

Modern Organic Synthesis

**by Barry M. Trost
and Edwin Vedejs**

**University
of Wisconsin**

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A WORD TO THE USER

ACS AUDIO COURSES are instructional units on subjects of significant interest that are suitable for both individual study and group use.

The ACS AUDIO COURSE on "Modern Organic Synthesis," by Professors Barry M. Trost and Edwin Vedejs of the University of Wisconsin, is intended for individuals who are concerned with putting organic molecules together. A survey of important modern synthetic techniques is presented within a context of several recent contributions in organic synthesis. Emphasis is placed on general methods. For maximum benefit the student is expected to have a background knowledge of basic organic chemistry as well as a familiarity with classical synthetic techniques.

This volume is the reference manual that is integrated with the audiotape of "Modern Organic Synthesis." The two together--the tape and manual--comprise the ACS AUDIO COURSE; neither is complete without the other. Because the lecturers refer constantly to the manual, each listener should have a copy of the manual as he listens, so he may follow these references.

The manual was not written to be a self-sufficient textbook. It was designed, rather, to be used as a workbook while listening to the tape. The listener is urged to take notes with the expectation that this activity will reinforce the learning process. The product is a personally annotated volume which should serve as an authoritative and up to date introduction to the subject.

Your comments and suggestions have proved to be exceptionally valuable guides for improving our educational programs. We hope you will continue to send them to us.

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General Outline*

I. Planning a synthesis

- A. Synthetic goal -- definition of problem
- B. Consideration of properties of product
- C. Stereochemical relationships
- D. Recognition of structural types
- E. Correlation with simple building blocks
- F. Methods of structural alteration

II. Reaction types

A. Reductions

- 1. Catalytic hydrogenation
 - a. Heterogeneous catalysis
 - b. Homogeneous catalysis
- 2. Dissolving metals
 - a. Reduction of unsaturated systems
 - b. Replacement of halide by hydrogen
 - c. Olefin formation by reductive vicinal cleavage
- 3. Metal hydrides (aluminum, boron, and tin hydrides)
 - a. Carbonyl compounds
 - b. Halides

B. Oxidations

- 1. Cr(VI)
- 2. Permanganate
- 3. Lead tetraacetate and sodium metaperiodate
- 4. Osmium tetroxide
- 5. Ozonolysis
- 6. Selenium dioxide
- 7. Peracids
- 8. Halogenation
- 9. Peresters
- 10. Photosensitized oxidation

C. Carbon-carbon bond formation

- 1. Alkylations (including Michael reaction)
 - a. Activating and blocking groups
 - b. Specific enolate generation
 - (1) Enol acetate
 - (2) Enol silanes
 - (3) α,β -unsaturation
 - (4) Cleavage of α -substituents

c. Enolate derivatives

- (1) Enamines
- (2) Salts of Schiff bases

2. Condensations at the carbonyl group

- a. Aldol and related condensation
- b. Ylide reactions

- (1) Phosphorus ylides
- (2) Sulfur ylides

c. Claisen and related condensations

3. Cycloadditions

- a. Diels-Alder
- b. Carbenes
- c. Thermal and photolytic 2 + 2 additions

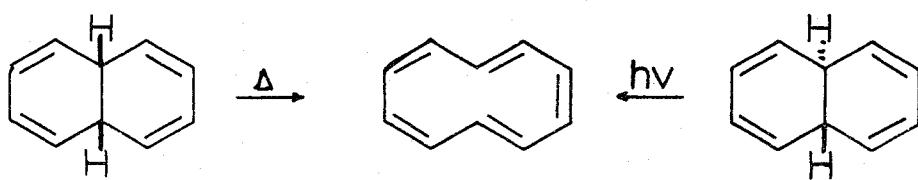
- (1) Reactions of allenes and ketenes
- (2) Reactions of activated olefins
- (3) Enone cycloadditions

E. Rearrangements

- 1. Valence isomerizations
- 2. Rearrangements involving carbonium ions
- 3. Ring contractions; pinacol rearrangements

* Note: The course lectures do not follow the order of this outline.

I. Synthesis of Cyclodecapentaene



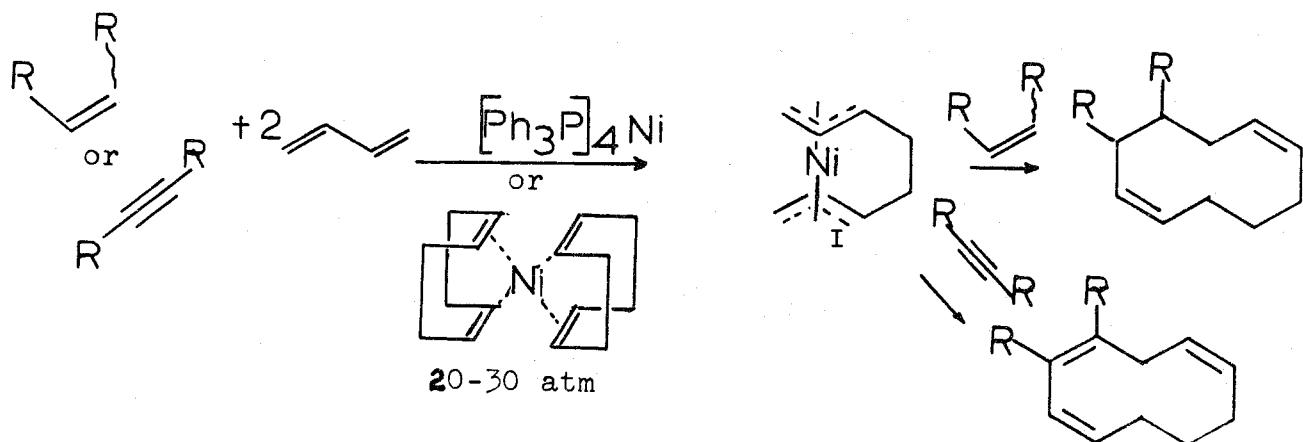
References

S. Masamune and R. T. Seidner, Chem. Commun., 542 (1969).

E. E. van Tamelen and T. L. Burkoth, J. Amer. Chem. Soc., 89, 151 (1963).

A. Synthesis of medium sized rings

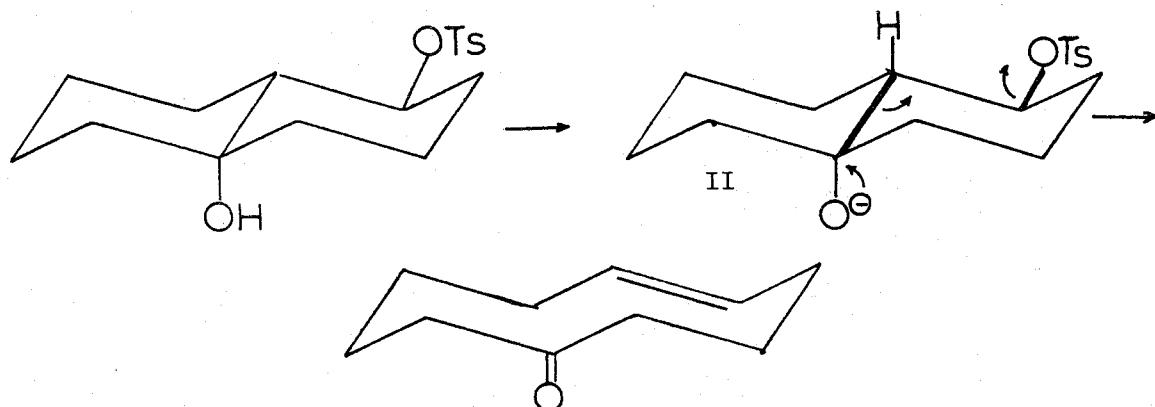
1. Transition metal catalyzed cycloadditions



Reference

P. Heimbach and G. Wilke, Ann. Chem., 727, 183, 194 (1969).

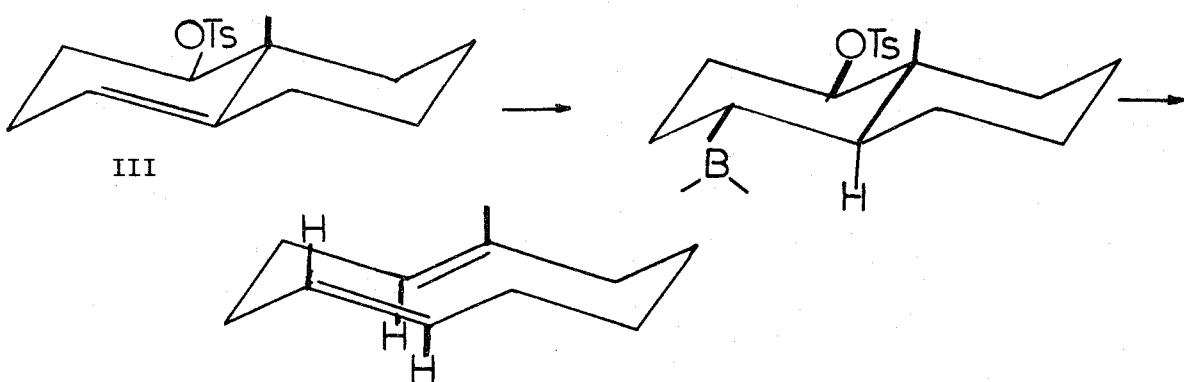
2. Four bond fragmentation



Reference

P. S. Wharton and G. A. Hiegel, J. Org. Chem., 30, 3254 (1965).

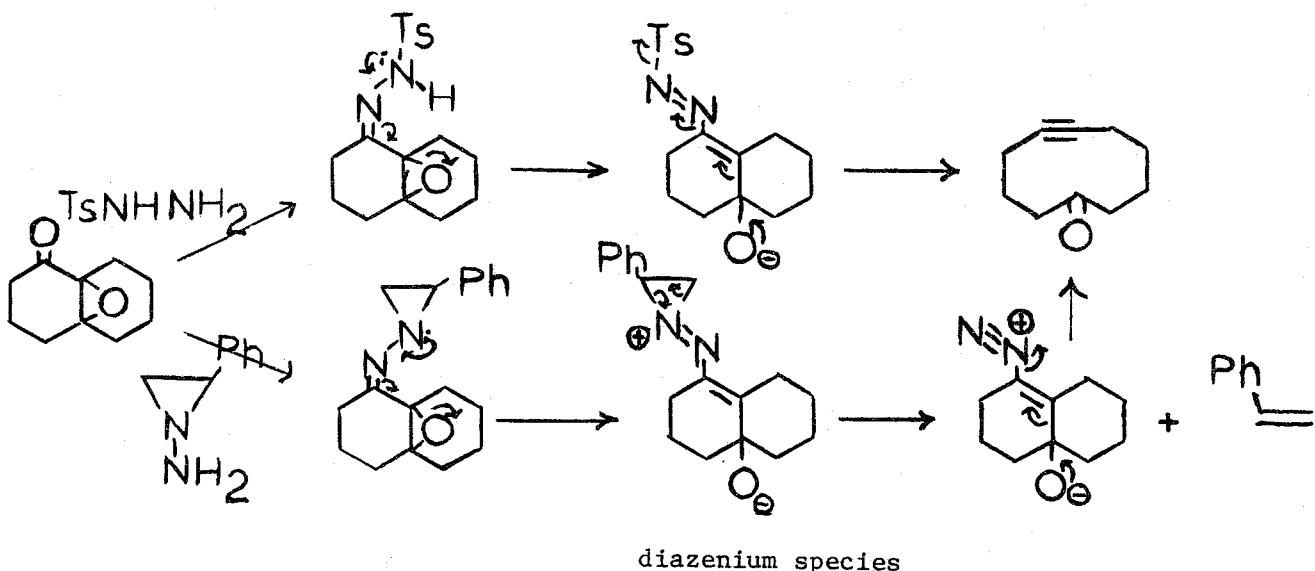
3. Five bond fragmentation



Reference

J. A. Marshall and G. L. Bundy, J. Amer. Chem. Soc., 88, 4291 (1966).

4. Hydrazine induced fragmentations of epoxyketones



Reference

A. Eschenmoser, et al., Helv. Chim. Acta, 51, 1461 (1968).

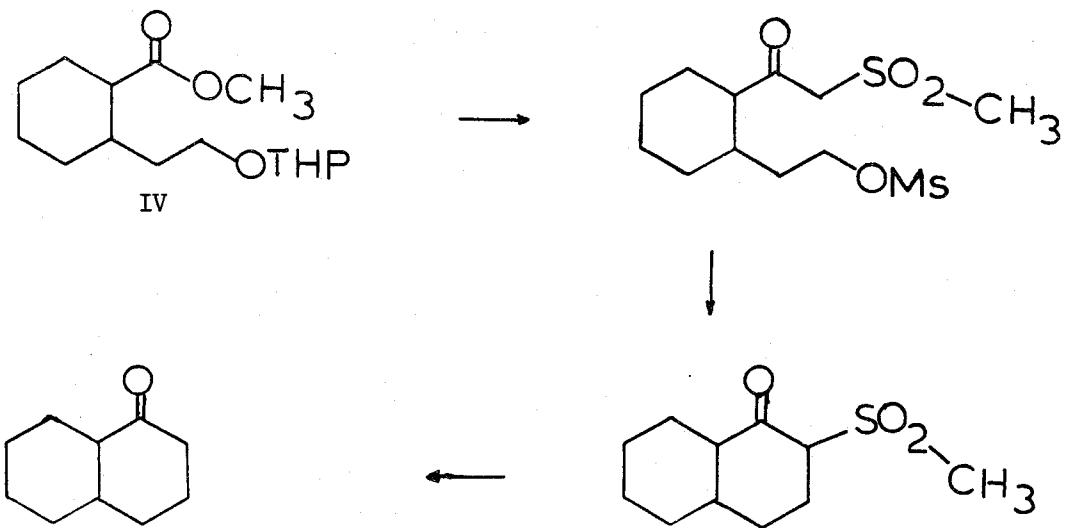
B. Six-membered ring formation

1. Robinson annelation procedure

Reference

T. A. Spencer, H. S. Neel, D. C. Ward and K. L. Williamson, J. Org. Chem., 31, 434 (1960).

2. Alkylation and/or acylation



References

P. G. Gassman and G. D. Richmond, J. Org. Chem., 31, 2355 (1966).

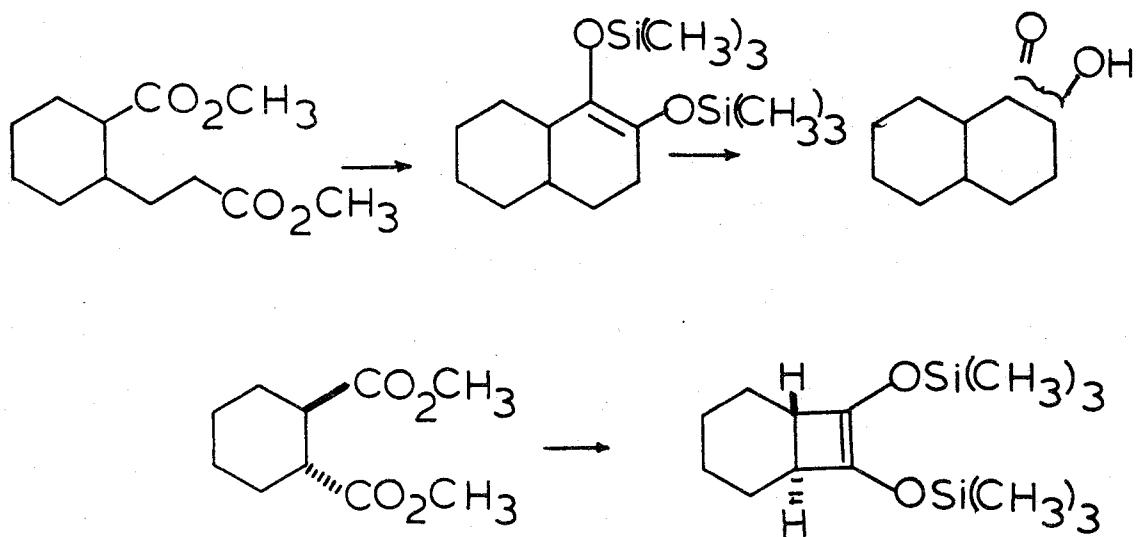
H. O. House and J. K. Larson, J. Org. Chem., 33, 61 (1968).

3. Dieckman or Thorpe Cyclizations

Reference

C. R. Krüger and E. G. Rochow, Angew. Chem. Int. Ed. Eng., 2, 617 (1963).

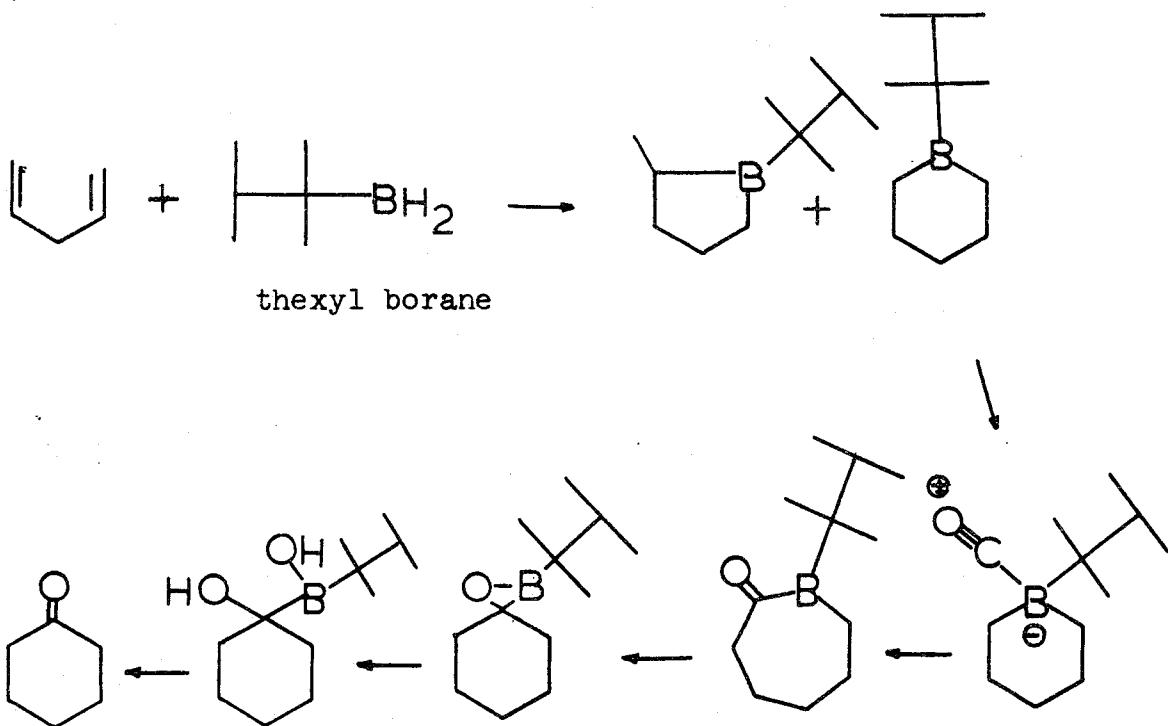
4. Acyloin condensation



Reference

J. J. Bloomfield, J. R. S. Irelan and A. P. Marchand,
Tetrahedron Lett., 5647 (1968).

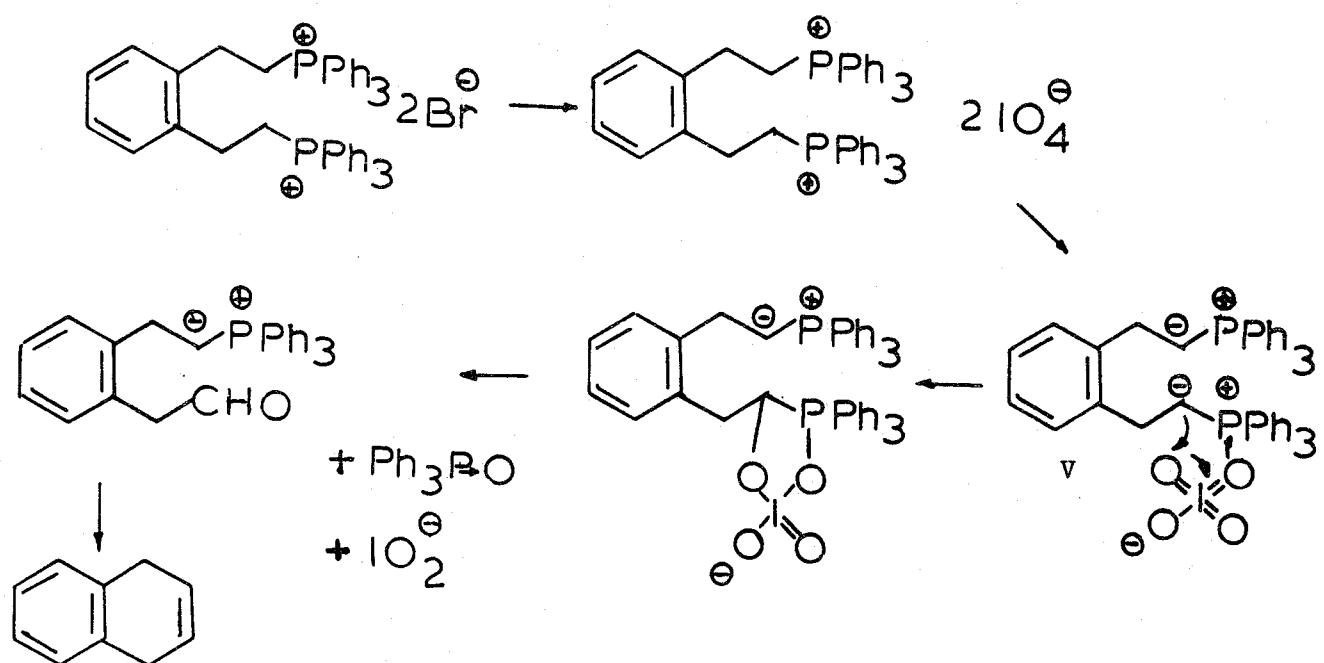
5. Hydroboration-carbonylation



Reference

H. C. Brown and E. Negishi, J. Amer. Chem. Soc., **89**, 5258, 5477 (1967).

6. Ylides

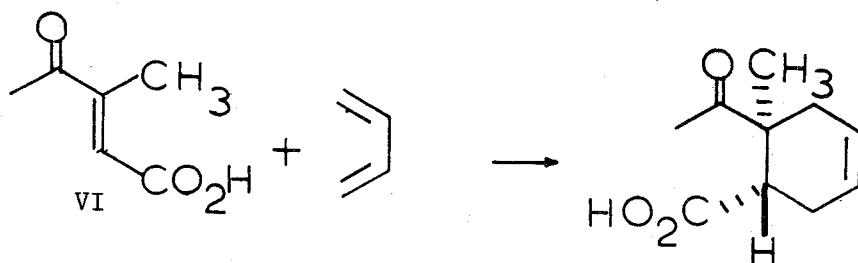
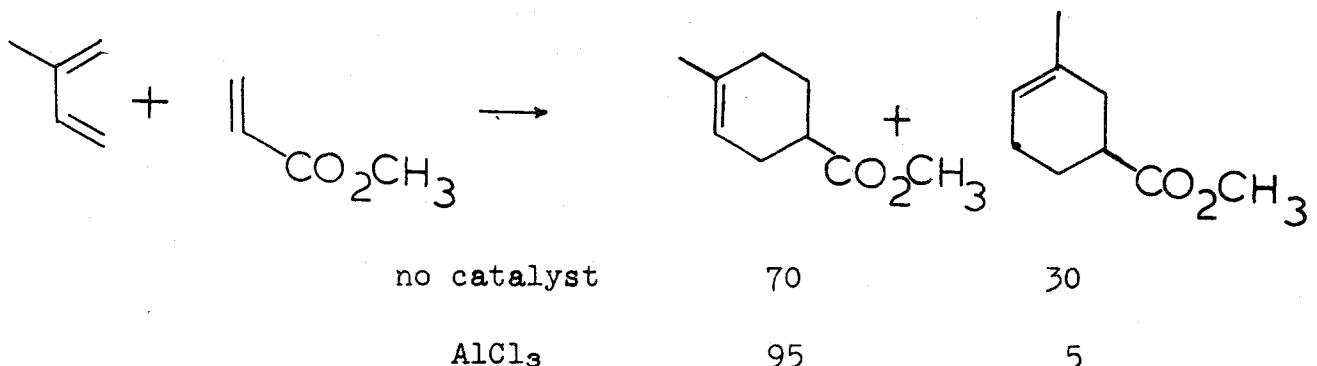


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H. J. Bestmann, R. Arnsen and H. Wagner, Chem. Ber., 102, 2259 (1969).

A. Nurrenbach and H. Pommer, Ann. Chem., 721, 34 (1969).

7. Cycloadditions



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- G. A. Berchtold, J. Ciabattoni and A. A. Tunick, J. Org. Chem., 30, 3679 (1969).
R. F. Farmer and J. Hamer, J. Org. Chem., 31, 2418 (1966).
T. Inukai and T. Kojima, J. Org. Chem., 35, 1342 (1970).
J. Sauer and J. Kredel, Tetrahedron Lett., 731, 6359 (1966).

C. Olefin formation

1. Dehydration

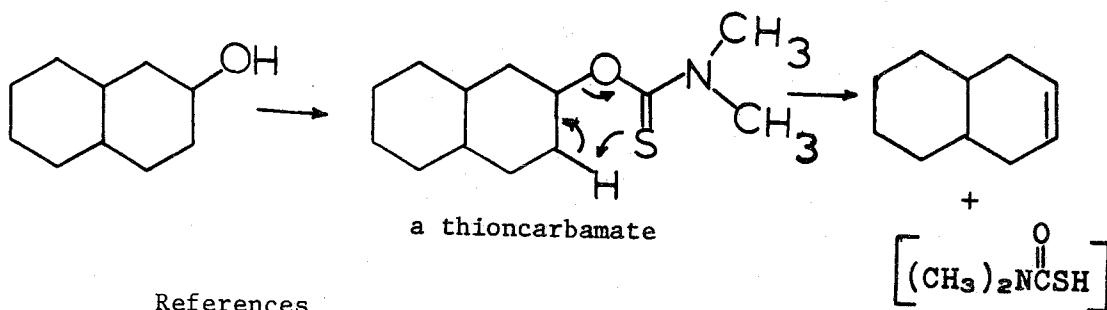
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G. G. Hazen and D. W. Rosenburg, J. Org. Chem., **9**, 1930 (1964).

G. J. Karabatsos, J. M. Corbett and K. L. Krumel, J. Org. Chem., 30, 689 (1965).

V. J. Traynelis, W. L. Hergenrother, H. T. Hanson and J. A. Valicenti, *J. Org. Chem.*, 29, 123 (1964).

2. Ester pyrolysis



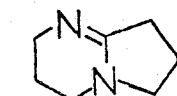
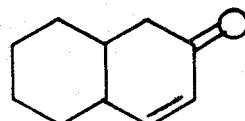
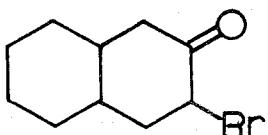
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W. S. Briggs and C. Djerassi, J. Org. Chem., 33, 1625 (1968)

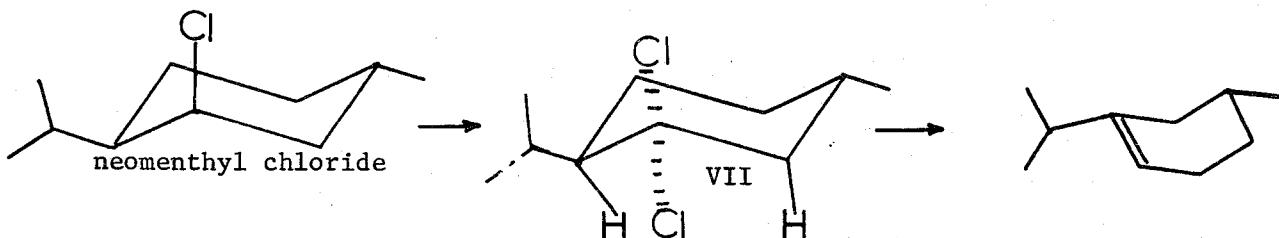
G. J. Karabatsos and K. L. Krumel, J. Amer. Chem. Soc., **91**, 3324 (1969).

M. S. Newman and F. W. Hetzel, J. Org. Chem., 34, 3604 (1969).

3. Dehydrohalogenation



1,5-diazabicyclo
[4.3.0.]non-5-ene



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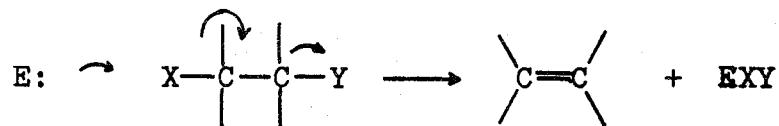
G. Biale, A. J. Parker, S. G. Smith, I. D. R. Stevens and S. Winstein, J. Amer. Chem. Soc., 92, 115 (1970).

R. Hanna, Tetrahedron Lett., 2105 (1968).

H. Oediger, et al., Chem. Ber., 99, 2012 (1966).

4. Reductive elimination and fragmentations

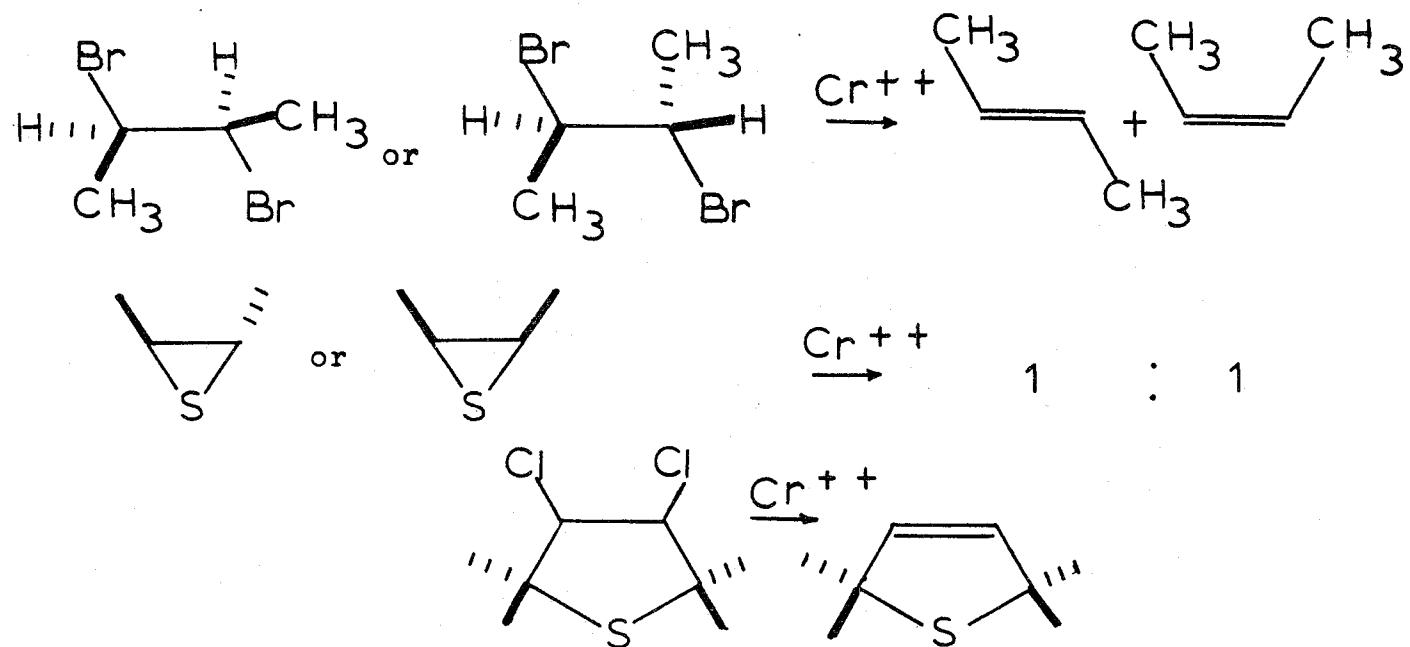
a) General



Reference

J. F. King and R. G. Pews, Can. J. Chem., 42, 1295 (1964).

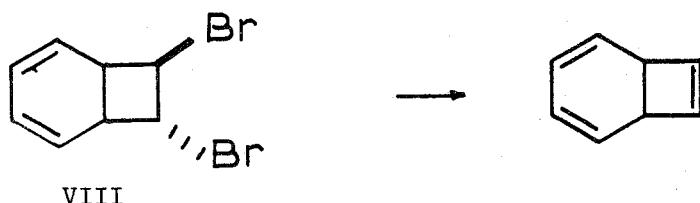
b) Chromous ion



Reference

J. K. Kochi, D. M. Singleton and L. J. Andrews, Tetrahedron, 24, 3503 (1968).

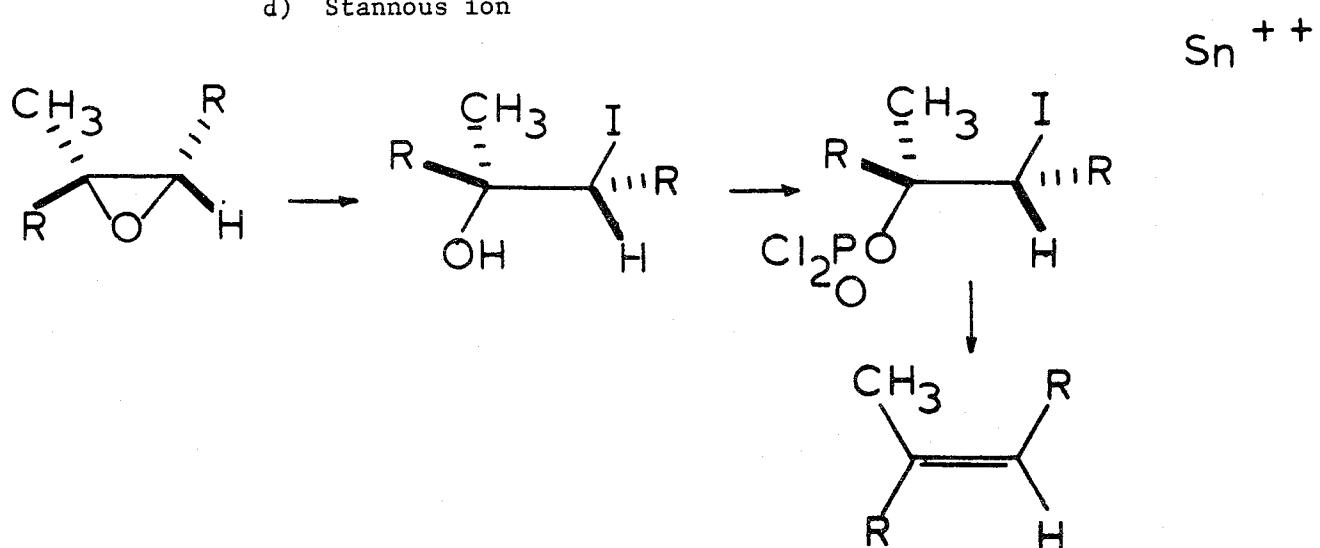
c) Sodium arylides



Reference

C. G. Scouton, F. E. Barton, J. R. Burgess, P. R. Story
and J. F. Garst, Chem. Commun., 78 (1969).

d) Stannous ion



Reference

J. W. Cornforth, R. H. Cornforth and K. K. Mathew, J. Chem. Soc., 2539 (1959).

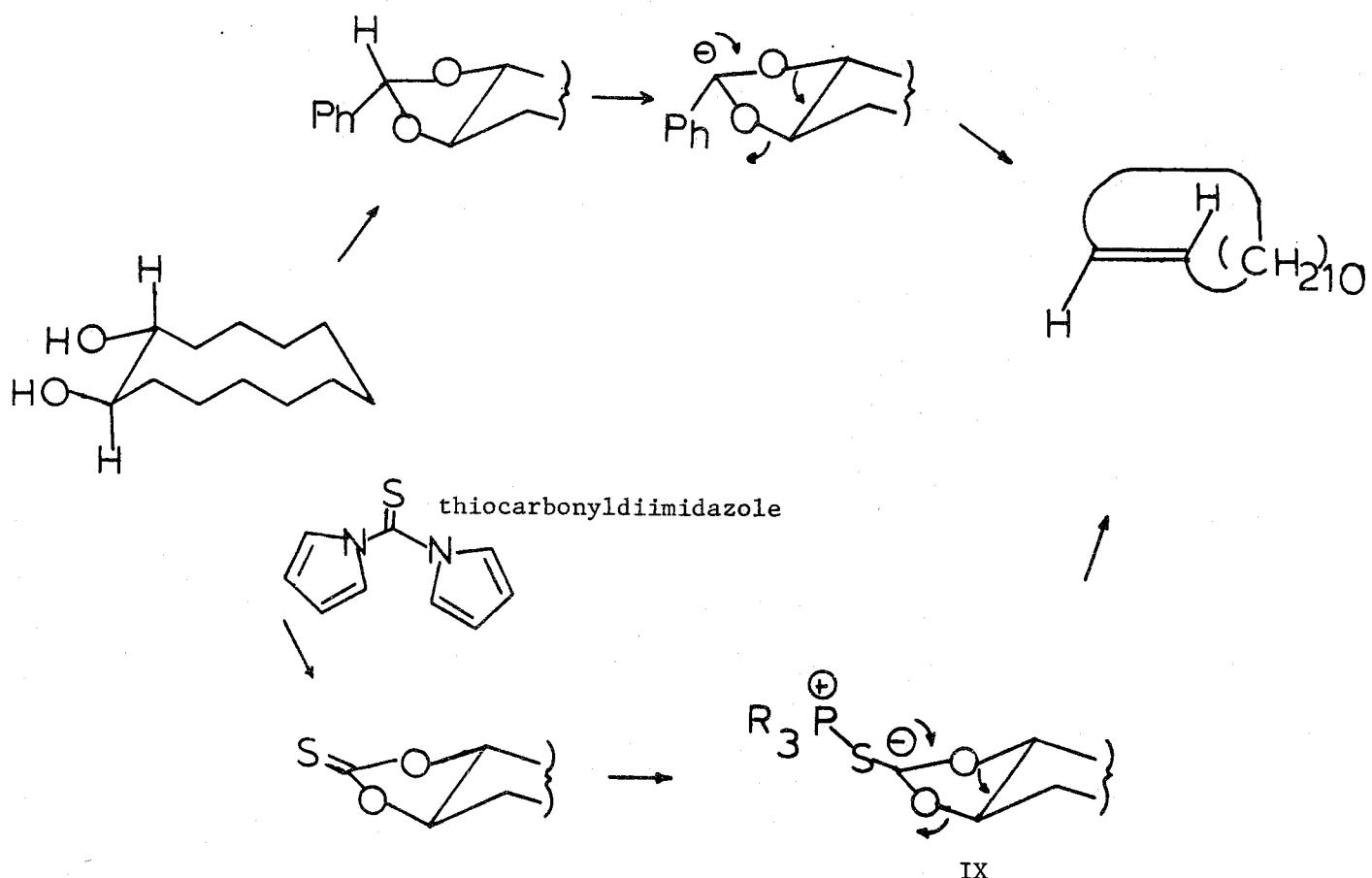
e) Epoxide deoxygenation



Reference

F. Pertini, P. Grasselli, G. Zubiani and G. Cainelli,
Chem. Commun., 144 (1970).

(f) Acetal and thioncarbonate fragmentation

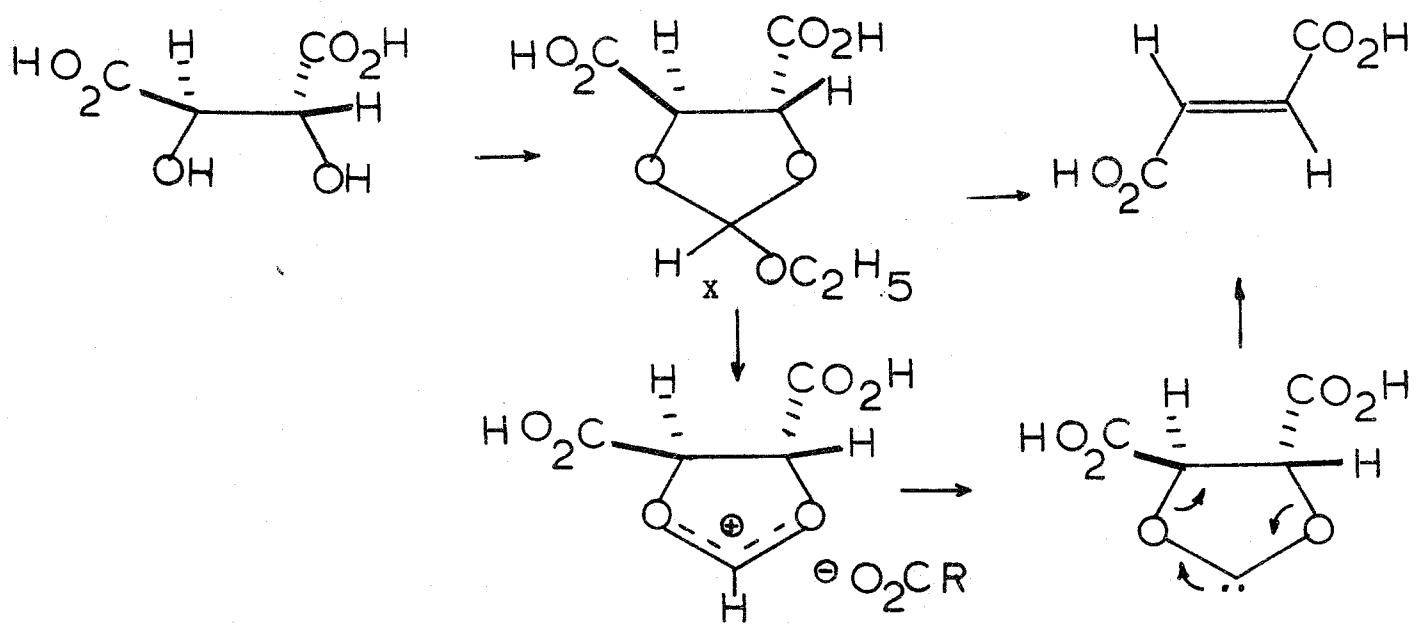


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J. N. Huses, M. J. Peagram, G. H. Whitham and M. Wright,
Chem. Commun., 1593 (1968).

g) Orthoester fragmentation



References

G. Crank and F. W. Eastwood, Aust. J. Chem., 17, 1392 (1964).

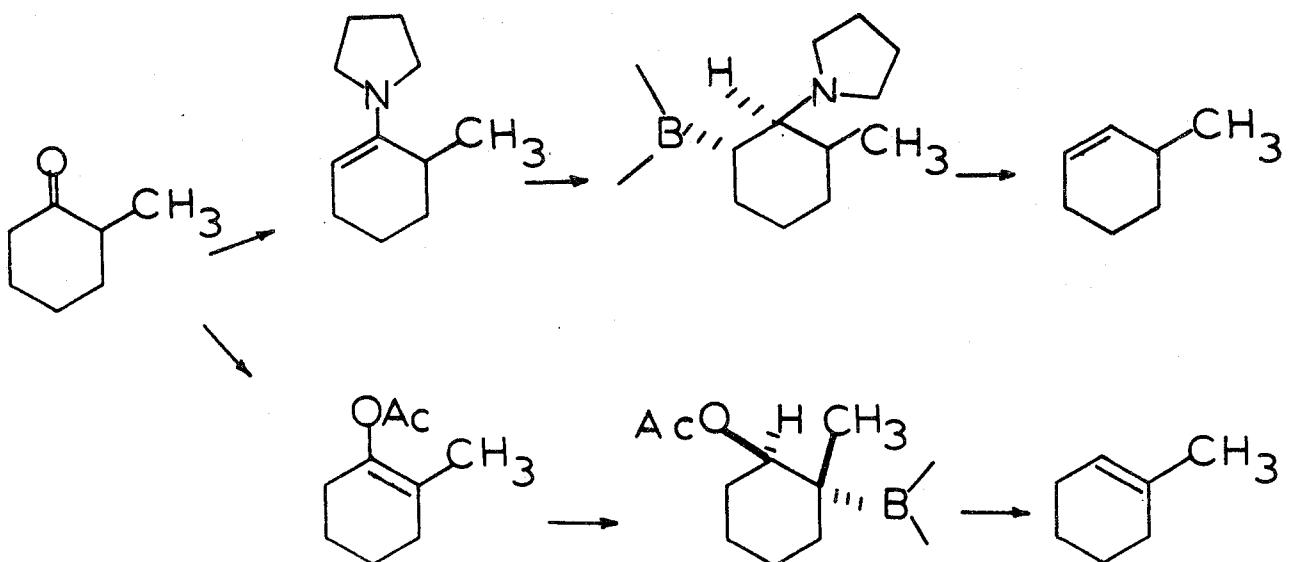
J. S. Josan and F. W. Eastwood, Aust. J. Chem., 21, 2013 (1968).

h) Decarboxylative elimination

Reference

J. A. Marshall and H. Faubl, J. Amer. Chem. Soc., 89, 5965 (1967).

i) Diborane reduction of keto derivatives

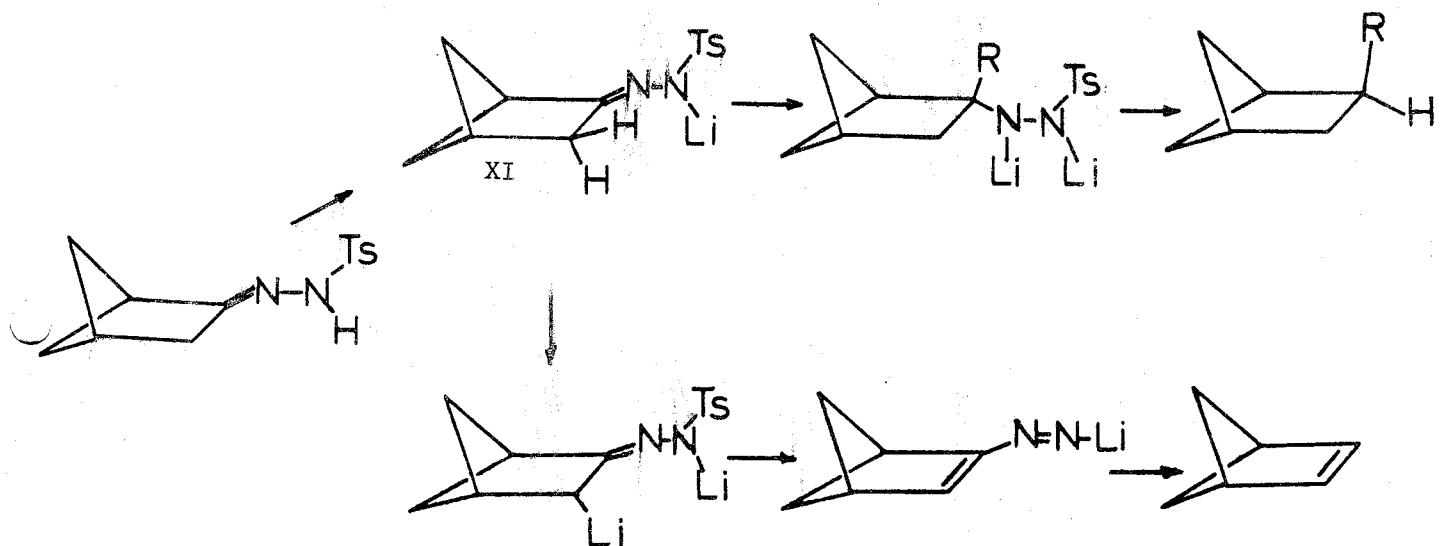


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J. M. Coulter, J. W. Lewis and P. P. Lynch, Tetrahedron, 24, 4489 (1968).

J. W. Lewis and A. A. Pearce, Tetrahedron Lett., 2039 (1964).

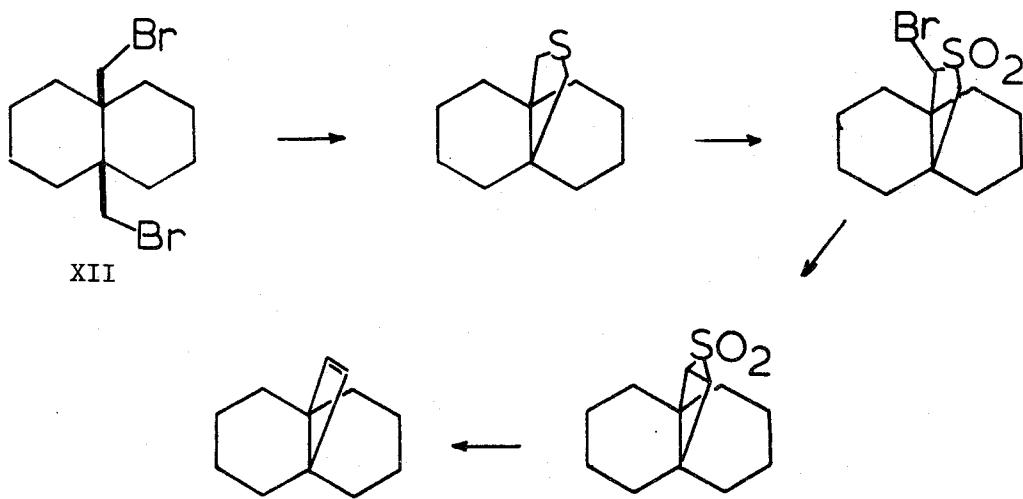
j) Tosylhydrazone decomposition

References

W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan and K. Tomer, J. Amer. Chem. Soc., 90, 4762 (1968).

R. H. Shapiro, Tetrahedron Lett., 345 (1968).

k) Ramberg-Bäcklund rearrangement



Reference

L. A. Paquette and R. W. Houser, J. Amer. Chem. Soc., 91, 3870 (1969).

5. Oxidative decarboxylations

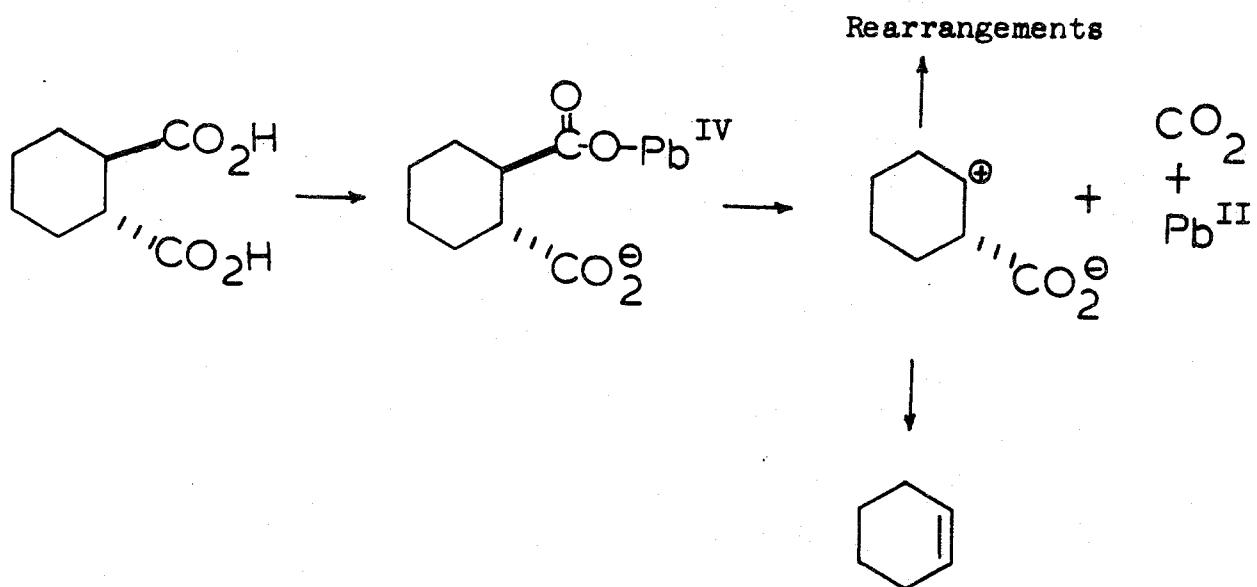
a) Monoacid

References

J. K. Kochi and J. K. Bacha, J. Org. Chem., 33, 2847 (1968); Tetrahedron, 24, 2215 (1968).

J. Tsuji, Advan. Org. Chem. M., 6, 109 (1969).

b) Diacids - lead(IV)

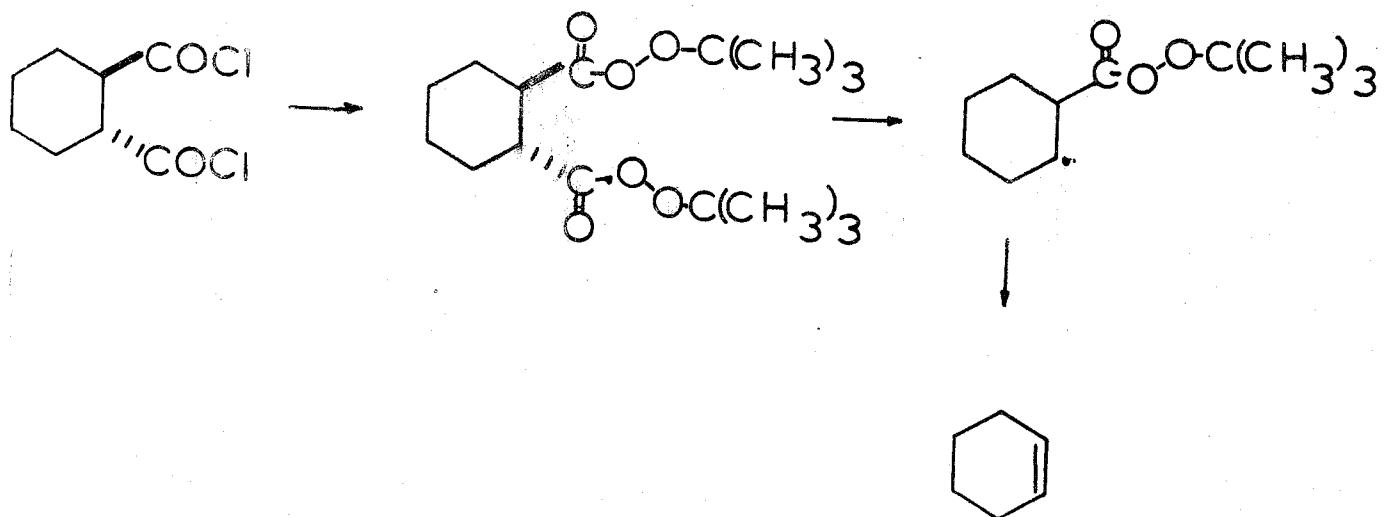


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C. M. Cimarusti and J. Wolinsky, J. Amer. Chem. Soc., 90, 113 (1968).

F. Huber and M. S. A. El-Meligy, Chem. Ber., 102, 872 (1969).

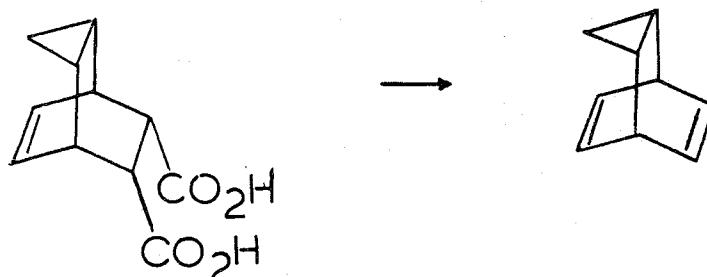
c) Diacids - perester



Reference

E. N. Cain, R. Vukov and S. Masamune, Chem. Commun., 98 (1969).

d) Diacids - electrolytic



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P. Radlick, et al., Tetrahedron Lett., 5117 (1968).

H. H. Westberg and H. J. Dauben, Jr., Tetrahedron Lett., 5127 (1968).

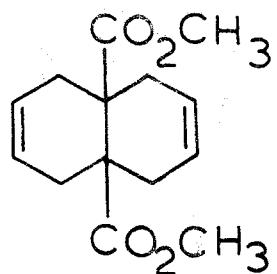
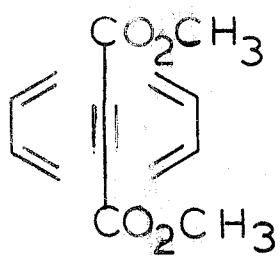
6. Hofmann and Cope elimination

References

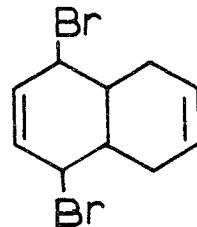
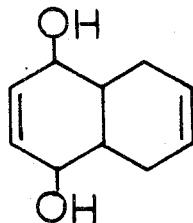
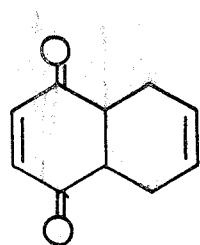
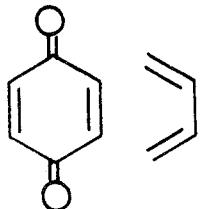
M. P. Cooke, Jr., and J. L. Coke, J. Amer. Chem. Soc., 90, 5556, 5561 (1968).

D. J. Cram, M. R. V. Sahyun and G. R. Knox, J. Amer. Chem. Soc., 84, 1734 (1962).

D. Preliminary solution



XIII

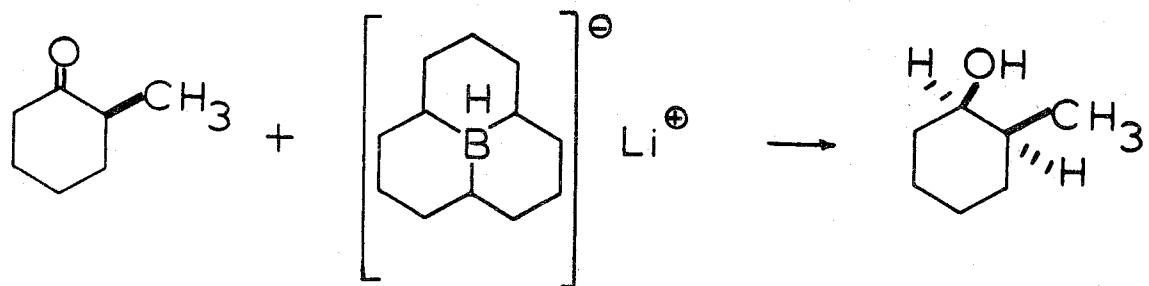


XIV

E. Reduction of ketone to alcohol

1. Boron hydrides

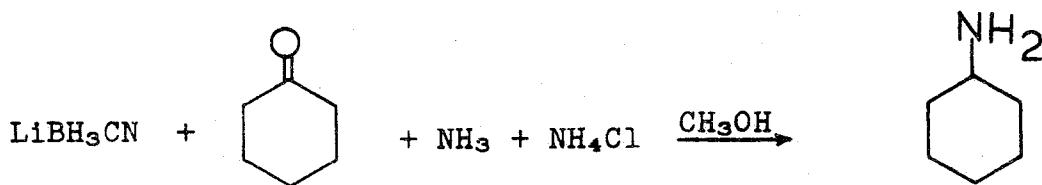
a) Lithium perhydro-9b-boraphenalylhydride



Reference

H. C. Brown and W. C. Dickason, J. Amer. Chem. Soc., 92, 709 (1970).

b) Lithium cyanoborohydride



Reference

R. F. Borch and H. D. Durst, J. Amer. Chem. Soc., **91**, 3996 (1969).

c) Sodium borohydride and cobaltous chloride



Reference

T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji and Z. Imai, Tetrahedron Lett., 4555 (1969).

2. Sodium di(2-methoxyethoxy)aluminum hydride



Reference

M. Cerny, J. Malek, M. Capka and V. Chvalovsky, Coll. Czech. Chem. Commun., **34**, 118, 1025, 1033 (1969).

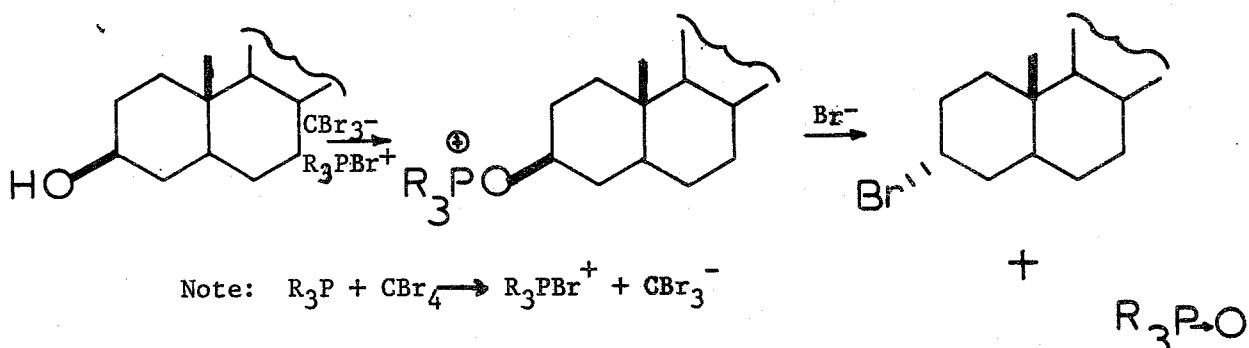
F. Conversion of alcohol to halide

1. Iodide

Reference

E. J. Corey and J. E. Anderson, J. Org. Chem., 32, 4160 (1967).

2. Bromide

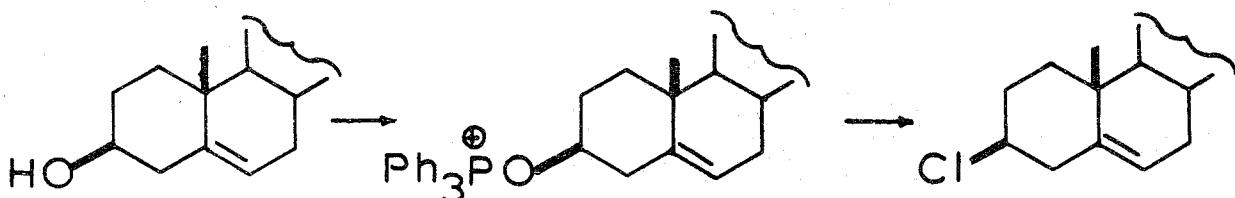


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D. Levy and R. Stevenson, Tetrahedron Lett., 341 (1965).

J. B. Schaefer and D. S. Weinberg, J. Org. Chem., 30, 2635 (1965).

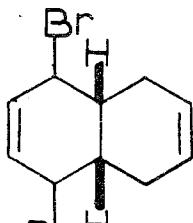
3. Chloride



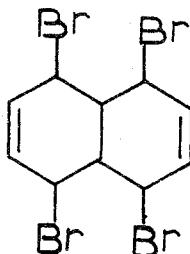
Reference

I. M. Downie, J. B. Lee and M. F. S. Matough, Chem. Commun., 1358 (1968).

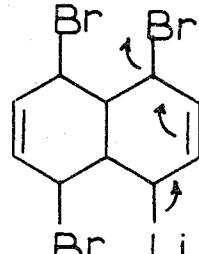
G. Final solution



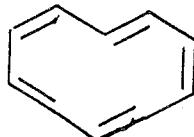
XV



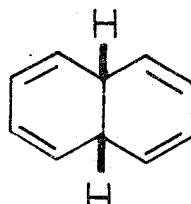
XVI



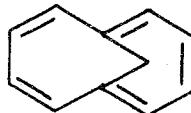
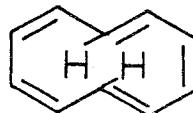
XVII



non-aromatic



cis-9,10-dihydronaphthalene



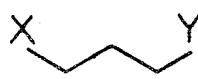
methanocyclodecapentaene



XVIII

H. Cyclopropane formation

1. 1,3-Eliminations



Z = SO₂, N=N

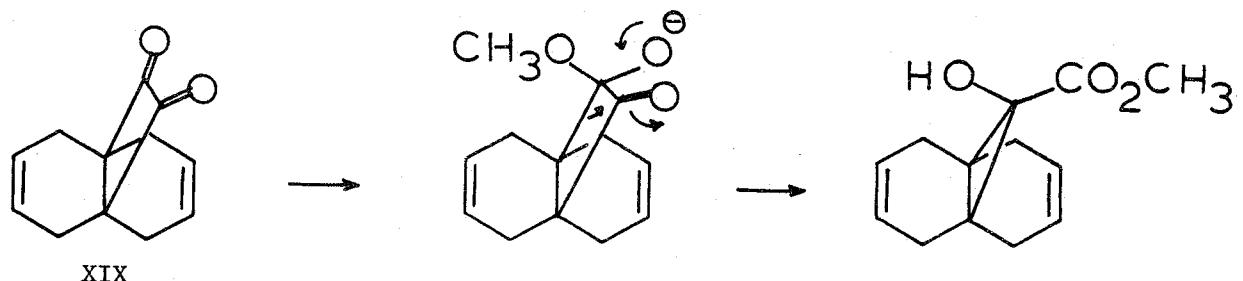
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R. J. Crawford and A. Mishra, J. Amer. Chem. Soc., 88, 3963 (1966).

J. K. Kochi and D. M. Singleton, J. Org. Chem., 33, 1027 (1968).

2. Ring contractions*

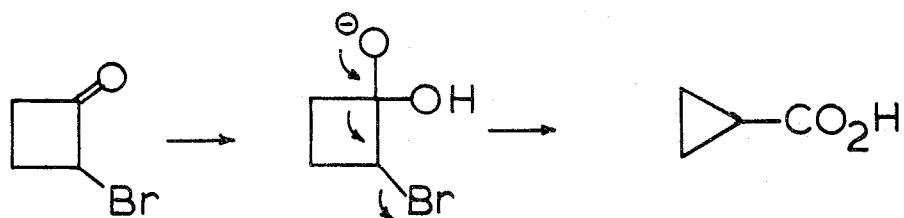
a) Benzillic acid rearrangement



Reference

A. de Groot, D. Oudman and H. Wynberg, Tetrahedron Lett., 1529 (1969).

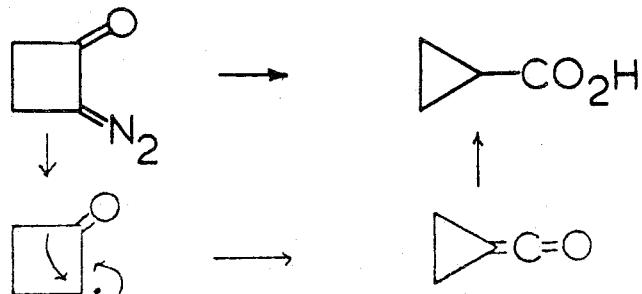
b) Semibenzillic acid rearrangement



Reference

J. Salaun and J. M. Conia, Tetrahedron Lett., 4545 (1968).

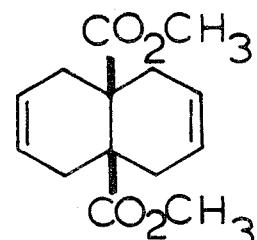
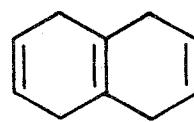
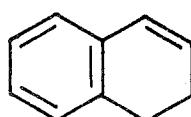
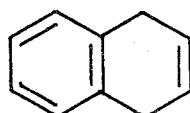
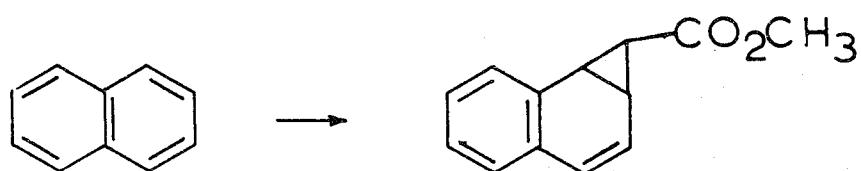
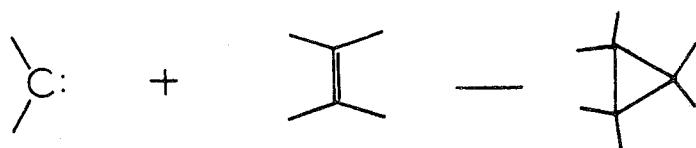
c) Diazoketone



Reference

M. Regitz and J. Rüter, Chem. Ber., 102, 3877 (1969).

3. Additions to double bonds



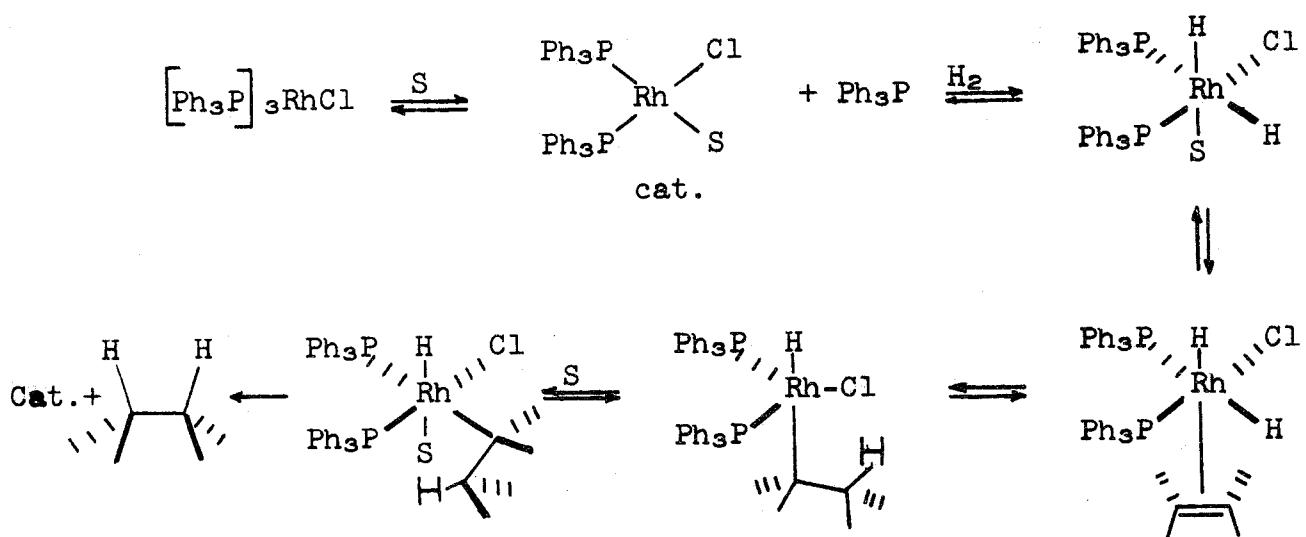
a) Reductions of olefins and aromatics

(1) Heterogeneous catalysis

Reference

F. J. McQuillin, et al., J. Chem. Soc. (C), 260 (1969).

(2) Homogeneous catalysis



References

E. N. Frankel and R. Butterfield, J. Org. Chem., 34, 3930, 3936 (1969).

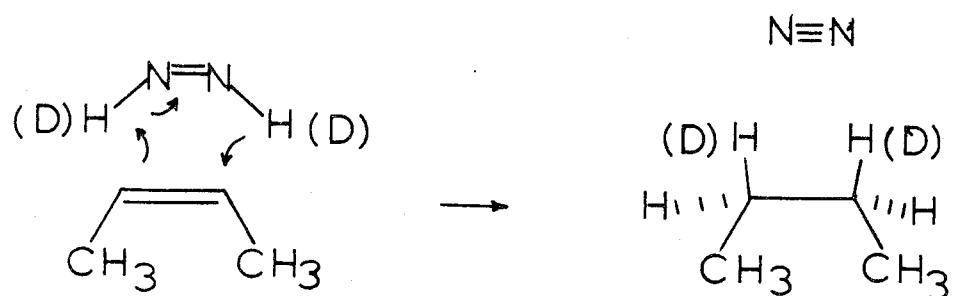
R. E. Harmon, et al., J. Org. Chem., 34, 3684 (1969).

I. Jardine and F. J. McQuillin, Chem. Commun., 477, 503 (1969).

S. Montelatici, A. van der Ent, J. A. Osborn and G. Wilkinson, J. Chem. Soc., (A), 1054 (1968) and references therein.

(3) Diimide

prepared from NH_2NH_2 TsNNH_2
 $\text{KO}_2\text{CN}=\text{NCO}_2\text{K}$ $\text{NH}_2\text{OSO}_3\text{Na}$



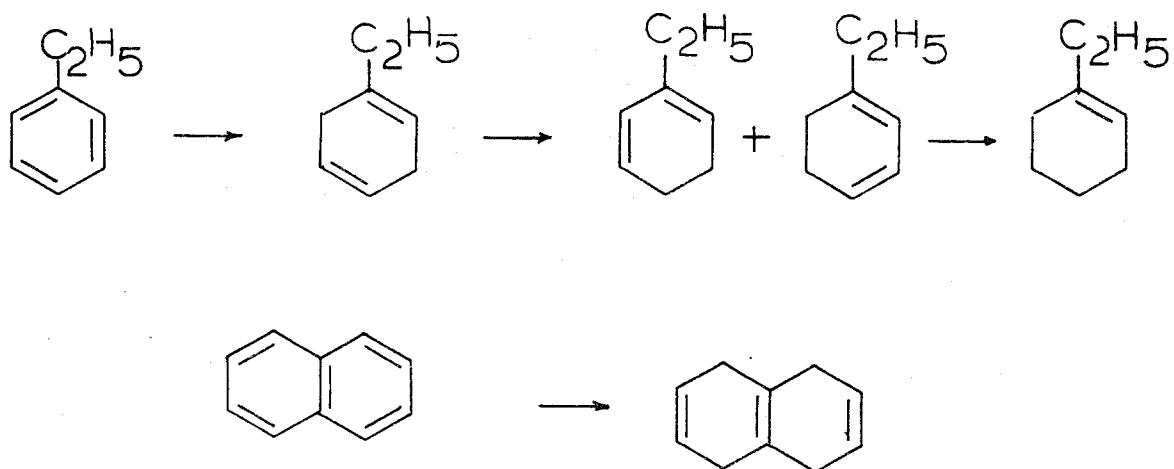
References

E. W. Garbisch, Jr., et al., J. Amer. Chem. Soc., 87, 2932 (1965).

J. W. Hamersma and E. I. Snyder, J. Org. Chem., 30, 3985 (1965).

S. Hunig, H. R. Müller and W. Thier, Angew. Chem. Int. Ed. Eng., 4, 271 (1965).

(4) Dissolving metals



References

R. G. Harvey and K. Urberg, J. Org. Chem., 33, 2206 (1968).

J. J. Sims and L. H. Selman, Tetrahedron Lett., 561 (1969).

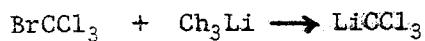
L. H. Slaugh and J. H. Raley, J. Org. Chem., 32, 2861 (1967).

b) Carbenes and carbenoids

(1) Dihalocarbenes



HCX_3 $\text{CX}_3\text{CO}_2\text{H}$ derivatives



Stability of anion



Leaving group ability



Stability of carbene



References

G. Köbrich, K. Flory and H. R. Merkel, Tetrahedron Lett., 973 (1965) and references therein.

D. Seyferth, et al., J. Amer. Chem. Soc., 87, 4259 (1965).

(b) Reductions of dihalocyclopropanes

- 1) Dissolving metal
- 2) Tin hydride

References

G. L. Grady and H. G. Kuivila, J. Org. Chem., 34, 2014 (1969).

D. Seyferth, H. Yamazaki and D. L. Alleston, J. Org. Chem., 28 703 (1963).

- 3) Dimsyl anion

Reference

C. L. Osborn, T. C. Shields, B. A. Shoulders, C. G. Cardenas and P. D. Gardner, Chem. Ind., (London), 766 (1965).

- 4) Electrolysis

Reference

A. J. Fry and R. H. Moore, J. Org. Chem., 33 1283 (1968).

- 5) Organomagnesium

Reference

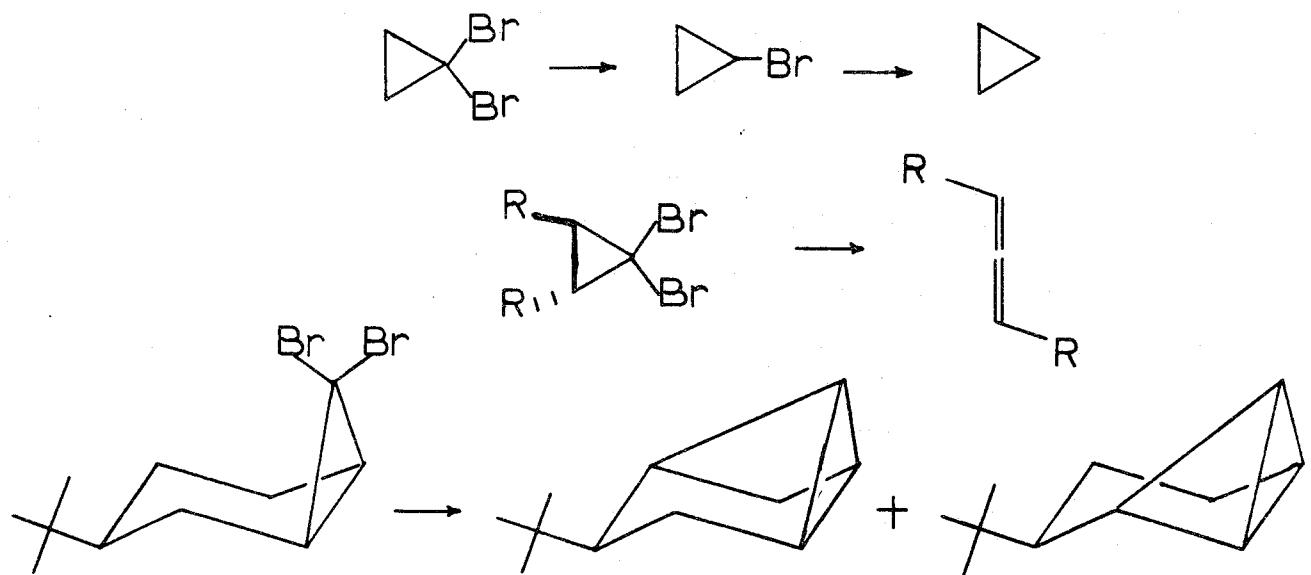
D. Seyferth and B. Prokai, J. Org. Chem., 31, 1702 (1966).

6) Chromous ion

Reference

N. Nozaki, T. Aratani and R. Noyori, Tetrahedron, 23, 3645 (1967).

7) Organolithium



Reference

L. Skattebol, Tetrahedron, 23, 1107 (1967)
and references therein.

(c) Selectivity

Olefin	CBr ₂	CCl ₂	Carbene
	3.5	6.5	1.1
	3.2	2.8	1.1
	1.0	1.0	1.0
	0.3	0.2	0.7
	0.3	0.1	0.7
	—	0.01	0.8

(2) Diazo compounds

(a) Diazo formation by diazo transfer

Reference

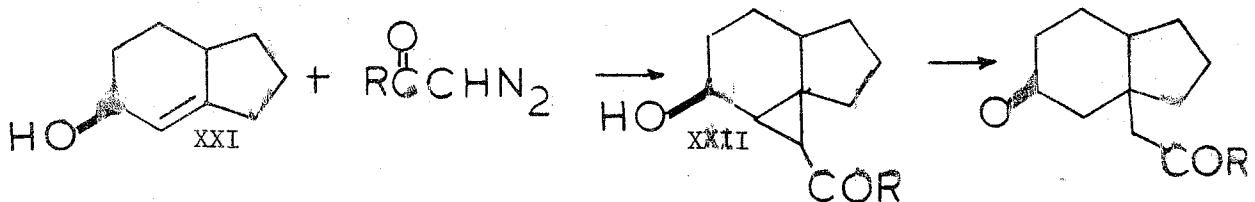
J. B. Hendrickson and W. A. Wolf, J. Org. Chem., 33, 3610 (1968).

(b) Tosylhydrazone method

Reference

W. Kirmse and K. H. Pook, Angew. Chem., 78, 603 (1966).

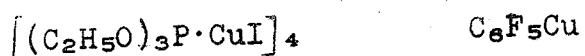
(c) Photolytic



Reference

M. Jones, Jr., and W. Ando, J. Amer. Chem. Soc., 90, 2200 (1968).

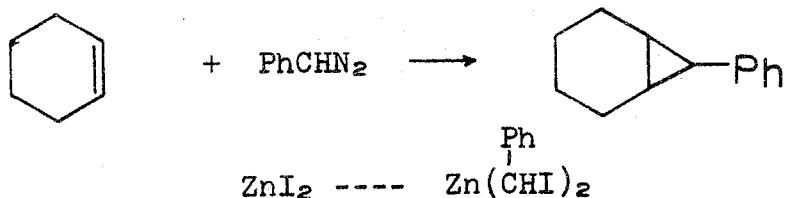
(d) Copper catalyzed addition



Reference

W. R. Moser, J. Amer. Chem. Soc., 91, 1135, 1141 (1969).

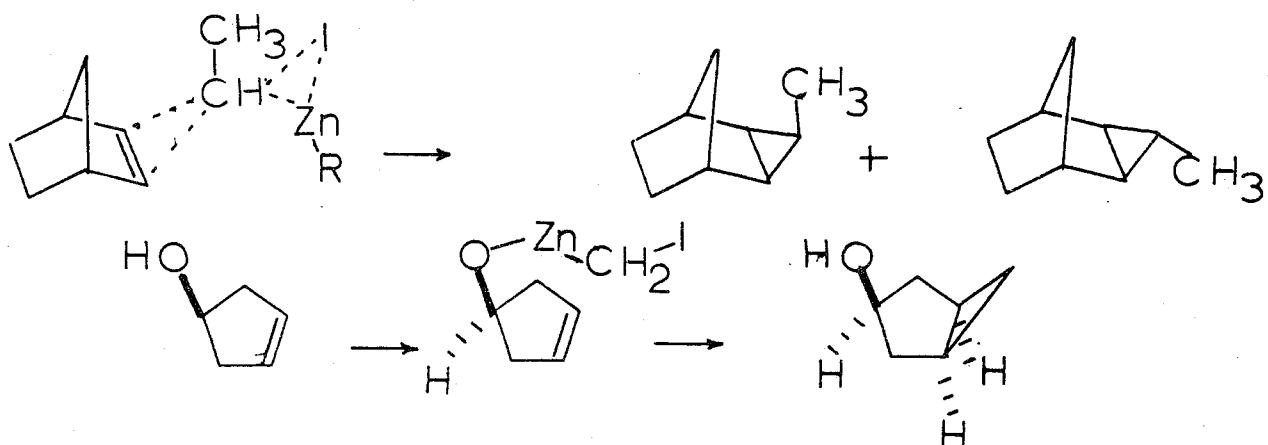
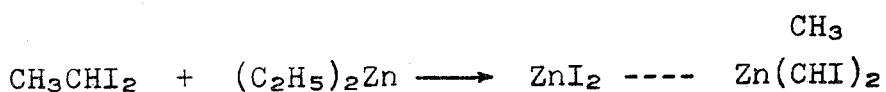
(e) Zinc iodide catalyzed addition



Reference

S. H. Goh, L. E. Gloss and G. L. Gloss, J. Org. Chem., 34, 25 (1969).

(3) Simmons-Smith reaction

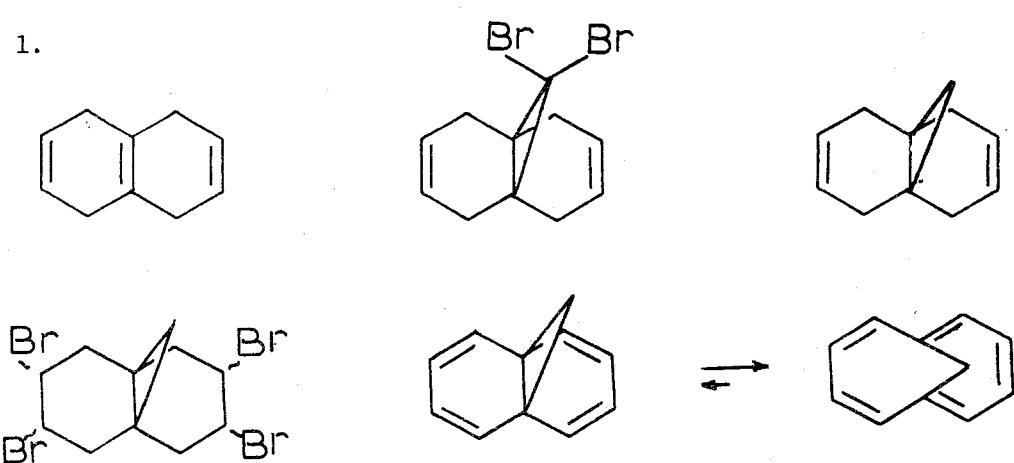


Reference

J. Nishimura, N. Kawabata and J. Furukawa,
Tetrahedron, 25, 2647 (1969).

I. Solution

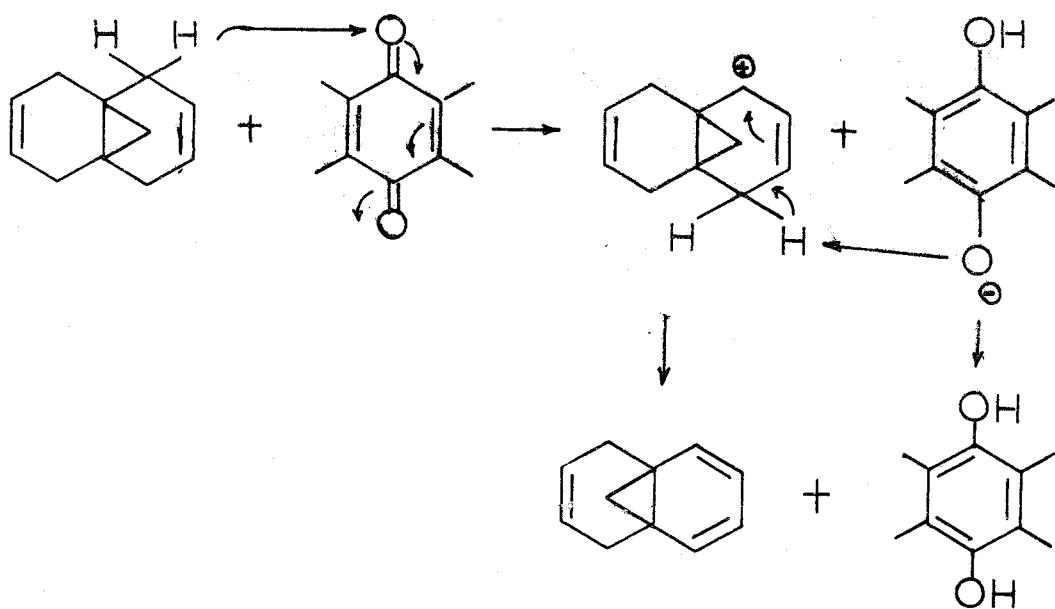
1.



Reference

E. Vogel, et al., Angew. Chem., 76, 145, 535, 784, 785 (1964).

2. Dehydrogenation



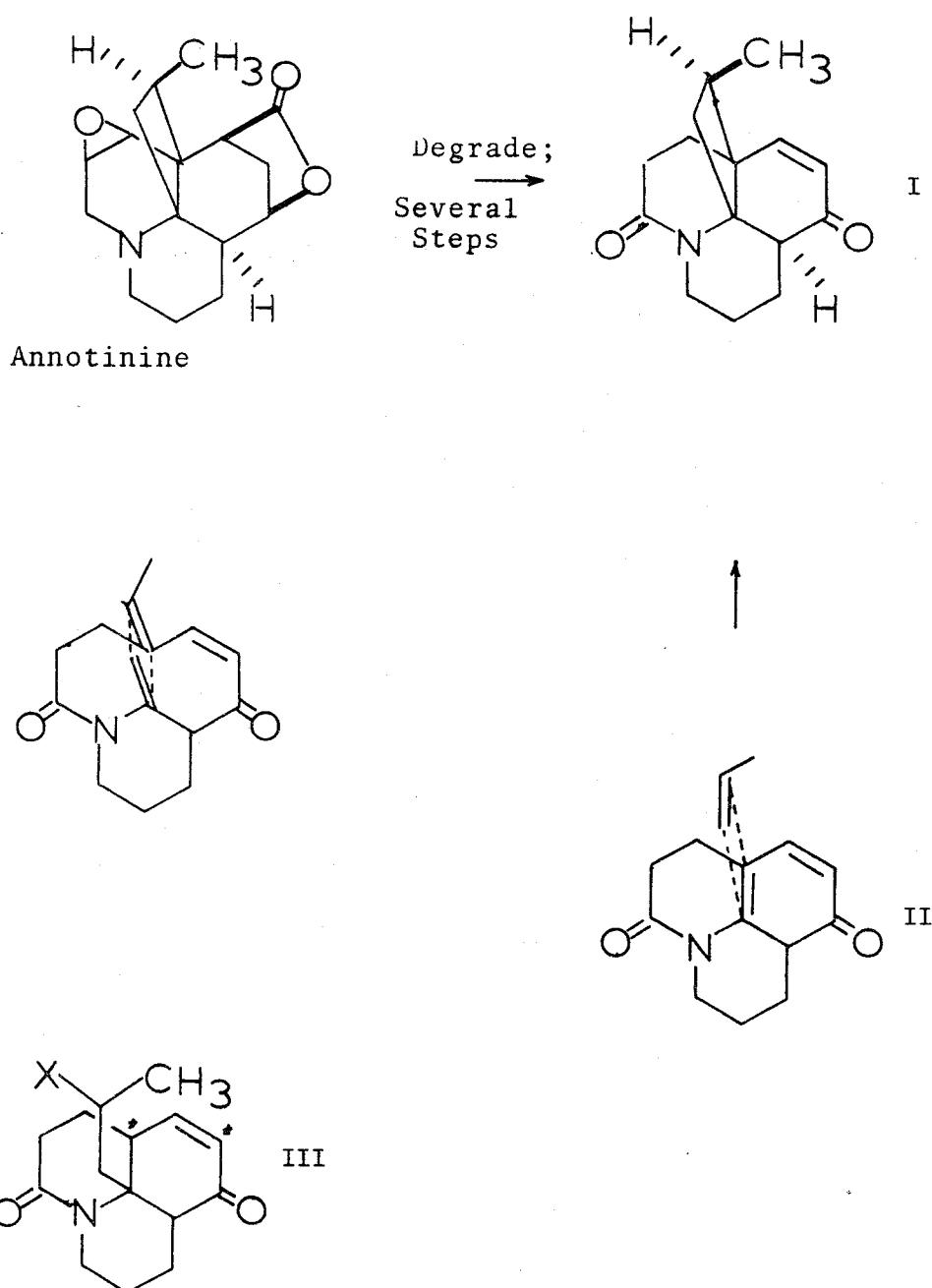
Reference

P. H. Nelson and K. G. Untch, Tetrahedron Lett., 4475 (1969).

B. M. Trost, J. Amer. Chem. Soc., 89, 1847 (1967).

II. Synthesis of a Degradation Product of Annotinine
[See Wiesner, et al., Tetrahedron Lett., 1523, 4937 (1967).]

A. Analysis; isolation of synthetic problems



B. Synthesis of Cyclobutanes

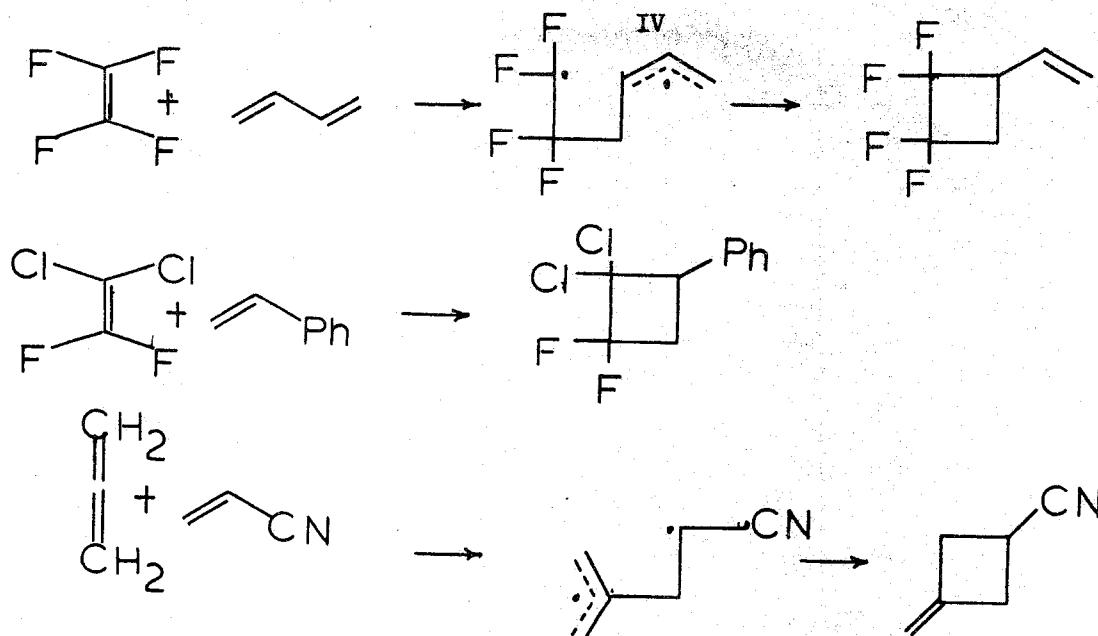
1. Thermal cycloadditions

References

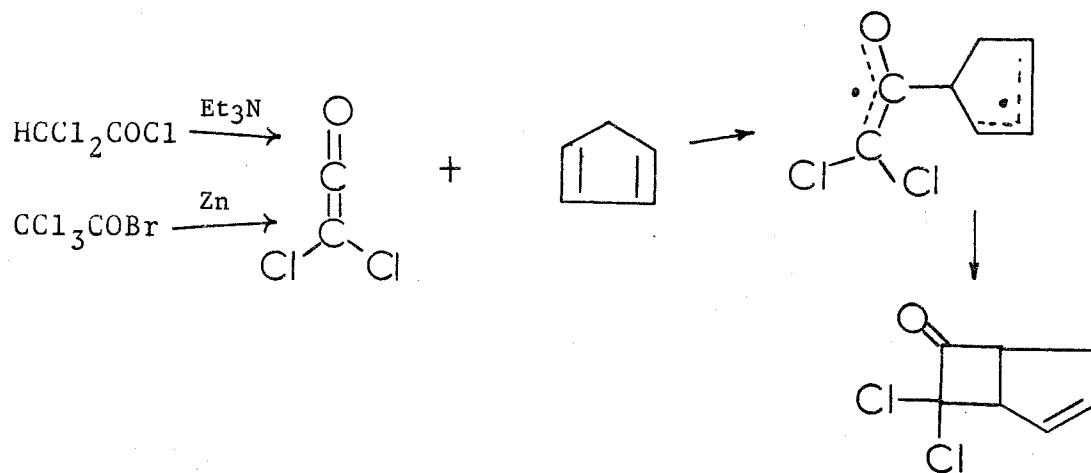
J. D. Roberts and C. M. Sharts, Org. React., **12**, 1 (1962).

H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, Inc., New York, N. Y., 1967.

a) Halogenated olefins, cumulenes, conjugated olefins



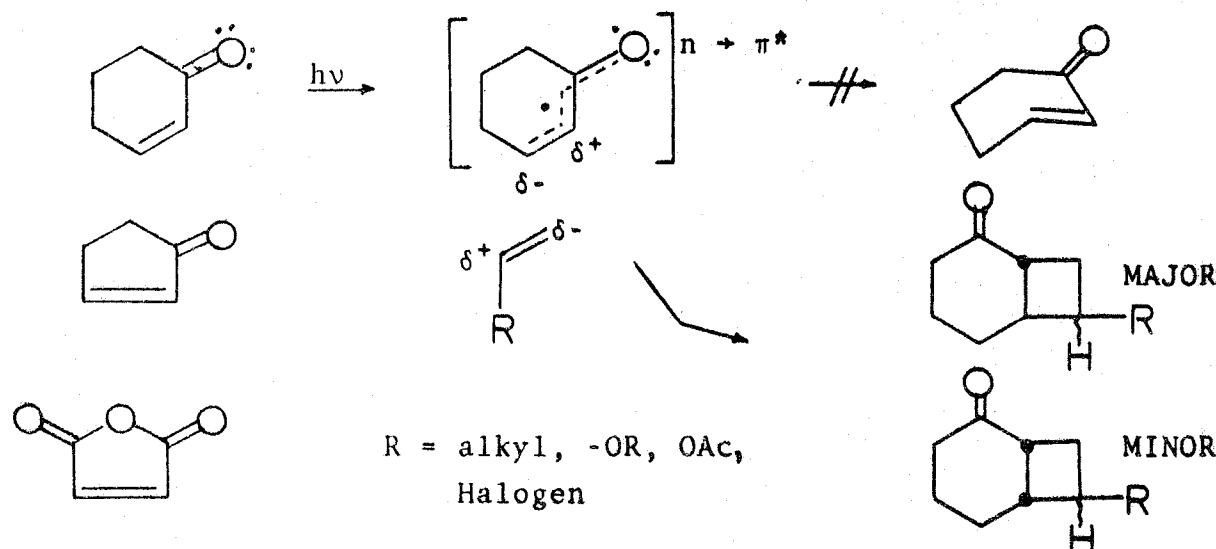
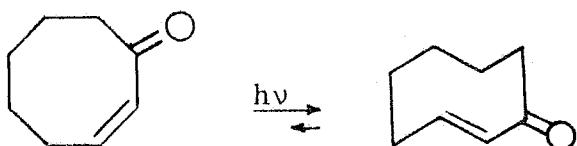
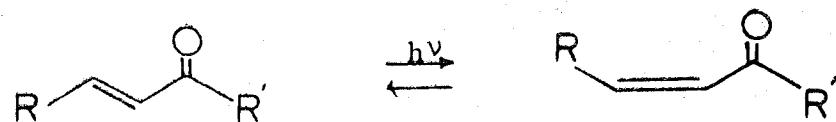
b) Cycloaddition of ketenes and haloketenes.



Reference

W. T. Brady and E. F. Hoff, Jr., J. Amer. Chem. Soc., 90, 6256 (1968).

2. Photochemical cycloadditions.



R = alkyl, -OR, OAc,
Halogen

References

B. D. Challand, H. Hikino, G. Kornis, G. Lange and P. DeMayo, J. Org. Chem., 34, 794 (1969).

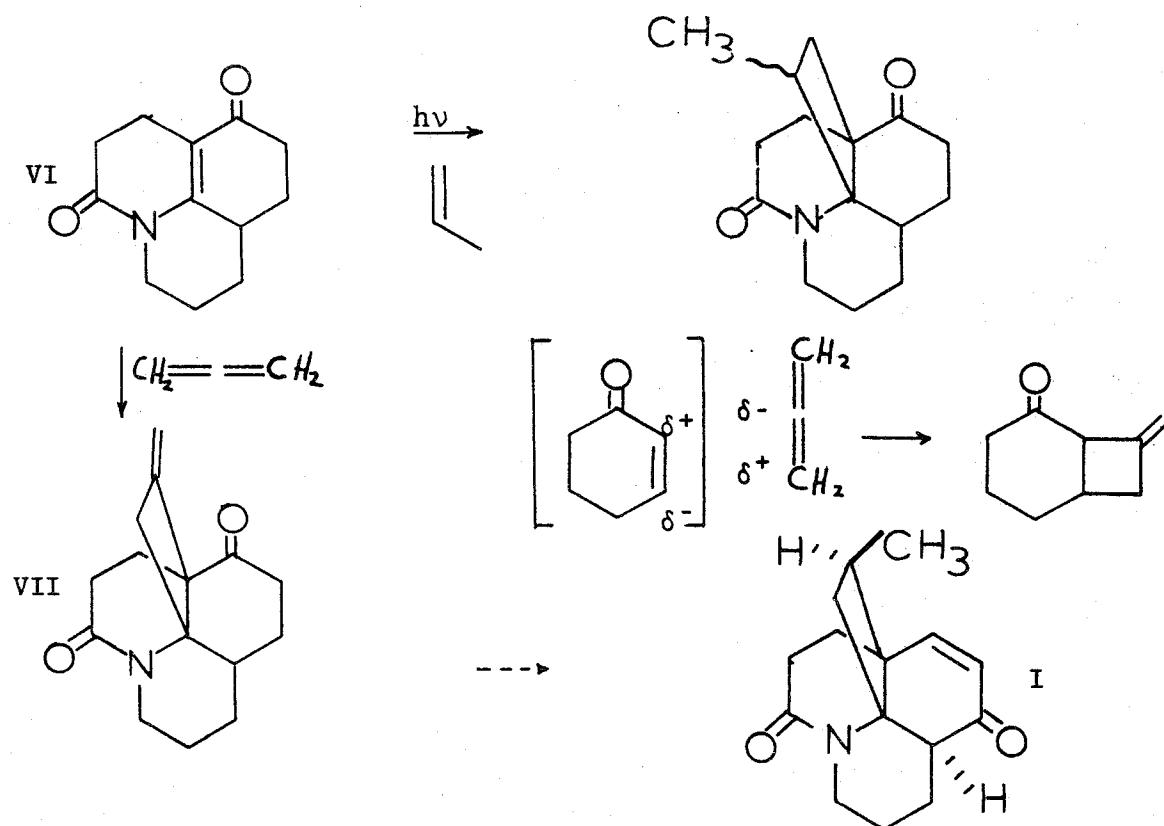
E. J. Corey, J. D. Bass, R. Lemahieu and R. B. Mitra, J. Amer. Chem. Soc., 86, 5570 (1964).

W. L. Dilling, Chem. Rev., 69, 845 (1969).

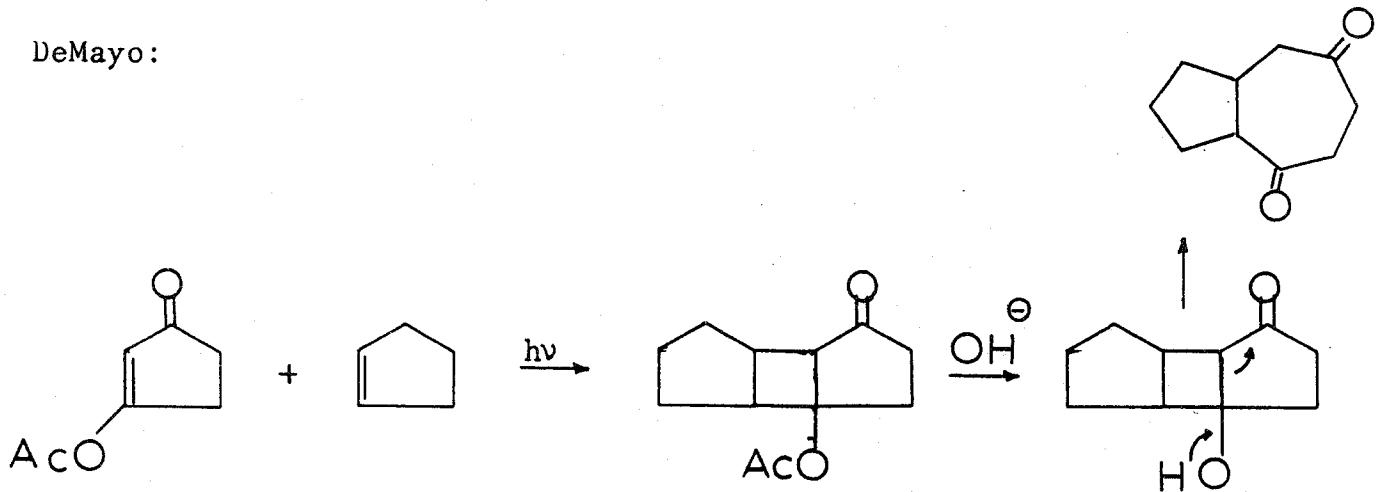
N. J. Turro in "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 8.

3. Miscellaneous methods: intramolecular alkylation, ring contraction, acyloin condensation discussed in sections I & IV.

4. Choice of a synthetic precursor to the tetracyclic skeleton.

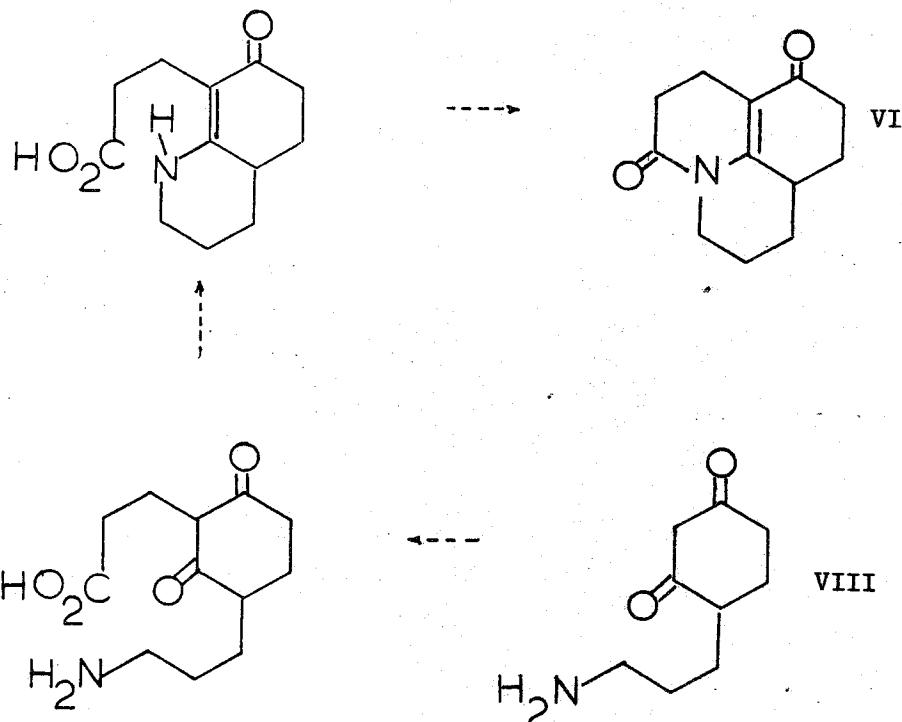


DeMayo:

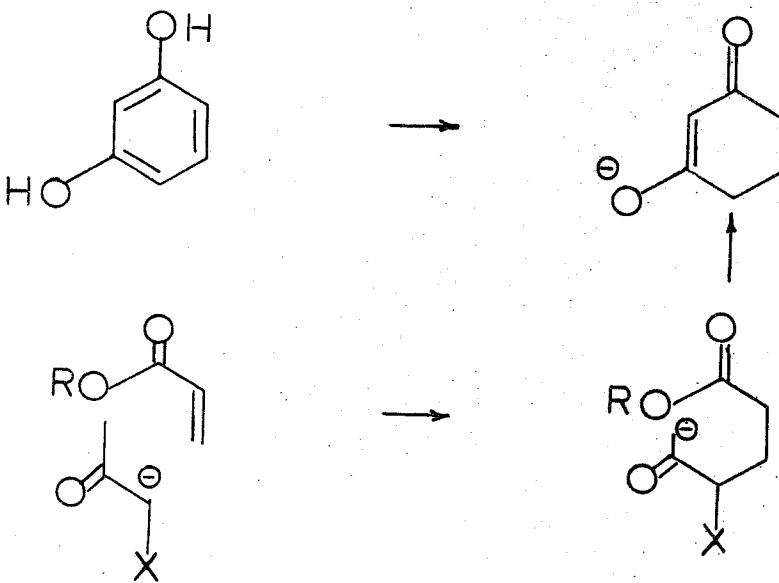


C. Synthesis of the tricyclic backbone.

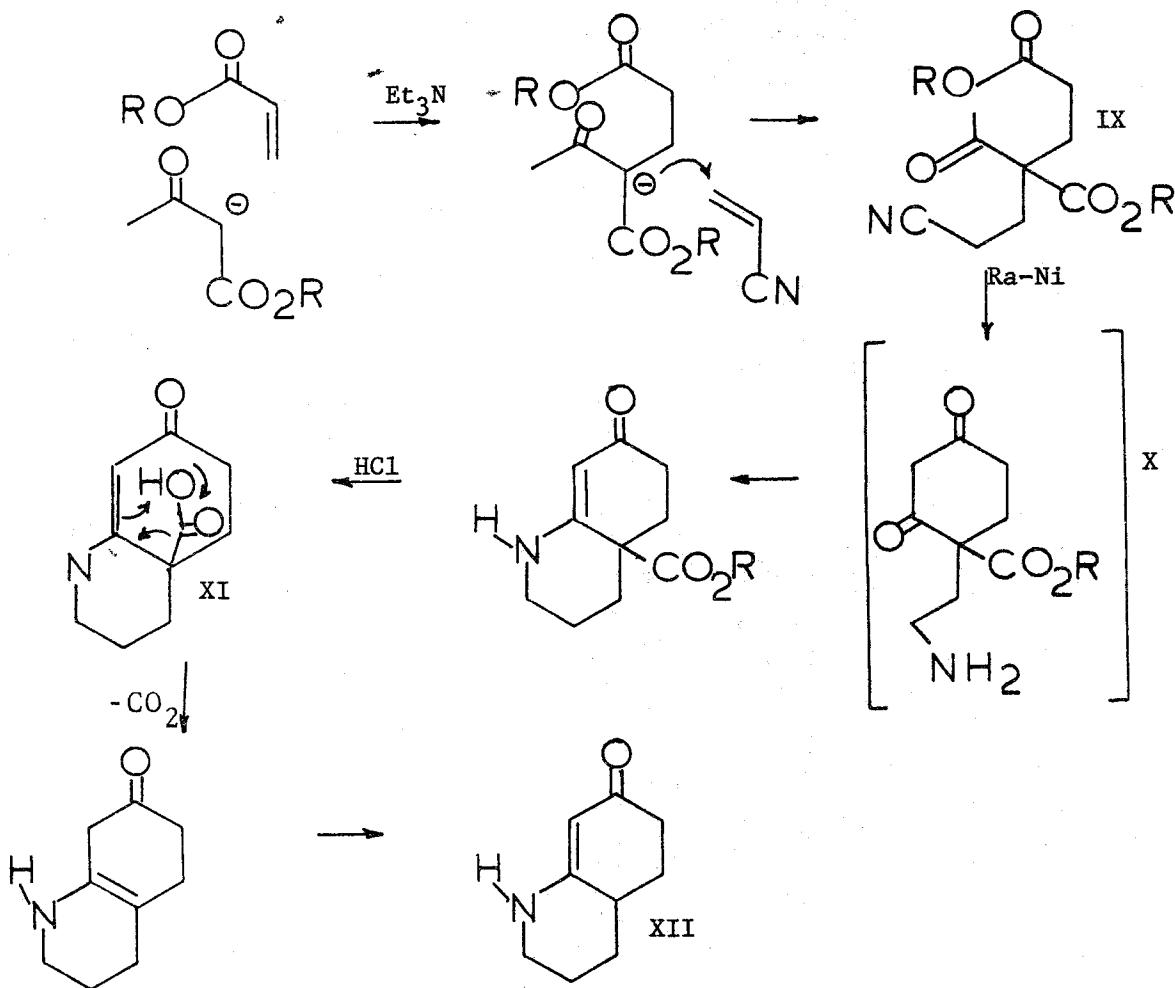
1. Analysis; dissection at bonds which are easily made or broken



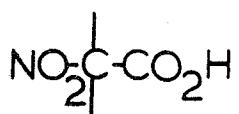
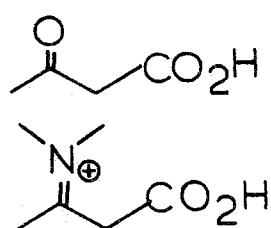
2. Synthesis of cyclohexane 1,3-diones



3. The bicyclic unit



Other facile decarboxylations:
In general, $\text{R}-\text{CO}_2\text{H}$ where R can accept a pair of electrons.



4. Properties of Enamines

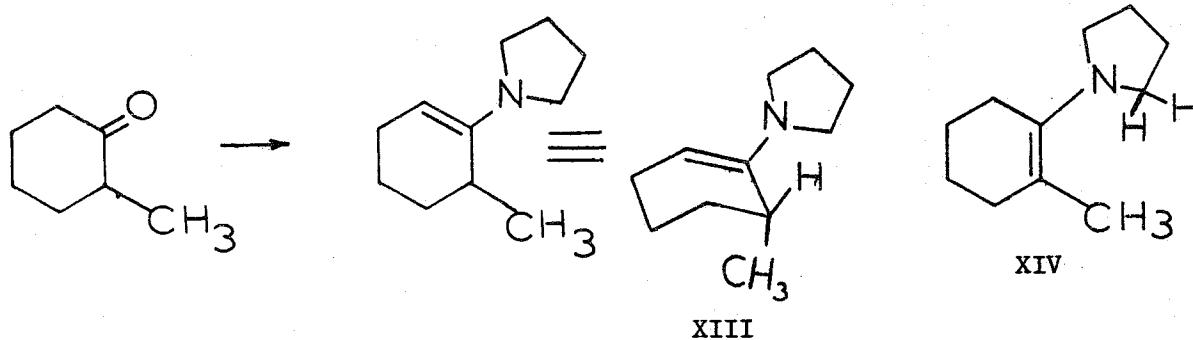
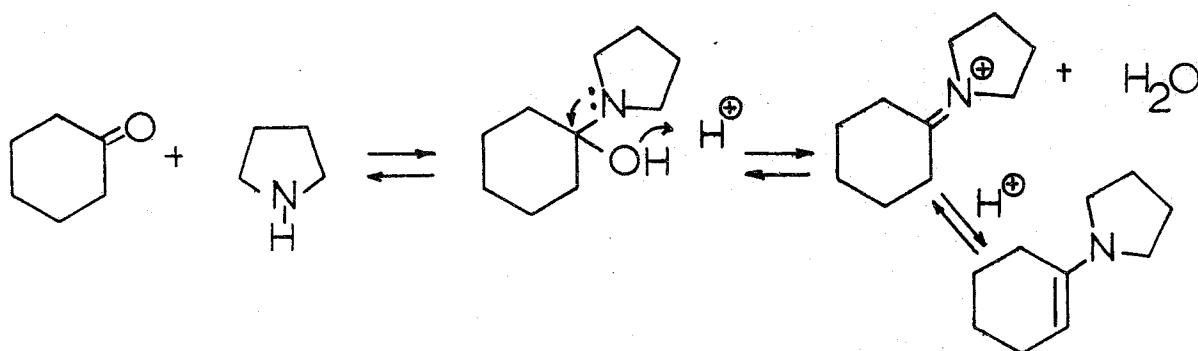
References

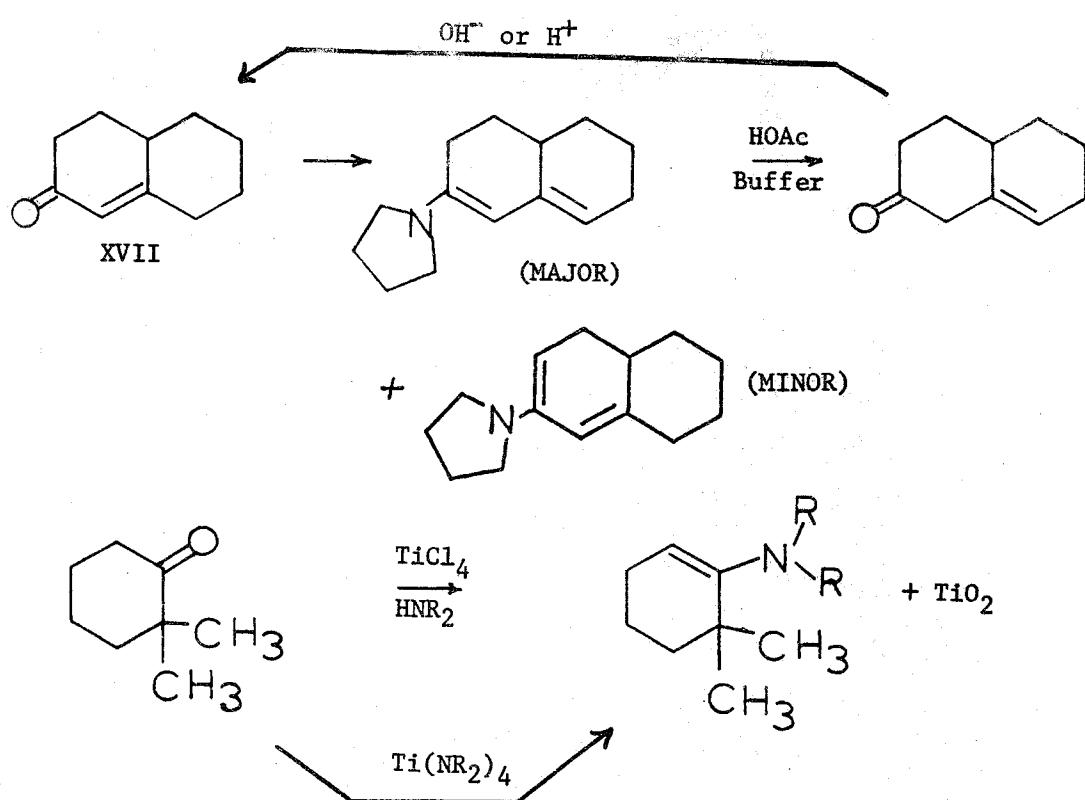
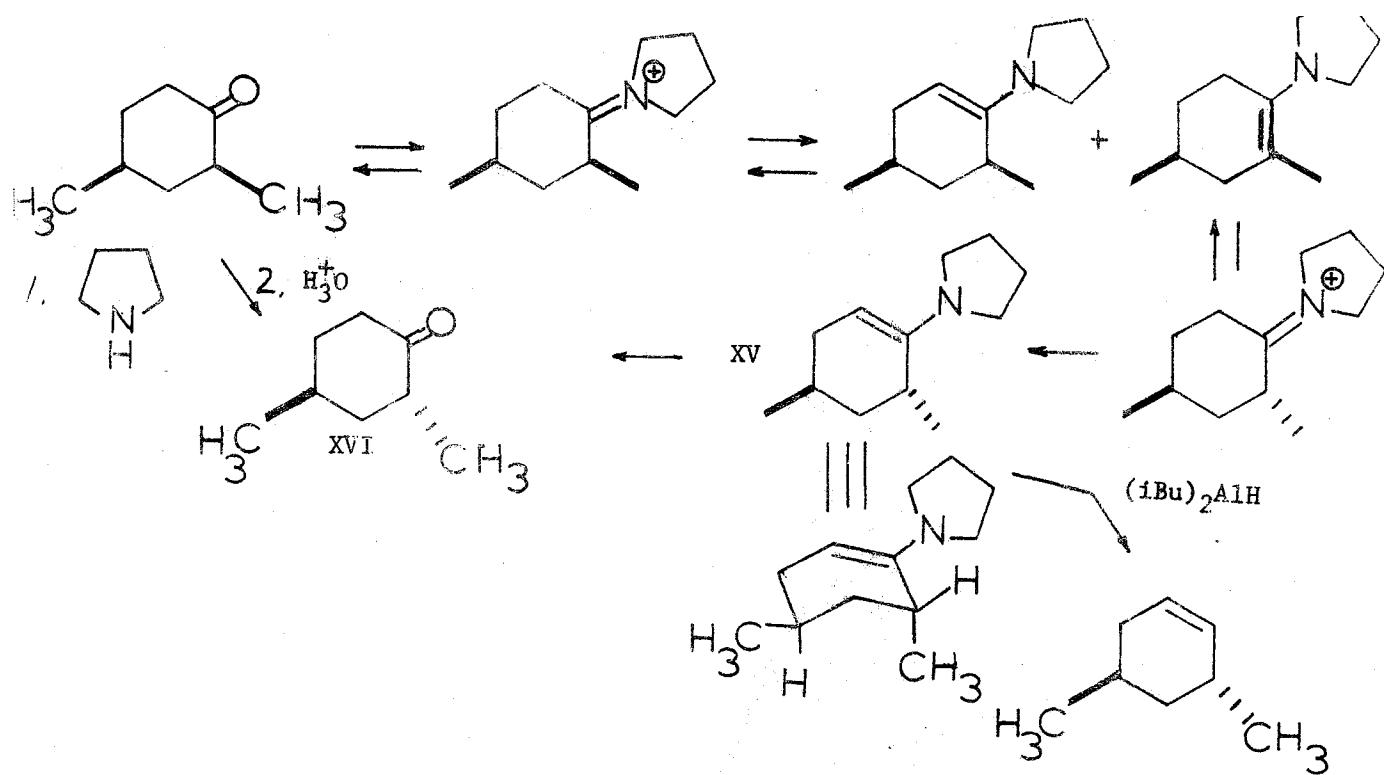
Advan. Org. Chem. M., 4, 1-113 (1963).

A. G. Cook, Ed., "Synthesis, Structure and Reactions,"
Marcel Dekker, Inc., New York, N. Y., 1969.

M. E. Kuehne and T. Garbacik, J. Org. Chem., 35, 1555
(1970).

a) Preparation and structure





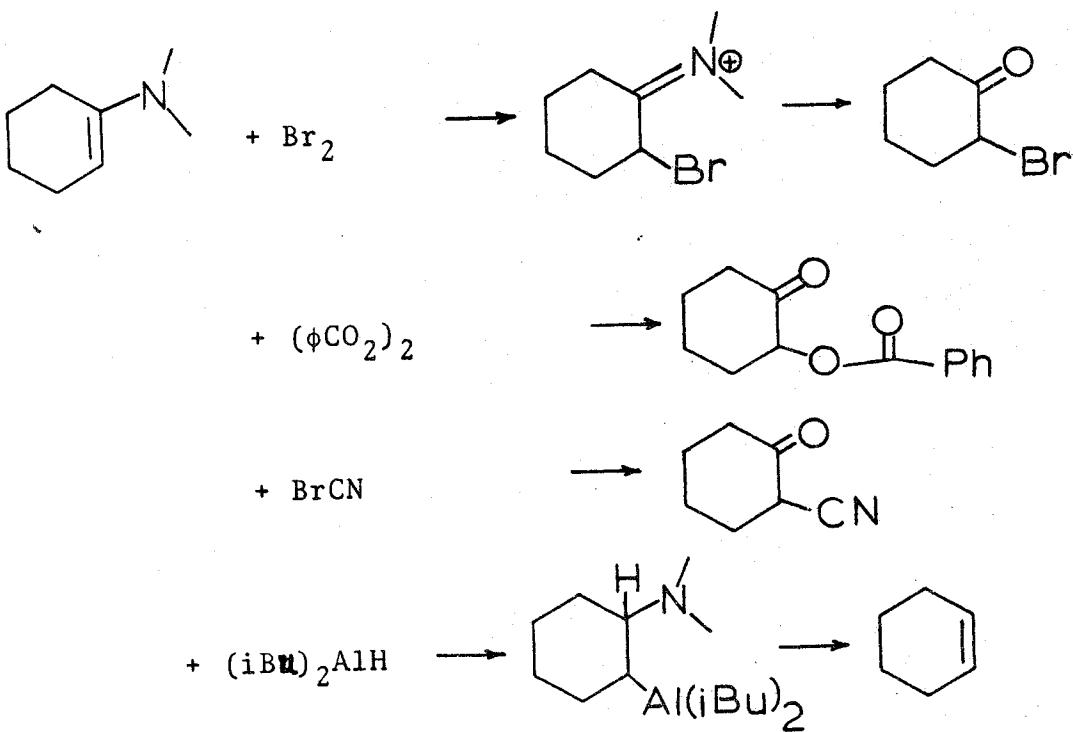
References

F. Johnson and A. Whitehead, Tetrahedron Lett., 3825 (1964).

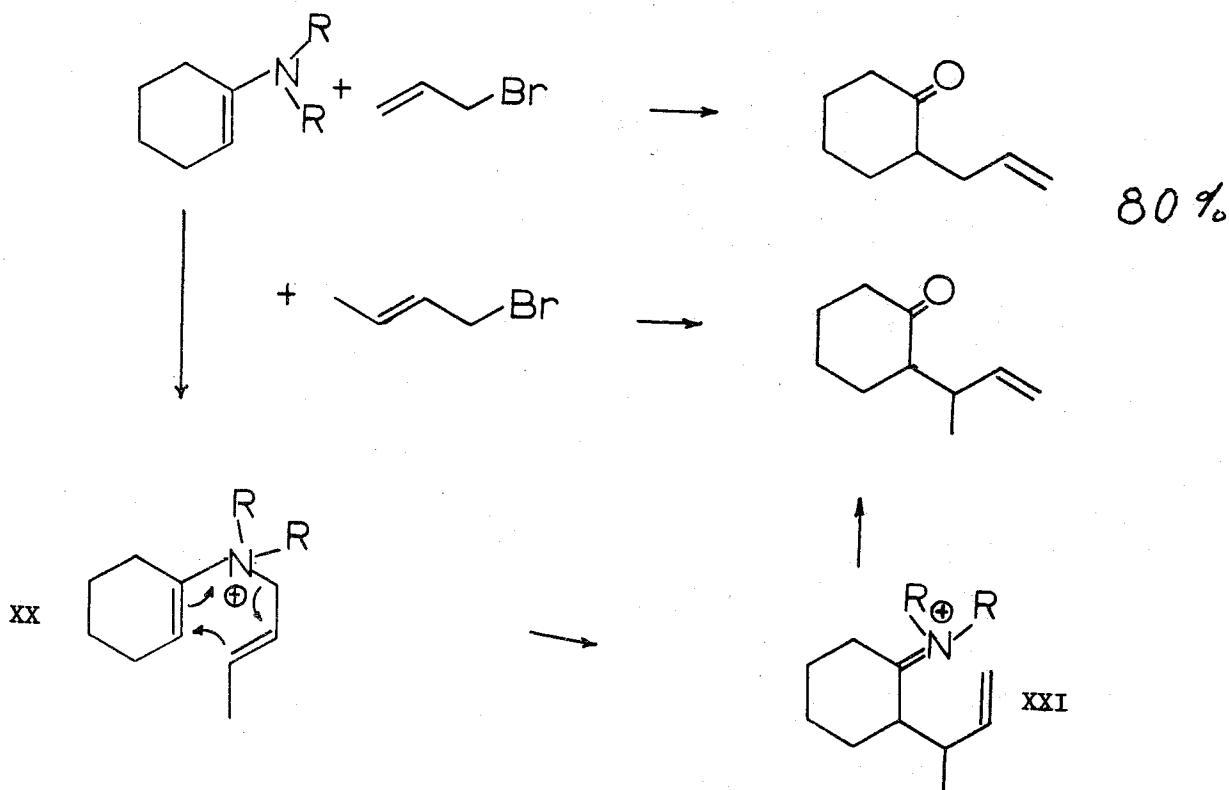
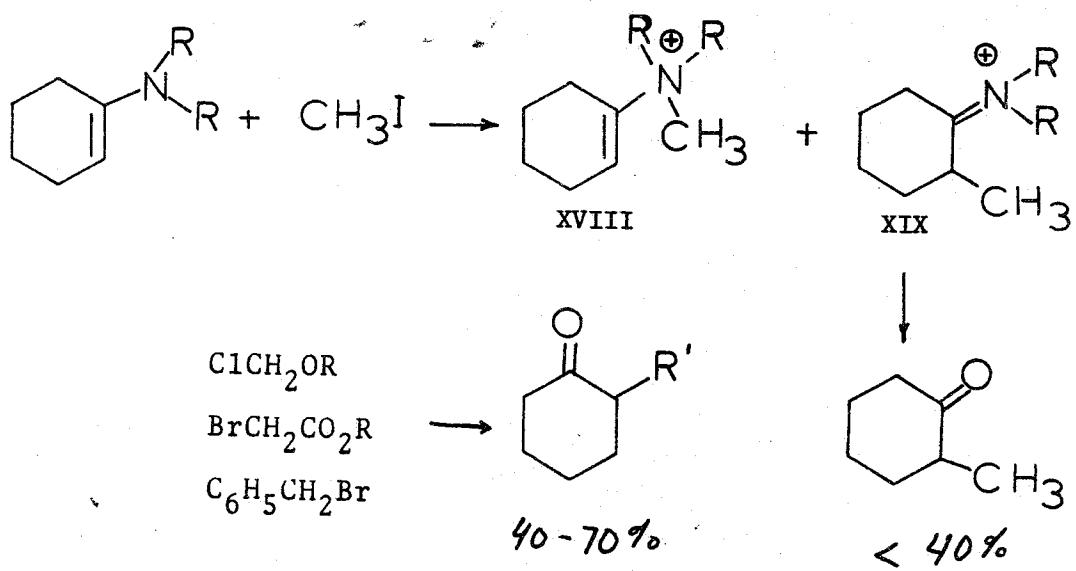
G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovics and R. Terrell, J. Amer. Chem. Soc., 85, 207 (1963).

W. A. White and H. Weingarten, J. Org. Chem., 32, 213 (1967).

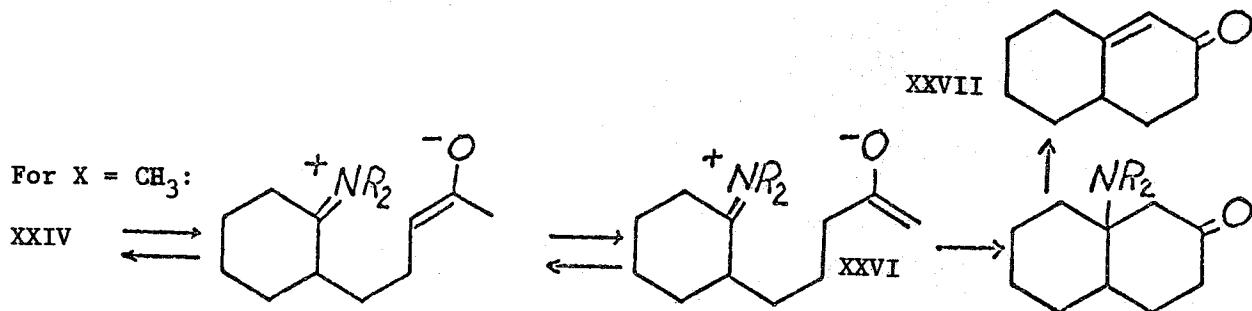
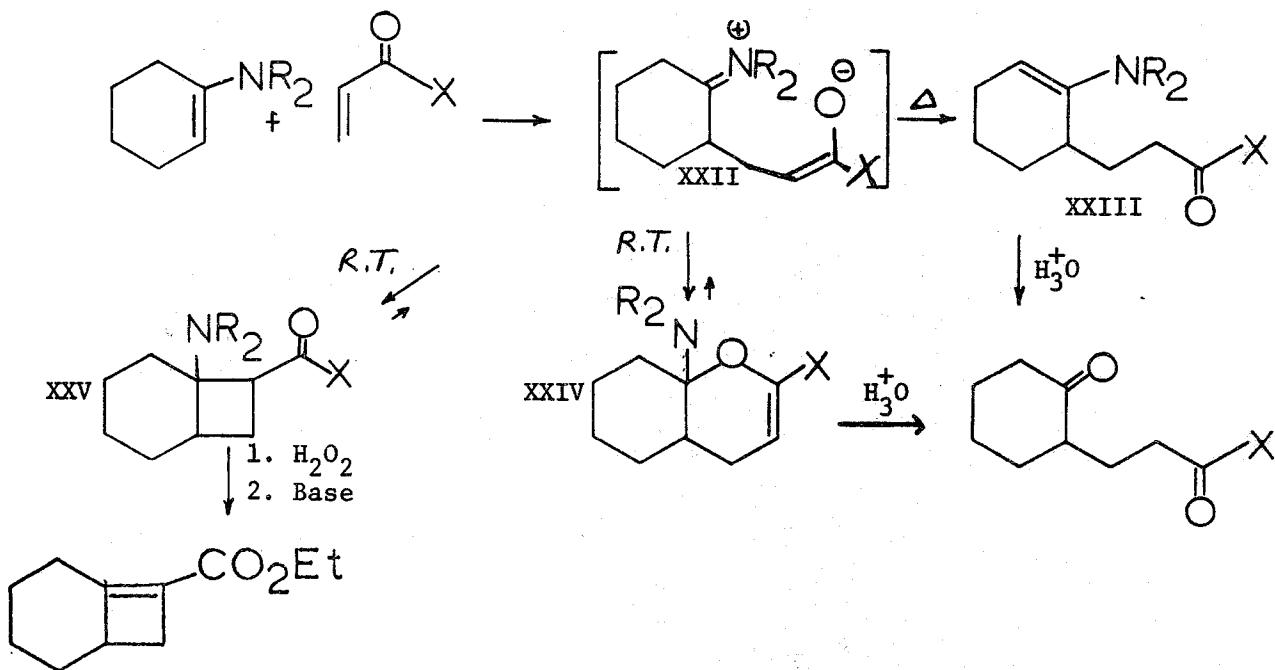
b) Reactions with heteroatom electrophiles (A. G. Cook, etc)

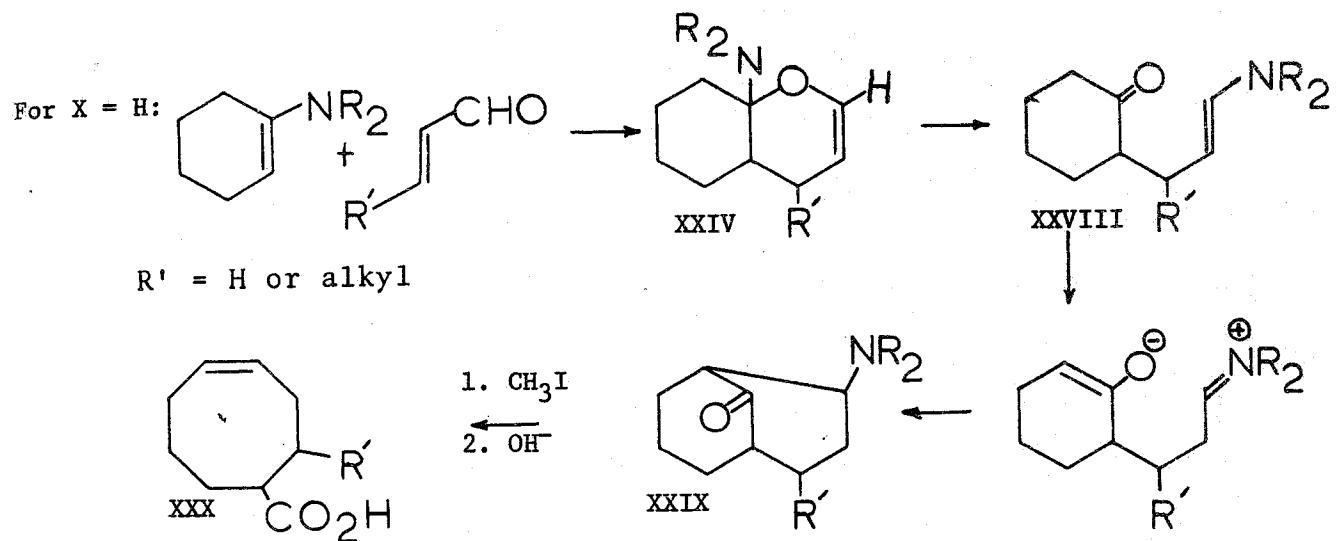


c) Reactions with alkyl halides (Stork)



d) Reactions with conjugated carbonyls



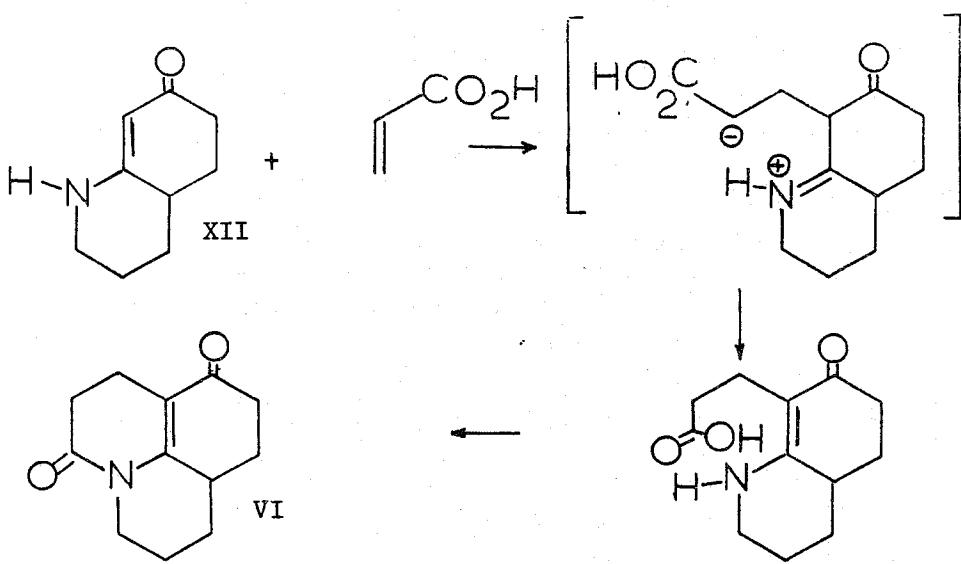


References

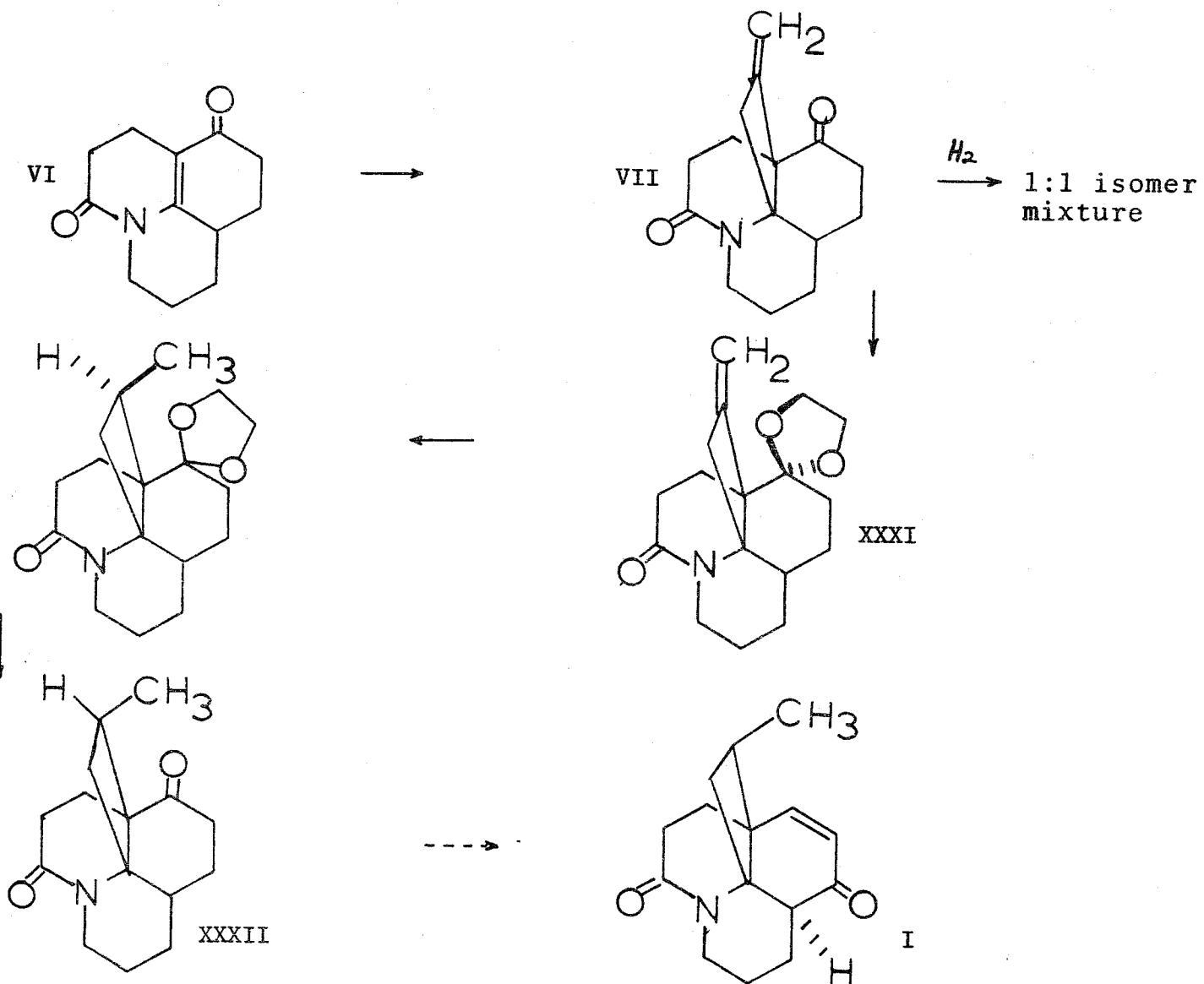
K. C. Brannock, et al., J. Org. Chem., 29, 801, 813, 818 (1964).

H. O. House in "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 212.

5. Completion of tricyclic backbone

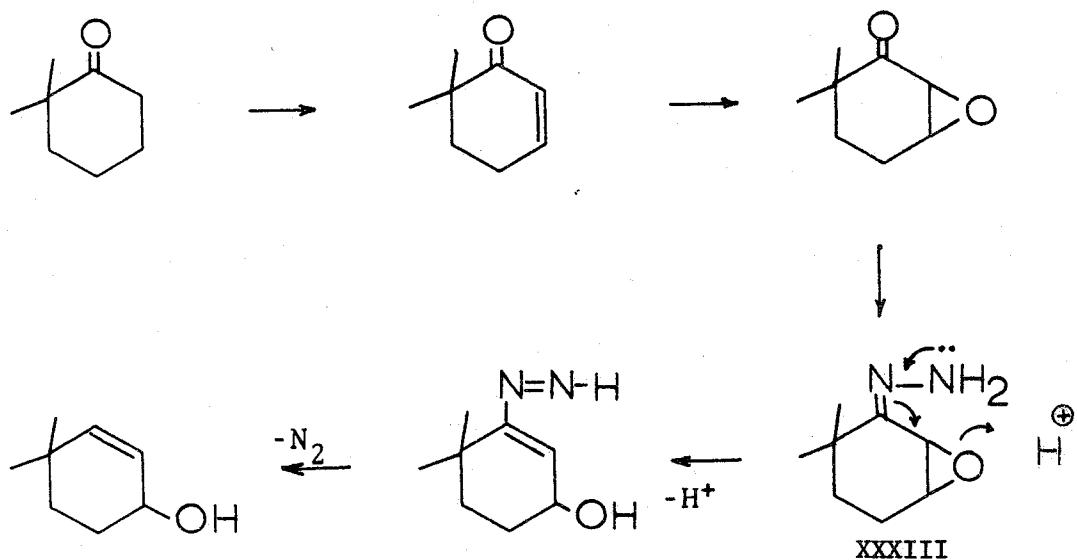


D. The tetracyclic skeleton; stereochemical control.



E. The oxidation pattern

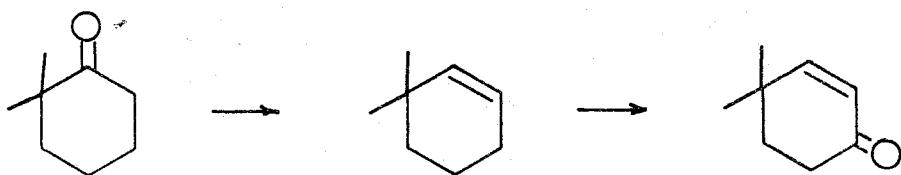
1.



Reference

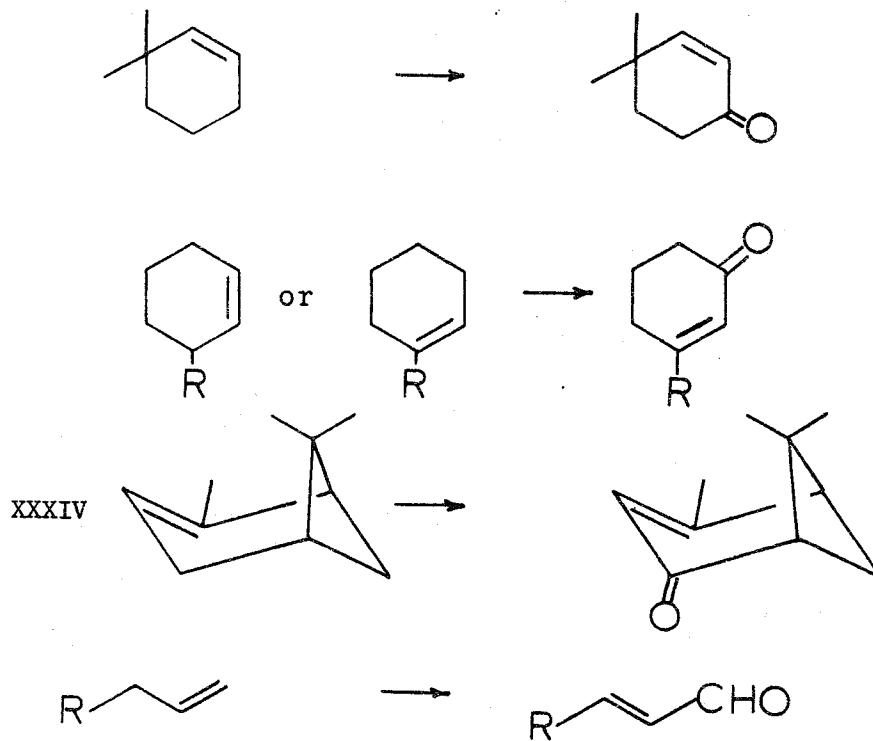
P. S. Wharton and D. H. Bohlen, J. Org. Chem., 26, 3615
(1961).

2.



a) Preparation of olefins; discussed in Section I.

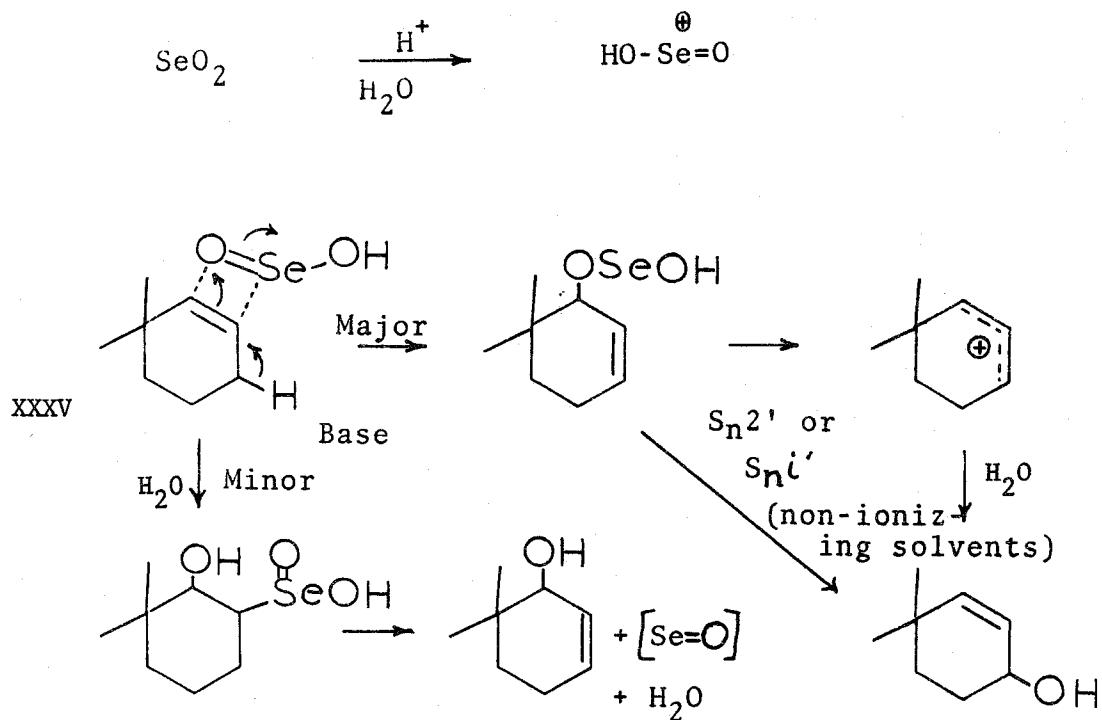
b) Allylic oxidation with $\text{CrO}_3(\text{pyridine})_2$ in CH_2Cl_2



Reference

W. G. Dauben, M. Lorber and D. S. Fullerton, J. Org. Chem., 34, 3587 (1969).

c) Allylic oxidation with SeO_2 .

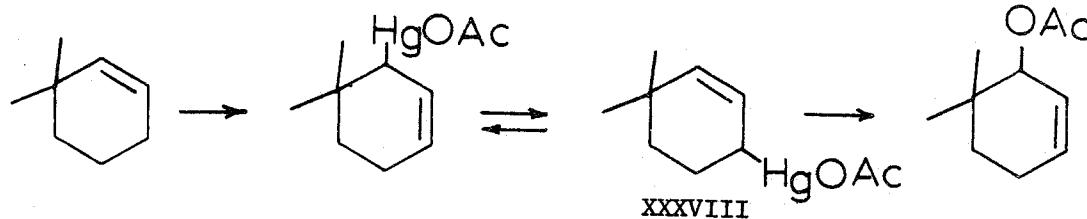
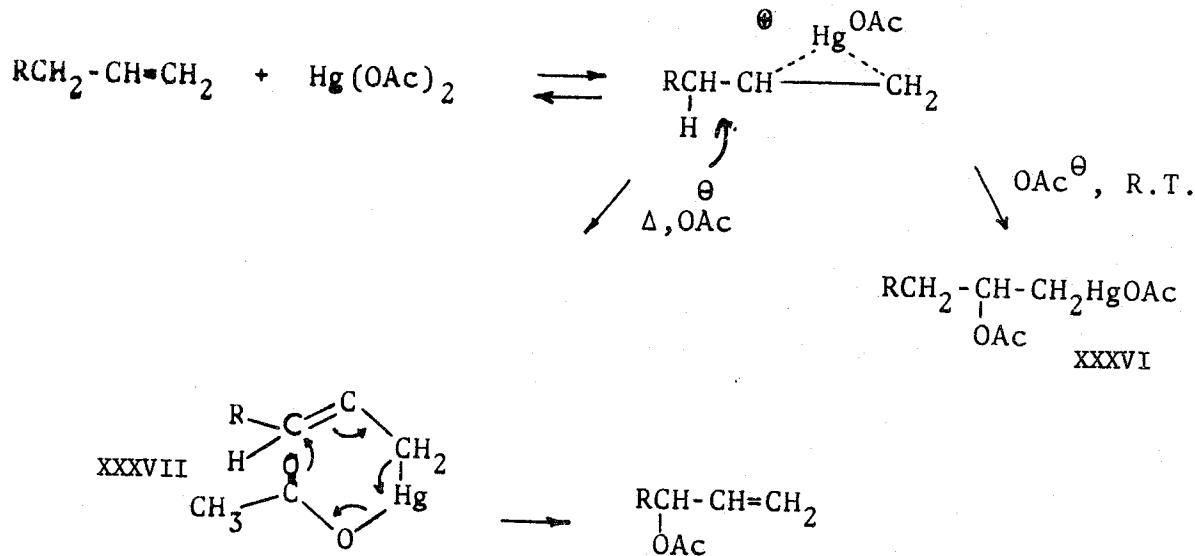


References

N. Rabjohn, Org. React., 5, 331 (1949).

E. N. Trachtenberg, C. H. Nelson and J. R. Carver,
J. Org. Chem., 35, 1653 (1970).

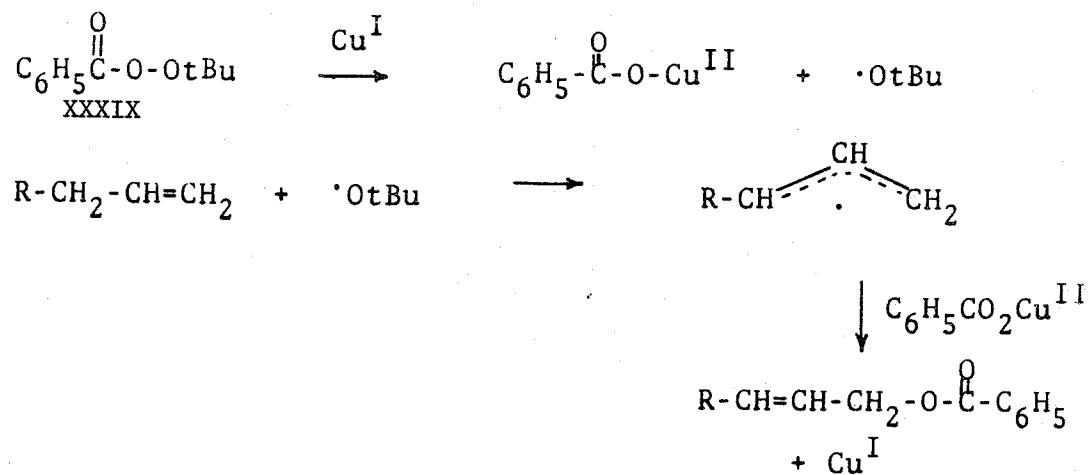
d) Allylic oxidation with Hg(OAc)_2 .



Reference

Z. Rappoport, P. D. Sleezer, S. Winstein and W. G. Young, Tetrahedron Lett., 3719 (1965).

e) t-Butyl perbenzoate oxidations.

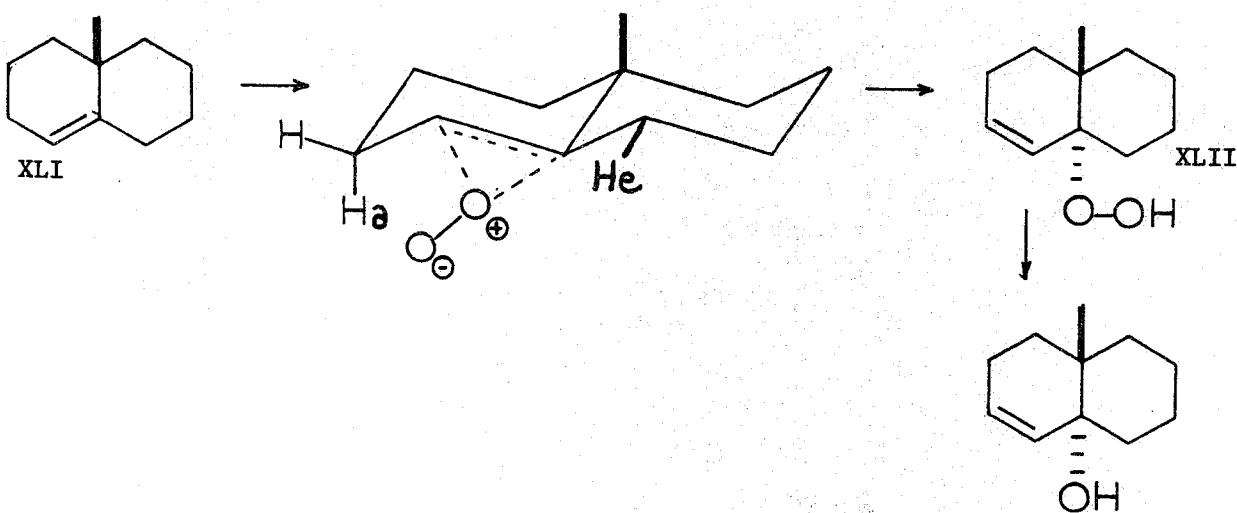
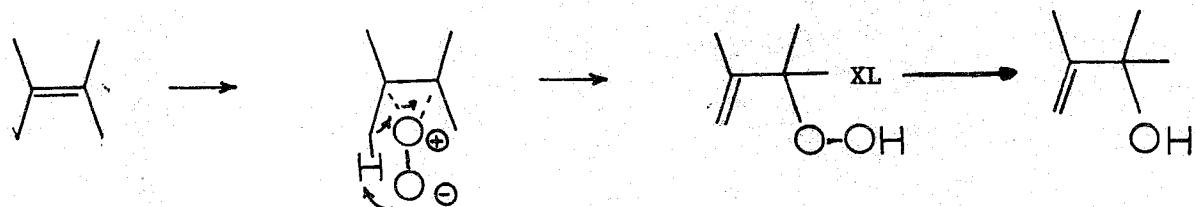
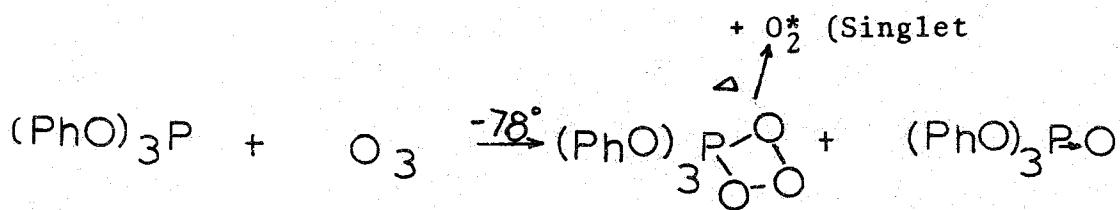
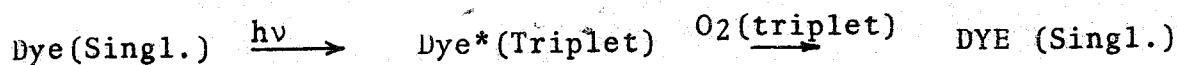


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H. L. Goering and U. Mayer, J. Amer. Chem. Soc., 86, 3753 (1964).

J. K. Kochi, J. Amer. Chem. Soc., 84, 774 (1962).

f) Allylic oxidation by singlet oxygen:



References

W. Fenical, D. R. Kearns and P. R. Radlick, J. Amer. Chem. Soc., 91, 7771 (1969).

R. W. Murray and M. L. Kaplan, J. Amer. Chem. Soc., 91, 5358 (1969).

A. Nickon, N. Schwartz, J. B. DiGiorgio and D. A. Widdowson, J. Org. Chem., 30, 1711 (1965).

g) Mild and selective oxidants; alcohol \longrightarrow aldehyde or ketone

1) $\text{CrO}_3(\text{pyridine})_2/\text{CH}_2\text{Cl}_2$

Reference

J. C. Collins, W. W. Hess and T. J. Frank, Tetrahedron Lett., 3373 (1968).

2) N-chlorobenzotriazole

Reference

C. W. Rees and R. C. Storr, J. Chem. Soc., C., 1474, 1478 (1969).

3) active MnO_2

Reference

L. Crombie and J. Crossley, J. Chem. Soc., 4983 (1963).

4) azodicarboxylate derivatives

Reference

R. C. Cookson, I. D. R. Stevens and C. T. Watts, Chem. Commun., 754 (1966).

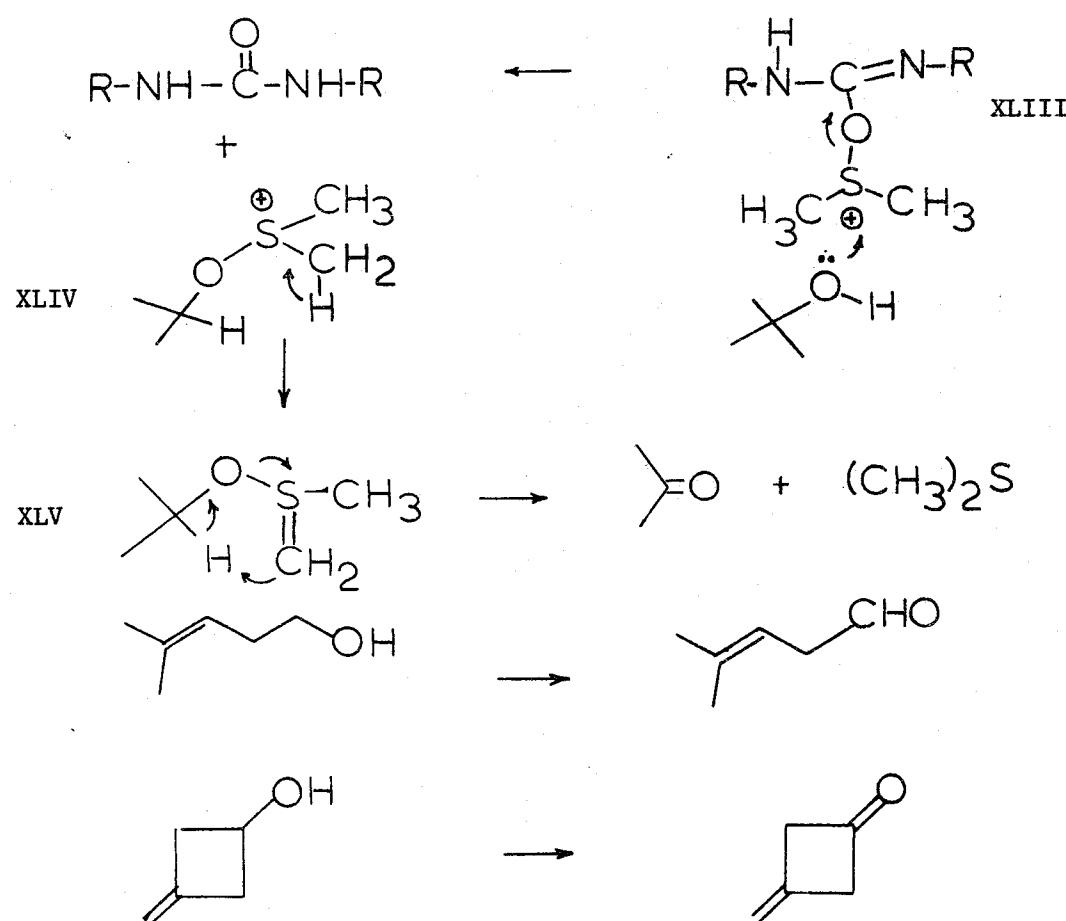
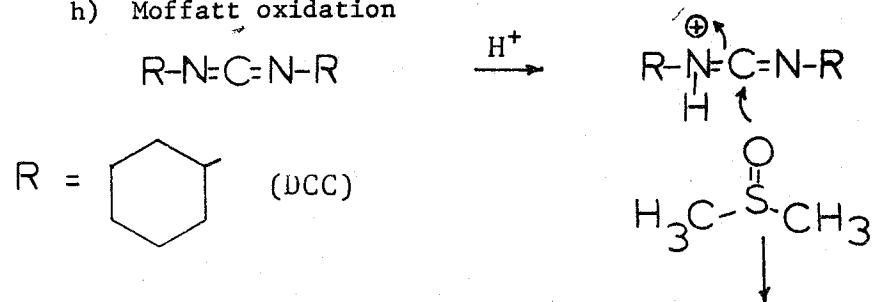
5) silvercarbonate/celite

References

M. Fetizon, M. Golfier, C. R. Acad. Sci. Paris, Ser. C, 267, 900 (1968).

M. Fetizon, M. Golfier and J. M. Tours, Chem. Commun., 1102, 1118 (1969).

h) Moffatt oxidation

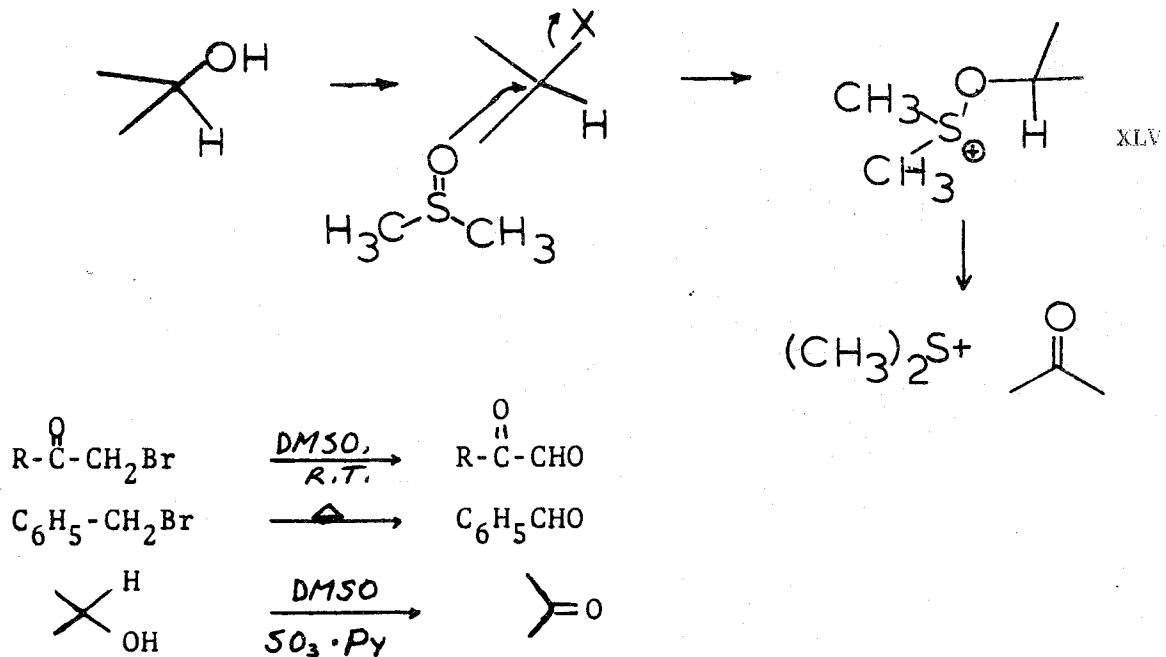


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J. D. Albright and L. Goldman, J. Amer. Chem. Soc., 89, 2416 (1967).

A. H. Fenselau and J. G. Moffatt, J. Amer. Chem. Soc., 88, 1762 (1966).

i) Kornblum Oxidations

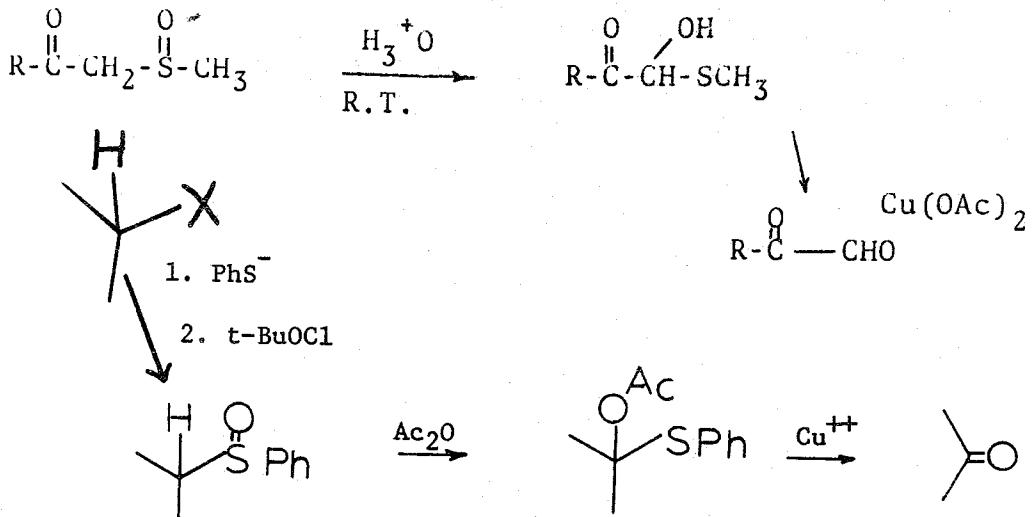


References

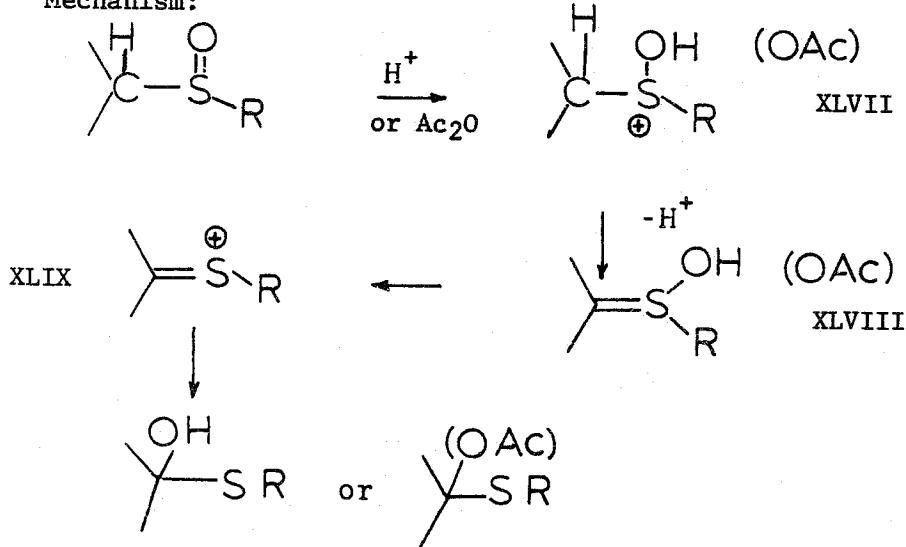
N. Kornblum, et al., J. Amer. Chem. Soc., 79, 6562 (1957); ibid., 81, 4113 (1959).

J. R. Parikh and W. E. Doering, J. Amer. Chem. Soc., 89, 5505 (1967).

j) Pummerer Rearrangement



Mechanism:



References

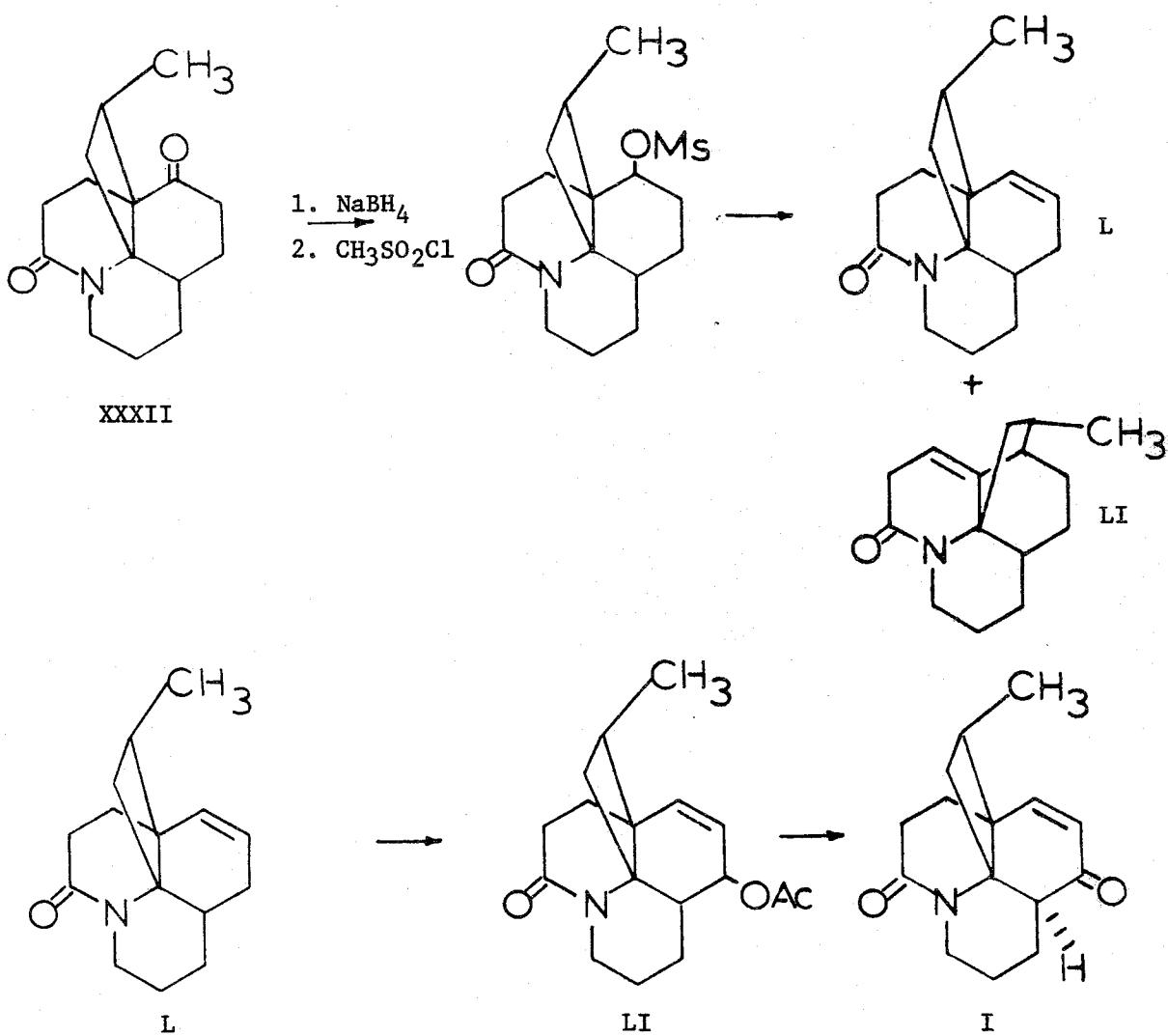
C. R. Johnson and W. G. Phillips, J. Amer. Chem. Soc., 91, 682 (1969).

W. D. Kingsbury and C. R. Johnson, Chem. Commun., 365 (1969).

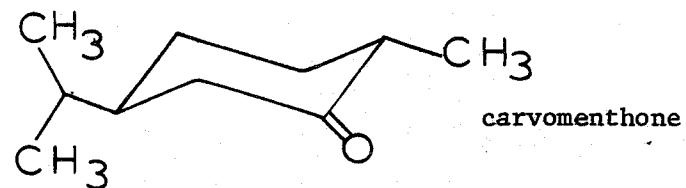
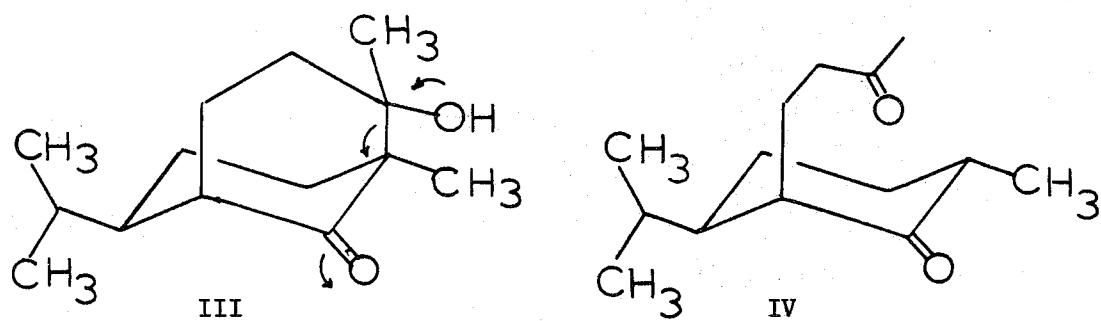
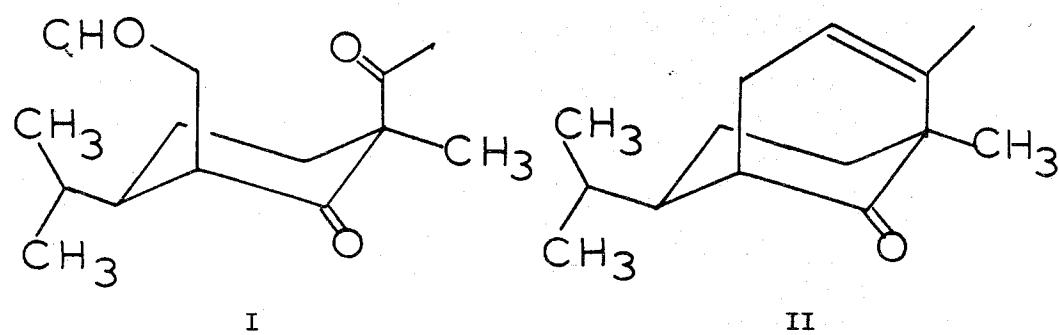
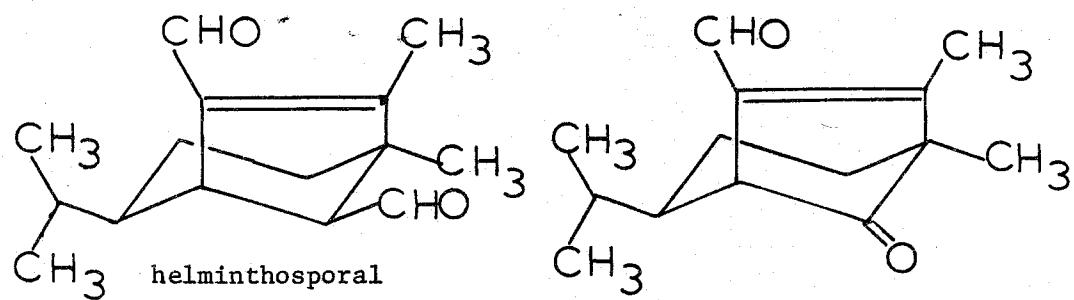
W. E. Parham and L. D. Edwards, J. Org. Chem., 33, 4150 (1968).

G. A. Russell and G. J. Mikol, J. Amer. Chem. Soc., 88, 5498 (1966).

F. Final synthetic transformations of the tetracyclic structure.



III. Synthesis of Helminthosporal

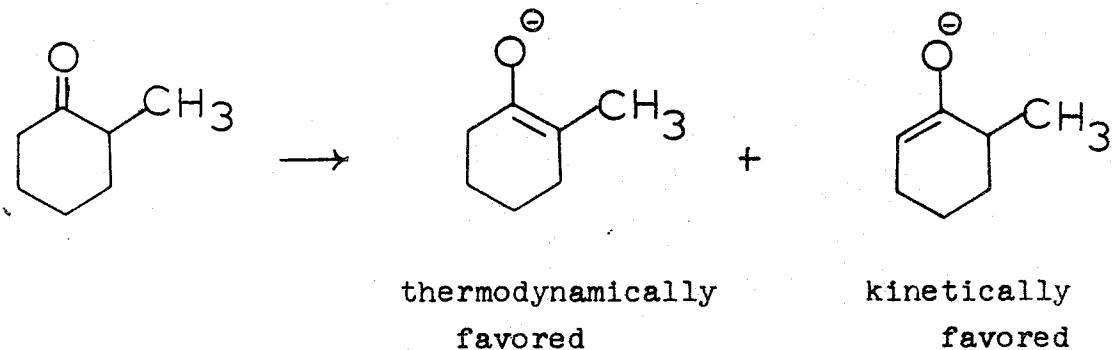


Reference

E. J. Corey and S. Nozoe, J. Amer. Chem. Soc., 87, 5728 (1965).

A. Enolization carbonyl components

1. Simple enolization



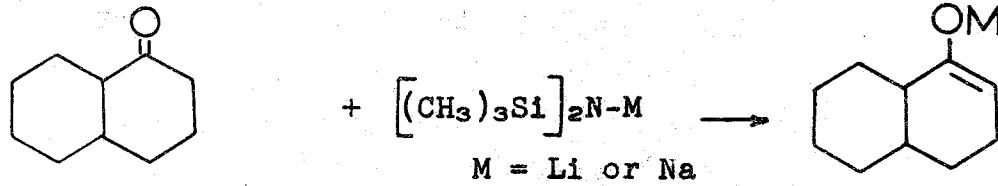
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H. O. House, Rec. Chem. Progr., 28, 99 (1967).

H. O. House and B. M. Trost, J. Org. Chem., 30, 2502 (1965).

B. J. L. Huff, F. N. Tuller and D. Caine, J. Org. Chem., 34, 3070 (1969).

2. Bistrimethylsilylamides



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- D. H. R. Barton, R. H. Hesse, G. Tarzie and M. M. Pechet, Chem. Commun., 1497 (1969).
- C. R. Krüger and E. G. Rochow, J. Organometal. Chem., 1, 476 (1964).
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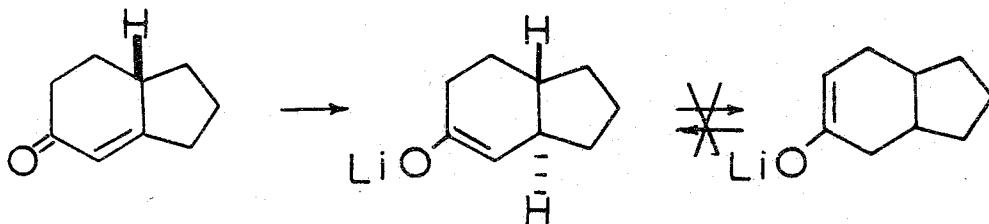
3. Sodium hydride

Reference

- S. Bank and T. A. Lois, J. Amer. Chem. Soc., 90, 4505 (1968).

B. Specific enolate (or its equivalent) generation

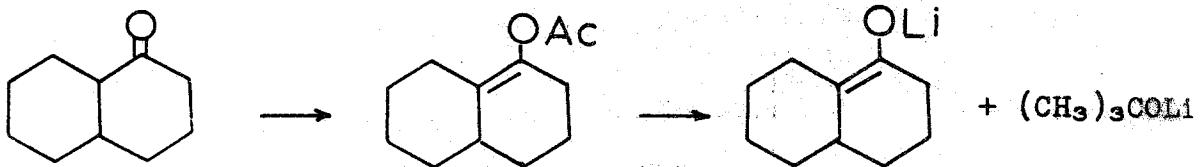
1. Reduction of enones



Reference

G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsifyi,
J. Amer. Chem. Soc., 87, 275 (1965).

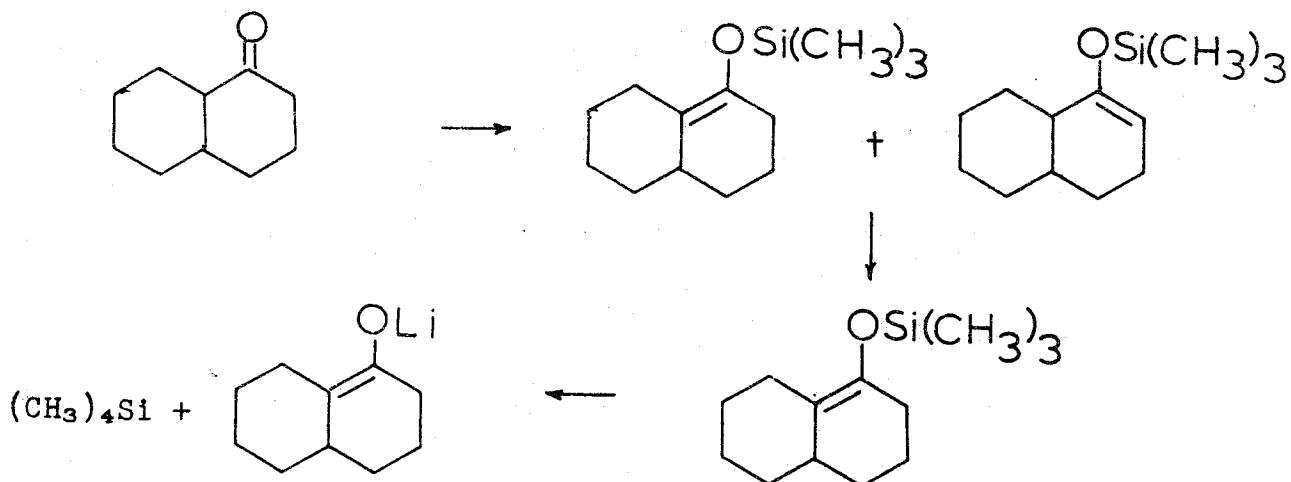
2. Enol acetates



Reference

H. O. House and B. M. Trost, J. Org. Chem., 30, 2502 (1965).

3. Enol silanes



References

H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead,
J. Org. Chem., 34, 2324 (1969).

G. Stork and P. F. Hudelik, J. Amer. Chem. Soc., 90,
4462, 4464 (1968).

4. Enamines

See previous discussion

C. Blocking groups

1. Enamine

Reference

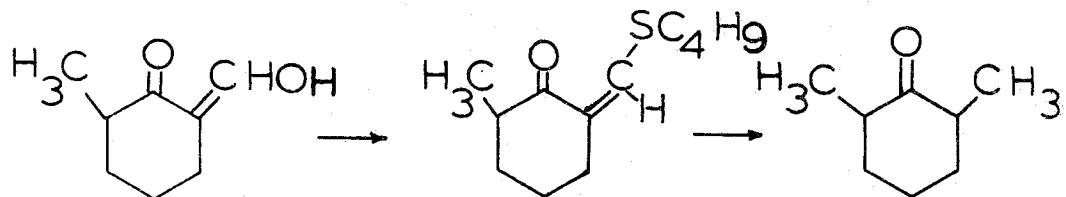
A. J. Birch and R. Robinson, J. Chem. Soc., 501 (1944).

2. Enol Ether

Reference

W. S. Johnson and H. Posvic, J. Amer. Chem. Soc., 69, 1361 (1947).

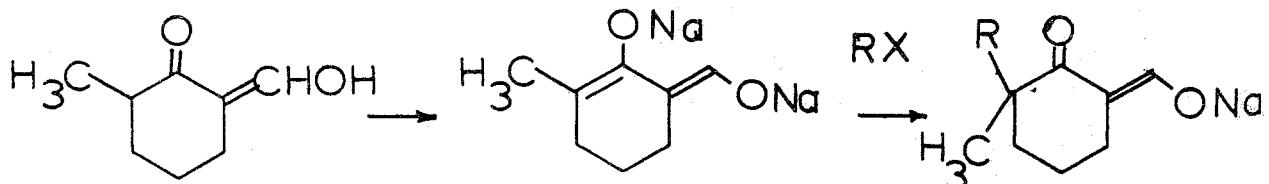
3. Enol thioether



Reference

R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1615, 1620 (1962).

4. Dianion



Reference

T. M. Harris and C. R. Hauser, J. Amer. Chem. Soc., 84, 1750 (1962).

D. Activating groups

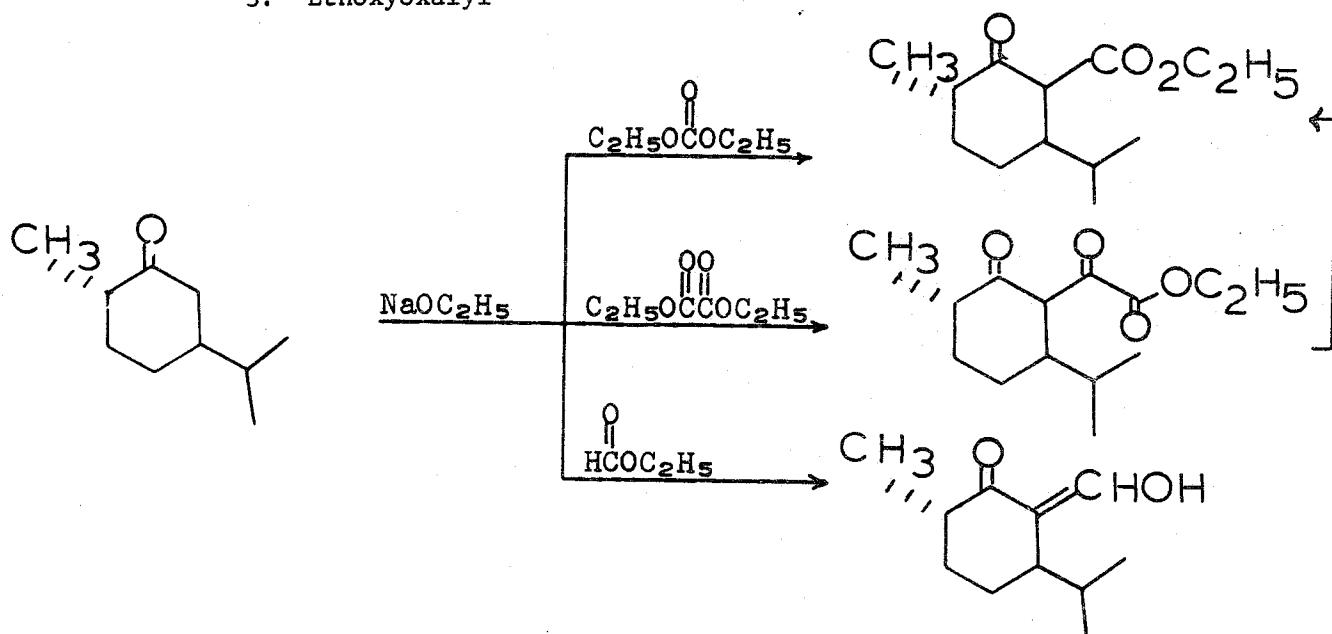
1. Formyl

Reference

R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, J. Amer. Chem. Soc., 74, 4223 (1952).

2. Carbethoxy

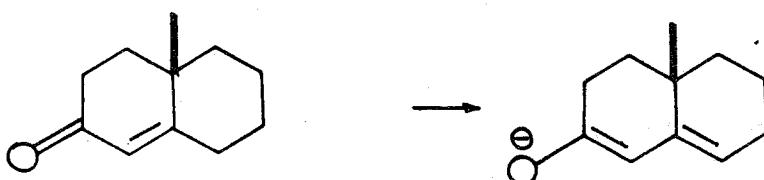
3. Ethoxycarbonyl



Reference

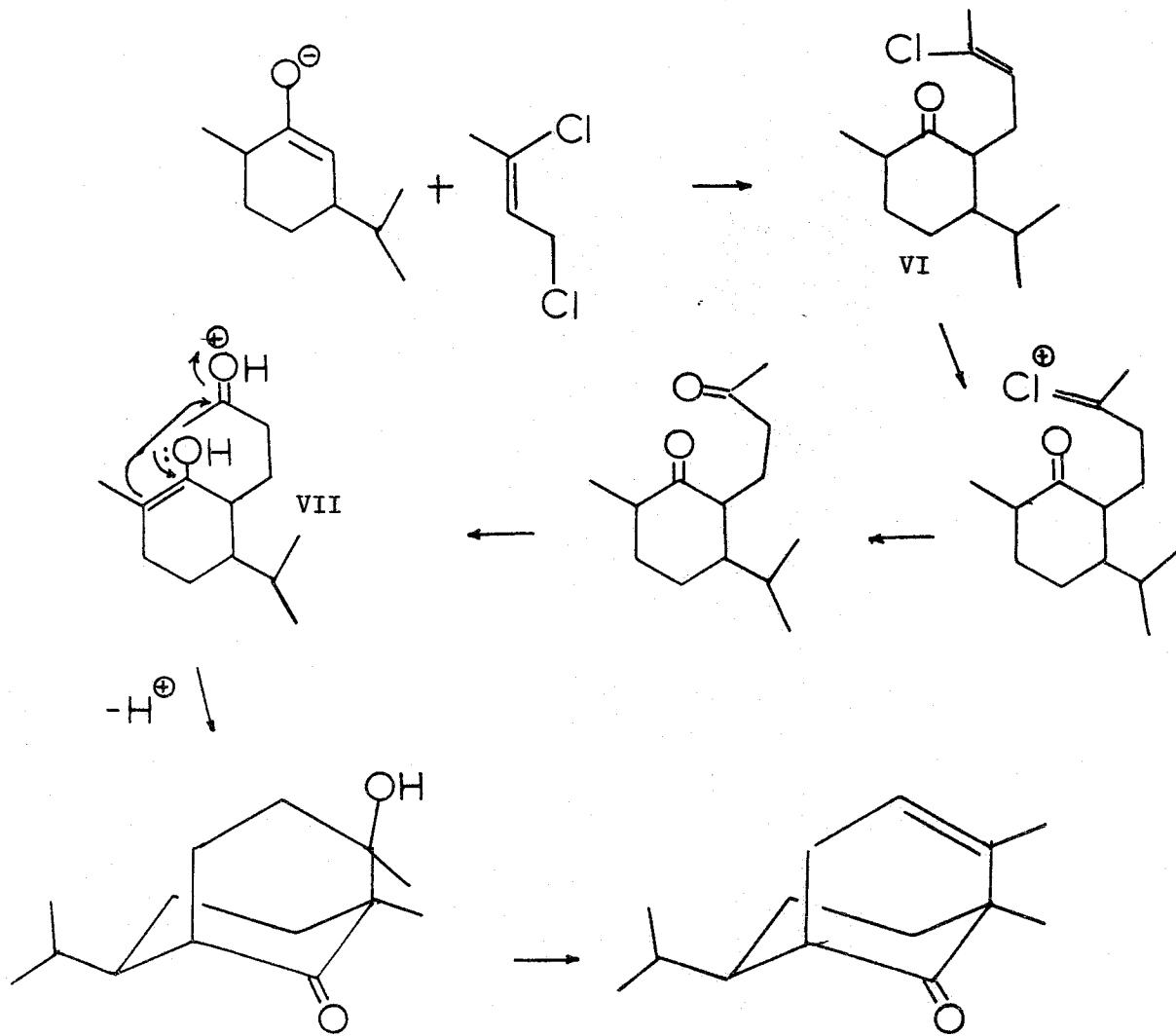
Y. Mazur and F. Sondheimer, J. Amer. Chem. Soc., 80, 5220, 6296 (1958).

4. Double bonds and phenyl rings



E. Robinson annelation procedure

1. 1,3-Dichloro-2-butene approach

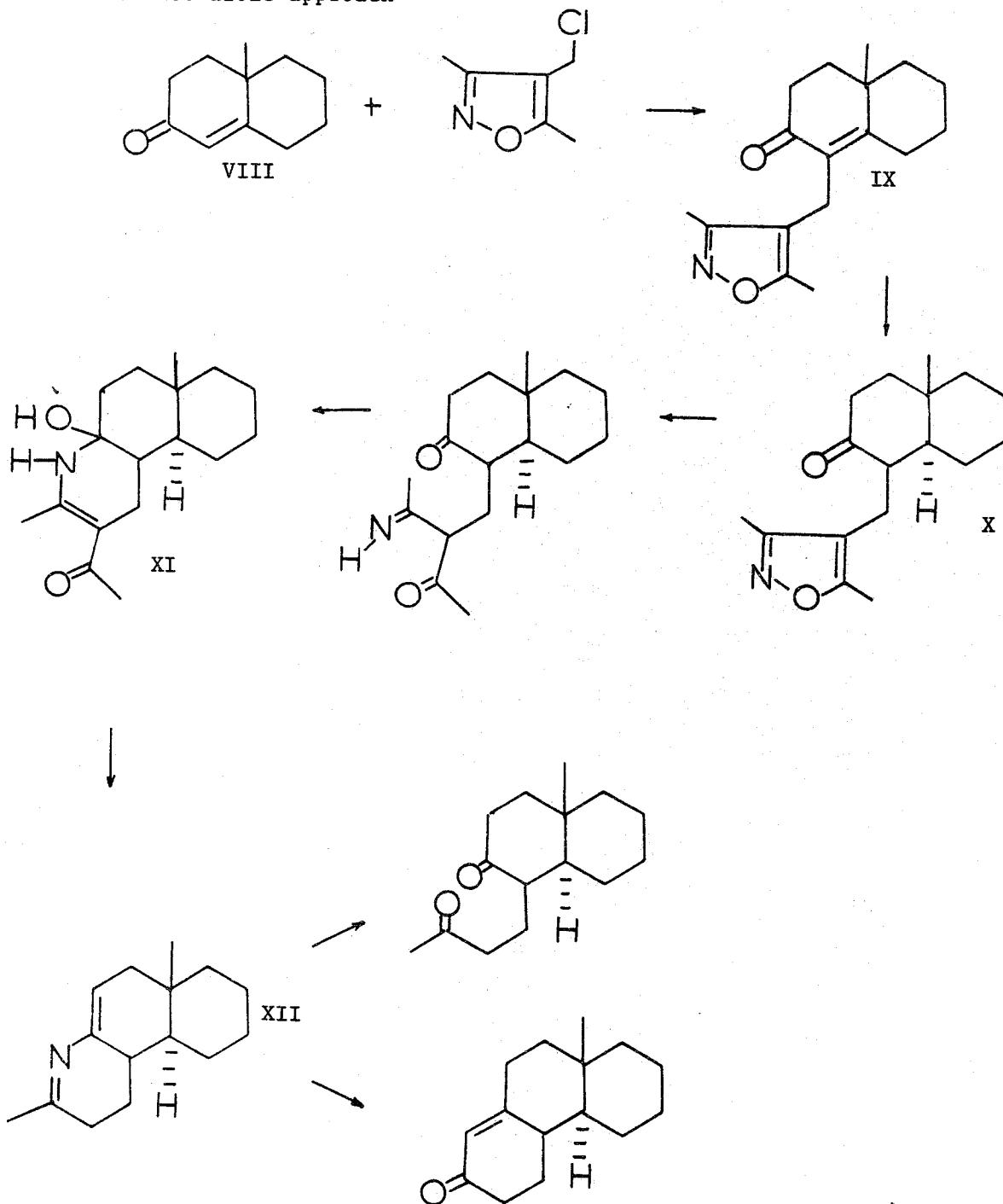


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Y. L. Chow, Tetrahedron Lett., 1337 (1964).

J. A. Marshall and J. J. Partridge, Tetrahedron, 25, 2159 (1969).

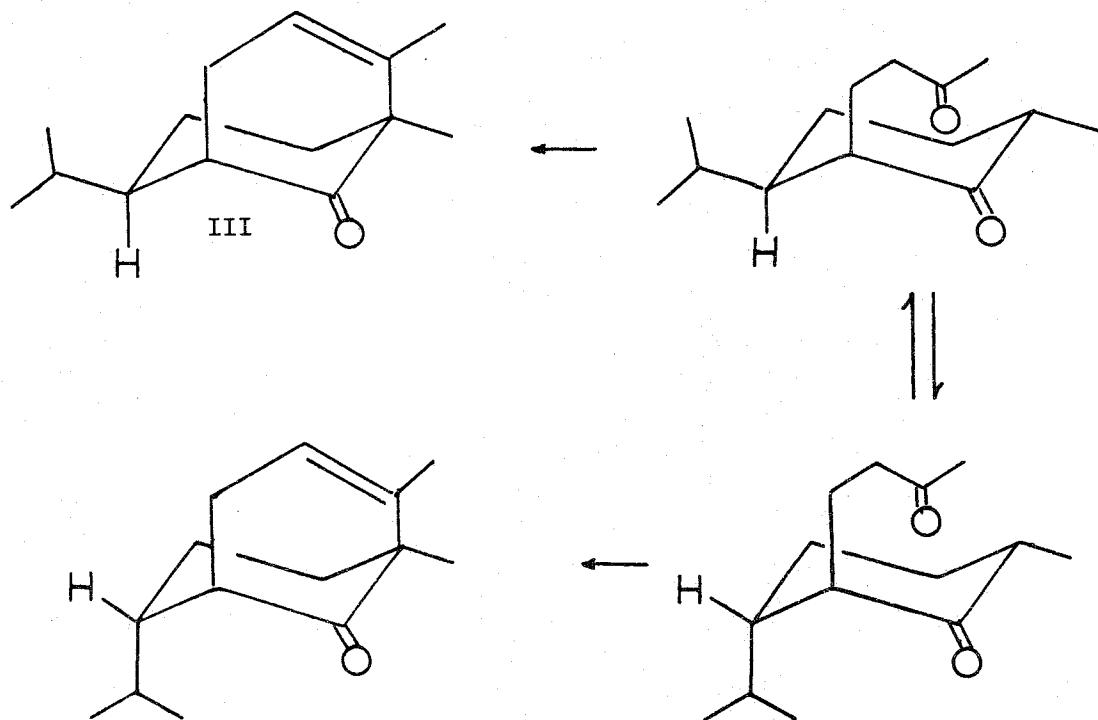
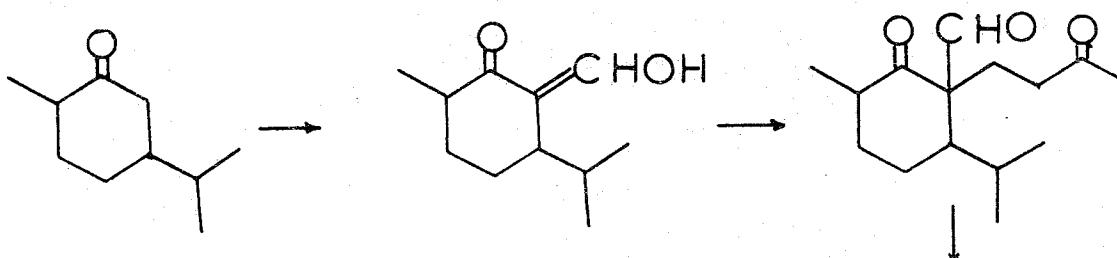
2. Isoxazole approach



References

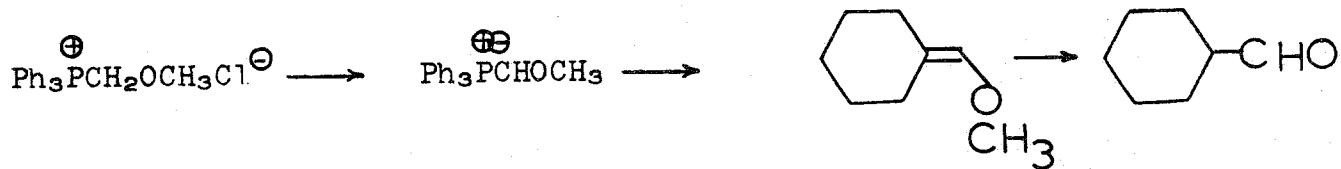
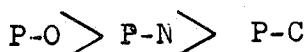
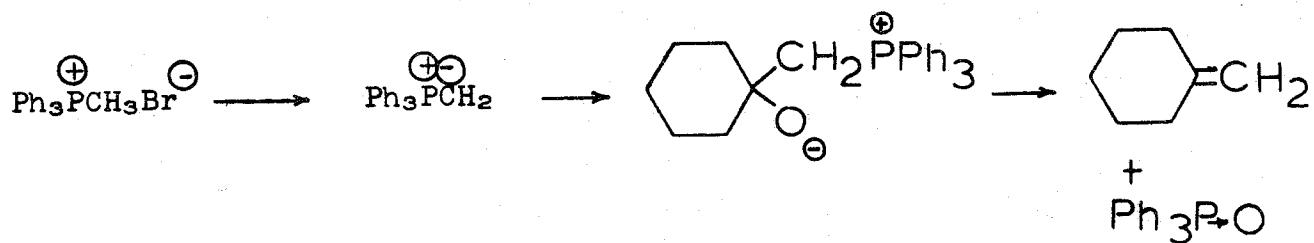
G. Stork, et al., J. Amer. Chem. Soc., 89, 5459, 5461, 5463, 5464 (1967).

3. Michael reaction



F. One carbon chain extension

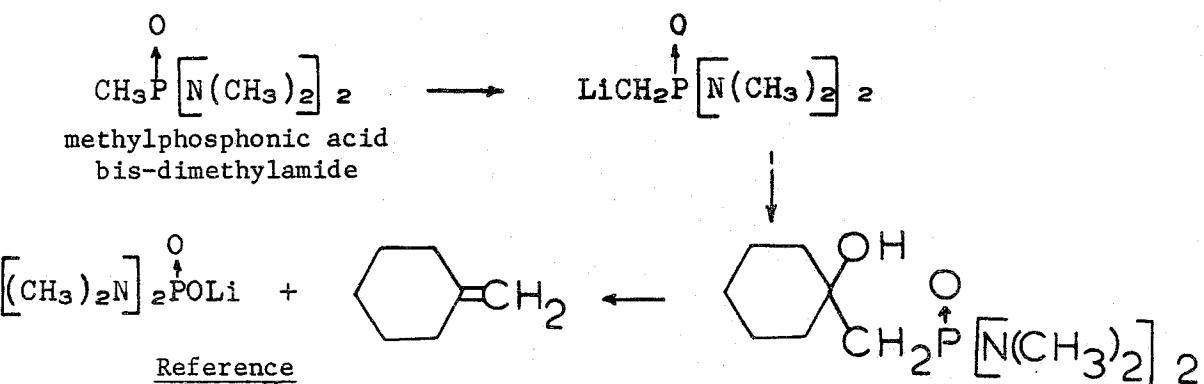
1. Phosphorus ylides



Reference

A. Maercker, Org. React., 14, 270 (1965).

2. Phosphonic acid bis-amides



Reference

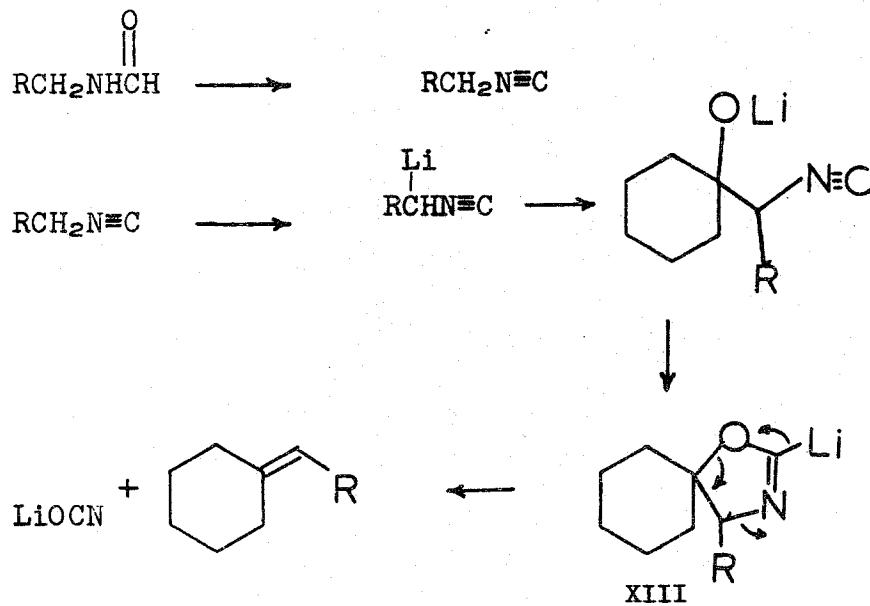
E. J. Corey and G. T. Kwiatkowsky, J. Amer. Chem. Soc., 90, 6816 (1968).

3. Sulfonamides

Reference

E. J. Corey and T. Durst, J. Amer. Chem. Soc., 90, 5548, 5553 (1968).

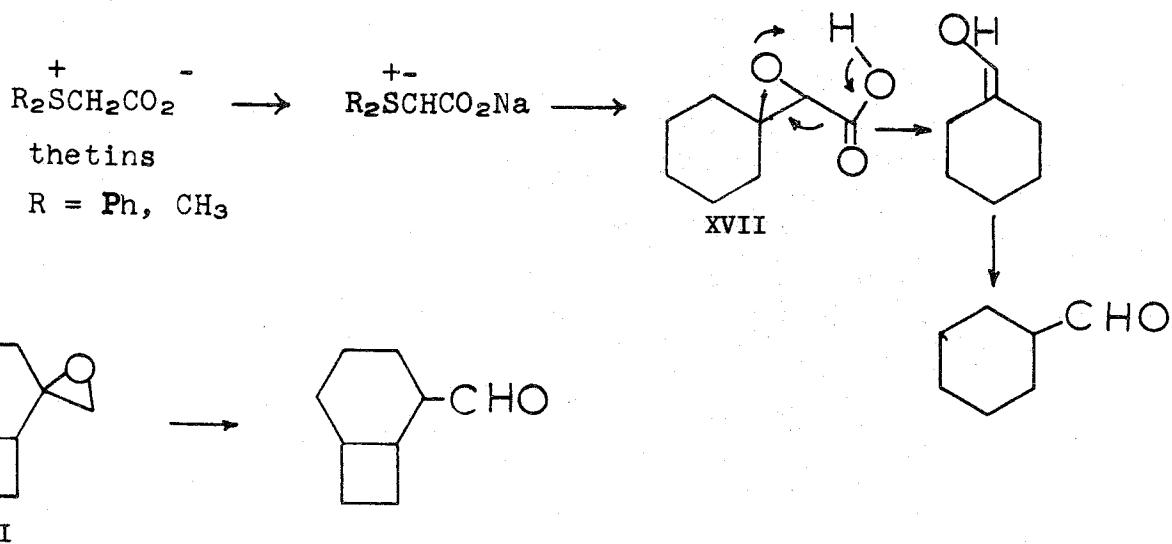
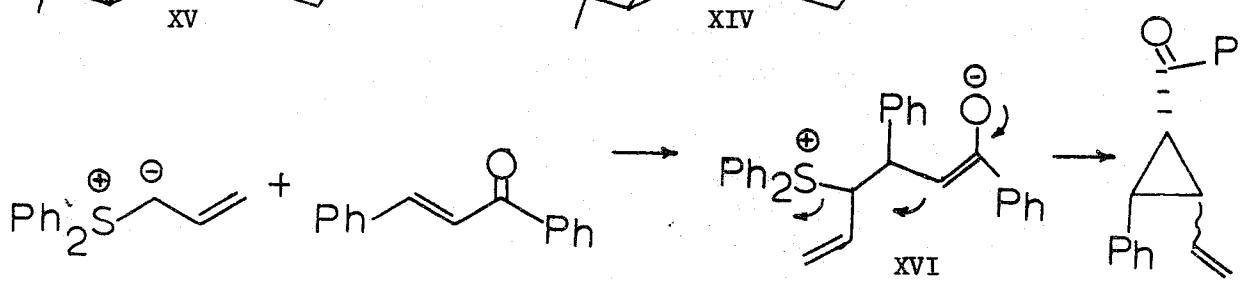
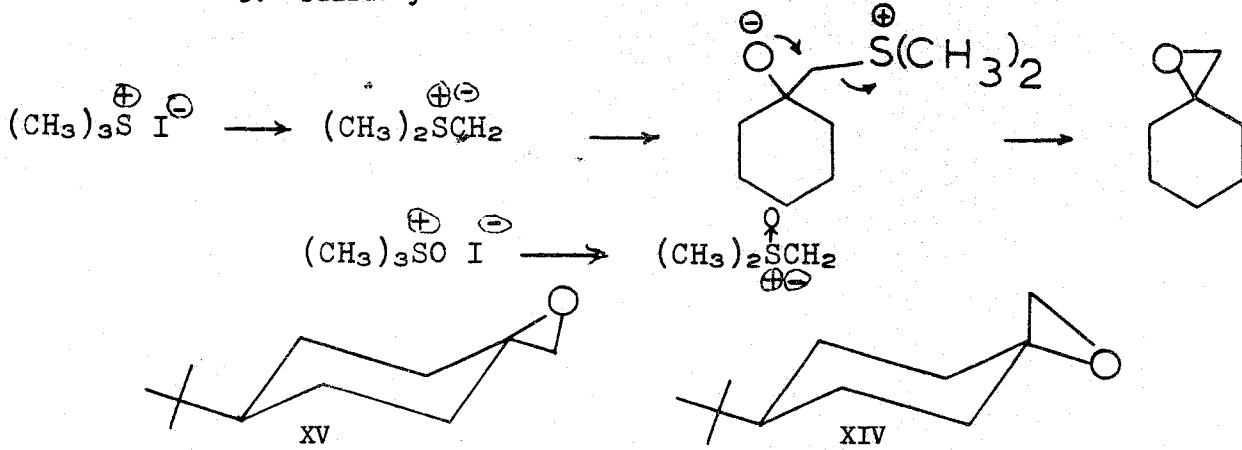
4. Isonitriles



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U. Schollkopf and F. Gerhart, Angew. Chem. Int. Ed. Eng., 7, 805 (1968).

5. Sulfur ylides



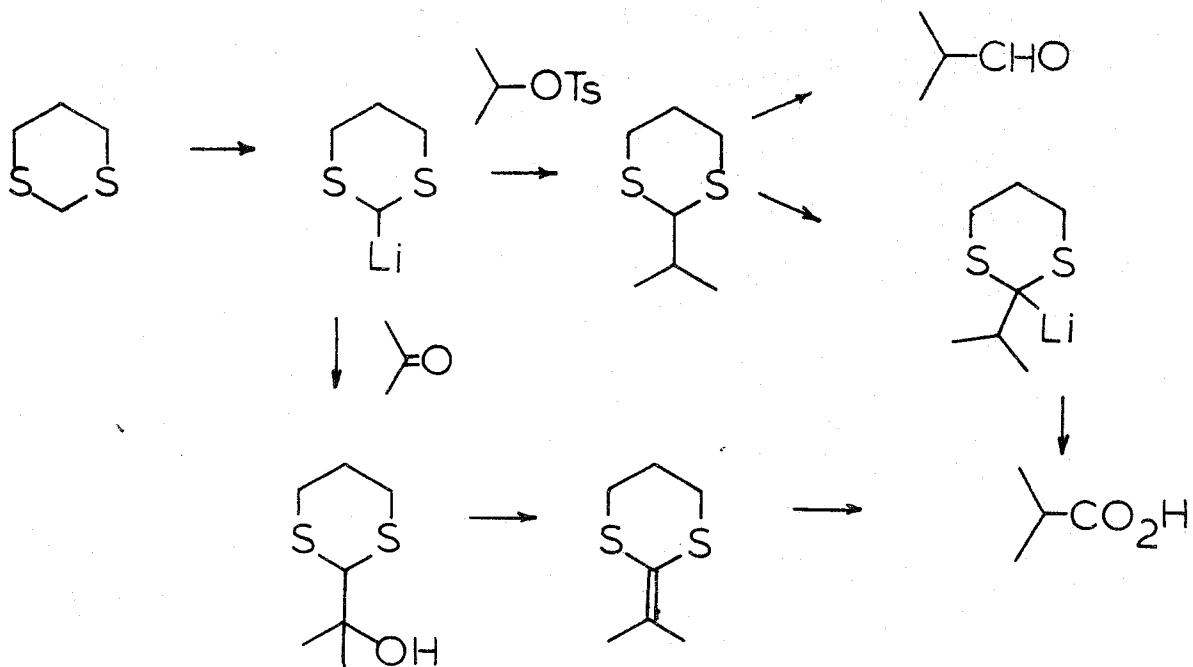
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J. Adams, L. Hoffman, Jr., and B. M. Trost, J. Org. Chem., 35, 1600 (1970).

E. J. Corey and M. Jautelat, J. Amer. Chem. Soc., 89, 3912 (1967).

M. J. Hatch, J. Org. Chem., 34, 2133 (1969).

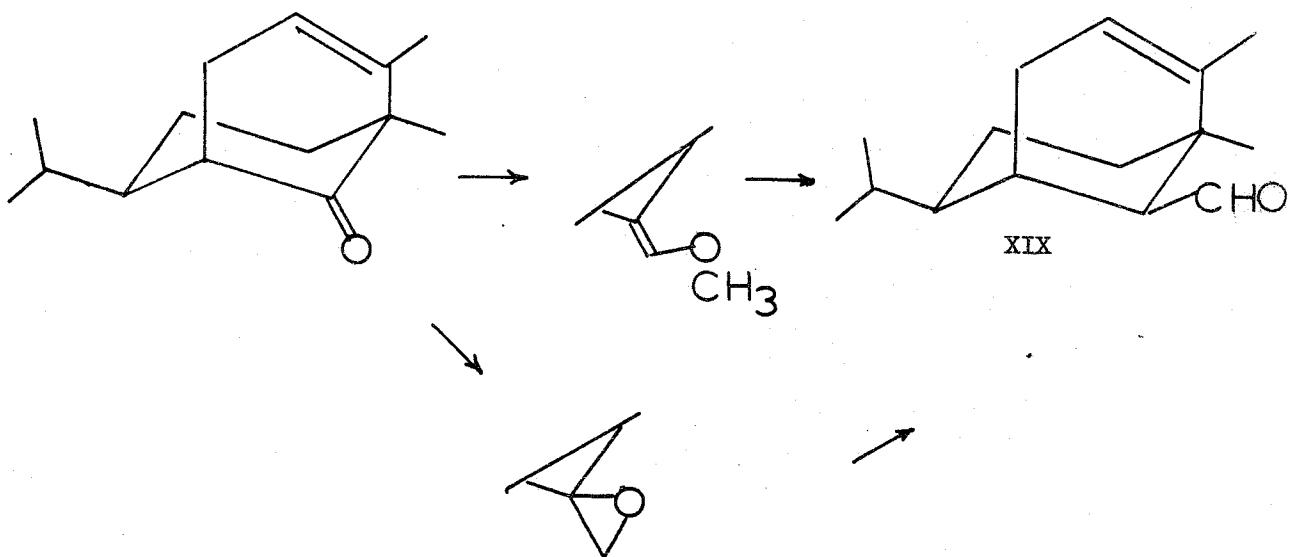
6. Dithianes



Reference

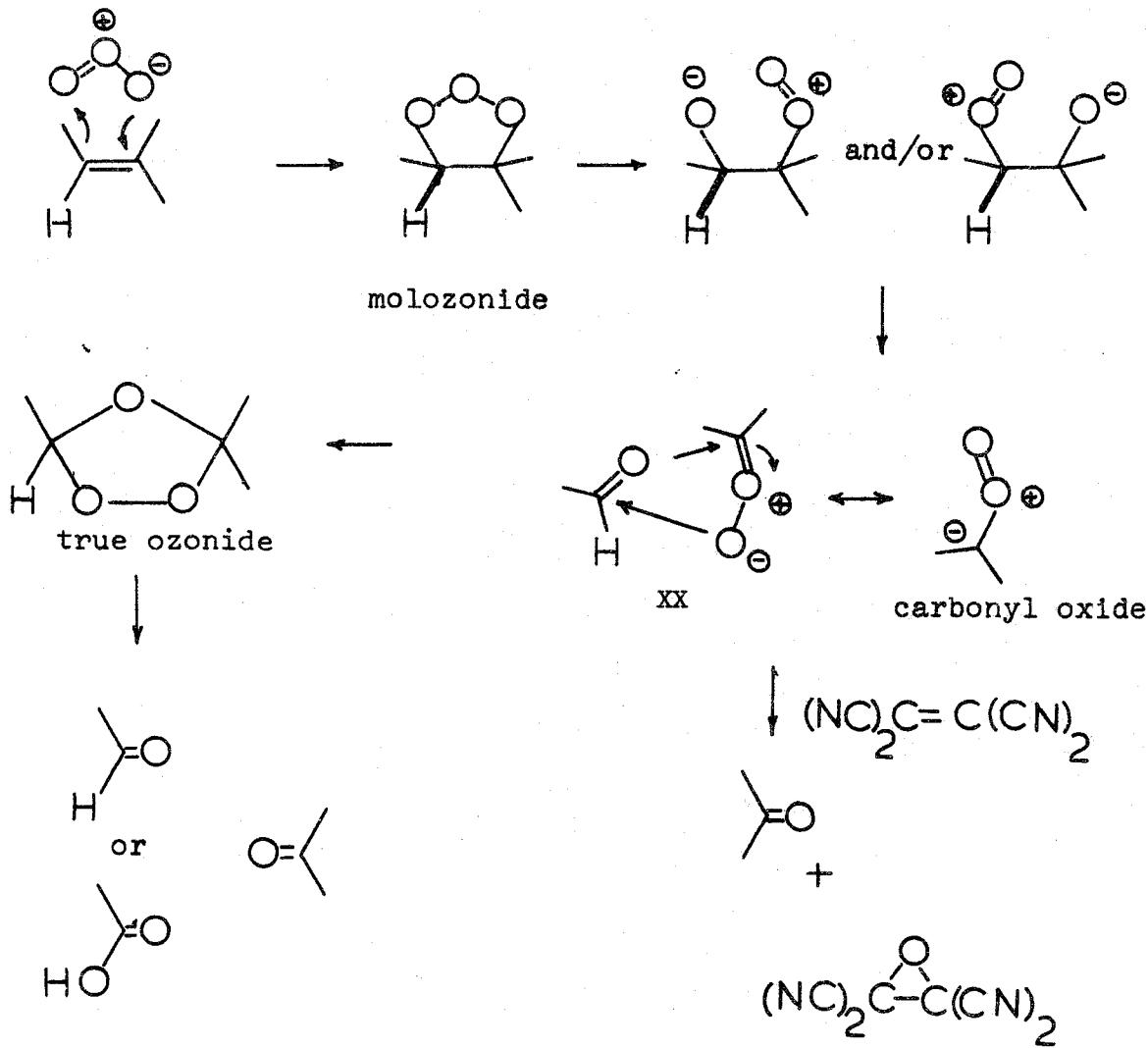
D. Seebach, Angew. Chem. Int. Ed. Eng., **8**, 639 (1969);
Synthesis, **1**, 17 (1969).

7. Desired transformation



G. Oxidative cleavage of double bond

1. Ozonolysis

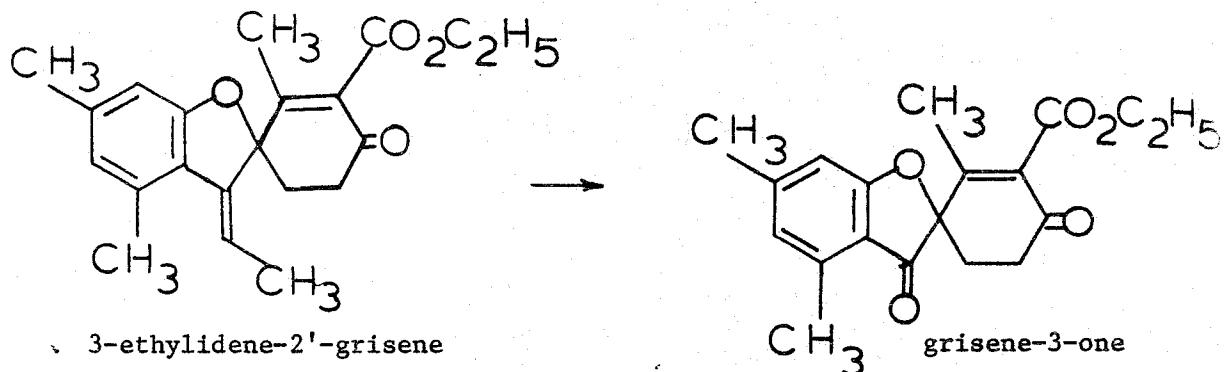


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S. Munavalli and G. Ourisson, Bull. Soc. Chim. France, 729 (1964).

R. W. Murray, Accounts Chem. Res., 1, 313 (1968).

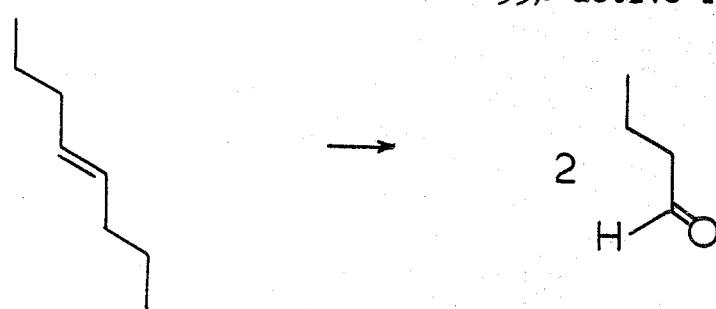
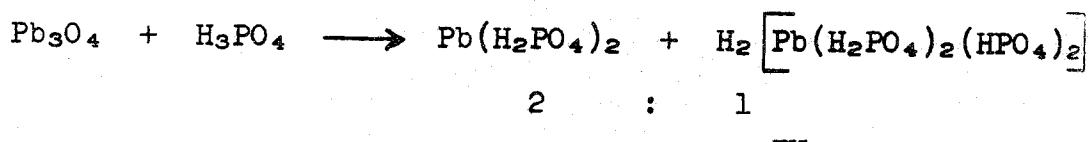
2. Ruthenium tetroxide (RuO_4)



Reference

F. M. Dean and J. C. Knight, J. Chem. Soc., 4745 (1962).

3. Pb^{IV} phosphate



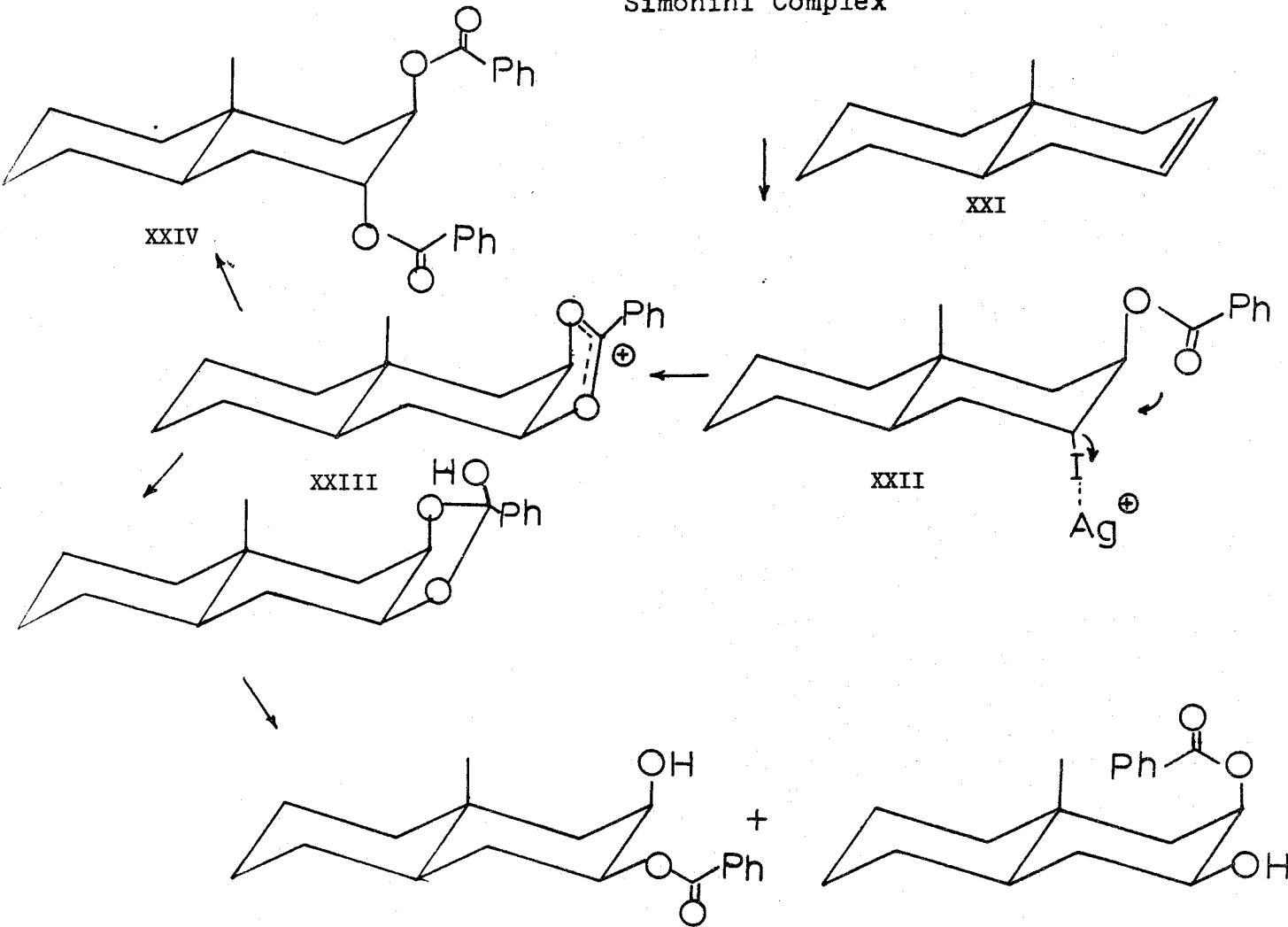
Reference

F. Huber and M. S. A. El-Meligy, Chem. Ber., 102, 872 (1969).

4. Prevost procedure



Simonini Complex

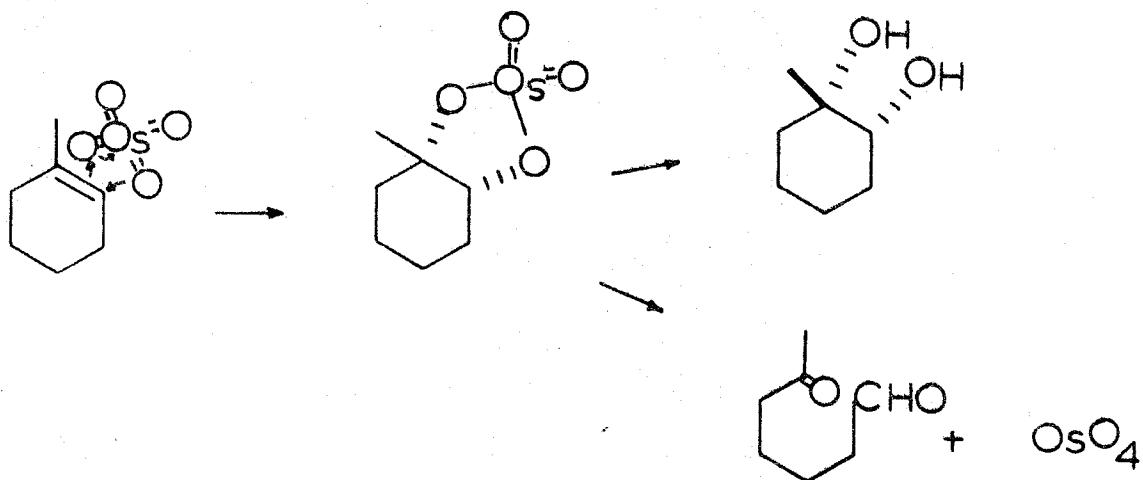


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5. Osmium tetroxide procedure



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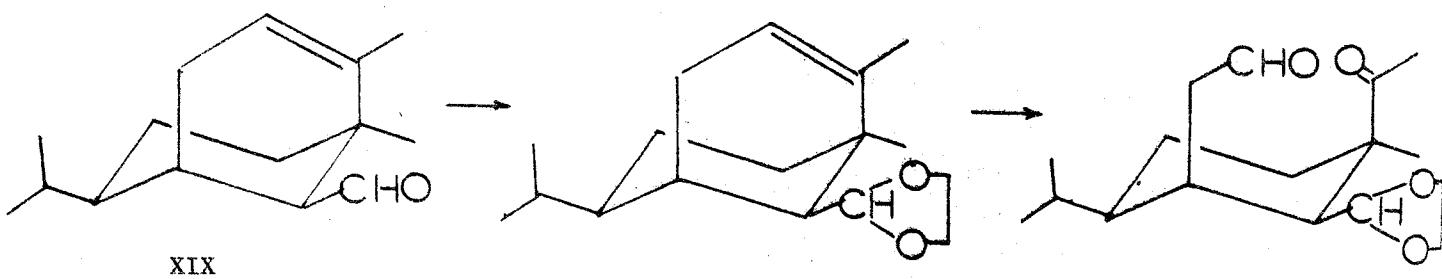
R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, J. Org. Chem., 21, 478 (1956).

6. Permanganate procedure

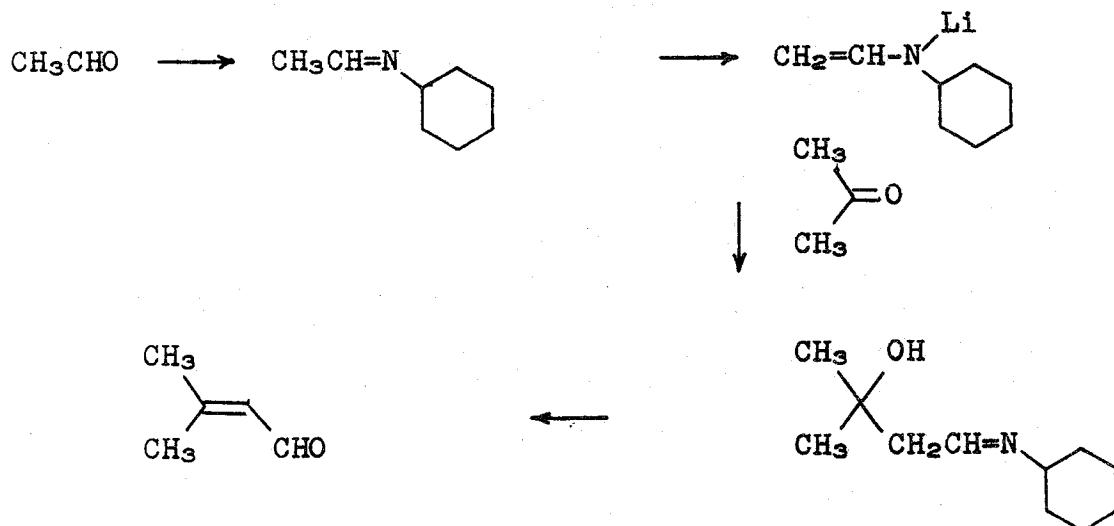
Reference

M. Jacobson, M. Beroza and W. A. Jones, J. Amer. Chem. Soc., 83, 4819 (1961).

7. Cleavage reaction



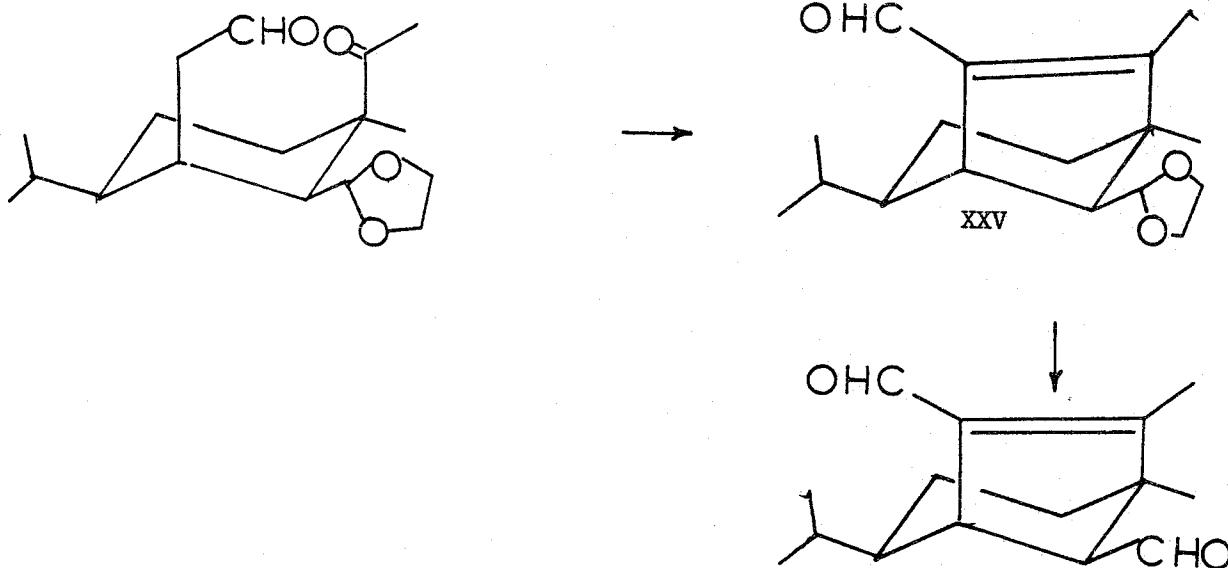
H. Directed aldol condensation



Reference

G. Wittig and H. Reiff, Angew. Chem. Int. Ed. Eng., 7, 7 (1968).

I. Final solution

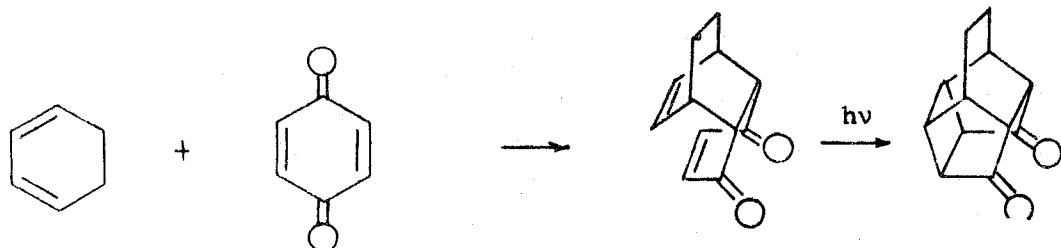


IV. Synthesis of Cubane

[See P. E. Eaton and T. W. Cole, Jr., J. Amer. Chem. Soc., 86, 3157 (1964).]

A. Synthetic approach

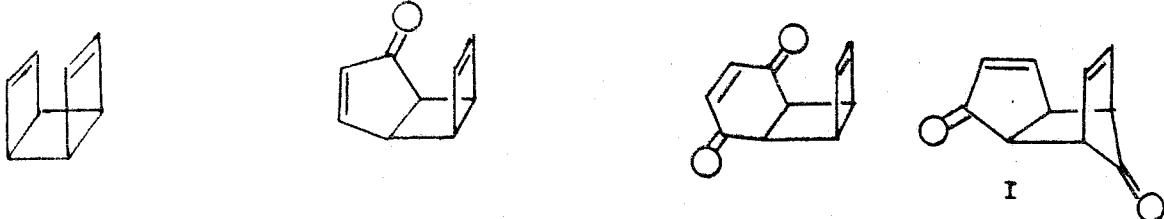
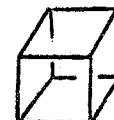
1. Cage Synthesis



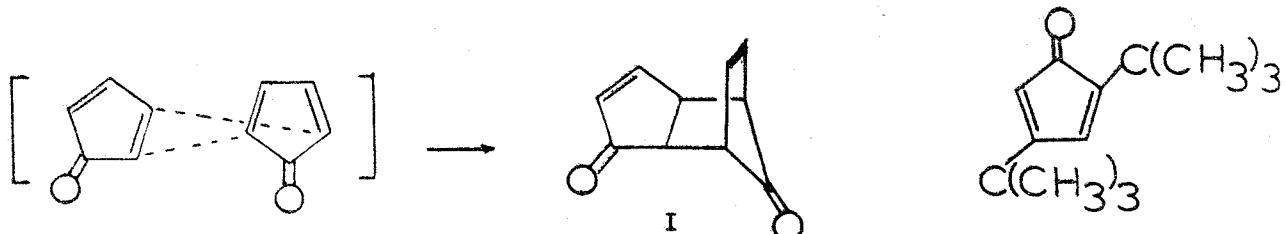
Reference

R. C. Cookson, E. Crundwell, R. R. Hill and J. Hudec, J. Chem. Soc., 3062 (1964).

2. Logical synthetic precursors



3. Properties of cyclopentadienones

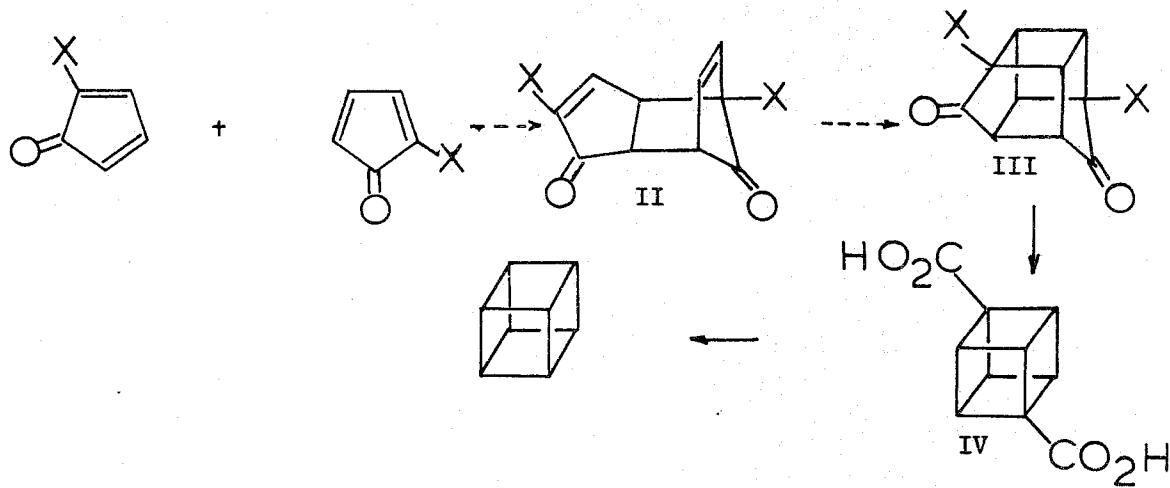


References

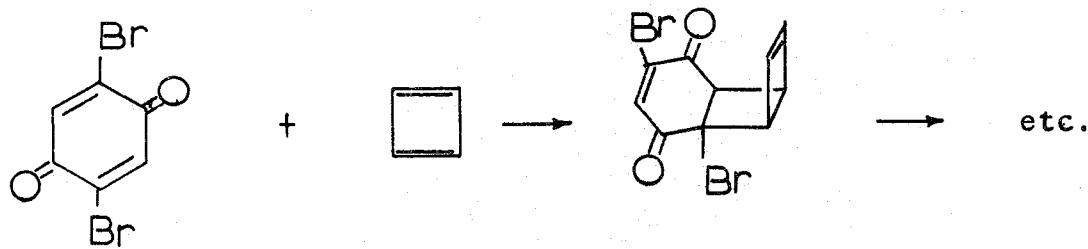
C. H. DePuy, M. Isaks, K. L. Eilers and G. F. Morris, J. Org. Chem., 29, 3503 (1964).

E. W. Garbisch, Jr., and R. F. Sprecher, J. Amer. Chem. Soc., 88, 3433 (1966).

4. Adaptation to cubane



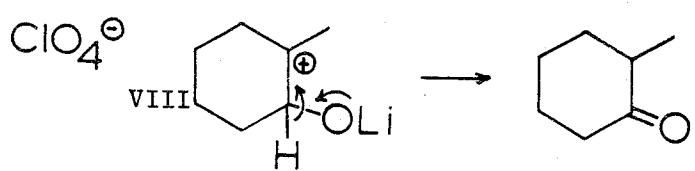
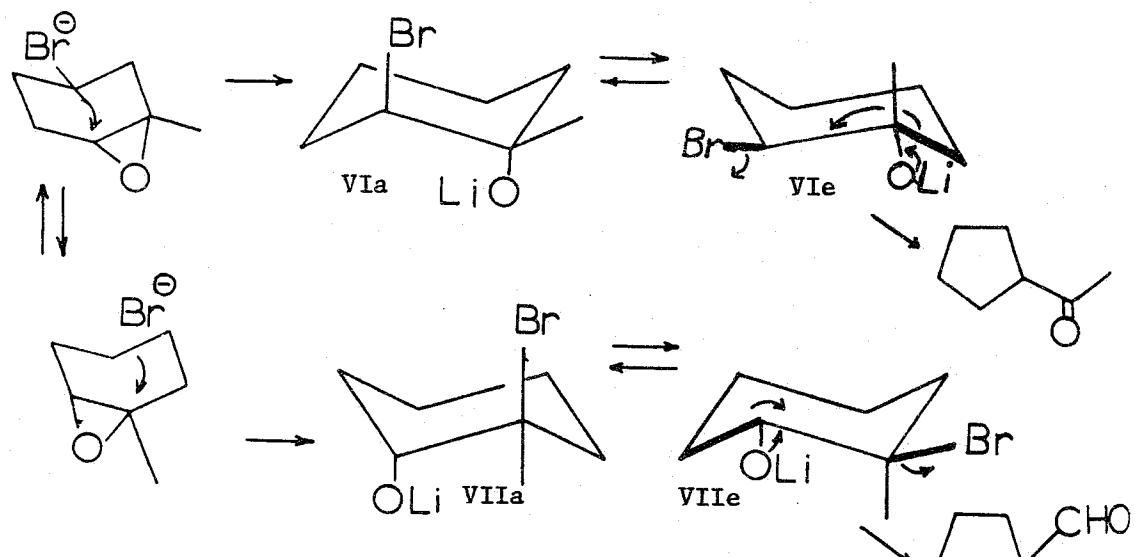
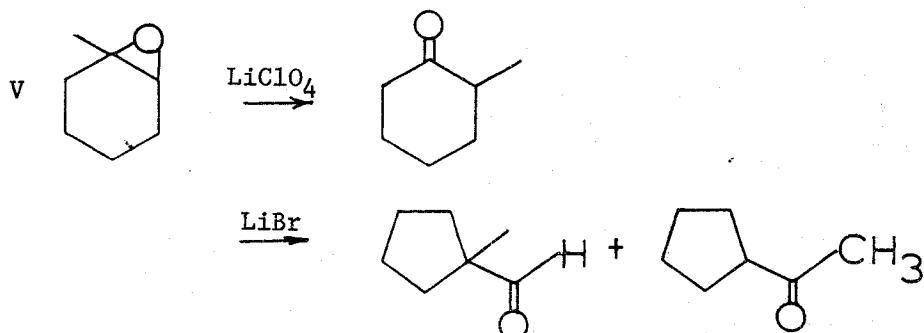
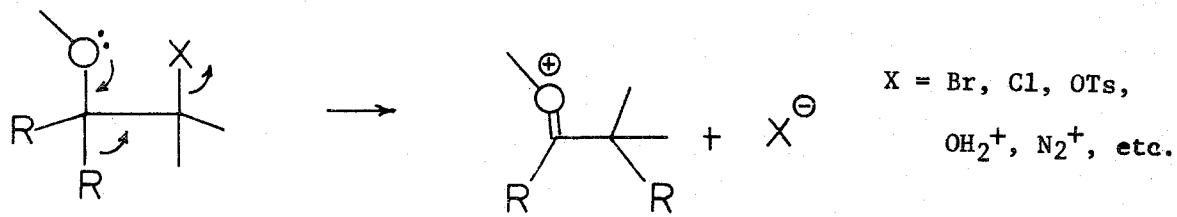
Compare to approach of J. C. Barborak, L. Watts and R. Pettit, J. Amer. Chem. Soc., 88, 1328 (1966).



B. Methods for ring size modification

1. Pinacol rearrangements

a) General considerations; ring contraction via epoxides

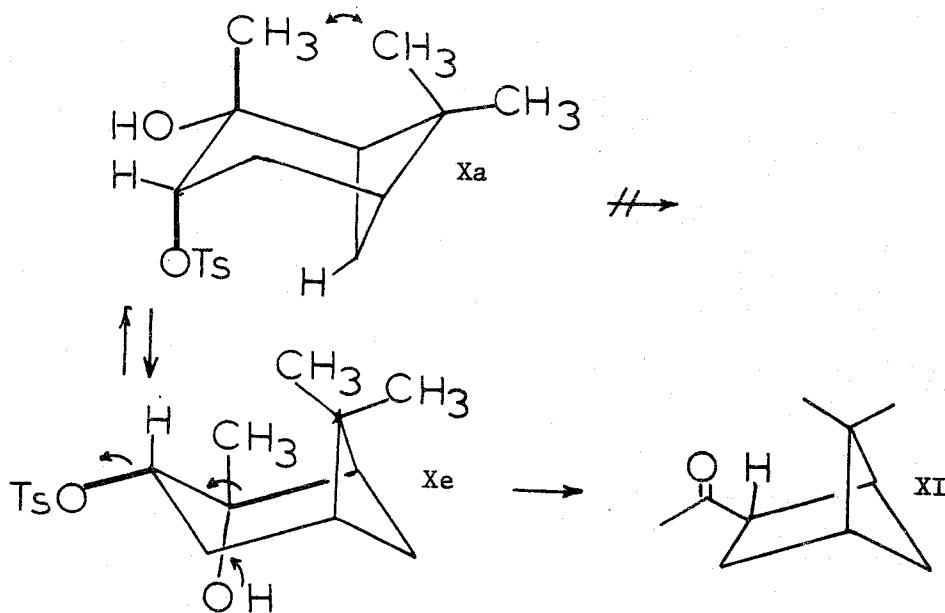
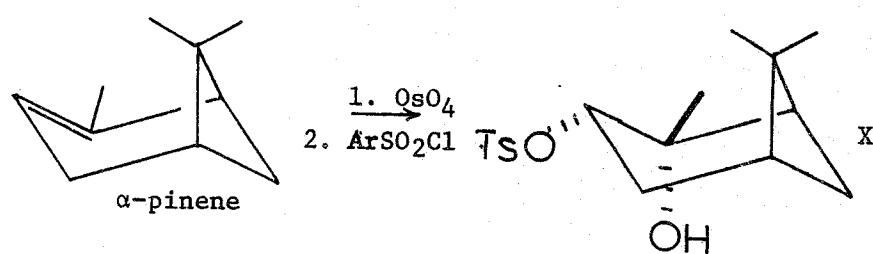
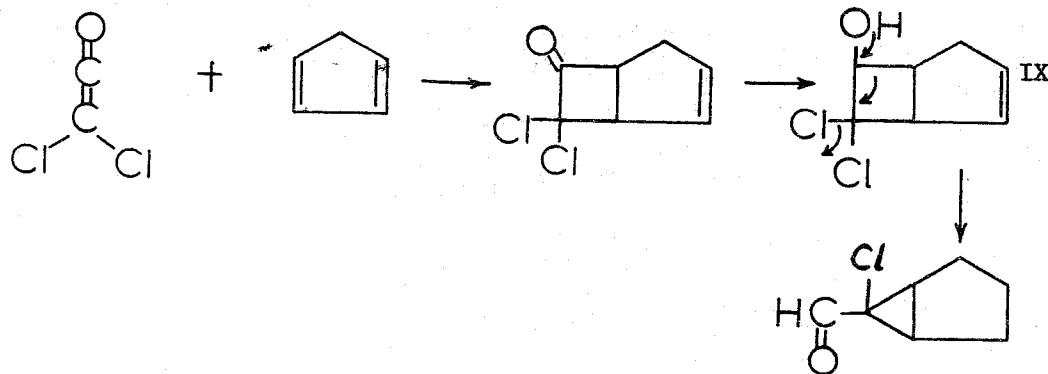


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C. J. Collins, Quart. Rev. Chem. Soc., 14, 357 (1960).

B. Rickborn, R. M. Gerkin, J. Amer. Chem. Soc., 90, 4193 (1968).

b) Rearrangements involving the common leaving groups

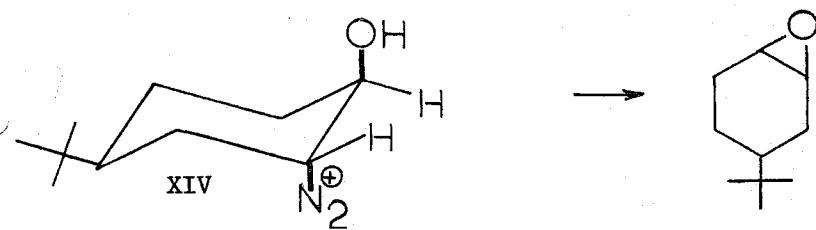
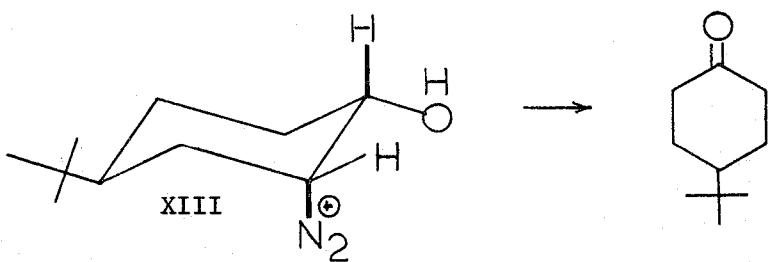
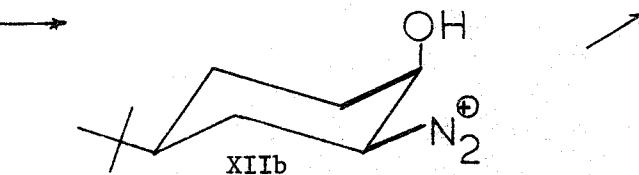
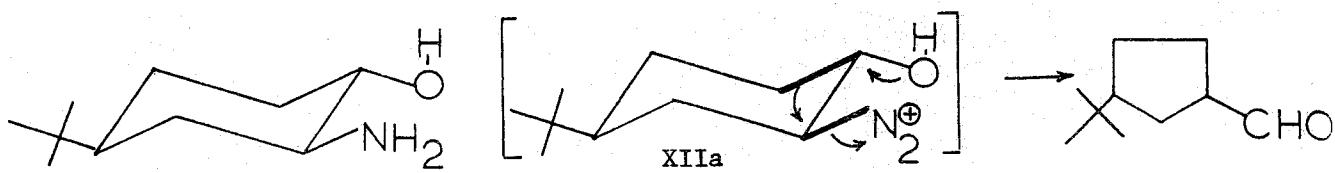


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P. R. Brook, Chem. Commun., 565 (1968).

T. Suga, et al., Tetrahedron Lett., 5553 (1968).

c) Deamination of 2-amino alcohols; nitrogen as the leaving group.

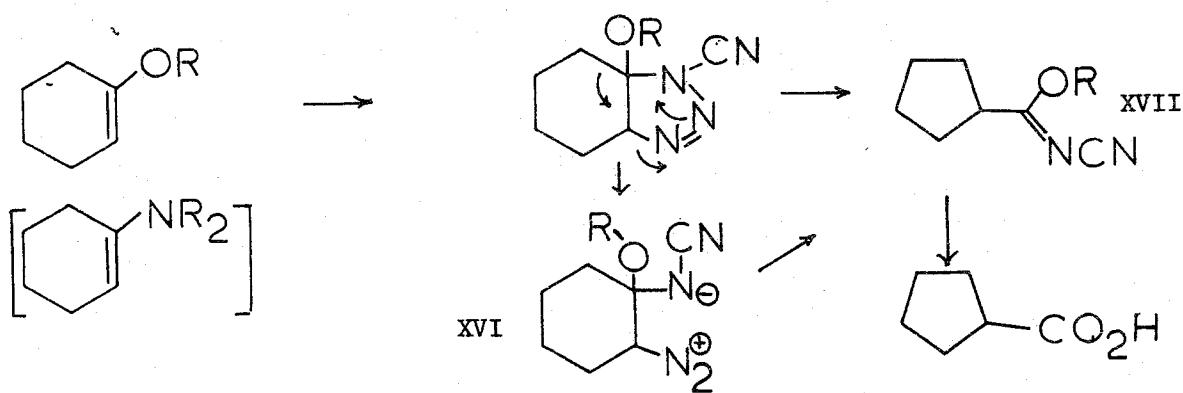
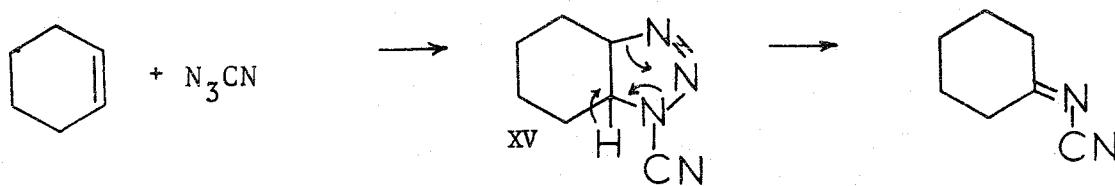


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M. Cherest, H. Felkin, J. Sicher, F. Sipos, and M. Ticky, J. Chem. Soc., 2513 (1965).

K. Ebisu, L. B. Batty, J. H. Higaki and H. O. Larson, J. Amer. Chem. Soc., 87, 1399 (1965).

d) Cyanogen azide ring contraction

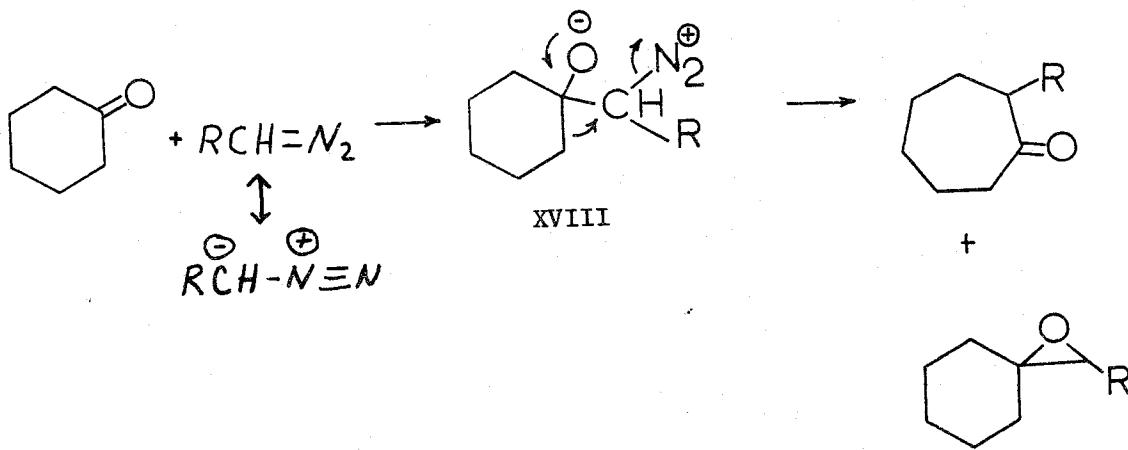


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F. D. Marsh and M. E. Hermes, J. Amer. Chem. Soc., 86, 4506 (1964).

R. M. Scribner, Tetrahedron Lett., 4737 (1967).

e) Modifications for ring expansion

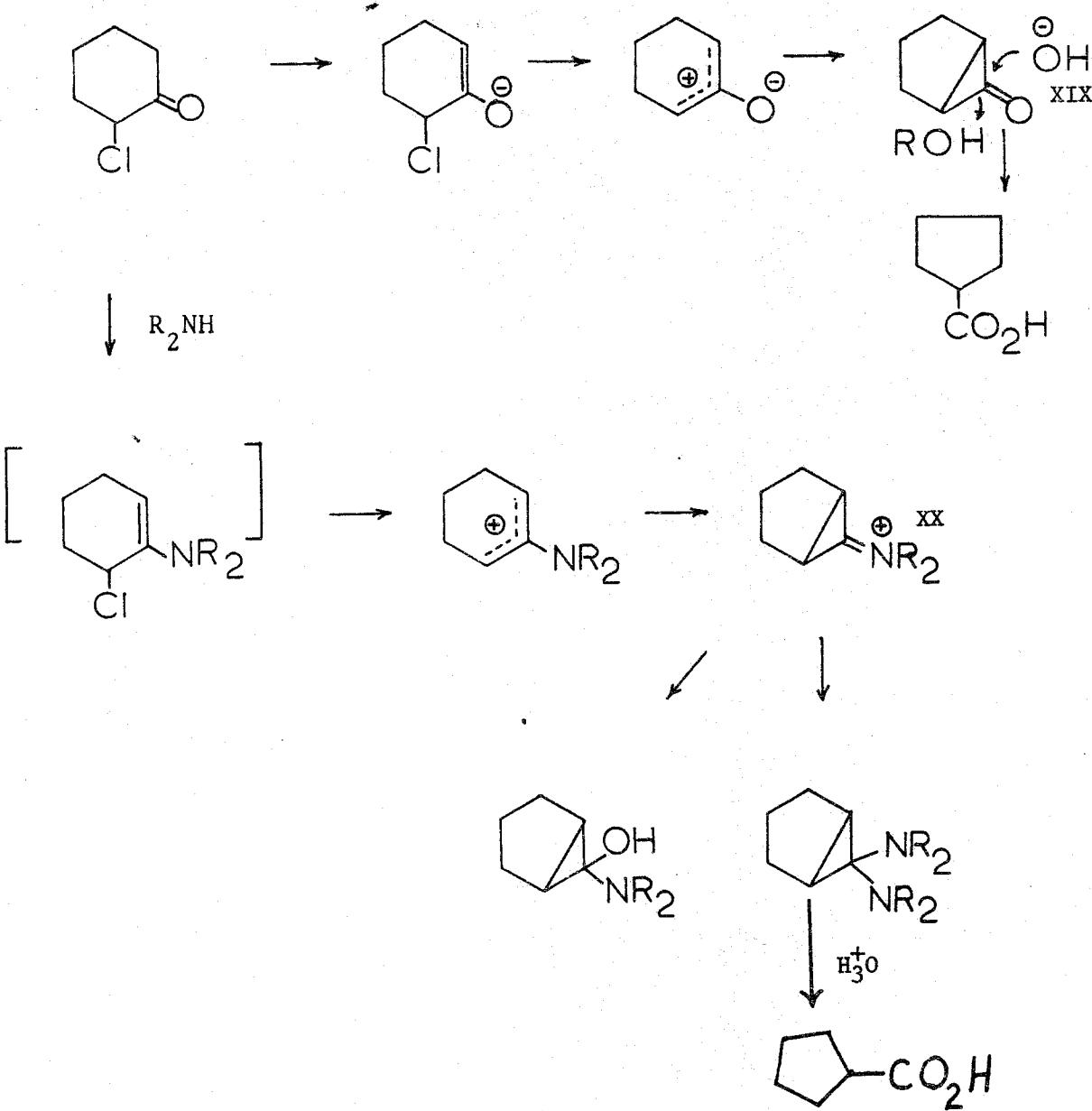


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J. A. Marshall and J. J. Partridge, J. Org. Chem.,
33, 4090 (1968).

2. Favorskii rearrangements

a. Enolizable ketones



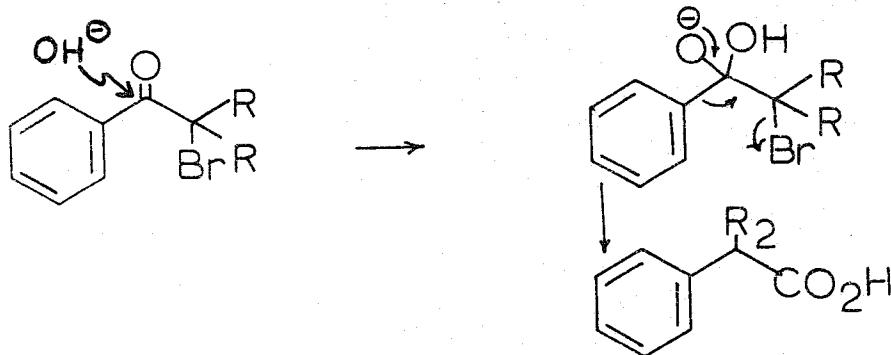
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F. G. Brodwell and R. G. Scamehorn, J. Amer. Chem. Soc., 90, 6751 (1968).

H. O. House and F. A. Richey, Jr., J. Org. Chem., 32, 2151 (1967).

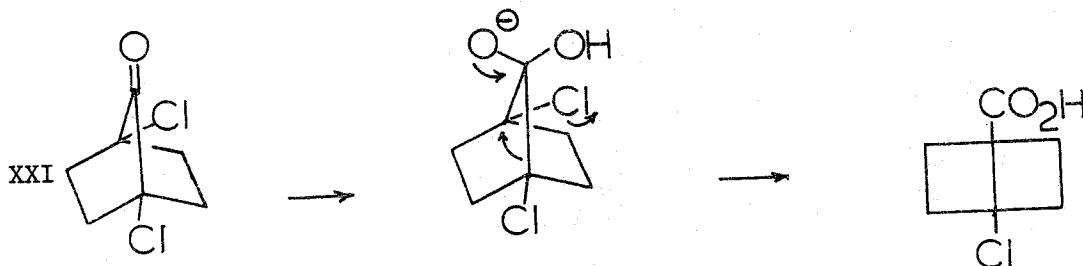
J. Szmuszkovicz, et al., Tetrahedron Lett., 1309 (1969).

b) Nonenolizable ketones



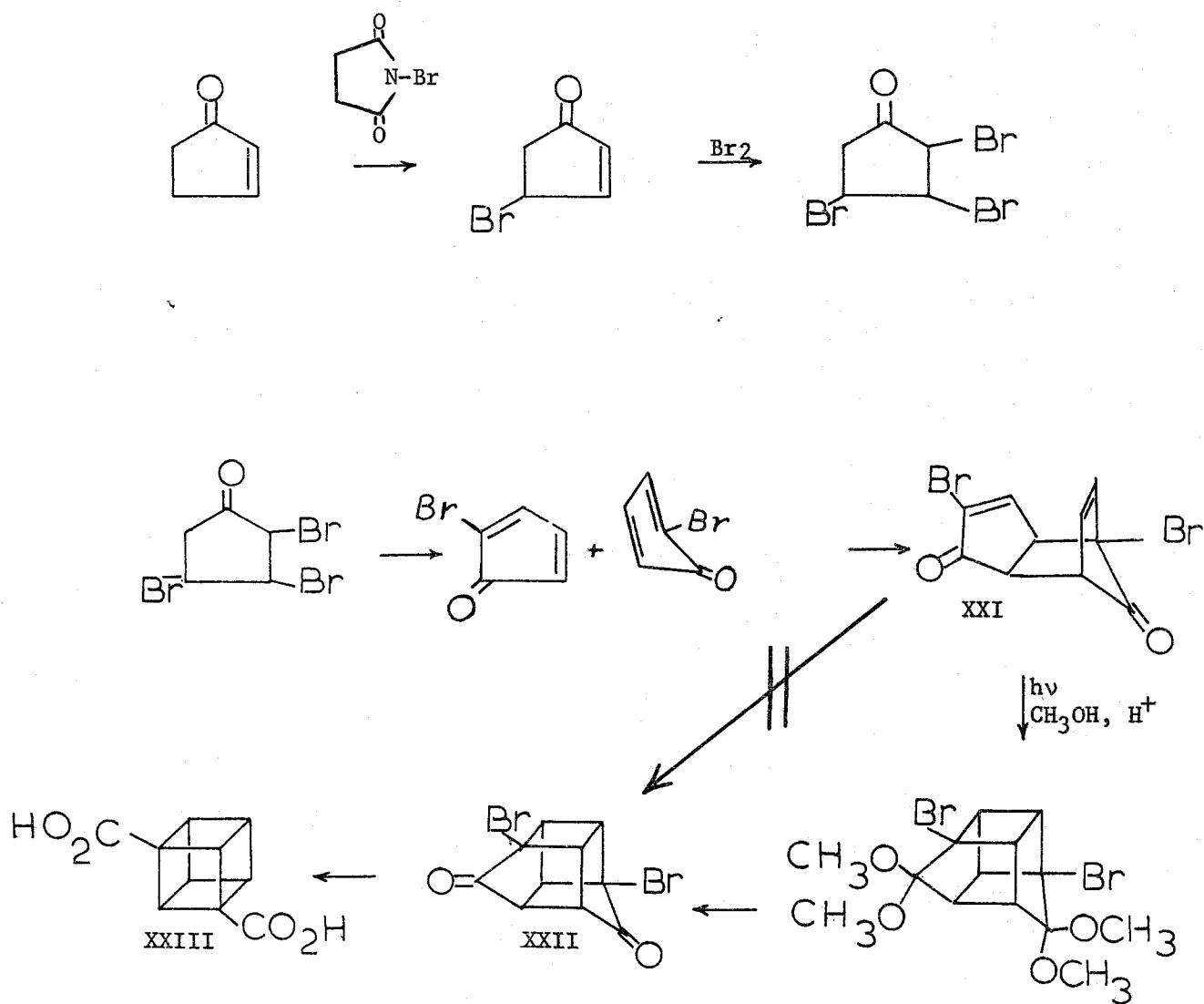
Reference

K. V. Scherer, Jr., Tetrahedron Lett., 5685 (1966).



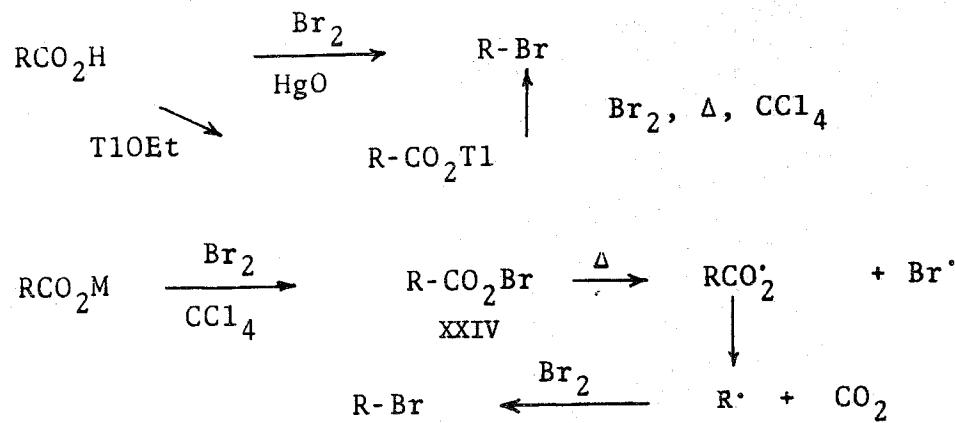
3. α -Diazoketone ring contractions; discussed in Section I.

C. Synthesis of cubane dicarboxylic acid.



D. Removal of carboxylate groups

1. Hunsdiecker reaction; Hg^{II} , Ag^I or Tl^I carboxylates



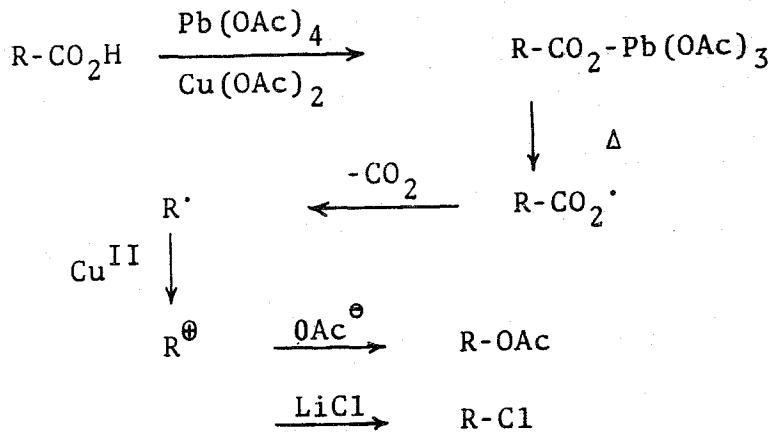
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J. A. Davis, J. Herynk, S. Carroll, J. Bunds and D. Johnson,
J. Org. Chem., 30, 415 (1965).

A. McKillop and D. Bromley, J. Org. Chem., 34, 1172 (1969).

2. Lead tetraacetate decarboxylation

For R=tertiary, secondary, allylic or benzylic:



Reference

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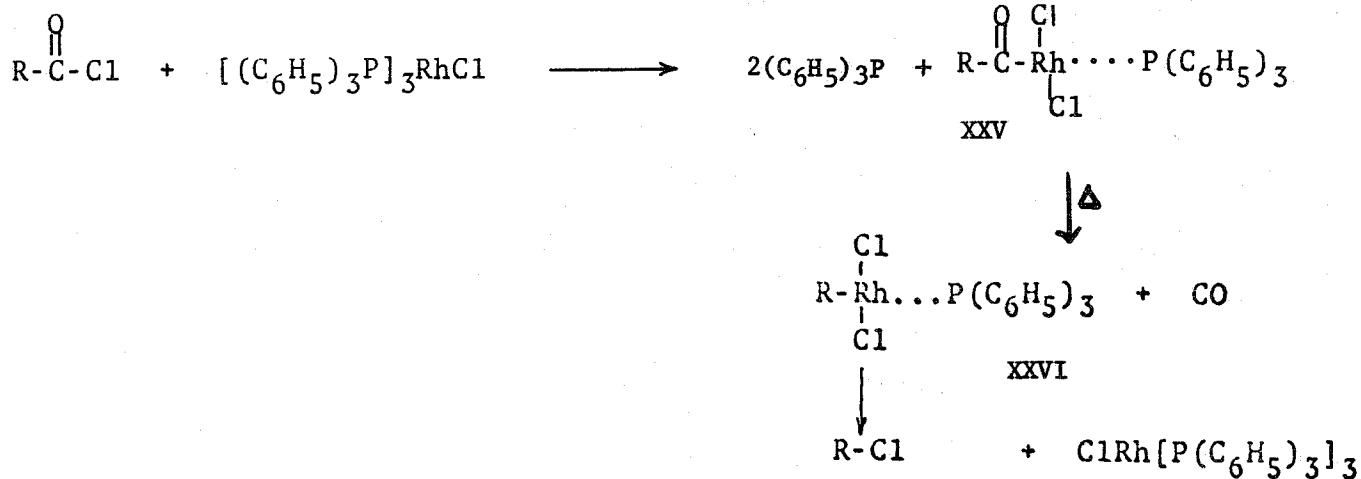
3. Aromatic acids and aldehydes; Rhodium (I) catalyzed decarbonylation

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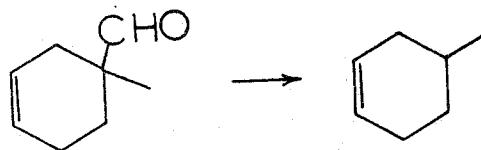
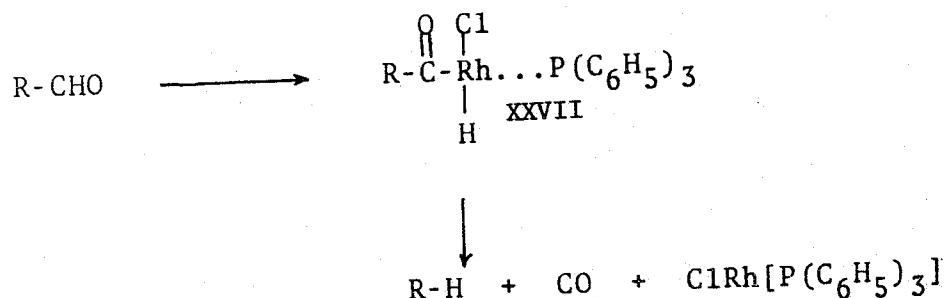
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a) Acid chlorides

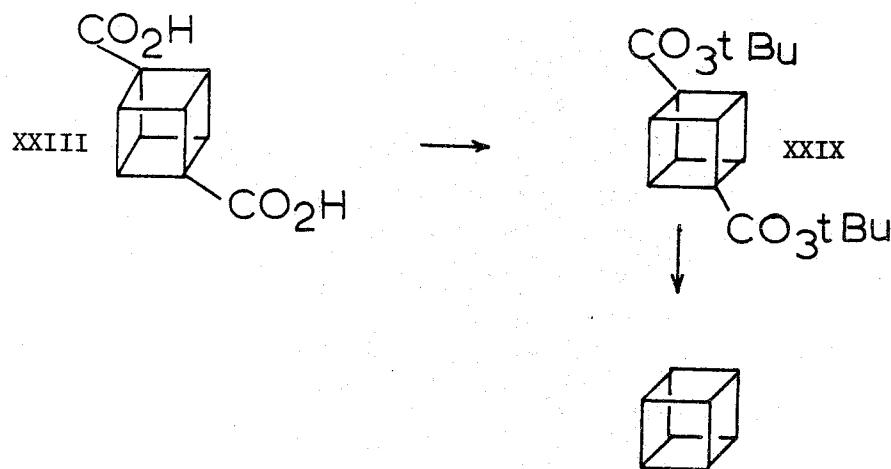
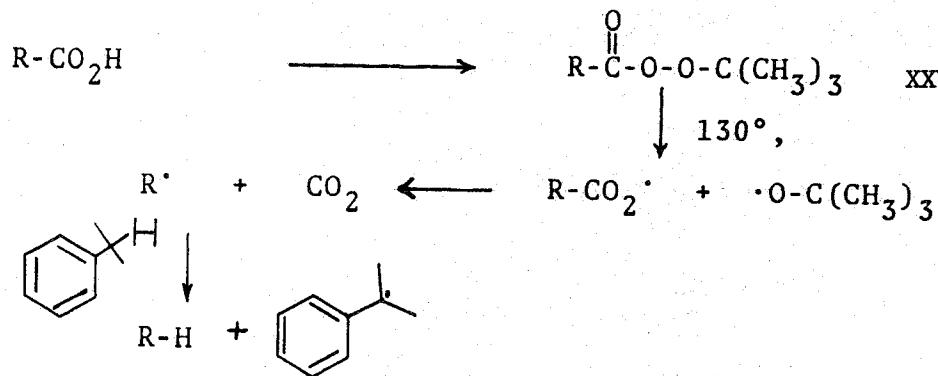


b) Aldehydes



(Olefins often are major products upon attempted
decarbonylation of aliphatic acid chlorides or
aldehydes.)

4. Decarboxylation via t-butyl peresters



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