(CCl_4) δ 2.1–4.0 (multiplet, 8 aliphatic H), 7.17 (broad singlet, 10 aromatic H).

Anal. Calcd for $C_{18}H_{18}OS$: C, 76.50; H, 6.37. Found: C, 75.30; H, 6.17.

Acknowledgments. We are grateful to the National Science Foundation and the U. S. Army Research Office (Durham) for generous support of this research. In addition, we thank Professor A. L. Wilds for a generous supply of 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (**24**), which was used to synthesize **25**, as well as an authentic sample and spectra of the latter.

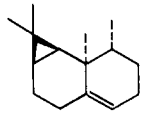
Total Synthesis of (±)-Calarene[1]

Robert M. Coates and James E. Shaw[2]

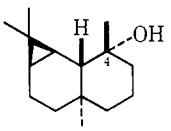
Contribution from the Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois 61801. *Received January 19, 1970*

Abstract: A stereochemically defined synthetic route to the tricyclic sesquiterpene calarene (**1**) is described. The key intermediates, *cis*- and *trans*-4,4a-dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (**3a** and **3b**), were prepared by annulation of 2-methylcyclohexane-1,3-dione as its monopyrrolidine enamine (**6**) with 3-penten-2-one (**4**). The stereochemistry of **3b** was established by independent chemical and spectroscopic evidence. Pyrolysis of the 2-pyrazolines derived separately from *cis*- and *trans*-2(3H)-isopropylidene-8,8a-dimethyl-4,6,7,8-tetrahydronaphthalene-1(8aH)-one (**20** and **22**) by reaction with hydrazine served as an efficient means for introducing the fused dimethylcyclopropane ring. (±)-Calarene was obtained stereoselectively from **20**, whereas two stereoisomers (**25** and **26**), both distinctly different from calarene, were formed from **22**.

The naturally occurring hydrocarbon calarene (**1**) is one member of a small group of tricyclic sesquiterpenes which contain a dimethylcyclopropane ring fused to the nonisoprenoid octalin nucleus of the eremophilone family.[3] Structure **1** was first proposed by Büchi, Greuter, and Tokoroyama as the result of an extensive chemical study[4] and their conclusion was confirmed by concurrent investigations in other laboratories.[5] The structural and stereochemical assignment was supported by a correlation with 4-epimaaliol (**2**),[4] a synthetic isomer of the well-known natural sesquiterpene alcohol maaliol.[6] In this paper we describe a total synthesis of (±)-calarene which fully confirms the proposed structure and provides independent evidence regarding the relative stereochemistry depicted in **1**.[7,8]

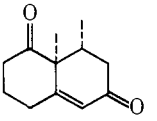


1

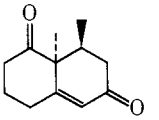


2

Our synthetic plan involved the initial preparation of the *cis*-unsaturated bicyclic ketone **3a**.[9] This substance not only appeared well suited for transformation into calarene, but also could serve as an intermediate in the total synthesis of other sesquiterpenes in the eremophilone family.[10] It seemed likely that the two carbonyl groups in **3a** could be chemically distinguished since the *peri*-like secondary methyl group sterically hinders the nonconjugated ketone. Furthermore, the angular methyl group might enable stereochemical control in reactions introducing the three-membered ring, or possibly other functionality.



3a



3b

A variant of the Robinson annulation reaction with 3-penten-2-one **4** in place of methyl vinyl ketone was used to prepare the requisite dimethyl octalone derivative.[11] Although a successful annulation reaction with **4** had been previously reported,[12] the stereochemistry of the product was not determined. Attempts to effect the annulation of 2-methylcyclohexane-1,3-

(1) Taken in part from the Ph.D. Thesis of J. E. S., University of Illinois, 1969.

(2) National Science Foundation Trainee, 1965–1969.

(3) For a recent review see A. R. Pinder, *Perfum. Essent. Oil. Rec.*, **59**, 645 (1968).

(4) G. Büchi, F. Greuter, and T. Tokoroyama, *Tetrahedron Lett.*, 827 (1962).

(5) (a) J. Vrkoč, J. Krepinský, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **29**, 795 (1964); (b) P. Pesnelle and G. Ourisson, *Bull. Soc. Chim. Fr.*, 912 (1963); (c) J. Streith, P. Pesnelle, and G. Ourisson, *ibid.*, 518 (1963).

(6) (a) Structure: G. Büchi, M. Schach, M. Schach v. Wittenau, and D. M. White, *J. Amer. Chem. Soc.*, **81**, 1968 (1959); (b) total synthesis: R. B. Bates, G. Büchi, T. Matsuura, and B. R. Schaffer, *ibid.*, **82**, 2327 (1960).

(7) Portions of this investigation have been briefly reported: R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47, 515 (1968).

(8) For recent syntheses of the closely related sesquiterpene ketone aristolone see (a) C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968); (b) E. Piers, R. W. Britton, and W. de Wall, *Can. J. Chem.*, 47, 831 (1969).

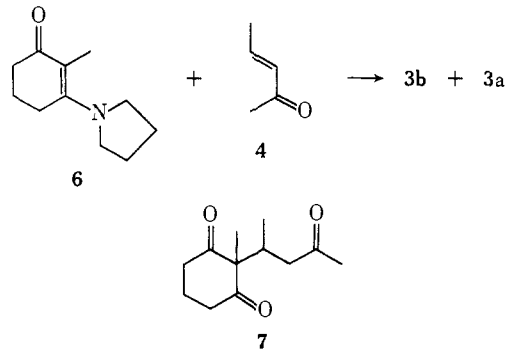
(9) All structural formulae except **1**, **2**, and **14** designate only one enantiomorph of a racemic mixture.

(10) (a) R. M. Coates and J. E. Shaw, *Tetrahedron Lett.*, 5405 (1968); (b) "Symposium on the Chemistry of Essential Oils," 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstract 46; (c) *J. Org. Chem.*, **35**, 2597 (1970).

(11) This synthetic approach toward sesquiterpenoids of the eremophilone family has been employed in several recent investigations: (a) J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); (b) H. C. Odom and A. R. Pinder, *ibid.*, 26 (1969); (c) R. L. Hale and L. H. Zalkow, *ibid.*, 1249 (1968); (d) L. W. Piszkiewicz, Ph.D. Thesis, California Institute of Technology, 1967; *Diss. Abstr. B*, 27, 3865 (1967); (e) C. J. V. Scanio, "Symposium on the Chemistry of Essential Oils," 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstracts, AGFD 47.

(12) W. S. Rapson, *J. Chem. Soc.*, 1626 (1936).

dione (**5**) with 3-penten-2-one by potassium hydroxide catalyzed conjugate addition followed by aldol cyclization[13] afforded poor yields (2–17%) of a bicyclic product subsequently shown to be **3b**. The use of other catalysts such as sodium ethoxide[11a,14] or potassium fluoride[15] were unsuccessful.



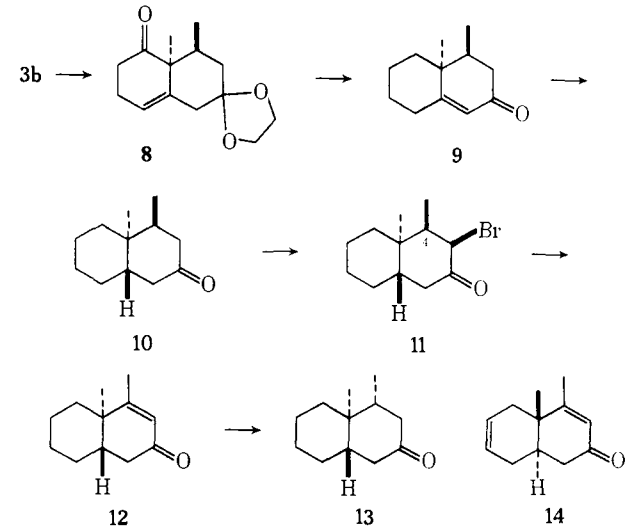
We found, however, that the monopyrrolidine enamine (**6**) of 2-methylcyclohexane-1,3-dione reacted readily with **4**[16] in a heterogeneous medium consisting of benzene, acetic acid, and aqueous sodium acetate at reflux, affording the crystalline *trans*-diketone **3b** in 59% yield along with a small amount (~5%) of the *cis*-isomer **3a**.[17] Although the general structure of the major product is evident from the spectral characteristics, the more subtle stereochemical designation required the lengthy chemical transformations which are described below.

Since the vicinal methyl groups in calarene (and all other sesquiterpenoids having the rearranged methyl group pattern of eremophilone) are in a *cis* relationship, we sought experimental modifications which might alter the stereochemical course of this annulation reaction. The use of a pentenone mixture enriched in the *cis*-geometrical isomer did not affect the product. However, increasing the polarity of the organic solvent led to significantly higher proportions of the desired isomeric diketone **3a** in the product mixture. With formamide as solvent, a 1:1 mixture of the isomers **3a** and **3b** was obtained in a total yield of 27%. Other solvents such as ethanol, dimethylformamide, and dimethyl sulfoxide gave varying proportions which seemed to correspond roughly to the polarity of the solvent.

Although the detailed mechanism of these reactions is unclear, we can make the following observations. There is no reaction between **4** and **6** in benzene in the absence of acetic acid. Hence, mechanisms involving an uncatalyzed Michael reaction or cycloaddition step must be excluded in this case.[16,18] The *trans* diketone is stable to the reaction conditions (dimethyl sulfoxide as solvent), eliminating equilibration of the isomers by a reverse aldol reaction. The *trans* isomer was also formed exclusively (but in lower yield) by the method of Newman and Ramachandran[13] in which the Michael adduct, triketone **7**, is presumably formed first, then cyclized by treatment with pyrrolidine in benzene. If the free triketone is indeed an intermediate in these reactions, the stereochemistry must be determined in the intramolecular aldol cyclization stage rather than in the Michael addition. The change in stereochemistry would then be the result of a solvent effect upon the course of the aldol cyclization step. With the cyclohexanone reactants which have been employed in other Robinson annulations with pentenone,[11,12] the stereochemistry must be fixed in the Michael addition step of the overall reaction.

The *trans* relationship between the adjacent methyl groups in **3b** was established by the reaction sequence in Scheme I. The monoethylene ketal was obtained

Scheme I



(49%) by reaction with ethylene glycol and *p*-toluenesulfonic acid in benzene. The selective reaction at the conjugated carbonyl group provides evidence for the steric effect of the secondary methyl group. In the absence of the methyl group ketalization occurs selectively in the opposite sense.[19]

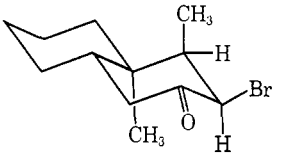
Wolff–Kishner reduction of the exposed carbonyl group in **8** followed by removal of the ketal protecting group affords the dimethyloctalone **9** (91%). Conjugate reduction to the decalone **10** was effected with lithium in liquid ammonia in 72% yield.[20] The bromoketone (**11**) was obtained after exposure of **10** to bromine in acetic acid. The bromine atom must be equatorial and adjacent to the secondary methyl group in view of the shift in the carbonyl frequency (**10** → **11**, $\Delta\nu = +20$ cm^{-1}) and dehydrobromination (calcium carbonate in dimethyl acetamide) to the new dimethyloctalone 12.

The nmr spectrum of **11** exhibits a doublet at τ 4.84 with $J = 5.1$ Hz for the proton on carbon-bearing bromine. The low magnitude of this coupling constant requires that the adjacent hydrogen be equatorial (assuming chair conformations only); hence, the methyl group at this position must be axial (*cf.* **11a**).[21]

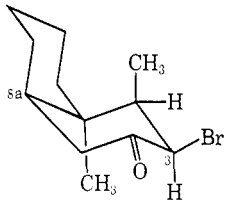
(13) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).
(14) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(15) S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *Tetrahedron Lett.*, 3489 (1966); Y. Kitahara, A. Yoshikoshi, and S. Dida, *ibid.*, 1763 (1964).
(16) *Cf.* G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(17) Diketones **3a** and **3b** have been independently prepared from 4 and **5** by Hale and Zalkow[11c] under somewhat different conditions.
(18) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 212–214, and references cited.
(19) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964); J. E. McMurry, *ibid.*, **90**, 6821 (1968).
(20) Glpc analyses showed the presence of a minor (10%) impurity in the crude product, possibly, corresponding to the *cis*-fused isomer of **10**.

If the reaction sequence in Scheme I had originated with the *cis*-diketone **3a**, we can safely predict[22] that the lithium–ammonia reduction of the corresponding *cis*-dimethyloctalone (*i.e.*, *cis*-**9**) would have produced a dimethyl decalone with a *trans*-ring fusion (*i.e.*, **13**) in which the secondary methyl group can only be equatorial. Since this is not the case, we conclude that the methyl groups are, in fact, *trans* as shown in **3b**.[23,24] This assignment is reinforced by the observation that hydrogenation of **12** with palladium on carbon in methanol affords the isomeric dimethyl decalone **13**. These conditions have previously been shown to reduce the optically active dienone (+)-**14** stereoselectively to the enantiomer of **13**.[25]

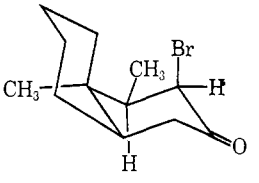
Having established that the methyl groups are *trans* in **3b** and **8–11** and that the secondary methyl group is axial in **11**, we may conclude further that the ring fusion is *trans* as indicated in **10–13**.[26] The chair conformation of a *cis*-fused bromo decalone with the secondary methyl group axial (**15a**) should be unstable (two 1-3 dialkyl diaxial interactions) with respect to its conformational isomer (**15b**) in which the methyl group would be equatorial (one 1-3 alkyl–bromine diaxial interaction). Thus the lithium–ammonia reduction **9** → **10** produced the *trans*-decalone with an ostensibly high stereoselectivity.[20] While there is considerable precedent for the reductions of analogous octalone derivatives to produce *trans*-decalones,[22] the selectivity appears to be greater than would be predicted from consideration of the *trans* and "stereoelectronically-allowed" *cis* transition states derived from **9**.[22a,27a] However, this result seems to be in line with the empirical trend that the *trans*/*cis* product ratio is higher than expected on the basis of the conformational energies involved.[27b]



11a



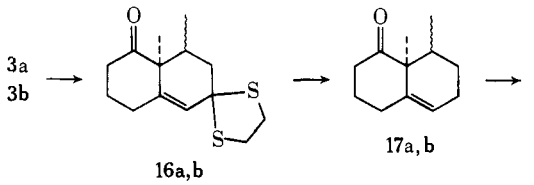
15a



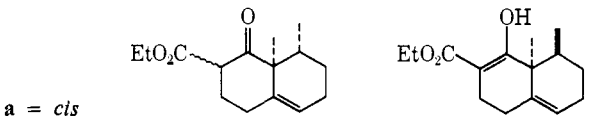
15b

The next stage of the synthesis requires removal of the allylic oxygen function in diketone **3a**, then introduction of a substituent adjacent to the remaining ketone. The first requirement was met by selective thioketal formation and desulfurization, the second by carbethoxylation. Although **3a** could be obtained in relatively pure form by chromatography, it proved to be more expedient to defer the isomer separation. The stereochemical identity of the intermediates was assured by performing these transformations separately with the pure *trans* diketone **3b**.

Reaction of the **3a** + **3b** mixture (or pure **3b**) with ethanedithiol in acetic acid with *p*-toluenesulfonic acid as catalyst furnished the monothioketals **16a** + **16b** (or **16b**) in good yield. The appearance of an unsplit vinyl proton signal in the nmr spectrum of **16** ensures that the double bond position was unaltered in this conversion. Desulfurization was effected by treatment with freshly prepared W-2 Raney nickel in absolute ethanol for 30 min at 5°. The use of longer reaction times, higher temperatures, or Raney nickel previously boiled in acetone[28] promoted serious side reactions. The two ketones, **17a** and **17b**, could be separated from the mixture by careful distillation with an annular-type Teflon spinning band column, or alternatively carried through the carbethoxylation reaction.



16a,b **17a,b**



a = *cis*
b = *trans*

18 **19**

Treatment of **17a** and/or **17b** with sodium hydride and diethyl carbonate in 1,2-dimethoxyethane furnished the corresponding β-keto esters **18** and/or **19**. The nmr spectra indicate that the former exists mainly (~80%) as the keto tautomer, while the equilibrium in the latter case favors the enol form. The two esters could be separated from a mixture by chromatography on neutral alumina.

For the introduction of the dimethylcyclopropane unit of calarene, we elected to use the pyrazoline method[29,30] originally employed by Kishner and

(21) For examples see: W. D. McLeod, Jr., *Tetrahedron Lett.*, 4779 (1965); J. A. Marshall and N. H. Anderson, *J. Org. Chem.*, **31**, 667 (1966); J. A. Marshall, N. H. Anderson, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967).

(22) (a) G. Stork and S. D. Darling, *ibid.*, **86**, 1761 (1964); (b) for numerous examples see "Steroid Reactions," C. Djerassi, Ed., Holden Day, San Francisco, Calif., 1963, Chapter 7; (c) for some exceptions see W. Herz and J. J. Schmid, *J. Org. Chem.*, 34, 3473 (1969).

(23) The same conclusion has been reached by Zalkow and Hale[12c] on the basis of optical rotatory dispersion evidence.

(24) Both **9** and *cis*-**9** have recently been prepared independently by a quite different route by J. J. Sims and L. H. Selman [*Tetrahedron Lett.*, 561 (1969)]. The identity of the former compound from both laboratories has been established by the correspondence of the infrared spectra, nmr spectral data, and 2,4-dinitrophenylhydrazone melting point. The stereochemistry of the latter was proven in a similar manner by these workers.

(25) L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 6354 (1960).

(26) The *trans*-ring fusion assignment has been verified by comparison of the properties (infrared and nmr spectra, melting point and mixture melting point of the 2,4-dinitrophenylhydrazone derivative) of **13** with those of the same compound obtained by lithium–ammonia reduction of *cis*-**9**.[24] We are grateful to Professor Sims for making this comparison.

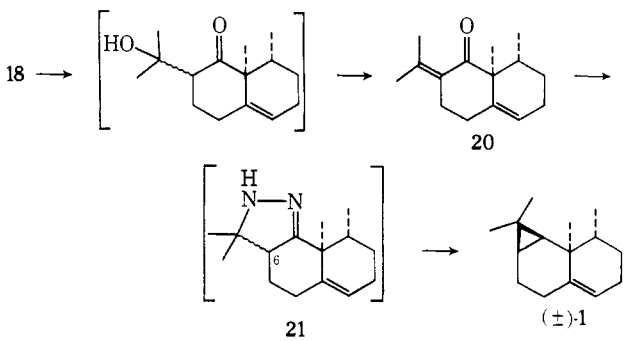
(27) (a) The lithium–ammonia reduction of **9** is to our knowledge the first reported case in which the stereoelectronicaly allowed *cis* conformation is essentially equivalent in energy to the *trans*. On this basis one would have predicted[22a] the formation of perhaps 40–50% of the *cis*-fused isomer of **10**. (b) M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965); F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(28) G. Rosenkranz, St. Kaufmann, and J. Romo, *J. Amer. Chem. Soc.*, **71**, 3689 (1949).

(29) N. Kishner and A. Zavadovsky, *J. Russ. Phys. Chem.*, **43**, 1132 (1911); *Chem. Abstr.*, **6**, 854 (1912); N. Kishner, *ibid.*, 43, 1554 (1911); *Chem. Abstr.*, **6**, 1430 (1912).

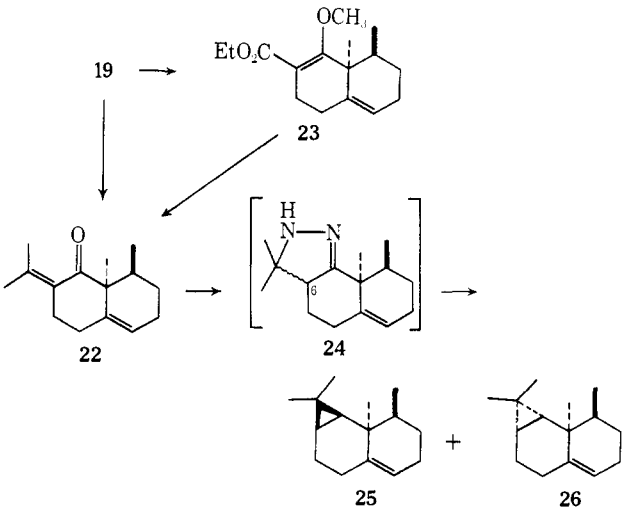
(30) (a) Y. R. Naves and G. Papazian, *Helv. Chim. Acta*, **25**, 984 (1942); (b) E. D. Andrews and W. E. Harvey, *J. Chem. Soc.*, 4636 (1964).

Zavodovsky in the synthesis of carane.[31] The required isopropylidene ketone **20** could be prepared in 89% yield by direct reaction of **18** with excess methyllithium in ether followed by dehydration of the ketol intermediate with 1% concentrated hydrochloric acid in methanol. The steric congestion in the proximity of the annular carbonyl group is no doubt responsible for the selective reaction at the ester function in **18**,[32] and obviated a ketone protecting group[30b] in the present case.



The 2-pyrazoline **21** was formed by reaction of **20** with 1 equiv of hydrazine in absolute ethanol. Pyrolysis of the unpurified pyrazoline over powdered potassium hydroxide[30b] at 240–250° gave rise to (±)-calerene (**1**) with only traces of impurities. The synthetic material proved to be identical with natural (+)-calarene[33] on the basis of infrared, 100-MHz nmr, mass spectral, and glpc comparisons.

In order to confirm the relative stereochemistry proposed for calarene, we have also prepared two of the three possible stereoisomers. The isopropylidene ketone in the *trans* series (**22**) was secured from the enolic ester **19** in the same way as before in 90% yield.



A less efficient alternative procedure for the preparation of **22** involved preliminary conversion to the methyl enol ether **23** by prolonged exposure to diazomethane, followed by reaction with methyllithium and subsequent acid-catalyzed hydrolysis.

Pyrolysis of the 2-pyrazoline **24** obtained from **22** resulted again in smooth formation of the dimethylcyclopropane ring. However, in this case two isomers were obtained in a 3:1 ratio. The major product was isolated in a pure state by preparative glpc and recrystallization. The spectral properties of the minor isomer were inferred from the spectra of the mixture. The nmr spectral data (see Experimental Section) leave no doubt that the two products are the cyclopropane isomers **25** and **26**. The nmr and infrared spectra and glpc retention times of both isomers are distinctly different from those of the natural and synthetic calarene, thus assuring that the vicinal methyl groups in calarene are *cis* as originally assigned.[4,5]

The major product is tentatively assigned the relative stereochemistry **25** with the cyclopropane attached *anti* to the angular methyl group. The assignment is based upon the similarity of the chemical shifts for the *gem*-dimethyl groups in the nmr spectra of the predominant isomer (τ 8.96 and 9.04) and calarene (one pair from the three methyl signals τ 8.94, 8.99, and 9.02) as contrasted to the less abundant isomer (τ 8.84 and 8.99). Examination of models indicates that the orientation of the three-membered ring significantly alters the spatial relationship between the double bond and the *endo*-methyl group in the three isomers, and is presumed to be responsible for the observed differences in chemical shifts.

While it seems certain that the mechanism of formation of cyclopropanes from 2-pyrazolines involves prior tautomerization to the 1-pyrazoline followed by thermal ejection of molecular nitrogen,[34] the factors which dictate the stereochemistry of the three-membered ring are less certain. The proposal that the configuration of the cyclopropane ring will be that resulting from the conformationally more stable 2-pyrazoline in fused ring systems[35] is consistent with the limited stereochemical information available.[35,36] The stereoselective formation of the *anti*-cyclopropane isomers (±)-**1** and **25** seems to be in line with this suggestion since models indicate that the respective *anti*-2-pyrazoline epimers (*i.e.*, with the C-6 proton *cis* to the angular methyl group) should be more stable than the *syn*-pyrazolines for which boat-like conformations are unavoidable. The formation of a substantial proportion of the *syn*-cyclopropane product (**26**) requires that either the pyrazoline precursor **24** was a mixture of the *syn* and *anti* isomers or that epimerization of the 6 position *via* a 3-pyrazoline occurred under the rigorous conditions of pyrolysis. In either case, it is apparent that the stereoselectivity in the overall conversion from the isopropylidene ketones **20** and **22** to the fused-ring cyclopropanes is influenced significantly by the orientation of the secondary methyl group.

(31) For other methods see ref 6b and 8 and the following: G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Amer. Chem. Soc.*, **91**, 6473 (1969); G. Büchi and H. J. E. Loewenthal, *Proc. Chem. Soc.*, 280 (1962); J. Streith and A. Blind, *Bull. Soc. Chim. Fr.*, 2133 (1968); E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); E. J. Corey and M. Jautelat, *ibid.*, **89**, 3912 (1967).

(32) When this reaction sequence is applied to 2-carbethoxycyclohexanone, a mixture of several components is produced in contrast to the reactions with **18** and **19**.

(33) Authentic samples of natural calarene were contributed by Professor V. Herout[5a] and Professor G. Ourisson[5b,c] to whom we are very grateful.

(34) W. M. Jones, P. O. Sanderfer, and D. G. Baarda, *J. Org. Chem.*, **32**, 1367 (1967), and references cited therein.

(35) B. Ramamoorthy and G. S. Krishna Rao, *Tetrahedron Lett.*, 5145 (1967).

(36) D. E. Evans, G. S. Lewis, P. J. Palmer, and D. J. Weyell, *J. Chem. Soc. C*, 1197 (1968); H. G. Heller and R. A. N. Morris, *ibid.*, 1004 (1966).

Experimental Section[37]

4α,4aα-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (3a) and 4β,4aα-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5-(3H,6H)-dione (3b). A solution of 5.0 g (40 mmol) of 2-methyl-1,3-cyclohexanedione, 3.1 g (44 mmol) of pyrrolidine, and 75 ml of benzene was heated at reflux for 3 hr using a Dean–Stark trap to collect the water. The benzene and excess pyrrolidine were then removed under reduced pressure. To the resulting crude enamine was added 3.7 g (44 mmol) of *trans*-3-penten-2-one[38] and 30 ml of benzene followed by a solution consisting of 5.3 g (88 mmol) of acetic acid, 5.0 ml of water, and 2.5 g of sodium acetate. The mixture was heated at reflux under nitrogen with stirring for 4 hr. The reaction mixture was cooled and then thoroughly extracted with benzene. The benzene solution (approximately 80 ml) was washed with four 10-ml portions of 10% concentrated hydrochloric acid and then once with saturated sodium bicarbonate, dried with sodium sulfate, and evaporated to give 6.9 g of a yellow-orange oil which partially solidified upon standing in a refrigerator. Glpc analysis (column A, 163°, 75 ml/min) of the material revealed three peaks: 88% of diketone **3b**, 9% of diketone **3a**, and 3% of a ketonic impurity. The relative retention times were 1.00, 1.09, and 0.75, respectively. The material was chromatographed on 150 g of Woelm neutral alumina (activity III). Elution with 10–30% ether in petroleum ether (bp 30–60°) and evaporation of most of the solvent from the fractions gave 4.55 g (59%) of diketone **3b** as white crystals, mp 79.5–81°. Recrystallization from ether–petroleum ether (bp 30–60°) gave an analytical sample: mp 82.5–83.5°; ν_{max} 1715 (C=O), 1675 (C=O), 1625 (C=C), 1460, 1322, 1238, 1013, and 945 cm^{-1}; τ 4.25 (s, 1 H), 8.55 (s, 3 H), and 9.12 (d, 3 H, J = 7.0 Hz).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.20; H, 8.47.

The mother liquors from the chromatography fractions were combined and evaporated to give an oil which contained a significant percentage of diketone **3a** as well as **3b**. Preparative glpc (column A, 160°) gave **3a** as a colorless oil which crystallized. Recrystallization from ether–petroleum ether (bp 30–60°) gave an analytical sample: mp 58–60°: ν_{max} 1717 (C=O), 1674 (C=C), 1628 (C=C), 1455, 1345, 1285, 1012, and 939 cm^{-1}; τ 4.23 (s, 1 H), 8.69 (s, 3 H), and 8.98 (d, 3 H, J = 6.2 Hz).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.44.

Preparation of the Diketones 3a and 3b in Formamide. A solution of 100.0 g (0.800 mol) of 2-methyl-1,3-cyclohexanedione, 62.5 g (0.880 mol) of pyrrolidine, and 600 ml of benzene was heated at reflux for 3 hr using a Dean–Stark trap to collect the water. The benzene and excess pyrrolidine were then removed under reduced pressure. To the resulting crude enamine was added 800 ml of formamide, 74.0 g (0.880 mol) of *trans*-3-penten-2-one,[38] and a solution of 100 g (1.67 mol) of acetic acid, 100 ml of water, and 50 g of sodium acetate. The resulting solution was heated at 85° with stirring for 4 hr under nitrogen. Glpc analysis (column A, 167°, 200 ml/min) of small aliquots taken at various times during the reaction revealed that heating more than 3 hr did not produce more diketone. The reaction mixture was cooled and thoroughly extracted with a total of 1500 ml of benzene. The benzene solution was washed with five 200-ml portions of 10% concentrated hydrochloric acid and then once with saturated sodium bicarbonate, dried with sodium sulfate, and evaporated to give 54 g of an orange-red oil. The material was chromatographed on 400 g of Woelm neutral alumina (activity III). Elution with 10–30% ether in petroleum ether (bp 30–60°) gave 41.0 g (27%) of a slightly yellow oil which contained equal amounts of diketones **3a** and **3b** according to glpc and nmr analysis.

The diketones **3a** and **3b** were also prepared in formamide by the following procedure. A solution of 80.0 g (0.635 mol) of 2-methyl-1,3-cyclohexanedione, 49.7 g (0.700 mol) of pyrrolidine, and 500 ml of benzene was heated at reflux for 4 hr using a Dean–Stark trap to collect the water. The benzene and excess pyrrolidine were then removed under reduced pressure. To the resulting crude enamine was added 640 ml of formamide, 58.8 g (0.700 mol) of *trans*-3-penten-2-one, and 42 g (0.70 mol) of acetic acid. The solution was heated at 80° with stirring for 16 hr under nitrogen. A solution consisting of 21 g (0.35 mol) of acetic acid, 60 ml of water, and 30 g of sodium acetate was then added, and the solution was heated at 80° for an additional 3.5 hr. Isolation as described previously gave 27.4 g (23%) of a 1:1 mixture of diketones **3a** and **3b**. A summary of the effect of various solvents on the stereoselectivity and yield of the reaction is as follows: solvent (**3b**/**3a** ratio, combined yield of **3a** and **3b**), benzene (10, 59%), ethanol (4, ~20%), N,N-dimethylformamide (2.5, ~30%), N-methylformamide (2, ~30%), hexamethylphosphoramide (2, ~30%), formamide (1, 27%), and dimethyl sulfoxide (1, ~20%).

4β,4aα-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione 2-Ethylene Ketal (8). A mixture of 900 mg (4.7 mmol) of diketone **3b**, 20 mg of *p*-toluenesulfonic acid monohydrate, 1.6 g (26 mmol) of ethylene glycol, and 35 ml of benzene was heated at reflux with stirring under nitrogen for 4 hr with water being removed using a Dean–Stark trap. The reaction mixture was then cooled, washed with saturated sodium bicarbonate solution, saturated sodium chloride and water, dried over sodium sulfate, and evaporated to give a yellow oil. This material was chromatographed on 50 g of Woelm neutral alumina (activity III). Elution with 10% ether in petroleum ether (bp 30–60°) gave 520 mg (47%) of ketal **8** as colorless crystals, mp 81.5–83.5°. Further elution with 25–50% ether in petroleum ether gave some diketone **3b**. Recrystallization of the ketal from ether–petroleum ether (bp 30–60°) gave an analytical sample: mp 87–88°; ν_{max} 1715, 1359, and 1101 cm^{-1}; τ 4.34 (m, 1 H), 6.17 (m, 4 H, $-OCH_2CH_2O-$ protons), 8.73 (s, 3 H), and 9.17 (d, 3 H, J = 7.0 Hz).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.14; H, 8.61.

4β,4aα-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (9). A solution of 10.3 g (43.6 mmol) of ketal **8** 6.0 ml of 85% hydrazine hydrate (105 mmol), and 7.90 g (141 mmol) of potassium hydroxide in 84 ml of diethylene glycol was heated at reflux under nitrogen for 1.5 hr. The condenser was removed and liquid was allowed to distill until the pot temperature rose to 200°. The solution was cooled, diluted with water, and thoroughly extracted with ether. The combined ether extracts were washed with 10% concentrated hydrochloric acid and then with water, dried over magnesium sulfate, and evaporated to give a yellow oil which showed no carbonyl band in the infrared spectrum. The oil was then heated with 40 ml of 90% acetic acid in water on a steam bath for 35 min. The reaction mixture was cooled and diluted with ether. The ether solution was carefully washed with saturated sodium bicarbonate and then with water, dried with magnesium sulfate, and evaporated. The residual oil (7.15 g, 91%) showed a single peak on analysis by glpc (column A, 139°, 200 ml/min): ν_{max} 1668 (C=O), 1618 (C=C), 1445, 1379, 1357, 1287, and 1246 cm^{-1}; τ 4.39 (s, 1 H), 8.72 (s, 3 H), and 9.02 (d, 3 H, J = 7.0 Hz). Compound **9** was further characterized as a red 2,4-dinitrophenylhydrazone derivative,[39] mp 134–136° from 95% ethanol.

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19. Found: C, 60.60; H, 6.44.

4β,4aα-Dimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1H)-one (10). A solution of 7.0 g (39 mmol) of ketone **9** in 100 ml of tetrahydrofuran was added dropwise over a period of 30 min to a stirred, dark blue solution of 700 mg (0.10 g-atom) of lithium in 300 ml of anhydrous ammonia under argon. After the addition

(37) All melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 137 or Model 521 spectrometer using sodium chloride cells. All spectra were determined in carbon tetrachloride solution unless otherwise specified and were calibrated with the polystyrene band at 1603 cm^{-1}. Proton magnetic resonance spectra were determined with a Varian Associates Model A-60A or A-56-60 spectrometer using tetramethylsilane as an internal standard. A Varian Associates Model HA-100 spectrometer was used where indicated. All nmr spectra were determined in carbon tetrachloride solution unless otherwise specified. Mass spectra were determined on an Atlas CH4 mass spectrometer. Microanalyses were determined in the University of Illinois microanalytical laboratory. Gas chromatography (glpc) was performed on a Wilkens Aerograph A-90-P instrument employing helium as the carrier gas. The following columns were used: a 5 ft × 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column A), a 6 ft × 3/8 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column B), a 5 ft × 0.25 in. column of 3% SE-30 on 60–80 mesh Chromosorb W (column C), a 6 ft × 0.25 in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column D), a 6 ft × 3/8 in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column E), and a 5 ft × 0.25 in. column of 15% FFAP on 60–80 mesh Chromosorb W (column F).

(38) S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, 28, 928 (1963); J. E. Baldwin, *ibid.*, 30, 2423 (1965).

(39) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 253.

was completed, the solution was stirred an additional 40 min. Ammonium chloride was then added to discharge the blue color. The ammonia was allowed to evaporate and the residue was extracted with ether. The ether solution was washed with 10% concentrated hydrochloric acid and then with water, dried with magnesium sulfate, and evaporated to give 6.5 g of a yellow oil. The infrared spectrum of the crude ketone revealed that it contained an alcoholic impurity. This impurity was removed by treating the material with chromium trioxide reagent in acetone.[40] Glpc analysis (column D, 134°, 150 ml/min) of the crude oxidation product showed ketone **10** (90%) and an unidentified compound (10%) of slightly longer retention time which may have been the *cis*-fused isomer of **10**. Distillation provided 5.0 g (72%) of **10** as a colorless oil: bp 133–137° (9 mm); ν_{max} 1713 (C=O), 1451, 1423, 1382, 1278, 1242, and 1158 cm^{-1}; τ 8.84 (s, 3 H) and 9.08 (d, 3 H, J = 7.0 Hz). Ketone **10** gave an orange 2,4-dinitrophenylhydrazone derivative,[39] mp 164–166° from 95% ethanol.

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.96; H, 6.84; N, 15.35.

4β,4aα-Dimethyl-3β-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2-(1H)-one (11). To a stirred solution of 1.00 g (5.56 mmol) of ketone **10** in 5 ml of acetic acid at 10° was added dropwise over a period of 10 min a solution of 0.90 g (5.62 mmol) of bromine in 6 ml of acetic acid. After an additional 20 min, the reaction mixture was poured into 40 ml of water, whereupon a viscous oil separated and solidified in an ice bath. The supernatant liquid was decanted and the residue was dissolved in ether. The ether solution was washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried over sodium sulfate, and evaporated to give a white solid which upon recrystallizaton from ether–petroleum ether (bp 30–60°) gave 1.08 g (75%) of **11** as white crystals, mp 105–108°. Two more recrystallizations from ether–petroleum ether gave an analytical sample: mp 107.5–108.5°; ν_{max} 1733 (C=O), 1449, 1386, and 1167 cm^{-1}; τ 4.84 (d, 1 H, J = 5.1 Hz), 8.72 (s, 3 H), and 8.99 (d, 3 H, J = 7.0 Hz).

4,4aα-Dimethyl-4a,5,6,7,8,8aβ-hexahydronaphthalen-2(1H)-one (12). A mixture containing 1.00 g (3.86 mmol) of α-bromoketone **11** (8.40 mg, 8.40 mmol) of calcium carbonate, and 33 ml of N,N-dimethylacetamide was heated at mild reflux with stirring under nitrogen for 17 min. The reaction mixture was cooled and then thoroughly extracted with petroleum ether (bp 30–60°). The combined extracts were washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried with sodium sulfate, and evaporated to give 623 mg of a yellow oil. This material was chromatographed on 20 g of Woelm neutral alumina (activity III). Elution with 5–10% ether in petroleum ether gave 455 mg of a colorless oil. Glpc analysis (column D, 159°, 160 ml/min) revealed two components: **12** (87%) and what appeared to be **9** (13%). Preparative glpc (column B, 135°) provided an analytical sample of **12**: ν_{max} 1668 (C=O), 1617 (C=C), 1449, 1381, 1329, and 1259 cm^{-1}; τ 4.42 (quartet, 1 H, J = 1.5 Hz), 8.14 (d, 3 H, J = 1.5 Hz), and 8.91 (s, 3 H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.17. Found: C, 80.75; H, 10.26.

4α,4aα-Dimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1H)-one (13). A mixture of 250 mg (1.40 mmol) of **12** (contaminated with 13% of an impurity, presumably **9**), 50 mg of 5% palladium on carbon, and 20 ml of absolute methanol was stirred under 1 atm of hydrogen for 20 min. The solvent was removed from the filtered reaction mixture to give 255 mg of a colorless oil. Glpc, thin layer chromatography, and the infrared spectrum of the product indicated that it was a mixture of ketone **13** and its methyl ketal (hemiketal) as was previously reported by Djerassi, Zalkow, and Markley.[25] Therefore, the material was stirred at room temperature for 0.5 hr with 3 ml of a 1:1 mixture of 3 *N* hydrochloric acid and dioxane. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed with saturated sodium bicarbonate and saturated sodium chloride, dried with sodium sulfate, and evaporated to give 242 mg of a colorless oil. Glpc analysis (column D, 158°, 160 ml/min) revealed that the ketal was gone and that only **13** remained except for 13% of an impurity which probably resulted from the hydrogenation of **9**. The material was purified by preparative glpc (column E, 156°) to yield 162 mg (64%) of **13** as a colorless oil: n^{25}D 1.4903 (lit.[25] n^{25}D 1.4907); ν_{max} 1714 (C=O), 1449, 1418, 1388, 1290, 1245, and 1158 cm^{-1}; τ 9.09 (s, 3 H) and 9.12 (d, 3 H, J = 6.2 Hz). Compound **13** gave an orange-yellow 2,4-dinitrophenylhydrazone derivative,[39] mp 141–142° from 95% ethanol (lit.[25] 136–138°, optically active). A direct comparison between our hydrozone and that of the ketone reported by Sims and Selman was kindly performed by Professor Sims:[26] our derivative mp 145–146°, their derivative mp 144–145°, mmp 144–145°.

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.13; H, 6.76; N, 15.28.

4α,4aα-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione 2-Ethylene Thioketal (16a) and 4β,4aα-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione 2-Ethylene Thioketal (16b). A solution of 26.0 g (0.135 mol) of the 1:1 mixture of diketones **3a** and **3b**, 13.4 g (0.143 mol) of ethanedithiol, and 10.0 g of *p*-toluenesulfonic acid monohydrate in 325 ml of acetic acid was stirred for 8 hr at room temperature. The reaction mixture was then poured into water and thoroughly extracted with chloroform. The chloroform solution was washed with water, 5% sodium hydroxide, and again with water, dried over sodium sulfate, and evaporated to give 36.0 g (99%) of a yellow oil which was used without further purification. The infrared spectrum shows only one carbonyl band at 1713 cm^{-1}. Since thioketal **16b** was also prepared from pure diketone **3b** by the above procedure, it was possible to distinguish between the nmr absorptions of the two isomers: **16b** τ 4.43 (s, 1 H), 6.70 (m, 4 H, $-SCH_2CH_2S-$), 8.72 (s, 3 H), and 8.98 (d, 3 H, J = 6.5 Hz); **16a** τ 4.93 (s, 1 H), 6.70 (m, 4 H, $-SCH_2CH_2S-$), 8.83 (s, 3 H), and 9.02 (d, 3 H, J = 6.0 Hz).

8α,8aα-Dimethyl-3,4,6,7,8,8a-hexahydronaphthalen-1(2H)-one (17a) and 8α,8aβ-Dimethyl-3,4,6,7,8,8a-hexahydronaphthalen-1(2H)-one (17b). A mixture of 31.5 g (0.118 mol) of the 1:1 mixture of thioketals **16a** and **16b** and 255 g of freshly prepared W-2 Raney nickel[41] in 1500 ml of absolute ethanol was stirred for 30 min at 5°. The ethanol solution was then decanted and the Raney nickel was washed with two 500-ml portions of ethanol. The combined fractions were filtered and concentrated to give an oily residue which was diluted with petroleum ether (bp 30–60°), washed with water, dried over sodium sulfate, and evaporated to give 15.5 g of a yellow oil. Chromatography of the oil on 50 g of Woelm neutral alumina (activity II) and elution with 0–5% ether in petroleum ether (bp 30–60°) gave 14.0 g (67%) of a slightly yellow oil which contained ketones **17a** and **17b** as a 1:1 mixture according to glpc and nmr data. This mixture was sufficiently pure to be used in the synthesis of a mixture of the β-keto esters **18** and **19**. Separation of ketones **17a** and **17b** was achieved by fractional distillation on a Nester–Faust annular spinning band column with a 30:1 reflux ratio. Pure fractions of both isomers were obtained along with some mixed fractions. Since ketone **17b** was also prepared from pure thioketal **16b** by the above procedure, it was possible to assign the stereochemistry of the two isomers. Ketone **17b** crystallized upon distillation, bp 121.5° (8.5 mm). Recrystallization from petroleum ether (bp 30–60°) provided an analytical sample: mp 45–47°; ν_{max} 1709, 1662, 1380, 1322, 1259, 1236, 1089, and 1039 cm^{-1}; τ 4.60 (m, 1 H), 8.75 (s, 3 H), and 9.17 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.17. Found: C, 80.91; H, 10.04.

No further purification was required to obtain an analytical sample of ketone **17a**: bp 123.5° (8.5 mm); n^{25}D 1.5073; ν_{max} 1709, 1658, 1377, 1309, 1226, 1215, 1149, 1081, and 1012 cm^{-1}; τ 4.55 (m, 1 H), 8.83 (s, 3 H), and 9.07 (d, 3 H, J = 6.2 Hz).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.17. Found: C, 80.64; H, 10.29.

Ethyl 8α,8aα-Dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (18). A mixture of 712 mg (4.00 mmol) of ketone **17a**, 1.91 g (16.2 mmol) of diethyl carbonate, 540 mg (12.6 mmol) of a 56% dispersion of sodium hydride in mineral oil, and 8 ml of 1,2-dimethoxyethane was heated to 85° with stirring under nitrogen. To assure that the reaction had started, 0.02 ml of absolute ethanol was then added. After heating at 85° for 1.5 hr, the reaction mixture was cooled to 0–5°, and absolute ethanol was added dropwise to destroy excess sodium hydride. A solution of 0.84 g (14 mmol) of acetic acid in 10 ml of water at 0–5° was then added to the cold reaction mixture with rapid stirring under nitrogen. The resulting solution was thoroughly extracted with benzene. The benzene solution was washed with sodium bicarbonate and then water, dried over sodium sulfate, and evaporated to give a yellow oil which was found by glpc (column A, 162°, 200 ml/min) to

(40) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(41) R. Mozingo, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 181.

contain in addition to the ester small amounts of three impurities of lower retention time. The material was chromatographed on 30 g of Woelm neutral alumina (activity II). Initial elution with petroleum ether (bp 30–60°) gave a mixture of the three impurities and a small amount of unreacted ketone **17a**. Elution with 10% ethyl ether in petroleum ether gave 524 mg (53%) of ester **18** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 170°): $n^{25}D$ 1.5028; ν_{max} 1745, 1713, 1641, 1601, 1374, 1309, 1255, 1236, 1184, and 1040 cm^{-1}. The nmr spectrum is complicated due to the presence of both the β-keto ester and its enol tautomer. Absorptions appear at τ −2.80 (s, ~0.2 H), 4.48 (m, H, C-5 proton), and 6.42 (m, 0.8 H, C-2 proton). There are two overlapping quartets at τ 5.78 and 5.82 (total of 2 H, J = 7.0 Hz). The region from τ 8.50 to 9.20 integrates as 9 protons and contains the following: a partially hidden triplet at τ 8.71 (J = 7.0 Hz, methyl of the ethoxy group), two singlets at τ 8.73 and 8.76 (C-8a methyl), two doublets at τ 9.02 and 9.06 (J = 6.2 Hz, C-8 methyl), and a singlet at τ 8.94. The fact that the absorption at τ 6.42 appears as a multiplet instead of a quartet indicates that the keto tautomer may be present with the ester group both axial and equatorial. The singlet at τ 8.94 may be the quaternary methyl of the axial epimer of the keto form.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.08; H, 8.64.

Preparation of the β-Keto Ester 18 from a Mixture of the Ketones 17a and 17b. A solution of 5.00 g (28.1 mmol) of the 1:1 mixture of the ketones **17a** and **17b**, 13.2 g (112 mmol) of diethyl carbonate, 3.36 g (84.0 mmol) of a 60% dispersion of sodium hydride in mineral oil, and 55 ml of 1,2-dimethoxyethane was heated to 85° with stirring under nitrogen. To assure that the reaction had started, 0.15 ml of absolute ethanol was added. After heating for 2 hr the reaction mixture was cooled to 0–5°, and 3.0 ml of absolute ethanol was added. After stirring the solution at 0–5° for 20–25 min, a solution of 5.56 g (92.7 mmol) of acetic acid in 60 ml of water at 0–5° was added with rapid stirring under nitrogen. Isolation as described previously gave 8.7 g of a yellow oil which was chromatographed on 210 g of Woelm neutral alumina (activity II). Elution with petroleum ether gave 2.50 g (36%) of β-keto ester **19** which was also synthesized from pure ketone **17b** (see below). Elution with 10% ether in petroleum ether (bp 30–60°) gave 2.01 g (29%) of β-keto ester **18**. The infrared and nmr spectra of **18** were identical with those previously reported.

2(3H)-Isopropylidine-8α,8aα-dimethyl-4,6,7,8-tetrahydronaphthalen-1(8aH)-one (20). Methyllithium was prepared by adding 5.65 g (40.0 mmol) of methyl iodide to 0.56 g (0.080 g-atom) of small lithium pieces in 32 ml of anhydrous ether under argon at a rate such that there was only very mild refluxing of the ether. After the addition was completed, the solution was stirred an additional 0.5 hr. To the stirred methyllithium solution under argon was added dropwise over a period of 15 min a solution of 600 mg (2.40 mmol) of ester **18** in 4 ml of ether. The ether solution was heated at reflux for 2.0 hr, then cooled, and poured into 40 ml of ice-cold 10% ammonium chloride. The solution was thoroughly extracted with ether, washed with water, dried over sodium sulfate, and evaporated to give a colorless oil which shows bands at 3460 and 1702 cm^{-1} in its infrared spectrum. The oil was treated with a solution of 0.10 ml of hydrochloric acid in 10 ml of absolute methanol. The solution was heated at reflux under nitrogen for 2.75 hr, then extracted with petroleum ether (bp 30–60°). The petroleum ether solution was washed with sodium carbonate and then water, dried over sodium sulfate, and evaporated to give a yellow oil which was chromatographed on 15 g of Woelm neutral alumina (activity II). Elution with petroleum ether (bp 30–60°) gave 466 mg (89%) of **20** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 168°): $n^{25}D$ 1.5216; ν_{max} 1689, 1668 (split carbonyl), 1626 (conjugated C=C bond), 1384, 1278, 1029, 992, and 848 cm^{-1}; τ 4.55 (m, 1 H), 8.19 (s, 3 H), 8.27 (s, 3 H) 8.94 (s, 3 H), and 9.08 (d, 3 H, J = 6.0 Hz).

A sample of **20** eventually crystallized and after two recrystallizations from petroleum ether (bp 30–60°) gave colorless crystals, mp 27.5–28.5°, which gave an infrared spectrum identical with that reported above.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.60; H, 10.25.

(±)-Calarene (1). To a stirred solution of 77 mg (0.075 ml, 1.5 mmol) of 99–100% hydrazine hydrate in 0.25 ml of absolute ethanol at 0–5° was added dropwise over a period of 15 min a solution of 327 mg (1.50 mmol) of **20** in 0.50 ml of absolute ethanol also at 0–5°. The resulting solution was heated at a gentle reflux under nitrogen for 1.5 hr. Solvent was then thoroughly removed under reduced pressure. Due to the unstable nature of the intermediate pyrazoline, the resulting viscous oil was immediately treated with 30 mg of powdered potassium hydroxide,[30b] and the mixture was heated in an oil bath at 240–250° under nitrogen for 1.5 hr. The resulting yellow oil (275 mg) was found by glpc (column A, 151°, 100 ml/min) to be approximately 87% (±)-**1**. Two small peaks (13%) of slightly longer retention time than (±)-**1** were not investigated. Preparative glpc (column B, 130°) of the crude product gave 135 mg (44%) of (±)-**1** as a colorless oil. The racemic calarene so obtained was identified by comparison of its infrared and 100-MHz nmr spectra with those of a sample of (+)-calarene donated by Professor G. Ourisson.[5b,c] The infrared and nmr spectra of the synthetic calarene were also identical with those of a sample of (+)-calarene from Professor V. Herout.[5c] Concentrated carbon tetrachloride solutions were used for the infrared spectra in order to ensure good comparison of the fingerprint regions. The mass spectra and glpc retention times (column A, 129°, 100 ml/min, and column D, 118°, 85 ml/min) of the synthetic and authentic samples were also identical.

Thioketal 16b from the Pure Diketone 3b. This reaction was performed using 12.0 g (62.5 mmol) of **3b**, 7.05 g (75.0 mmol) of ethanedithiol, 4.6 g of *p*-toluenesulfonic acid monohydrate, and 150 ml of acetic acid in the manner described above for the mixture of **16a** and **16b**. The reaction was completed in 5 hr and yielded 16.7 g (100%) of a yellow oil which was used without further purification. The nmr absorptions were identical with those previously reported. The infrared spectrum has bands at 1713, 1643, 1375, and 1032 cm^{-1}.

Ketone 17b from the Pure Thioketal 16b. This reaction was performed using 16.7 g (62.3 mmol) of **16b**, 135 g of freshly prepared W-2 Raney nickel, and 750 ml of absolute ethanol in the manner described above for the mixture of **17a** and **17b**. The reaction was completed in 20 min and yielded 9.0 g (81%) of **17b** as colorless crystals (mp 45–47°) which had properties identical with those previously reported.

Ethyl 8β,8aα-Dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (19). A mixture of 4.00 g (22.5 mmol) of **17b**, 10.5 g (89.0 mmol) of diethyl carbonate, 2.90 g (67.5 mmol) of a 56% dispersion of sodium hydride in mineral oil, and 45 ml of 1,2-dimethoxyethane was heated to 85° with stirring under nitrogen. To assure that the reaction had started, 0.10 ml of absolute ethanol was added. After heating for 2.5 hr, the reaction mixture was cooled to 0–5°, and absolute ethanol was added dropwise to destroy excess sodium hydride. A solution of 4.5 g (75 mmol) of acetic acid in 15 ml of water at 0–5° was then added to the cold reaction mixture with rapid stirring under nitrogen. Ester **19** was isolated as previously described for **18**. The resulting yellow oil was chromatographed on 140 g of Woelm neutral alumina (activity II). Elution with petroleum ether (bp 30–60°) gave 4.25 g (77%) of **19** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 164°): $n^{25}D$ 1.5160; ν_{max} 1648, 1609, 1381, 1263, 1233, and 1044 cm^{-1} and essentially no bands at 1745 or 1715 cm^{-1}; τ −2.53 (s, *ca.* 1 H), 4.66 (m, 1 H), 5.78 (quartet, 2 H, J = 7.0 Hz), 8.62 (s, 3 H), 8.69 (t, 3 H, J = 7.0 Hz), and 9.18 (d, 3 H, J = 6.7 Hz).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.97; H, 8.96.

Ethyl 3,4,6,7,8,8a-Hexahydro-8β,8aα-dimethyl-1-methoxy-2-naphthoate (23). Diazomethane in ether at 0° prepared from 1.0 g of nitrosomethylurea[42] was distilled under reduced pressure into a solution of 600 mg (2.40 mmol) of **19** in 3 ml of absolute methanol which was cooled in a Dry Ice–isopropyl alcohol bath. The solution was allowed to stand at room temperature until the yellow diazomethane color faded, and then more diazomethane was distilled into the solution as above. Since ether also distilled over with the diazomethane, more methanol was added to the reaction mixture so that it was always at least half methanol. After 7 days the reaction mixture was filtered and evaporated to give an oil which was chromatographed on 30 g of Woelm neutral alumina (activity II). Elution with petroleum ether (bp 30–60°) gave 450 mg (71%) of enol ether **23** as a colorless oil: ν_{max} 1707 and 1612 cm^{-1}; τ 4.72 (m, 1 H), 5.87 (quartet, 2 H, J = 7.0 Hz), 6.28 (s, 3 H), 8.71 (s, 3 H), 8.72 (t, 3 H, J = 7.0 Hz), and 9.21 (d, 3 H, J = 6.7 Hz).

2(3H)-Isopropylidene-8β,8aα-dimethyl-4,6,7,8-tetrahydronaphthalen-1(8aH)-one (22). The reaction was performed in the manner described above for **20**. Methyllithium was prepared from 8.53 g

(42) F. Arndt, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 165.

(60.0 mmol) of methyl iodide and 0.84 g (0.12 g-atom) of lithium in 48 ml of ether. To the methyllithium was added dropwise over a period of 15 min a solution of 1.00 g (4.00 mmol) of **19** in 5 ml of ether, and the solution was heated at reflux for 2 hr. The yellow oil obtained upon work-up was heated at reflux with a solution of 0.17 ml of hydrochloric acid in 17 ml of absolute methanol for 2 hr. Ketone **22** (785 mg, 90%) was isolated as previously described for **20**. An analytical sample was obtained by preparative glpc (column B, 164°): $n^{25}D$ 1.5260; ν_{max} 1683, 1663 (split carbonyl), 1599 (conjugated C=C bond), 1379, 1283, 1205, 997, and 840 cm^{-1}; τ 4.64 (m, 1 H), 7.98 (s, 3 H), 8.22 (s, 3 H), 8.77 (s, 3 H), and 9.26 (d, 3 H, J = 6.8 Hz).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.21; H, 10.25.

Preparation of 22 from Enol Ether 23. The enol ether **23** (100 mg, 0.38 mmol) in 2 ml of ether was added to a solution of methyllithium prepared from 0.14 g (0.020 g-atom) of lithium and 1.42 g (10.0 mmol) of methyl iodide in 7 ml of ether. The resulting solution was heated at reflux for 4.5 hr, cooled and poured into 10 ml of ice-cold 10% ammonium chloride which was then extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated to give an oil which shows a band at 3410 cm^{-1} but no carbonyl band in its infrared spectrum. The oil was then heated at 80° under nitrogen for 1.7 hr with a solution of 1.0 ml of methanol, 0.50 ml of water, and 0.015 ml of hydrochloric acid. The reaction mixture was extracted with ether. The ether solution was washed with saturated sodium carbonate and then water, dried over sodium sulfate, and evaporated. The resulting oil was purified by preparative glpc (column D, 171°) to give 45 mg (54%) of **22** which was identical with that obtained by the previous procedure.

4-*epi*-Calarene (25). To a stirred solution of 75 mg (0.073 ml, 1.5 mmol) of 99–100% hydrazine hydrate in 0.20 ml of absolute ethanol at 0–5° was added dropwise over a period of 15 min a solution of 327 mg (1.50 mmol) of **22** in 0.50 ml of absolute ethanol also at 0–5°. The resulting solution was heated at mild reflux under nitrogen for 1.9 hr. Solvent was then thoroughly removed under reduced pressure. To the remaining viscous oil was added 30 mg of powdered potassium hydroxide[30b] and the mixture was heated at 245–255° under nitrogen for 1.8 hr. Glpc analysis (column A, 130°, 200 ml/min) of the resulting yellow oil (300 mg) revealed it to be at least 95% one peak. This peak was collected by preparative glpc (column B, 133°) to give 151 mg (49%) of a colorless oil. An analytical sample was obtained by preparative glpc (column E, 142°). The mass spectrum of this sample showed the parent ion at *m/e* 204.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.21; H, 11.78.

The nmr spectrum of the product revealed that it was a 3:1 mixture of two compounds. The minor component **26** has nmr absorptions at τ 4.69 (m), 8.66, 8.84, 8.99 (s), 9.04 (d, J = 6–7 Hz), 9.45 (m). The major componen **25** was obtained pure by collecting only the first half of the peak on the above mentioned preparative SE-30 column. The collected material solidified, and three recrystallizations from methanol gave a white solid: mp 60.5–62°; ν_{max} 1667, 1372, 1142, 1126, 1067, 1029, 1014, 976, and 960 cm^{-1}. The nmr spectrum of **25** has a one-proton multiplet at τ 4.69, a three-proton singlet at 8.75, and two singlets at 8.96 and 9.04 which together integrate as 9 protons (C-4 methyl and two geminal methyls). The 100-MHz nmr spectrum shows that these two singlets hide a doublet at τ 9.00 (J = 6.8 Hz). The two cyclopropane protons appear as a multiplet with the major peak at τ 9.61 and other peaks at τ 9.33 and 9.76. The mass spectrum of **25** was essentially identical with that of the mixture of **25** and **26**.

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Molecular Rearrangements. XI.[1] The Synthesis and Neat, Thermal Rearrangement of (+)-(1*R*,3*R*)-2-Chloronorbornene *exo*-Oxide

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Abstract: The synthesis of (+)-(1*R*,3*R*)-2-chloronorbornene *exo*-oxide (**1**) *via* (+)-(1*R*,2*R*)-*exo*-2-norborneol and (−)-(1*R*)-norcamphor is reported. Neat, thermal rearrangement of **1** is found to proceed by >90% chlorine migration to yield (−)-(1*R*,3*R*)-*exo*-3-chloronorcamphor (**2a**), the major rearrangement product. This result together with product stability studies and hydrogen chloride and hydrogen bromide catalyzed rearrangements of this α-chloro epoxide is argued to be supportive evidence for the intermediacy of α-ketocarbonium ion–chloride ion pairs in these rearrangements.

Our results from the neat, thermal rearrangement of the mixture of 1-chloro-*cis*- and -*trans*-4-methylcyclohexene oxide where stereospecific chlorine migration is observed in the formation of *trans*-2-chloro-4-methylcyclohexanone led us to suggest that an α-ketocarbonium ion–chloride ion pair was the intermediate in this molecular rearrangement.[3] The product studies from neat, thermal rearrangement of 2-chloronorbornene *exo*-oxide (**1**),[4] while establishing Wagner–Meerwein rearrangement as a major process, fell short of the desired corroboration of the idea of such ionic intermediates. The major products of neat, thermal rearrangement of **1** are *exo*-3-chloronorcamphor (**2**) and *exo*-2-chloro-7-ketonorbornane (**3**) and the formation of **2** could be explained by either chlorine migration *via* the 3-ketonorborn-2-yl cation–chloride ion pair (**1** → **2a**) or by a hydride shift (**1** → **2b**).[5]

(1) (a) A portion of this work was previously communicated: R. N. McDonald and R. N. Steppel, *J. Amer. Chem. Soc.*, **91**, 782 (1969); (b) for paper X in this series see R. N. McDonald and D. G. Hill, *J. Org. Chem.*, **35**, 2942 (1970).

(2) NDEA Fellow, 1964–1967; NSF Cooperative Fellow, 1967–1968; taken from the Ph.D. Thesis of R. N. Steppel.

(3) R. N. McDonald and T. E. Tabor, *J. Amer. Chem. Soc.*, **89**, 6573 (1967).

(4) R. N. McDonald and T. E. Tabor, *J. Org. Chem.*, **33**, 2934 (1968).

(5) For a flowsheet of some possible pathways and intermediates for the neat, thermal and the hydrogen chloride and acetic acid catalyzed rearrangements of **1** see ref 4.