phase ether–water system at room temperature or preferably with $LiBF_4$[18] or $LiClO_4$[19] in refluxing benzene effects virtually quantitative rearrangement to cyclobutanones (see Table I).

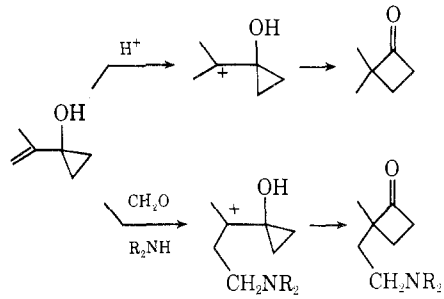
The stereochemistry depends upon the "acid" employed for the rearrangement. Thus, in the case of 4-*tert*-butylcyclohexanone, a sharp melting crystalline oxaspiropentane tentatively assigned the stereochemistry depicted (*i.e.*, **4**) is obtained upon condensation with the ylide. Changing from a protonic acid to a Lewis acid enhances the stereospecificity of the rearrangement. Assuming a carbonium ion intermediate, rationalization of this result requires bond migration to be competitive with conformational interconversion. The rate of bond migration will increase as the electron density on oxygen and consequently its electron-releasing power increases. Thus, the higher ionic character associated with an O–Li or O–Eu bond compared to an O–H bond should lead to k_2 being enhanced compared to k_1 with the consequent higher stereospecificity (see eq 1). These same cationic intermediates have been generated by reaction of 1-alkenyl-1-cyclopropanols with electrophiles.[20]



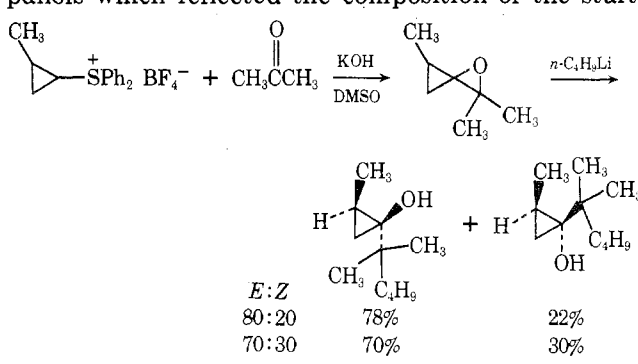
	5	**6**
HBF_4	82%	18%
$LiClO_4$	91%	9%
Eu(fod)$_3$	> 99%	> 1%



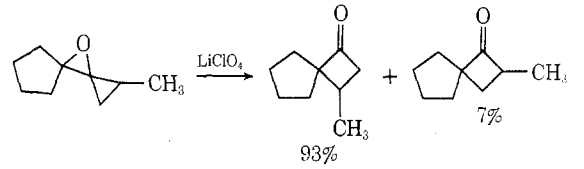
(1)



The methyl-substituted ylide **2** also forms oxaspiropentanes and cyclobutanones and offers insight into the mechanism of formation of these products.[21] Reaction of a cis–trans isomeric mixture of diphenyl-2-methylcyclopropylsulfonium tetrafluoroborate with acetone followed by nucleophilic epoxide opening with *n*-butyllithium produced a mixture of cyclopropanols which reflected the composition of the starting salt mixture.[9] Such an observation supports the straightforward mechanism for epoxide formation—addition of the carbanion center with retention of configuration followed by S_N2 displacement in the betaine. *Such a finding represents an unprecedented facile S_N2 displacement at a cyclopropyl carbon!* In the rearrangement of the oxaspiropentane to the cyclobutanone, there exists a high preference for migration of the more substituted cyclopropyl carbon.[17] The rearrangement of the cyclopentanone adduct gave a 13:1 ratio of the 3-methyl- and 2-methylcyclobutanones, respectively.



E:*Z*		
80:20	78%	22%
70:30	70%	30%



As will be seen by the subsequent discussion, cyclobutanones obtained from carbonyl groups play a myriad of useful roles in organic synthesis.[22] The unworkability of this method for obtaining cyclobutanones from α,β-unsaturated carbonyl compounds became a handicap. To overcome this difficulty, a more reactive (harder?) annelating agent was developed.[23] Treatment of cyclopropyl phenyl sulfide with *n*-butyllithium in tetrahydrofuran at 0° effected metalation in nearly quantitative yield, as determined

(17) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 5321 (1973).

(18) B. M. Trost, K. Smith, M. Preckel, and W. J. Frazee, unpublished observations.

(19) *Cf.* B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, **93**, 1693 (1971).

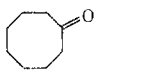
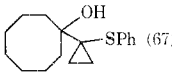
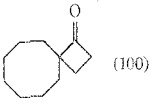
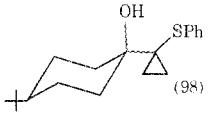
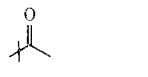
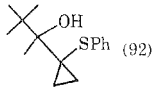
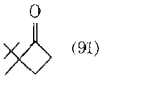
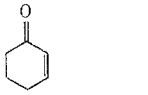
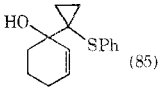
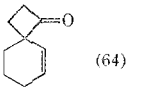
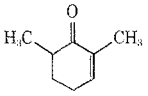
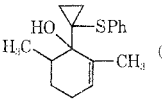
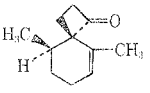
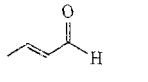
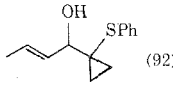
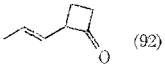
(20) J. R. Salaun and J. M. Conia, *Tetrahedron Lett.*, 2849 (1972); H. H. Wasserman and D. C. Clagett, *J. Amer. Chem. Soc.*, **88**, 5368 (1966).

(21) For a related study, see J. M. Townsend and K. B. Sharpless, *Tetrahedron Lett.*, 3313 (1972).

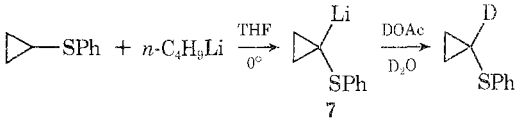
(22) For reviews, see J. M. Conia and J. R. Salaun, *Accounts Chem. Res.*, **5**, 33 (1972), and D. Seebach, S. Beckman, and H. Geiger in "Methoden der Organischen Chemie," Band IB, Teil 4, E. Mueller, Ed., Georg Thieme Verlag, Stuttgart, 1971.

(23) B. M. Trost, D. Keeley, and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 3068 (1973).

Table II
Annelations with 7[23,25]

Ketone	Adduct (% yield)	Cyclobutanone (% yield)
	 (67)	 (100)
	 (98)	5 + 6 (90) (7) (93)
	 (92)	 (91)
	 (85)	 (64)
	 (74–81)	 (85)
	 (92)	 (92)

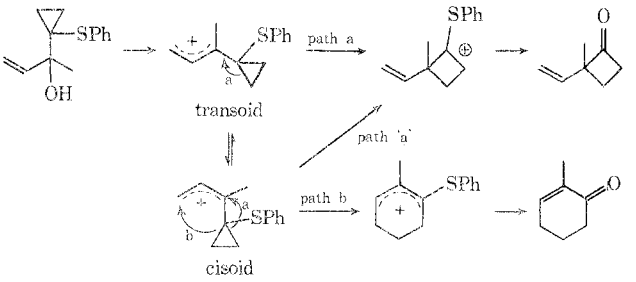
by greater than 95% deuterium incorporation upon quenching with deuterioacetic acid.[24] Treatment of saturated ketones with this organolithium (7) gave the desired adducts in high yields. Table II lists some representative examples.[23,25]



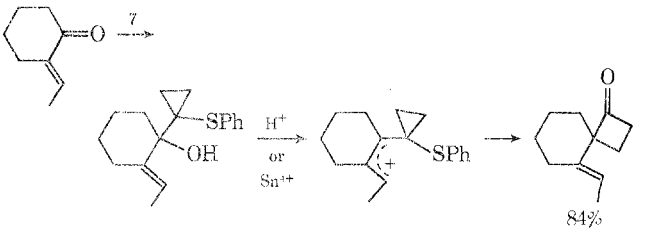
7

Hindered ketones reacted as readily as unhindered ketones. Aqueous tetrafluoroboric acid, stannic chloride in methylene chloride, or *p*-toluenesulfonic acid in refluxing moist benzene rearranged these adducts to the corresponding cyclobutanones. It is important to note that the choice of acid varied among the adducts. With the establishment of the method, application to unsaturated substrates was examined. Only 1,2 addition occurred in a wide variety of enones including such notoriously good Michael acceptors as methyl vinyl ketone. Likewise, treatment under one of the above sets of acid conditions produced the spiroannelated cyclobutanones in moderate to excellent yields.

The exclusive formation of cyclobutanones from acyclic enones was surprising. In such cases the presumed allyl cation intermediates may be envisioned to undergo 1,4-cyclopropyl bond migration (path b) to produce cyclohexenones in addition to the 1,2-migration products (path a). Virtually exclusive formation of the transoid conformer, which is geometrically restricted to the 1,2-shift pathway, rationalizes the result. Alternatively, both conformers may be forming; however, for stereoelectronic reasons,[26] only 1,2 migration occurs. To test these ideas, the adduct



of 2-ethylidenecyclohexanone, in which a conformationally rigid cisoid allyl cation would be the intermediate, was examined. Again, only cyclobutanone product was detectable. This observation suggests the reaction is controlled by stereoelectronic factors.

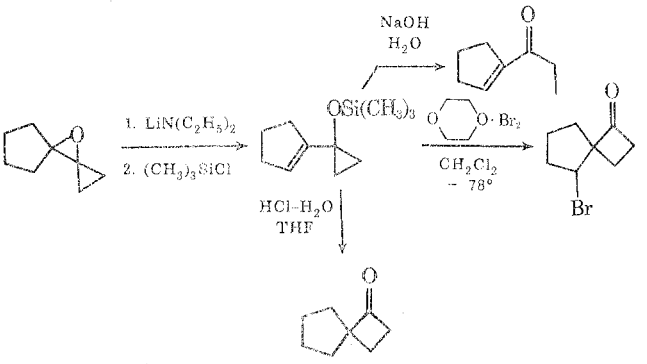


Like the reaction of ylide 1 with ketones, high stereoselectivity is found. 4-*tert*-Butylcyclohexanone produces the isomers 5 and 6 in a 1:17 ratio—complementing the behavior of the ylide. Similarly, 2,6-dimethyl-2-cyclohexenone generates mainly one isomer, assigned the stereochemistry depicted in Table II. If cations are involved, these results suggest preferable bond migration in a (pseudo) axial orientation.

With the firm establishment of facile synthetic entries to oxaspiropentanes and cyclobutanones from the ubiquitous carbonyl compounds, investigations were begun into their utilization for elaboration of organic structures.

Cyclopentane Annelation

Attention initially focused on the reactive oxaspiropentanes. As reactive epoxides, base opening should lead to allylic alcohols.[27] Indeed, treatment with lithium diethylamide in hexane at room temperature followed by quenching with trimethylchlorosilane generated the 1-alkenyl-1-cyclopropanols protected as the trimethylsilyl ethers. Base-catalyzed ring



(24) For other sulfide stabilized anions in synthesis, see E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966); R. L. Sowerby and R. M. Coates, *J. Amer. Chem. Soc.*, **94**, 4758 (1972); J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, *ibid.*, **95**, 3429 (1973).

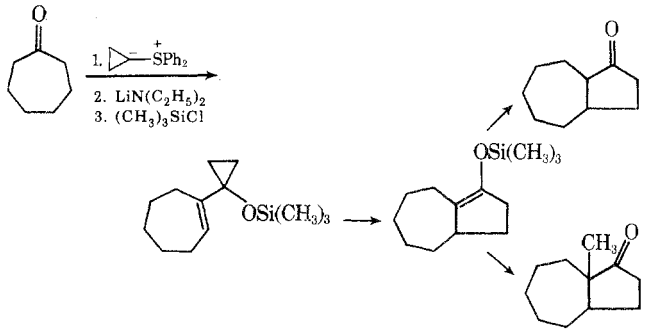
(25) B. M. Trost and D. Keeley, unpublished observations.

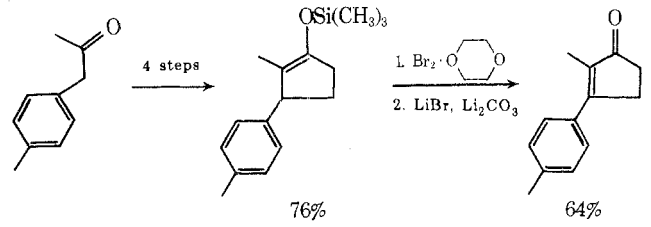
(26) According to orbital symmetry, 1,2 shift involves retention of configuration whereas 1,4 shift involves inversion of configuration. See R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, GmbH, Weinheim, 1970; J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).

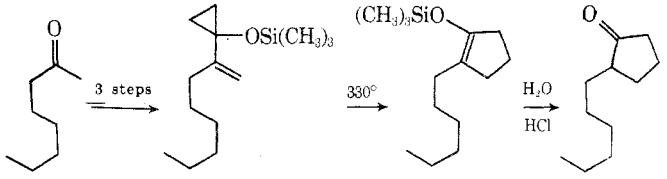
(27) R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **37**, 3919, 4250 (1972), and earlier references cited therein.

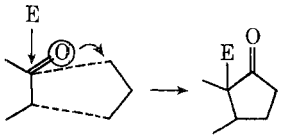
cleavage of the cyclopropanol and acid-catalyzed rearrangement to the cyclobutanone provided chemical characterization.[28]

These unique allyl alcohols have a vinylcyclopropane substructure—a structural unit capable of undergoing thermal rearrangement to a cyclopentene.[29] Passing the vinylcyclopropanol silyl ether derived from cycloheptanone through a conditioned hot tube at 330° with a contact time of less than 4 sec produced the cyclopentene with a 100% conversion and a 99% yield.[15,30] The olefin possessing a trimethylsiloxy group on the double bond is a masked carbonyl. Unmasking occurs upon simple acid hydrolysis to produce the annelated cyclopentanone. Alternatively, cleavage with methyllithium in 1,2-dimethoxyethane generates the enolate regiospecifically to the more substituted side.[31] Alkylation, as with methyl iodide, allows introduction of such groups specifically at the bridgehead position. Bromination of the alkenylcyclopropanol silyl ether followed by dehydrobromination effects a regiospecific cyclopentenone annelation.[32] With an unsymmetrical ketone such as 2-octanone, lithium diethylamide induced ring opening orients exclusively toward the methyl group.[27] This method of cyclopentane annelation formally involves the addition of a three-carbon unit to the carbonyl carbon and α carbon of a ketone, migration of the carbonyl to this three-carbon unit, and the additional ability of introduction of electrophiles at the former carbonyl carbon.









Lactone Annelation

The similar use of the cyclobutanones for creation of a wide range of structural units derives from the release of the approximately 27 kcal/mol of strain energy. One of the simplest examples of this effect is the unusual facility with which these cyclic ketones undergo the Baeyer–Villager oxidation. Even basic hydrogen peroxide, a reagent that does not normally affect acyclic or larger ring cyclic ketones, converts the cyclobutanones almost quantitatively into γ-butyrolactones.[33] As the examples in Table III illustrate, this unusual version of the Baeyer–Villager reaction possesses the same characteristics as the normal version, *i.e.*, preferential migration with retention of configuration of the more highly substituted carbon.[17,34] An advantage of this procedure over the peracid method resides in the lack of reactivity of double bonds to the oxidants, as illustrated in Table III, entry 2. Such lactones are known to cyclize to cyclopentenones upon acid treatment.[35] Thus, this lactone annelation also serves as a cyclo-

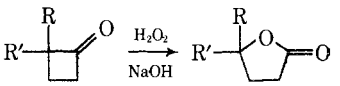
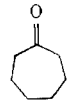
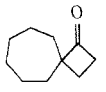
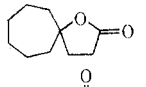
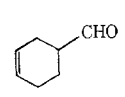
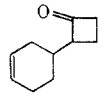
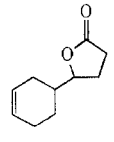
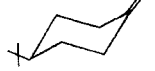
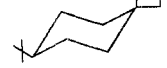
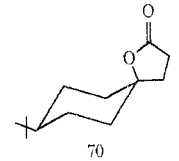
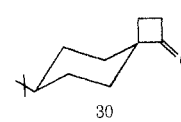
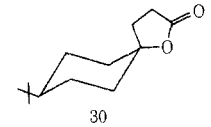


Table III
Representative Examples of Lactone Annelation

Entry	Ketone or aldehyde	Cyclobutanone	Lactone	Overall % yield
1				85
2				57
3		 70	 70	80
		 30	 30	

(28) Q. J. P. Barnier, B. Garnier, C. Girard, J. M. Denis, J. Salaun, and J. M. Conia, *Tetrahedron Lett.*, 1747 (1973).

(29) For a few pertinent references, see W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963); M. R. Willcott and V. H. Cargle, *J. Amer. Chem. Soc.*, **89**, 723 (1967); **91**, 4310 (1969); L. Skattebol, *Tetrahedron*, **23**, 1107 (1967).

(30) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 289 (1973).

(31) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

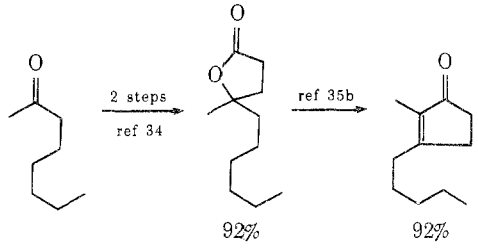
(32) B. M. Trost and S. Kurozumi, unpublished results.

(33) Y. Tsuda, T. Tanno, A. Ukai, and K. Isobe, *Tetrahedron Lett.*, 2009 (1971); E. J. Corey and T. Ravindranathan, ibid., 4753 (1971); P. A. Grieco, *J. Org. Chem.*, **37**, 2373 (1972); J. A. Horton, M. A. Laura, S. M. Kalbag, and R. C. Petterson, *ibid.*, **34**, 3366 (1969).

(34) M. J. Bogdanowicz, T. Ambelang, and B. M. Trost, *Tetrahedron Lett.*, 923 (1973).

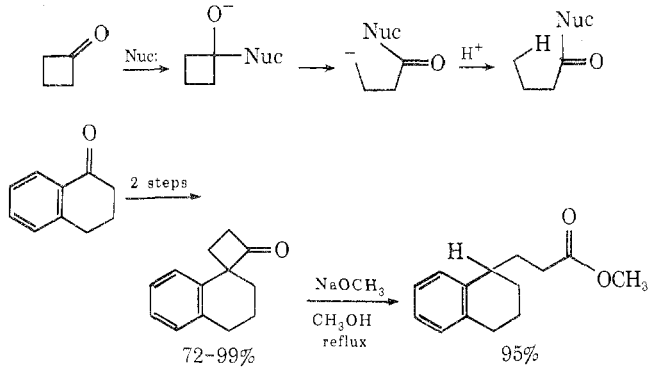
(35) (a) M. F. Ansell and M. H. Palmer, *Quart. Rev., Chem. Soc.*, **18**, 211 (1964); (b) P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).

pentenone annelation. Starting with 2-heptanone, dihydrojasmone is available in 81% overall yield.



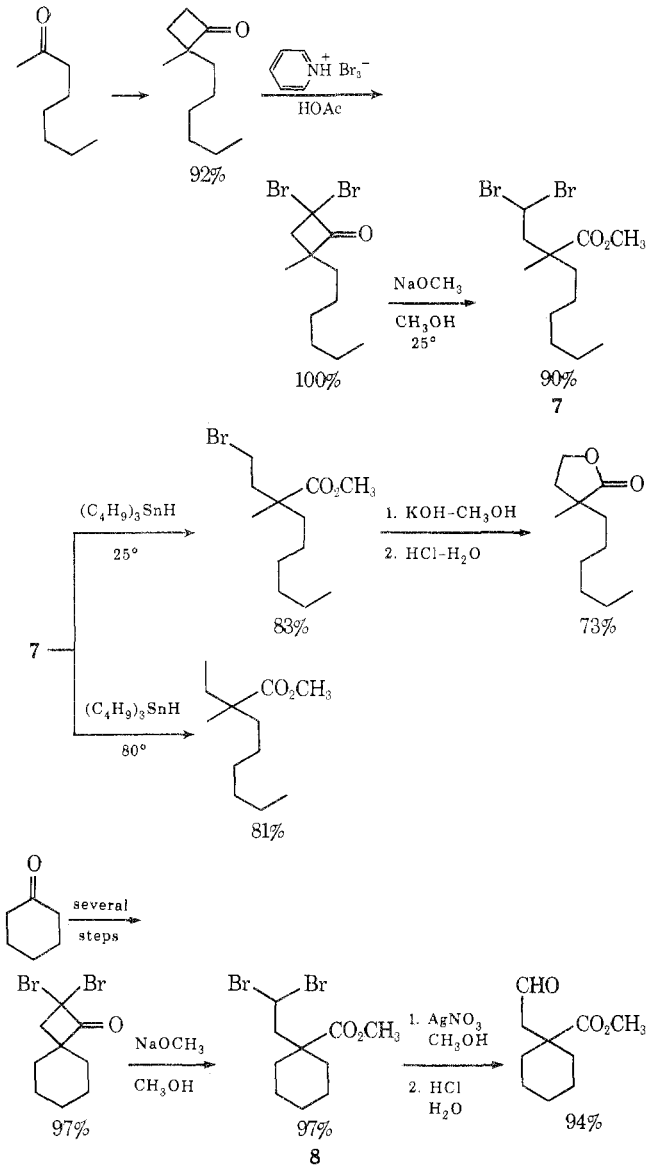
Secoalkylation

Ring cleavage of cyclobutanones by nucleophiles requires the presence of anion-stabilizing groups even though the reaction possesses a strong driving force in the release of strain energy. A phenyl ring provides enough anion stabilization to allow reaction to proceed.[36,37] The net process is the replacement of the two carbon–oxygen bonds of the carbonyl group with a carbon–hydrogen and a carbon–carbon bond—*i.e.*, a reductive alkylation.



Geminal bromine or chlorine substitution stabilizes an anion to such an extent that cyclobutanone cleavage with nucleophiles becomes unusually facile.[38,39] This cleavage is a modified haloform reaction. Furthermore, the geminal bromine substitution provides an unusual degree of versatility.[39] For example, the ring-cleaved product 7 derived from 2-octanone can be monodehalogenated and subsequently cyclized to a 2,2-disubstituted γ-butyrolactone. Alternatively, complete dehalogenation occurs upon utilizing excess tri-*n*-butyltin hydride at elevated temperatures to create an α-ethylcarboxylic ester. The geminal bromine substitution also represents a masked carbonyl. Unmasking occurs upon solvolysis in methanol in the presence of silver nitrate (to the acetal) followed by aqueous acid as exemplified for the ring-cleaved product 8 derived from cyclohexanone. The high overall yield of such processes makes this approach to geminal substitution very attractive.

In one case, base treatment of the 2,2-dibromocyclobutanone led to a semibenzylic acid-type rearrangement rather than ring cleavage.[37] Sulfur, while



possessing anion-stabilizing properties,[24] is not a good leaving group and thus would preclude such side reactions. Introduction of a geminal dithioether unit in the form of a dithiane requires activating the α position of the cyclobutanone by condensation with bis(dimethylamino)-*tert*-butoxymethane[40] followed by reaction with trimethylene dithiotosylate under solvolytic conditions[41] (see Scheme II).[42] Essentially quantitative cleavage occurs with methanolic sodium methoxide. In the case of tricyclic ketone **9**,[43] the high stereoselectivity associated with spiroannelation translates into stereoselective geminal alkylation in which the differential functionality of the two chains allows selective structural modification.[44] Thus, hydrolysis of the dithiane to the aldehyde followed by decarbonylation utilizing Wilkinsen's catalyst[45] creates an α-methyl carboxylic ester unit, a common structural unit of natural products. The net result of the sequence of Scheme II is the first utilization of tricyclic ketone **9** in a stereoselec-

(36) For cleavage of a 2,2-diphenylcyclobutanone see R. Huisgen and P. Otto, *Tetrahedron Lett.*, 4491 (1968).

(37) M. J. Bogdanowicz, Ph.D. Thesis, University of Wisconsin, Madison, Wis., 1972.

(38) L. Ghosez, R. Montsigne, A. Roussel, H. Vanlierde, and Molliet, *Tetrahedron*, **27**, 615 (1971); J. M. Conia and J. L. Ripoll, *Bull. Chim. Soc. Fr.*, 763 (1963).

(39) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 2038 (1973).

(40) H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **96**, 1350 (1963); **98**, 1078 (1965); **101**, 41 (1968).

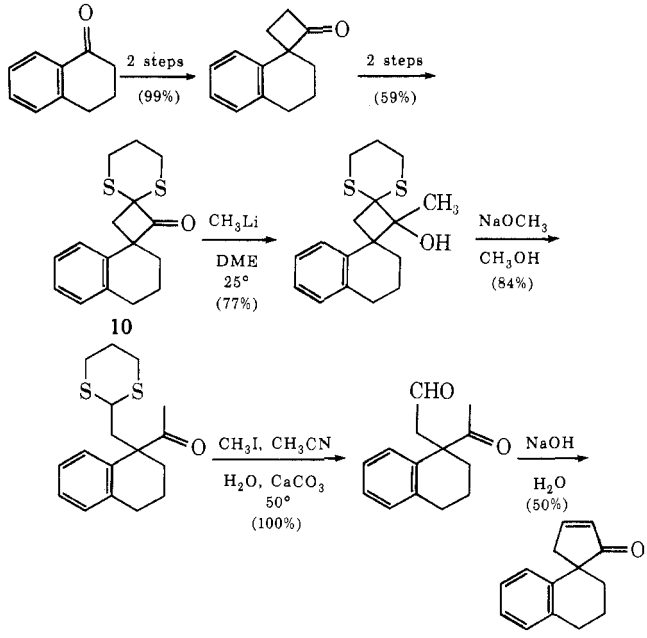
(41) J. C. A. Chivers and S. Simles, *J. Chem. Soc.*, 697 (1928); R. B. Woodward, I. J. Pachter, and M. L. Scheinbaum, *J. Org. Chem.*, **36**, 1137 (1971).

(42) B. M. Trost and M. Preckel, *J. Amer. Chem. Soc.*, **95**, 7862 (1973).

(43) G. Stork and A. Burgstahler, *J. Amer. Chem. Soc.*, **73**, 3544 (1951).

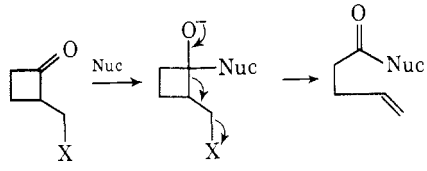
tive synthesis of a member of the resin acids, methyl desoxypodocarpate. The facilitation of ring cleavage by release of strain energy can be easily seen by the failure of similarly substituted larger ring ketones to cleave under these conditions.[46]

Methoxide need not be the nucleophile for initiation of ring cleavage. Addition of an organometallic followed by methanolic sodium methoxide produces a ketone dithiane derivative. Thus, condensation of



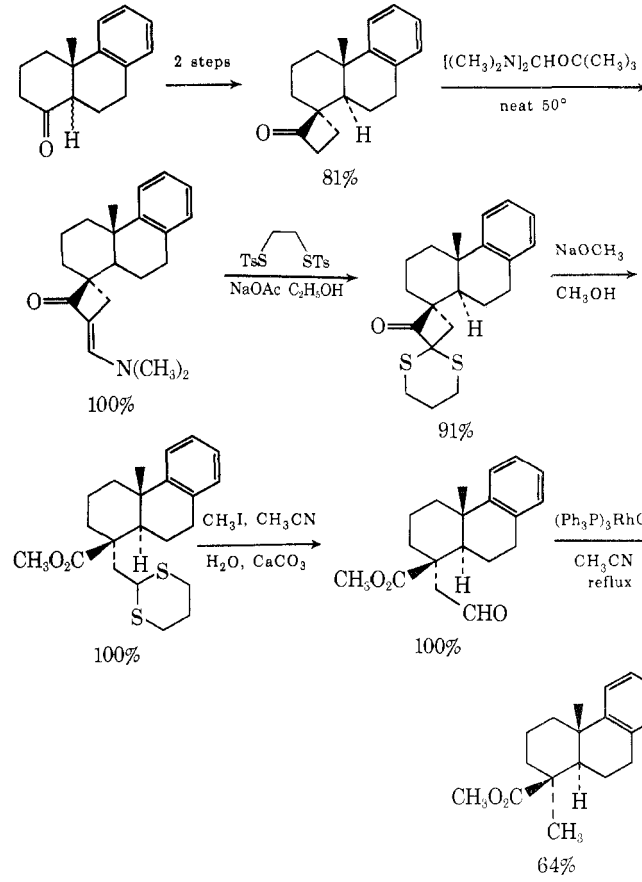
methyllithium with cyclobutanone **10** followed by methanolic sodium methoxide allows smooth ring cleavage to the methyl ketone.[42] Unmasking of the protected aldehyde to create the 1,4-dicarbonyl system permits subsequent aldol condensation for the synthesis of 5-monosubstituted or 5,5-disubstituted cyclopentenones. Such methodology provides unusually facile entry into a variety of natural products such as the spiro sesquiterpenes.

An alternative approach to effect cleavage of a cyclobutanone arises by allowing the developing nega-

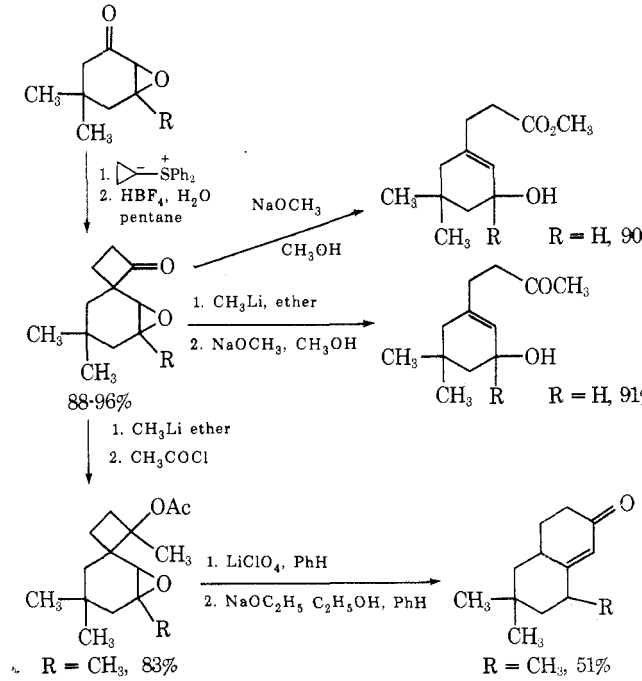


tive charge on one of the α carbons to effect an elimination reaction. Spiroannelation of an α,β-epoxy ketone creates such a structural unit (see Scheme III).[47] Fragmentation may be induced simply by dissolving the epoxycyclobutanone in methanolic sodium methoxide at reflux. Alternatively, addition of methyllithium followed by treatment with methanolic sodium methoxide also achieves ring cleavage. The net result is the addition of a $^{-}C—C—C(=O)—Nuc$ unit to a carbonyl group. Such a synthon represents an electronically inverse Michael acceptor system. Since the procedure represents creation of carbon–carbon bonds by ring formation followed by ring

Scheme II: Dithiane Introduction and Cleavage: Synthesis of Methyl Desoxypodocarpate



Scheme III: Secoalkylation



(44) (a) For other approaches, see W. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.*, 2175 (1964); K. Mori and M. Matsui, *ibid.*, 175 (1966); F. Giarruso and R. E. Ireland, *J. Org. Chem.*, **33**, 3560 (1968); M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 161 (1970); T. A. Spencer, T. D. Weaver, R. M. Villaricia, R. J. Friary, J. Posler, and M. A. Schwartz, *ibid.*, **33**, 712 (1968); S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *J. Amer. Chem. Soc.*, **90**, 2889 (1968); S. C. Welch and C. P. Hagan, *Syn. Commun.*, **2**, 221 (1972); **3**, 29 (1973). (b) For an alternative approach to the synthesis of cyclobutanones in this type of compound, see J. P. Tresca, J. L. Fourrey, J. Polonsky, and E. Wenkert, *Tetrahedron Lett.*, 895 (1973), and earlier references cited therein.

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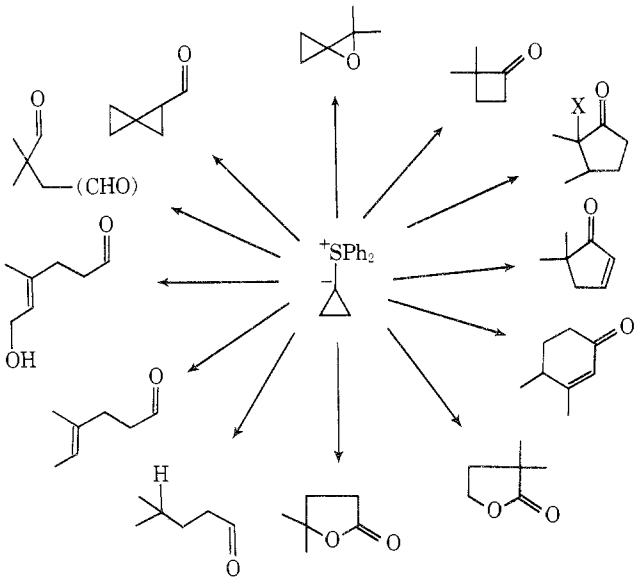
(46) J. A. Marshall and H. Roebke, *Tetrahedron Lett.*, 1555 (1970); J. A. Marshall, C. T. Buse, and D. E. Seitz, *Syn. Commun.*, **3**, 85 (1973).

(47) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **94**, 4777 (1972).

Scheme IV: Summary



cleavage, it has been termed secoalkylation. A particularly intriguing application is a cyclohexenone annelation sequence which complements the normal Robinson annelation procedure (see Scheme III). This secoalkylative annelation is particularly suitable for the addition of ring B to a preformed CD unit in steroid synthesis.

Conclusions

Scheme IV summarizes the variety of structural units that can be easily created by the above techniques. Starting with one class of reagents, the cyclopropylides, and two fundamental reactions, cyclopropanation and epoxide formation, creation of four-, five-, and six-membered carbocycles, γ-butyrolactones, and a wide variety of acyclic units are all possible. Clearly, the present work only points the way for future directions.

Carbon–carbon bond-forming reactions are among the oldest and most important to the synthetic chemist. Much new and important research in this area continues. Among the most exciting developments stand those new methods involving stereochemical purity and chemospecificity—the latter eliminating the need for protecting, blocking, or activating groups. The above methods contribute to these aspects.

I wish to thank my very able coworkers who transformed ideas into reality and the National Science Foundation and the National Institutes of Health for providing us all with sustenance.

Synthesis of Ribooligonucleotides Having Sequences of Transfer Ribonucleic Acids

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During the recent decade the chemical synthesis of polynucleotides has been explored by many investigators and there has been significant progress in methodology.[1] The most brilliant success in this field is perhaps the synthesis of a gene for yeast alanine tRNA by Khorana and his coworkers.[2]

This and other important syntheses were accomplished by a combination of chemical synthesis of deoxyribooligonucleotides and enzymatic joining of them to each other employing DNA ligase.[3] The methods utilized for the chemical synthesis of *deoxy*-ribooligonucleotides reached the level of deca- (10 units) to icosa- (20 units) nucleotides.

On the other hand, the chemical synthesis of *ribo*oligonucleotides, which have an additional 2′-hydroxyl group in each carbohydrate moiety, is rather difficult, mainly for the following reasons. (1) Selective protection of the 2′-OH while leaving the 3′-OH unprotected usually requires lengthy pathyways. (2) Migration of phosphate groups so as to change a ribose moiety with 2′-OH, 3′-phosphate to 2′-phosphate, 3′-OH, or *vice versa*, occurs rather easily under catalysis by acid or alkali. (3) Yields were relatively low in the condensation steps that join nucleotide units, presumably due to steric hindrance.

Problem 1 may be circumvented by using a nucleoside 3′-phosphate, in which the phosphate group acts both as a selective protecting group for the 3′-OH and as a reactive site for linking to other ribose moieties; also, acyl groups can be introduced successively either in the 2′-OH or in the heterocyclic amino group of a nucleoside 3′-phosphate. The second problem is partially solved by using 2′-O-acylated 3′-nucleotides. Also helpful is the use of trityl derivatives for the protection of the primary 5′-OH, which can later be exposed to further reaction by treating with mild acid. The third problem is the

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(1) H. G. Khorana, *Pure Appl. Chem.*, 71, 349 (1968).

(2) K. L. Agarwal, H. Büchi, M. H. Caruthers, N. Gupta, H. G. Khorana, E. Kleppe, A. Kumar, E. Ohtsuka, U. L. RajBhandari, J. H. Van de Sande, V. Sgaramella, H. Weber, and T. Yamada, *Nature (London)*, **227**, 27 (1970).

(3) B. S. Zimmerman, J. W. Little, C. K. Oshinski, and H. Gellert, *Proc. Nat. Acad. Sci. U. S.*, **57**, 184 (1967); B. Weiss and C. C. Richardson, *ibid.*, **57**, 1021 (1967).