formation of yellow solid. After 0.5 hr at −10° the suspension was poured into saturated ammonium chloride solution and additional ether was added. The organic phase was washed with saturated sodium bicarbonate and saturated brine and dried, and the solvent was removed to give 26 mg (98% yield) of the olefinic esters **2** and **37** (in the ratio 32:68, respectively). The products were identified by glpc, mass spectrum, tlc, ir, and nmr comparisons with authentic samples.

Alkylation of **35** with lithium dimethylcuprate in ether–tetrahydrofuran (1:5) for 17 hr at 0° gave a very similar ratio of **2** and **37**. Reaction of the acetate **34** in tetrahydrofuran–ether (6:1) or in pure tetrahydrofuran at −10° gave a mixture of **2** and **37** in the ratio of *ca.* 1:1 along with *ca.* 10% of the product from direct displacement of the ester.[16] A small sample of pure **2** was obtained from the latter reaction product by micropreparative glpc, and the mass spectrum was shown to be identical with that of an authentic sample.

Photooxygenation of 6. A 2.4-g sample of **6** in 50 ml of dry pyridine was placed in a glass chromatography column and 50 mg of hematoporphyrin was added. The mixture was irradiated with two 15-W fluorescent lamps while dry oxygen was passed through the solution for 10 hr (the reaction was followed by tlc). The solution was then cooled to 5° and 2.35 g of trimethyl phosphite added dropwise. After 1.5 hr at 5°, acetic anhydride (5.2 g) was added and the solution was left for 2 hr at room temperature. Ice was then added, followed by ice-cold aqueous HCl and extraction with ether. The ether layer was washed with water, brine, saturated $NaHCO_3$, and brine and dried, and the solvent was removed. The residue (2.5 g) was chromatographed on preparative tlc silica gel plates to give 0.80 g (23.4% yield) of **38**: ir (CCl_4) 3080, 1740, 1720, 1650, 1375, 1245, 1155, 920 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (t, 3, J = 7 Hz, CH_3CH_2), 1.77 (d, 3, J = 1 Hz, CH_3C=), 2.10 (s, 6, OAc), 2.18 (d, J = 1.5 Hz, C-3 CH_3), 4.17 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.02 (d, 4, CH_2=C), 5.18 (m, CHOAc), and 5.69 ppm (broad s, 1, H-2); mass spectrum (70 eV) *m/e* M^+ 380.

Ethyl 3,11-Dimethyl-7-ethyltrideca-2,6,10-trienoate (39). To a suspension of cuprous iodide (210 mg, 1.10 mmol) in 5 ml of ether at −10° under argon was added 1.27 ml (2.10 mmol) of methyllithium in ether (1.65 *M*). After a negative Gilman test[20] was obtained, 26 mg (0.055 mmol) of the acetate **38** in ether (1 ml) was added. After 0.5 hr at −10° the mixture was diluted with saturated NH_4Cl and the product (18 mg) recovered with ether. Analysis by glpc (comparison with authentic samples) showed the presence of 14% all trans, 8% trans,cis,cis, and 76% of the trans,cis,trans triene **39**: nmr ($CDCl_3$) δ 0.99 (t, 6, J = 7 Hz, CH_3CH_2C=C), 1.27 (t, 3, J = 7 Hz, CH_3CH_2O), 1.61 (s, 3, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 4.16 (q, 2, J = 7 Hz, CH_2O), 5.11 (CH=C), and 5.68 ppm (broad s, 1, H-2).

Acknowledgment. We thank L. Dunham and V. L. Hendry for invaluable technical assistance, and Dr. W. S. Johnson for a sample of **17**.

Stereoselective Total Synthesis of (±)-Zizaene[1]

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Contribution from the Department of Chemistry, University of Illinois, Urbana, Illinois 61801. *Received December 15, 1971*

Abstract: 1-(3′-Phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl acetate (**9**), obtained by rearrangement of the adduct (**7**) from 3-phenyl-1-propylmagnesium bromide and norcamphor, was converted stereoselectively, by way of unsaturated keto acetate **14**, to the 1′β methyl homolog (**17b**). The relative stereochemistry at the 1′ position was established independently with nmr spectral data from the δ-lactone (**22**) resulting from oxidative cleavage of the side chain phenyl group. The acetoxy acid (**19a**), produced by ozonolysis of the benzene ring in **17b**, was transformed through a sequence of functional group alterations, into a diazopentylnorcamphor intermediate (**3**) which cyclized spontaneously to 1,2,3,4,5,6β,7,8aα-octahydro-3α-methyl-8*H*-3aα,6-methanoazulen-8-one (**4a**). Reduction–methylation of the corresponding *n*-butylthiomethylene derivative (**30b**) of **4a** followed by epimerization at position 5 afforded (±)-13-norzizan-6-one (**32**). Introduction of the exocyclic methylene group into this sterically hindered ketone was achieved by addition of phenylthiomethyllithium, and then reductive elimination of the corresponding benzoate (**30b**) with lithium in liquid ammonia affording (±)-zizaene (**1**).

Zizaene (tricyclovetivene, **1**)[4–6] is the parent hydrocarbon of a small family of tricyclic sesquiterpenes found in vetiver oil. Degradative and spectral investigations with the more abundant zizanoic acid (**2**)[7–9] provided evidence for the 3a,6-methanoperhydroazulene ring system, a tricyclic carbon skeleton previously unknown among natural sesquiterpenes.[10] The structures of its various cogeneric relatives zizaene,[4d,8b] zizen-12-ol (khusimol),[7a,8b,11] ziz-

(1) Portions of this research have been presented at the following meetings: WOSNPC (Workshop on Organic Synthesis in Natural Product Chemistry) Conference, Aug 1970 (University of California, Santa Cruz, Calif.), and the XXIIIrd IUPAC Congress, Boston, Mass., July, 1971.

(2) A. P. Sloan Foundation Fellow, 1971–1973.

(3) University of Illinois Fellow, 1970–1971; Johnson and Johnson Fellow, 1971–1972.

(4) Isolation: (a) G. Chiurdoglu and P. Tullen, *Bull. Soc. Chim. Belg.*, **66**, 169 (1957); (b) M. Romanuk and V. Herout, *Collect. Czech. Chem. Commun.*, **25**, 2540 (1960); (c) K. Morikawa and Y. Hirose, *Nippon Kagaku Zasshi*, **88**, 795 (1967); *Chem. Abstr.*, **69**, 10554 (1968); (d) R. Sakuma and A. Yoshikoshi, *Chem. Commun.*, 41 (1968).

(5) For a review on early isolation and structural investigations, see N. T. Anh and M. Fetizon, *Amer. Perfum. Cosmet.*, **80**, 41 (1965). Unfortunately most of the structures contained therein have been revised subsequent to the publication of this article. See also N. H. Anderson, *Photochemistry*, **9**, 145 (1970).

(6) Alternative names appearing in the literature include tricyclovetivene,[4b] khusinene,[4c] and khusene.[8c]

(7) (a) F. Kido, H. Uda, and A. Yoshikoshi, *Tetrahedron Lett.*, 2815 (1967); (b) F. Kido, H. Uda, and A. Yoshikoshi, *ibid.*, 1247 (1968).

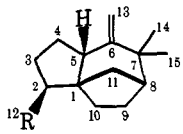
(8) (a) I. C. Nigam and H. Komae, *J. Pharm. Sci.*, **56**, 1299 (1967); (b) I. C. Nigam, C. Radecka, and H. Komea, *ibid.*, **57**, 1029 (1968); (c) I. C. Nigam, H. Komae, G. A. Neville, C. Radecka, and S. K. Paknikar, *Tetrahedron Lett.*, 2497 (1968); (d) H. Komae and I. C. Nigam, *J. Org. Chem.*, **33**, 1771 (1968).

(9) E. Klein, R. Siewert, and W. Rojahn, *Dragoco Rep. Ger. Ed.*, **2**, 23 (1969); *Chem. Abstr.*, 71, 102045 (1969).

(10) Other types of methanoperhydroazulene sesquiterpenes are well known: 1,4-methanoperhydroazulene (longifolene), 3a,7-methanoperhydroazulene (cedrene, cyperene), and 4,8-methanoperhydroazulene (α-caryophyllene alcohol). The B/C/D rings of the tetracyclic gibberellin diterpenes describe a 3a,6-methanoperhydroazulene.

(11) D. C. Umarani, K. G. Gore, and K. K. Chakravarti, *Tetrahedron Lett.*, 1255 (1966); *Perfum. Essent. Oil Rec.*, **60**, 307 (1969).

aen-3β-ol,[12] epizizanoic acid,[13] and epizizaene[13]) were secured by means of correlation with zizanoic acid and complementary chemical evidence.[14] An X-ray crystallographic analysis in our laboratories with khusimol *p*-bromobenzoate confirmed these structural and stereochemical assignments.[16]

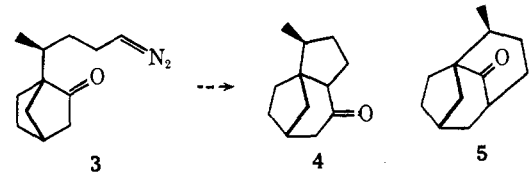


1, R = CH_3
2, R = CO_2H

Two distinct biogenetic schemes have been advanced in the literature to rationalize the unusual ring system, substitution pattern, and stereochemistry of zizaene. One scheme runs essentially parallel to the biogenesis of cedrene, but requires intermediates of different relative and absolute stereochemistry.[7,8c,d,17] The other relates zizaene to the spirovetivene sesquiterpene hinesol through a cyclization and a chemically precedented rearrangement.[18]

Consideration of the unique skeletal structure and biogenesis of zizaene lead us to select this tricyclic sesquiterpene as a goal for total synthesis. We describe herein a stereoselective total synthesis of (±)-zizaene which confirms structure **1** and provides independent evidence in support of the relative stereochemical designations.[19]

As the key reaction for construction of the 3a,6-methanoperhydroazulene ring system, we chose the intramolecular diazoalkane–carbonyl ring expansion method developed by Gutsche and coworkers.[21] Although the projected diazopentylnorcamphor intermediate **3** could conceivably produce the undesired bridged ring ketone **5**, the strain evident in this tricarbocycle[22] lead us to expect the required fused ring ketone (**4**) to be the principal product. With this plan in mind, the following critical points in the overall synthetic scheme become apparent: (1) synthesis of the appropriate bridgehead-substituted norcamphor derivative, (2) introduction and stereochemistry of the secondary methyl substituent (C_{12}), (3) incorporation of the *gem*-dimethyl grouping (C_{14} and C_{15}), (4) the relative configuration at the ring fusion position (C_5), and (5) introduction of the exocyclic methylene group (C_{13}) into the sterically congested 6 positions.

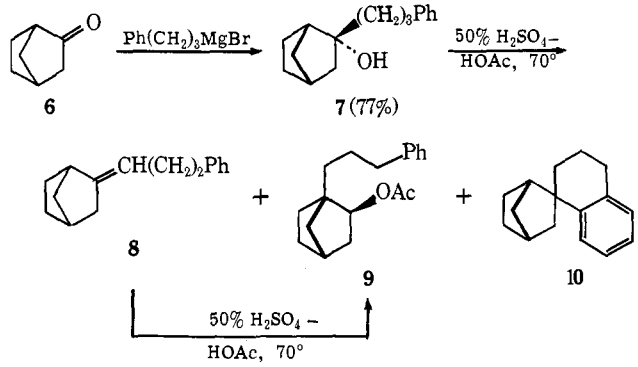


3 **4** **5**

The preparation of bridgehead-substituted 2-norbornyl derivatives is usually effected by the indirect approach of nucleophilic addition to norcamphor followed by Wagner–Meerwein rearrangement.[20b,23] For our purposes a four-carbon nucleophile, functionalized so as to permit elaboration of a nitrogen substituent yet at the same time stable to the strong acid conditions normally employed in the rearrangement,[23a] was required. After some experimentation[24] we found the 3-phenylpropyl group capable of accommodating this rather limiting pair of requirements. The aromatic ring thus serves essentially as a carboxyl protecting group, removable by ozone degradation.[25]

The rearrangement of tertiary alcohol **7** to acetate **9** is preceded by a relatively rapid dehydration to olefin **8** (Scheme I). The yield of the secondary acetate

Scheme I



slowly reaches a maximum of 51%, then declines with corresponding increases in the yield of the cyclodehydration by-product **10**. One recycle of the separated hydrocarbon fraction (**8**, **10**, and 1,6-diphenylhexane) increases the isolated yield of acetate **9** to 69%.

The secondary methyl group was incorporated into the side chain of **9** by way of the unsaturated keto acetate **14** (Scheme II). Despite the number of steps

(12) (a) A. Homma, M. Kato, M.-D. Wu, and A. Yoshikoshi, *Tetrahedron Lett.*, 231 (1970); (b) N. H. Andersen, *ibid.*, 1755 (1970).

(13) N. Hanayama, F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, *ibid.*, 6099 (1968).

(14) From the four different numbering systems in use[7a,8d,12b,15] we selected the one[8d] which logically derives from the designation of zizaane as a substituted tricyclo[6.2.1.$0^{1,5}$]undecane.

(15) G. A. Neville and I. C. Nigam, *Tetrahedron Lett.*, 837 (1969).

(16) R. M. Coates, R. F. Farney, S. M. Johnson, and I. C. Paul, *Chem. Commun.*, 999 (1969).

(17) N. H. Andersen and M. S. Falcone, *Chem. Ind. (London)*, 62 (1971).

(18) D. F. MacSweeney, R. Ramage, and A. Satter, *Tetrahedron Lett.*, 557 (1970).

(19) Total syntheses of 2-epizizanoic acid[20a] and zizanoic acid,[2c,b] which by virtue of correlations constitute total syntheses of zizaene, were published while this research was in progress.

(20) (a) F. Kido, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 1335 (1969); (b) D. F. MacSweeney and R. Ramage, *Tetrahedron*, 27, 1481 (1971). (c) See also A. Deljac, W. L. MacKay, C. S. J. Pan, K. K. Wiesner, and K. Wiesner, *Can. J. Chem.*, **50**, 726 (1972).

(21) (a) C. D. Gutsche and D. M. Bailey, *J. Org. Chem.*, **28**, 607 (1963); (b) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *ibid.*, **28**, 610 (1963); (c) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, Chapter IV.

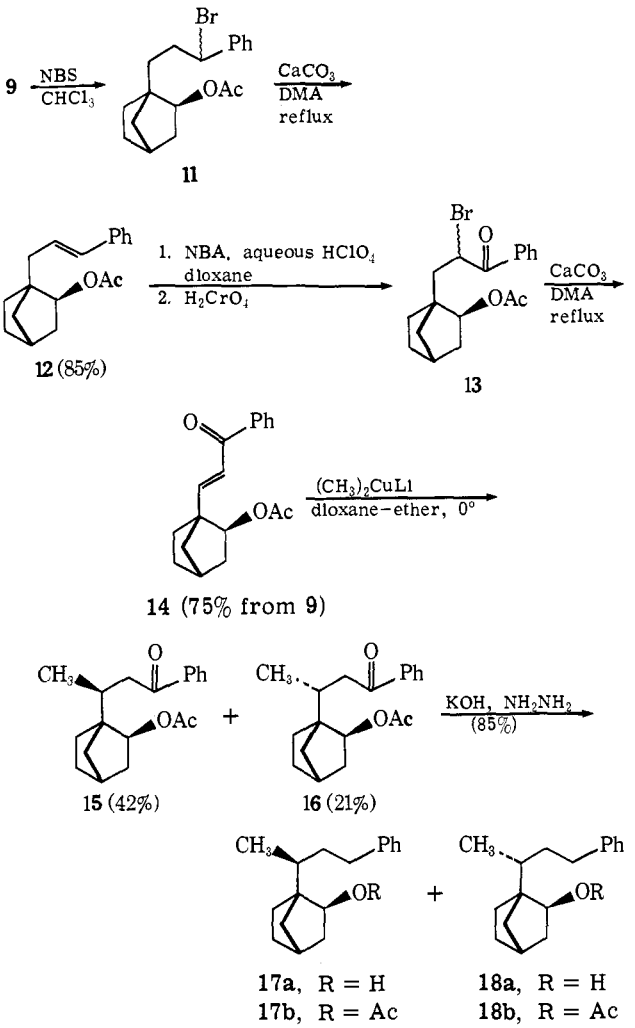
(22) Both six-membered rings must be in boat forms, not to mention severe transannular steric interactions.

(23) (a) D. C. Kleinfelter and P. v. R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961); (b) J. A. Berson, "Molecular Rearrangements," Part 1, Interscience, New York, N. Y., 1963, pp 133–138.

(24) Other substituents surveyed include the following. (a) 1-but-3-enyl. Addition of 1-but-3-enylmagnesium bromide to norcamphor (**6**) gave an adduct (42%) which rearranged (50% H_2SO_4–HOAc) to 1-(1′-but-3-enyl)-2-bicyclo[2.2.1]heptyl acetate (40%). Evidently cyclization into the side chain double bond giving 7-acetoxy-2,4a-methanodecahydronaphthalene was competitive with rearrangement. (b) 1-Pent-4-enyl. Exposure of the adduct from addition of 1-pent-5-enylmagnesium bromide to norcamphor (70%) to the rearrangement conditions afforded only olefin cyclization product (evidently 8-acetoxy-1,4-methanospiro[5.5]undecane). (c) β-Propionic acid. 2-Allylbicyclo[2.2.1]heptan-2-ol (allylmagnesium bromide + **6**, ~100%) after hydroboration and chromic acid oxidation (*cf.* A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 308 (1969)) gave 2′-*endo*-hydroxybicyclo[2.2.1]hept-2-yl-3-propanoic acid lactone which rearranged in part to its endo γ-lactone isomer; however no δ-lactone could be detected.

(25) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

Scheme II

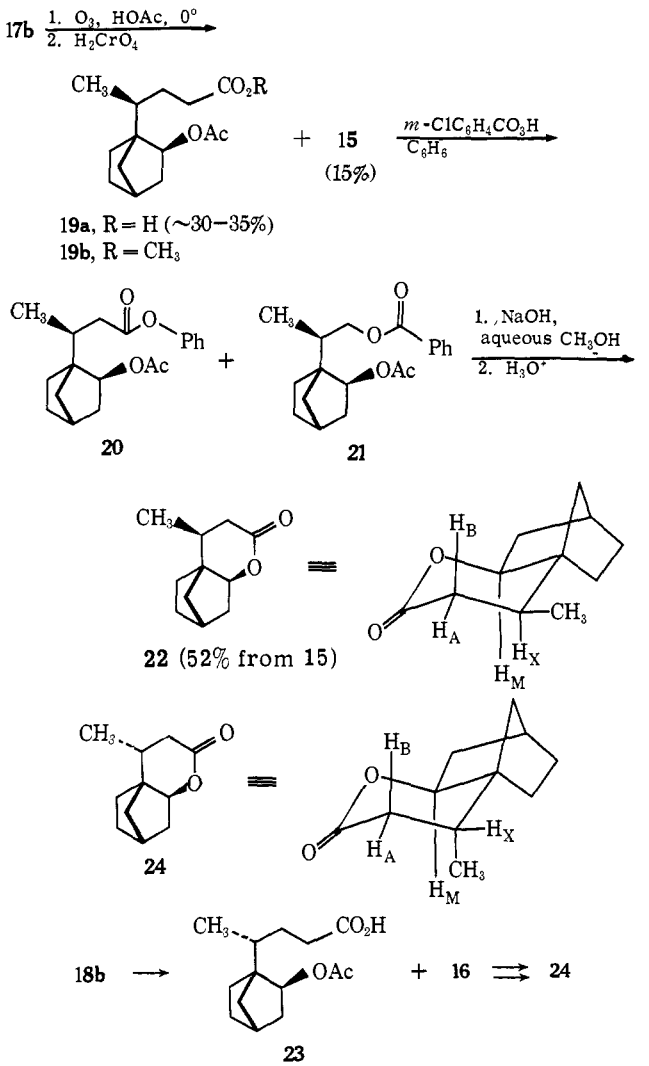


(eight) involved, the corresponding methyl-substituted acetate **17b** with the correct relative stereochemistry was obtained in about 25% overall yield.[26] The stereoselectivity in the conjugate addition of dimethylcopper lithium to **14** was controlled to some extent by solvent variation.[27] Whereas in ether isomers **15** and **16** were formed in a 1:2 ratio (75%), in a dioxane–ether mixture the isomer ratio reversed to a 2:1 distribution (63%). The isomers were separated after Wolff–Kishner reduction by a combination of chromatography and crystallization (**17a**, mp 88.5–90.5°, **18a**, liquid).

The relative stereochemistry at the new asymmetric center was established by oxidative cleavage of the side chain and conversion to the epimeric δ-lactones **22** and **24**. Baeyer–Villiger oxidation of keto acetate **15** (obtained free from **16** as a by-product in the ozonolysis reaction of **17b**) afforded a 2:1 mixture of diesters **20** and **21**, which, upon basic hydrolysis and acidification, yielded lactone **22**. Lactone **24** was similarly obtained from **16**.

The nmr spectrum of **22** in the presence of tris(dipivalomethanato)europium(III) (Eu(DPM)$_3$) shows an eight-line pattern for the methylene group adjacent to the lactone carbonyl. Analysis[28] of this multiplet as the AB part of an ABX spin system gives J_{AX} = 6 Hz and J_{BX} = 10 Hz. The corresponding coupling constants derived from the spectrum of isomeric lactone **24** are $J_{AX} = J_{BX}$ = 5 Hz. With the assumption that both δ-lactones exist preferentially in the half-chair, rather than half-boat, conformations (the rigid norbornyl structure precludes ring flip to the inverted half-chair conformer), we conclude that the large coupling constant (10 Hz) is due to an axial spin interaction and thus the secondary methyl in **22** is equatorial (β) as depicted in Scheme III.

Scheme III



The observation that the ratio of the chemical shift increments for the proton on carbon bearing oxygen (H_M) and the methyl group in the presence of Eu(DPM)$_3$ is greater in lactone **22** ($\Delta\delta H_M/\Delta\delta CH_3$ = 2.76) than lactone **24** ($\Delta\delta H_M/\Delta\delta CH_3$ = 1.95) also supports

(26) (a) An attempt to incorporate the methyl group prior to rearrangement was unsuccessful. The adduct obtained (poor yield) from the Grignard reagent of 2-bromo-4-phenylbutane and norcamphor apparently gave only simple dehydration product under the usual rearrangement conditions. (b) Bromo ketone **13** was also prepared (80%) by treatment of the corresponding keto acetate (1-(3′-oxo-3′-phenylpropyl)bicyclo[2.2.1]heptane-*exo*-2-yl acetate) with bromine in acetic acid. However, the latter was obtained at best in 64% yield by reaction of **11** with silver tetrafluoroborate in dimethyl sulfoxide (*cf.* D. M. Lemal and A. J. Fry, *Tetrahedron Lett.*, 775 (1961)) or less satisfactorily (33%) by direct oxidation of **9** with chromic acid in acetic acid.

(27) See, for example, J. A. Marshall and S. F. Brady, *J. Org. Chem.*, 35, 4068 (1970).

(28) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 105–113.

this conclusion. The equatorial methyl group in **22** is further removed from the site of complexation and hence shifted less with respect to the reference proton H_M. The constancy of the other increment ratios (for **22** $\Delta\delta H_M/\Delta\delta H_A = 0.49$, $\Delta\delta H_M/\Delta\delta H_B = 0.59$; for **24** $\Delta\delta H_M/\Delta\delta H_A = 0.53$, $\Delta\delta H_M/\Delta\delta H_B = 0.57$) suggests that both exist in similar chair conformations.[29]

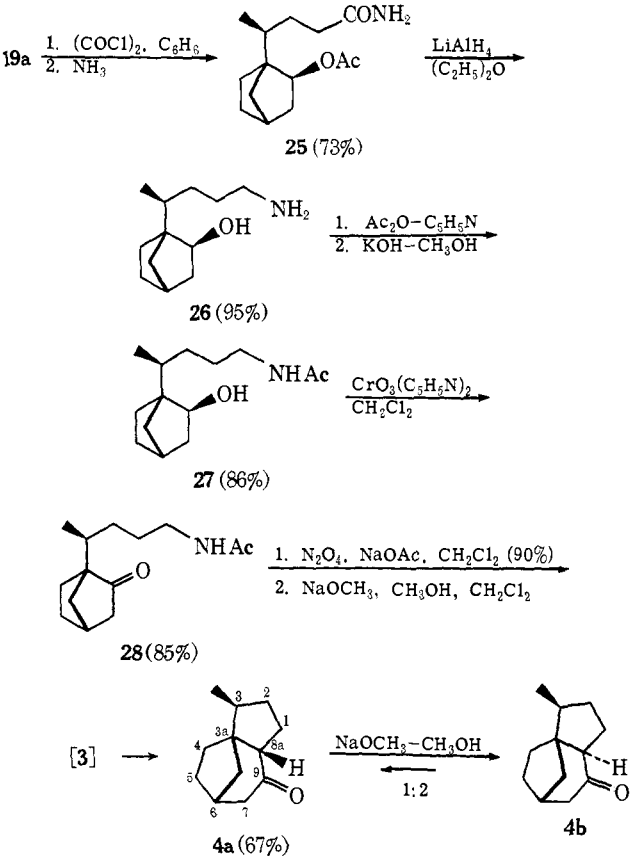
Acetoxy acid **19a**,[30] now known to have the correct stereochemistry, was converted into the keto amide **28** by standard functional group transformations which require no special comment. Both amine alcohol **26** (mp 101–104°) and hydroxy amide **27** (mp 104–106°) proved to be crystalline solids. Nitrosation of **28** with dinitrogen tetroxide[21a,31] followed by treatment with sodium methoxide[21b] liberated diazo ketone **3**, which underwent smooth cyclization to a single tricyclic ketone (**4a**)[32] (Scheme IV) (ir 1705 cm^{-1}). The alternative bridged ring structure **5** is excluded by the observation that the ketone forms a 1:2 equilibrium mixture in sodium methoxide–methanol with an isomer **4b**. Enolization in ketone **5** is not possible; furthermore only one, highly strained stereochemical form of **5** is feasible.

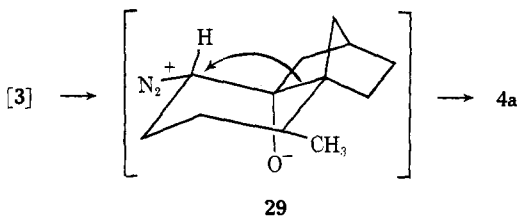
Tricyclic ketones **4** may be considered either as ethano-bridged 4-hydrindanones or methano-bridged 4(1*H*)-octahydroazulenones. Since the former is more stable cis fused (78:22)[33] while the equilibrium in the latter favors the trans isomer (20:80),[34] we assign stereochemistry **4b** to the more stable epimer.

The high stereoselectivity of the cyclization **3** → **4a** may be explained by an intramolecular exo approach to the carbonyl group forming diazonium alkoxide intermediate **29**. There is extensive precedent for exo attack on norcamphor and related norbornyl derivatives;[35] furthermore the alternative intermediates resulting from endo attack would be sterically destabilized relative to **29** by a 1:3 diaxial interaction.

If a gauche diazonium alkoxide zwitterion (**29**) is favored over the alternative diaxial array (axial N_2^+ in **29**) owing to minimization of charge separation,[21b] then concerted migration of the carbon–carbon bond antiparallel to the nitrogen leaving group affords directly the observed product, tricyclic ketone **4a**, to the exclusion of the isomeric epoxide. As a consequence of the rigid norbornyl moiety, there are no conformations of any of the possible diazonium alkoxide stereoisomers in which the alternative, methylene carbon attains antiparallel alignment with the diazonium function. Hence, the complete absence of bridged ring ketone **5** is understandable in the present case.

Scheme IV



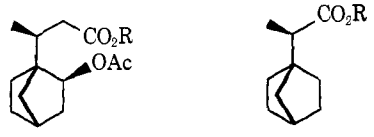


29

At this point it is necessary to introduce the *gem*-dimethyl group into ketone **4a**. We feared that direct base-catalyzed methylation might effect substitution at the ring fusion position (C_5) in competition with reaction at the methylene flank, and thus lead to separation and identification problems. This potential problem was solved by the discovery that α-*n*-butylthiomethylene derivatives[36a] of ketones undergo smooth reduction in lithium–ammonia solution to the corresponding methyl enolate anions which may then be alkylated *in situ* without loss of positional selectivity.[36b]

(29) For a study of Eu(DPM)$_3$ shift data with simple δ-lactones see F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970).

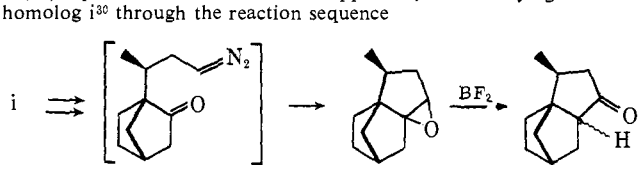
(30) This material was contaminated with lesser amounts of the lower homologs i and ii (R = H) evidently formed as by-products in the ozonolysis of **17b**. Esterification of the acids afforded **19b**, i (R = CH_3), and ii (R = CH_3) in a 4:1:1 distribution.



i ii

(31) E. H. White, *J. Amer. Chem. Soc.*, 77, 6008 (1955).

(32) Epoxide iii was also isolated apparently from carrying the lower homolog i[30] through the reaction sequence



iii iv

(33) (a) R. P. Linstead, *Annu. Rep. Chem. Soc.*, **32**, 305 (1935); (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, pp 177–180; (c) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964).

(34) J. A. Marshall and W. F. Huffman, *J. Amer. Chem. Soc.*, **92**, 6358 (1970); H. L. Goering, A. C. Olson, and H. H. Espy, *ibid.*, **78**, 5371 (1956).

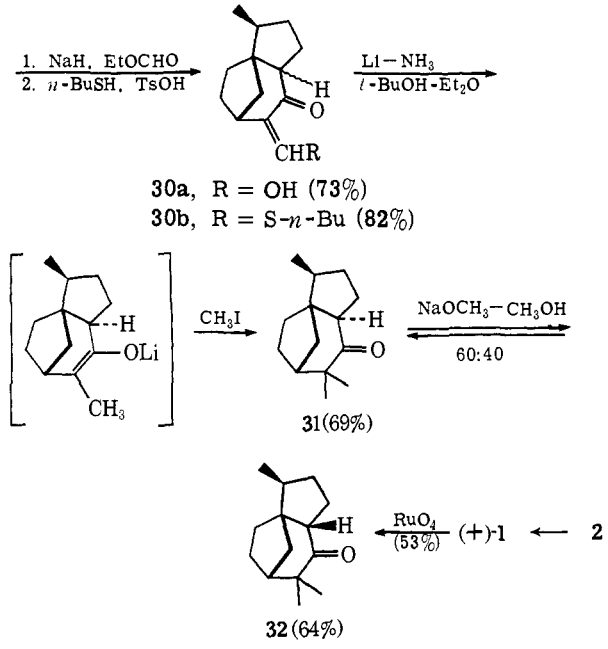
(35) For specific references, see G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 344 (1966).

(36) (a) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962); (b) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **92**, 1027 (1971).

Application of this method enabled a clean conversion of **4a** into **31** (5α-norzizanone).

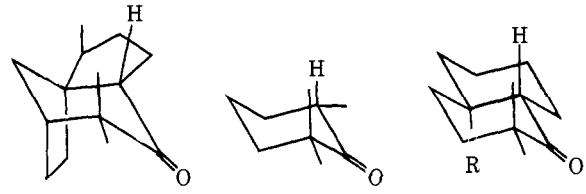
The nmr spectrum of the trimethyl ketone proved to be distinctly different from that of authentic (+)-norzizanone ((+)-**32**), prepared by ruthenium tetroxide oxidation[37] of (+)-zizaene. However, treatment with sodium methoxide in methanol gave rise to a 60:40 equilibrium mixture of epimers **31** and **32**, which could be separated by column chromatography. The new, less polar ketone ((+)-**32**), obtained in 64% yield after two reequilibrations of recovered **31**, was identical with (+)-norzizanone according to infrared, nmr, and chromatographic comparisons. Similarly equilibration of (+)-norzizanone gave an equilibrium mixture, the spectral properties of the new isomer corresponding to those of synthetic ketone, (±)-**31** (Scheme V).

Scheme V



The exclusive formation of **31** (<5% **32**) after the methylation operation upon **4a** is probably due to epimerization at the ring fusion position en route (either, or both, of the reactions **4a** → **30a** → **30b**). The introduction of a second trigonal carbon into the ring of **30a** and **30b** should further destabilize the β epimers, thus shifting the equilibrium further toward the α epimers.[38]

Although the stereochemistry at C_5 in the norketones **31** and **32** is unequivocally established by the previously mentioned comparisons with the naturally derived ketones, we offer the following spectral data as additional, and independent, evidence for the assignments. Inspection of models indicates that ketone **32** with the natural β stereochemistry may easily adopt a conformation with the cyclohexanone ring in a normal chair form. In contrast, the α epimer **31** must be distorted from a perfect chair as a consequence of a 1,3 diaxial dialkyl steric interaction. The close correspondence of the nmr chemical shifts for the methyl groups in the less polar ketone (**32**) compared with model cyclohexanones **33**,[36b] **34**,[36b] and **35**[39] suggests that this isomer has an essentially undistorted six-membered ring. The corresponding data from the more polar epimer (**31**) are distinctly different.[40]

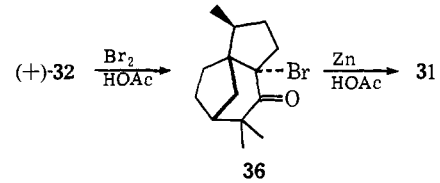


32 **33** **34**, R = H; **35**, R = CH_3

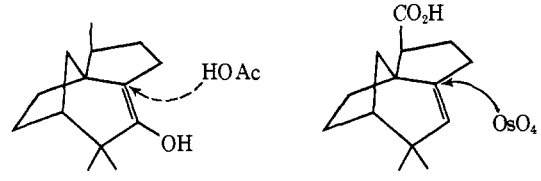
Table I

Ketone	$\delta_{(CH_3)_2}{}^{CCl_4}$	$\Delta\delta^{CCl_4}$	$\delta_{(CH_3)_2}{}^{C_6H_6}$	$\Delta\delta^{C_6H_6}$
31	1.02, 1.10	0.08	1.07, 1.07	0
32	1.01, 1.18	0.17	1.01, 1.09	0.08
33	1.02, 1.19	0.17		
34	1.00, 1.18	0.18	1.01, 1.07	0.08
35	0.98, 1.17	0.19	0.97, 1.09	0.11

In hopes of improving the stereoselectivity in the production of **32**, we examined the kinetically controlled protonation of its enol (**37**). However, zinc–acetic acid reduction[41] of bromo ketone **36** gave exclusively 5α-norzizanone (**31**). The evident high preference for protonation from the α direction is surprising since unsaturated acid **38** reacts with osmium tetroxide from the β side.[7b]



36



37 **38**

The recent suggestion that the stereoselectivity observed in addition reactions depends critically upon the transition-state geometry provides a reasonable explanation for this anomaly.[42] Although both reactants presumably approach perpendicular to the plane of the double bond, the proton transfer to **37** would be expected to attack directly at the C_5 end of the enol double bond. The cis addition of osmium tetroxide, on the other hand, probably involves a more symmetrical approach with a cyclic transition state.[43]

(37) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., p 987.

(38) Another possibility which cannot be exluded is selective reaction of the α epimers without concurrent epimerization in the sequence 4a → **30b**. Thus a less reactive (?) β epimer might be unchanged and lost in purification.

(39) R. M. Coates and S. K. Chung, unpublished results.

(40) See also D. H. Williams and D. A. Wilson, *J. Chem. Soc. B*, 144 (1966), and references cited therein, for additional data and discussion.

(41) H. E. Zimmerman and A. Mais, *J. Amer. Chem. Soc.*, **81**, 3644 (1959).

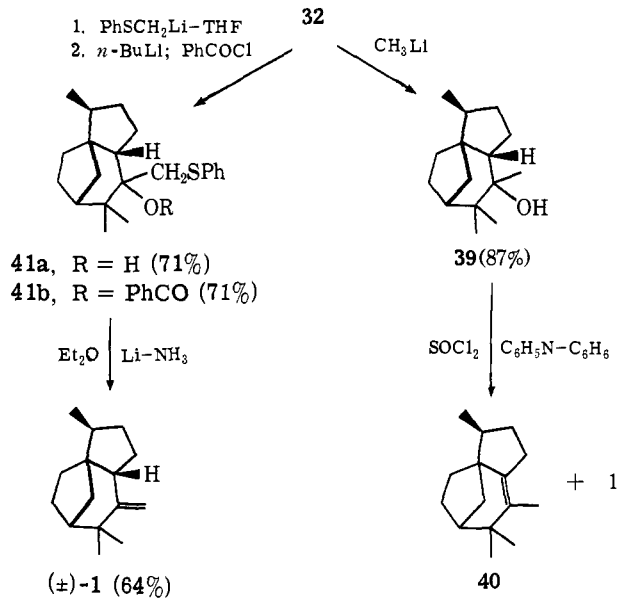
(42) H. C. Brown and J. A. Kawakami, *ibid.*, **92**, 201 (1970).

(43) For discussion and analysis of the effect of ring size upon relative reactivities in reactions with cyclic transition states see: A. K. Awasthy and J. Rocek, *ibid.*, **91**, 991 (1969); R. E. Erickson and R. L. Clark, *Tetrahedron Lett.*, 3997 (1969).

Thus, with potentially different steric effects (both long range and torsional) developing in the transition states, the stereochemical outcome might well be opposite in these two electrophilic addition reactions.

Completion of the synthesis requires the introduction of the exocyclic methylene group. Unfortunately, an efficient Wittig reaction of norzizanone with methylenetriphenylphosphorane is precluded by the hindered environment of the carbonyl group[44] and furthermore would very likely cause epimerization at C_5.[45] An alternative method employs methyllithium (or methylmagnesium reagents) addition followed by dehydration. While this method was in fact successful in the present case, both zizaene and its more stable endocyclic double bond isomer isozizaene (**40**) were formed (2:3 ratio) upon dehydration with thionyl chloride–pyridine in benzene solvent (Scheme VI).[46]

Scheme VI



We have found an alternative method which involves addition of a functionalized lithium reagent to the ketone followed by a reductive, vicinal elimination. Reaction of phenylthiomethyllithium[47] with synthetic (+)-norzizanone (**32**) affords adduct **41a** in good yield. The corresponding benzoate (**41b**) in ether undergoes smooth reduction in lithium–liquid ammonia to (±)-zizaene. The identity of the synthetic racemate ((±)-**1** with natural (+)-zizaene was established by ir, nmr, and glpc comparisons. The facile addition of phenylthiomethyllithium to the highly hindered norzizanone (no detectable enolate formation) and the smooth reduction of benzoate **38b** to (±)-zizaene indicate that this method for olefin synthesis should provide a useful complement to the Wittig reaction.

(44) Reaction of 2-epinorzizanoic acid with excess methylenetriphenylphosphorane in dimethyl sulfoxide for several days affords only about 10% of 2-epizizanoic acid.[20a]

(45) See C. H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, **93**, 1746 (1971), and references cited thereln.

(46) In pyridine as solvent only isozizaene (**40**) was formed. For other examples in which the use of benzene as solvent promotes exocyclic elimination see J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957); S. G. Levine and M. E. Wall, *J. Amer. Chem. Soc.*, **82**, 3391 (1960); E. Piers, W. de Waal, and R. W. Britton, *ibid.*, **93**, 5113 (1971).

(47) E. J. Corey and D. Seebach, *J. Org. Chem.*, 31, 4097 (1966).

Experimental Section

Nmr spectra were obtained with a Varian Associates Model A-60-A or A-56/60-A spectrometer using TMS as an internal standard, and CCl_4 as the solvent unless otherwise indicated. Reported values are on the δ scale. All infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer. The mass spectra were run on an Atlas CH-5 mass spectrometer. Elemental analyses were performed in the University of Illinois microanalytical laboratory. Melting points and boiling points are uncorrected. Glpc analyses were performed with a Varian Aerograph Model 90-P instrument using the following columns: A (5 ft × 0.25 in., 15% FFAP), B (5 ft × 3/8 in., 15% FFAP), C (6 ft × 0.25 in., 20% SE 30), D (6 ft × 3/8 in., 20% SE 30).

***exo*-2-(3′-Phenylpropyl)bicyclo[2.2.1]heptan-*endo*-2-ol (7).** To a stirred mixture of magnesium (18.21 g, 0.75 g-atoms) in 110 ml of ether at 0° under nitrogen was added a crystal of iodine and 3-phenyl-1-bromopropane (74.60 g, 0.375 mol) in 110 ml of ether over 30 min. The mixture was stirred an additional 1 hr at 0°, 1 hr at room temperature, and 1 hr at reflux. To this stirred solution (after decantation from residual magnesium) was slowly added norcamphor (33.05 g, 0.30 mol) in 110 ml of ether (ice bath cooling, nitrogen atmosphere). The mixture was allowed to warm slowly to room temperature and after 18 hr it was poured into an ice–1 *M* sulfuric acid mixture. After saturation with sodium chloride, the layers were separated and the aqueous phase was extracted with ether. The ether extracts were washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. Volatile impurities were first separated by vacuum distillation (6-in. Vigreux column, 0.2 mm, pot temperature 100°). The residue was distilled through a short path condenser to yield 60.5 g of a slightly discolored liquid (bp 126° (0.3 mm)). Glpc analysis (column A at 205°) indicated a purity of about 85% (*i.e.*, 77% yield of **7**). This, material was used in the next step without further purification.

A portion of this material was purified by chromatography on silica gel. Elution with 20% ether in benzene gave first a nonpolar component: ir (film 1605, 1495, and 1450 cm^{-1}; nmr 7.09 (s, 5 H), 2.56 (m, 2 H), and 1.39 (m, 4 H). These spectra match the corresponding spectra of 1,4-diphenylbutane (except for the nmr integration); this compound is accordingly identified as 1,6-diphenylhexane. Later fractions afforded alcohol **7**; ir (film) 3400, 1599, 1480, and 1400 cm^{-1}; nmr 7.10 (s, 5 H) and 2.54 (m, 2 H). Preparative glpc (column B at 225°) gave an analytical sample (glassy solid, mp 37–41°).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.11; H, 9.49.

1-(3′-Phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (9). A stirred solution of unpurified alcohol **7** (5.00 g, 19.0 mmol of **7**), glacial acetic acid (10.9 g, 0.182 mol), and 0.55 ml of 50% sulfuric acid was heated at 70° for 5 hr.[23a] The mixture became light brown almost immediately, and after 10 min two layers had formed which were mixed by rapid stirring. After cooling, the mixture was slowly poured into a cold mixture of 25 ml of 6.4 *M* sodium hydroxide and 25 ml of ether. The remaining acid was neutralized with potassium carbonate. The layers were separated and the aqueous portion was extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to yield 5.34 g of a yellow liquid which was chromatographed on silica gel (250 g). Elution with benzene gave a mixture of hydrocarbons (2.23 g) and rearranged acetate **9** (2.45 g): ir (film) 1725, 1599, 1485, and 1400 cm^{-1}; nmr 7.12 (s, 5 H), 4.06 (br d, 1 H, J = 7 Hz), 2.56 (m, 2 H), 2.13 (m, 1 H), and 1.80 (s, 3 H). Preparative glpc (column B at 225°) gave an analytical sample.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.38; H, 8.84.

A rapidly stirred mixture of the above hydrocarbon mixture (2.23 g), glacial acetic acid, and 0.3 ml of 50% sulfuric acid was heated at 70° for 4 hr. Isolation and purification as above gave 1.54 g of hydrocarbons and an additional 0.91 g of **9** (total yield 69%).

Preparative glpc (column B at 225°) of the hydrocarbon mixture gave **8**: ir (film) 1601, 1490, and 1447 cm^{-1}; nmr 7.09 (s, 5 H) and 5.15 (m, 1 H); and **10**: ir (film) 1480, 1450, and 746 cm^{-1}; nmr 7.04 (m, 4 H) and 2.81 (m, 2 H). A third component was identified as 1,6-diphenylhexane.

Anal. Calcd for $C_{16}H_{20}$ (**8**); C, 90.51; H, 9.49. Found: C, 90.43; H, 9.41.

Anal. Calcd for $C_{16}H_{20}$ (**10**); C, 90.51; H, 9.49. Found: C, 90.87; H, 9.49.

The time course of the reaction was followed by glpc (column A at 205°) and tlc analysis. After 1 hr the major product (>75%) is

8 with only about 20% of 9 and a very small amount of **10** (2–3%). Acetate 9 increases to a maximum of 51% at 5 hr, while **10** increases to about 9% and 9 decreases to about 40%.

When large batches of **7** were rearranged to 9, the crude product was first vacuum distilled through a 6-in. Vigreux column to remove a small amount of low boiling polar materials (bp 110° (0.2 mm)), and then the residue was purified by column chromatography as above, allowing repeated use of the same column.

1-(3′-Bromo-3′-phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (11). A stirred mixture of **9** (10.0 g, 36.8 mmol) and *N*-bromosuccinimide (7.85 g, 44.2 mmol) in 100 ml of chloroform was swept with nitrogen and irradiated with a heat lamp for 1 hr. When the mixture was nearly at reflux and most of the *N*-bromosuccinimide had dissolved, the reaction became very vigorous and irradiation had to be periodically interrupted. The solution became bright red, but after 10 min the color changed to tan. The chloroform was evaporated and petroleum ether was added to the residue. The solution was chilled in a freezer and the precipitate removed from the cold mixture. The filtrate was evaporated to give bromide **11** (13.05 g, 100%) as a yellow oil which was used without further purification: ir (film) 1725, 1445, 1365, and 695 cm^{-1}; nmr 7.43–7.00 (m, 5 H), 4.90–4.43 (m, 2 H), and 1.91 and 1.84 (singlets, 3 H total).

1-(3′-Phenyl-2′-propenyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (12). A mixture of **11** (26.96 g, 73.6 mmol), calcium carbonate (7.75 g, 75.5 mmol), and 250 ml of *N*,*N*-dimethylacetamide swept with nitrogen was refluxed for 20 min. The cooled mixture was poured into ice–water and extracted with pentane. The pentane extracts were washed with 250 ml each of saturated sodium bicarbonate, water, and saturated salt solutions, dried ($MgSO_4$), and evaporated to yield olefin **12** (19.93 g) as a brown oil which was used in the next step without further purification.

A 2.0-g portion was chromatographed on 100 g of silica gel. Elution with benzene gave 1.7 g (85%) of a yellow oil: ir (film) 1730 and 1370 cm^{-1}; nmr 7.17 (m, 5 H), 6.48–5.79 (m, 2 H), 4.63 (br d, 1 H, J = 7 Hz), 2.70–2.30 (m, 2 H), 2.18 (br s, 1 H), and 1.94 (s, 3 H). Preparative glpc (column C at 212°) gave an analytical sample.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.18; H, 8.01.

1-(2′-Bromo-3′-phenyl-3′-oxopropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (13). To a stirred solution of olefin **12** (15.0 g, ~55.5 mmol) and 32.2 ml of 0.46 *N* perchloric acid in 215 ml of peroxide free dioxane in the dark was added solid *N*-bromoacetamide (10.05 g, 73.0 mmol) in portions over 1 hr.[48] The solution was stirred an additional 1 hr, poured into chloroform, and washed with water. The $CHCl_3$ solution was dried ($MgSO_4$) and the solvents were evaporated to give the bromohydrin (24.68 g) as a yellow oil: ir (film) 3450, 1725, 1470, and 1350 cm^{-1}; nmr 7.23 (s, 5 H), 4.78 (m, 1 H), 4.54 (br d, 1 H, J = 7 Hz), 4.29 (m, 1 H), 2.84 (br s, 1 H), and 1.83 and 1.69 (2 s, 3 H total).

To a stirred solution of the crude bromohydrin (24.68 g, ~55.5 mmol) in 200 ml of acetone was slowly added Jones' reagent[49] until a brown color persisted. The mixture was stirred 5 min longer, added to 2 l. of saturated salt solution, and extracted with ether after adding a little sodium bisulfite. The ether extracts were washed with 1 *N* sodium hydroxide and saturated salt solutions, dried ($MgSO_4$), and evaporated to give crude bromo ketone **13** (20.52 g) as a yellow oil which was used in the next step without further purification. A portion of this material was purified by chromatography on silica gel. Elution with benzene enabled the two isomeric bromo ketones (**13**) to be separated.

The infrared spectra of the isomers are the same: (film) 1725, 1670, 1599, and 1445 cm^{-1}. The nmr spectrum of one isomer has: nmr 8.04–7.80 (m, 2 H), 7.57–7.27 (m, 3 H), 5.23 (quartet, 1 H, J = 4 and 10 Hz), 4.69 (br d, 1 H, J = 7 Hz), 2.86 (unsymmetrical quartet, 1 H, J = 15 and 10 Hz), 2.29 (unsymmetrical quartet, 1 H, J = 15 and 4 Hz), 2.15 (br s, 1 H), and 2.03 (s, 3 H). The other isomer has: nmr 8.04–7.80 (m, 2 H), 7.57–7.27 (m, 3 H), 5.28 (quartet, 1 H, J = 6 and 7 Hz), 4.53 (br d, 1 H, J = 7 Hz), 2.78 (unsymmetrical quartet, 1 H, J = 15 and 7 Hz), 2.25 (unsymmetrical quartet, 1 H, J = 15 and 6 Hz), 2.15 (br s, 1 H), and 1.92 (s, 3 H).

1-(3′-Phenyl-3′-oxo-1′-propenyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (14). A stirred mixture of bromo ketone **13** (17.8 g, 48.8 mmol) and calcium carbonate (6.1 g, 61 mmol) in 225 ml of *N*,*N*-dimethylacetamide swept with nitrogen was refluxed for 20 min.[50] Work-up as above for **12** gave 12.95 g of a brown oil which was purified by chromatography on 650 g of silica gel. Elution with 10% ether in benzene gave the unsaturated ketone **14** (10.41 g, 75% from **9**) as a yellow oil: ir (film) 1725, 1665, 1620, and 1440 cm^{-1}; nmr 7.87–7.67 (m, 2 H), 7.44–7.33 (m, 3 H), 6.82 (AB quartet, J = 15.5 Hz, $\Delta\nu$ = 16.7 Hz), 4.68 (br d, 1 H, J = 7 Hz), 2.23 (br s, 1 H), and 1.83 (s, 3 H). Preparative glpc (column D at 250°) gave an analytical sample.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.18; H, 7.05.

1-(1′-Methyl-3′-phenyl-3′-oxopropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (15 and 16). To a stirred mixture of cuprous iodide (24.44 g) in 450 ml of ether at 0° (under nitrogen) was added 250 ml of 1.0 *M* methyllithium. This mixture was then stirred an additional 5 min at 0°.[51] A solution of **14** (12.00 g, 42.2 mmol) in 350 ml of ether was then added over 20 min. After stirring at 0° for 2 hr, the reaction mixture was poured into 3.4 l. of 1.2 *N* hydrochloric acid with vigorous stirring. Concentrated ammonium hydroxide (275 ml) was slowly added to dissolve the resulting precipitate. The layers were separated, and the aqueous portion was extracted with ether. The ether extracts were washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The tan oil so obtained was chromatographed on 625 g of silica gel. Elution with 5% ether in benzene gave a 1:2 mixture of ketones **15** and **16** (9.50 g, 75%) as a yellow liquid: ir (film) 1725, 1680, 1599, and 1440 cm^{-1}; nmr 8.10–7.80 (m, 2 H), 7.58–7.27 (m, 3 H), 4.77 (br d, 1 H, J = 7 Hz), 3.14–2.38 (m, 3 H), 2.22 (br s, 1 H), 1.97 and 1.93 (singlets, 3 H total, 1:2 ratio), and 0.91 and 0.87 (2 d, 3 H total, J = 6.5 Hz); 2,4-dinitrophenylhydrazone, mp 160–163°.

Anal. Calcd for $C_{25}H_{28}N_4O_6$: C, 62.49; H, 5.87; N, 11.66. Found: C, 62.36; H, 5.88; N, 11.37.

The yield of **15** was enhanced by the use of a dioxane–ether mixture as solvent. To a stirred mixture of cuprous iodide (3.16 g, 16.6 mmol) in 28 ml of dry dioxane at 0° blanketed with nitrogen was added 19.9 ml of 1.66 *M* ethereal methyllithium. A thick yellow suspension formed. Stirring was continued for 20 min after which the suspension was less dense and tan colored. A solution of **14** (2.00 g, 7.03 mmol) in 56 ml of dioxane was added over 20 min. After stirring for 2 hr the product was isolated and purified as above to give a 2:1 mixture of ketones **15** and **16** (1.36 g, 63%). Other solvents and conditions gave the following results (solvent, temperature, addition time, reaction time, yield, isomer ratio): ether, −78°, 1 hr, 4 hr, ~25%, 1:1; tetrahydrofuran, 0°, 20 min, 2 hr, 43%, 3:1; tetrahydrofuran–ether, 0°, 20 min, 2 hr, 60%, 3:2; 1,2-dimethoxyethane–ether, 0°, 20 min, 2 hr, ~40%, 2:1.

1-(1′-Methyl-3′-phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-ol (17a and 18a). A 1:2 mixture of keto acetates **15** and **16** (8.70 g, 29.0 mmol) was treated with 85% hydrazine hydrate and potassium hydroxide in triethylene glycol[52] to give after work-up 6.76 g of a pale yellow oil. Purification by chromatography on 600 g of silica gel with 10% ether in benzene as eluent gave 2.35 g of **18a** (R_f value, 0.50): ir (film 3400, 1602, 1498, and 1450 cm^{-1}; nmr 7.27 (s, 5 H), 3.58 (d, 1 H, J = 7 Hz), 3.03–2.33 (m, 2 H), and 0.94 (d, 3 H, J = 6.5 Hz). Later fractions afforded 2.05 g of a 1:1 mixture of **17a** (R_f value, 0.45) and **18a**, and 1.67 g of 1:3 mixture of the isomers (85% total yield). The 1:3 mixture of isomers solidified upon standing. Recrystallization from *n*-hexane gave 0.79 g of a white solid (**17a**), mp 88.5–90.5: ir (Nujol) 3300, 1601, 1498, 1465, and 1450 cm^{-1}; nmr ($CDCl_3$) 7.27 (s, 5 H), 3.71 (d, 1 H, J = 7 Hz), 3.09–2.37 (m, 2 H), and 0.95 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{17}H_{24}O$ (**18a**): C, 83.55; H, 9.90. Found: C, 83.41; H, 9.90.

Anal. Calcd for $C_{17}H_{24}O$ (**17a**): C, 83.55; H, 9.90. Found: C, 83.39; H, 9.88.

A large scale run with 40.5 g (0.135 mol) of the ketone mixture obtained from several conjugate methylations using different solvent (containing 57% of **15**) gave the **17a–18a** mixture in 87% yield. Several column chromatographies and recrystallizations afforded 14.5 g (44%) of pure **17a** and 12.3 g (37%) of pure **18a**.

1-(1′-α-Methyl-3′-phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (18b). A stirred solution of alcohol **18a** (5.3 g, 21.7 mmol), acetic anhydride (3.9 ml, 33 mmol), and pyridine (7.4 ml, 98 mmol) was heated at 50° for 4 hr. The solution was then diluted with 100 ml of ether, washed with 3 *N* hydrochloric acid, saturated sodium

(48) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, 79, 1130 (1957).
(49) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weidon, *J. Chem. Soc.*, 39 (1946).
(50) R. M. Coates and J. E. Shaw, *J. Amer. Chem. Soc.*, 92, 5657 (1970).
(51) E. Piers and R. J. Keziere, *Can. J. Chem.*, 47, 137 (1969).
(52) Huang-Minlon, *J. Amer. Chem. Soc.*, 68, 2487 (1946).

bicarbonate, and once with saturated sodium chloride solutions, dried ($MgSO_4$), and evaporated to give 5.84 g (94%) of a yellow oil. Although the bulk of this crude acetate was used directly in the next step, a portion (0.30 g) was purified further by chromatography on silica gel. Elution with 10% ether in benzene gave a colorless liquid: ir (film) 1725, 1602, 1497, and 1450 cm^{-1}; nmr 7.10 (s, 5 H), 4.72 (br d, 1 H, J = 7 Hz), 2.81–2.36 (m, 2 H), 1.74 (s, 3 H), and 0.97 (d, 3 H, J = 6.5 Hz).

4α-Methyl-4-(*exo*-2′-acetoxybicyclo[2.2.1]hept-1′-yl)butanoic Acid (23) and Keto Acetate 16. Ozone was bubbled at a rate of 1 l./min into a rapidly stirred solution of **18b** (5.50 g, 19.2 mmol) in 140 ml of ethyl acetate cooled in an ice–water bath[53] for 5 hr. The solution was concentrated to about 20 ml, and 50 ml of acetone was added. Jones' reagent[49] was slowly added at room temperature until the brown color remained. Cold saturated salt solution (250 ml) was added, and sodium bisulfite was then added until the brown mixture became bright green. This mixture was extracted with ether and the ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil (5.99 g) which was chromatographed on 300 g of silica gel. Elution with 30% ether in benzene gave 0.81 g (14%) of ketone **16**; ir (film) 1730, 1690, 1601, 1580, and 1450 cm^{-1}; nmr 8.10–7.80 (m, 2 H), 7.58–7.27 (m, 3 H), 4.79 (br d, 1 H, J = 7 Hz), 3.20–2.43 (m, 3 H), 2.20 (br s, 1 H), 1.97 (s, 3 H), and 0.91 (d, 3 H, J = 6.5 Hz). Elution with 50% ether in benzene containing 1% acetic acid gave 2.20 g (45%) of impure acid **23**: ir (film) 3000 (v br), 1725, and 1700 cm^{-1}; nmr 10.8 (s, 1 H), 4.76 (d, 1 H, J = 7 Hz), 2.02 (s, 3 H), and 0.93 (d, 3 H, J = 7 Hz).

3α-Methyl-3-(*exo*-2′-hydroxybicyclo[2.2.1]hept-1′-yl)propionic Acid Lactone (24). A solution of keto acetate **16** (0.67 g, 2.23 mmol) and *m*-chloroperbenzoic acid (0.68 g, 3.33 mmol) in 11 ml of benzene was allowed to stand in the dark at room temperature for 4 days. The resulting mixture was added to 30 ml of ether and then washed successively with aqueous sodium bicarbonate, aqueous ferrous ammonium sulfate, aqueous oxalic acid, water, aqueous sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to give 0.82 g of a yellow oil: ir (film) 1725 and 1700 (weak) cm^{-1}.

This oil was treated with 25 ml of 1 *N* sodium hydroxide in 1:1 aqueous methanol solution at room temperature for 1 hr, diluted with water, and extracted with ether to remove any neutral material. The alkaline solution was then acidified (6 *N* HCl), saturated with salt, and extracted with ether and chloroform. The extracts were washed with saturated salt solution, dried ($MgSO_4$), and evaporated to give 0.35 g of a yellow semisolid. The nmr spectrum of this mixture showed peaks corresponding to benzoic acid (1 part) and phenol (2 parts) in addition to lactone **24**. This material was chromatographed on 20 g of silica gel. Elution with 20% ether in benzene removed the phenol and some of the benzoic acid. This partially purified material was dissolved in ether, washed with saturated sodium bicarbonate and saturated salt solutions, and dried ($MgSO_4$), and the ether evaporated to give 0.22 g (54% from **16**) of lactone **24**: ir (film) 1730, 1237 and 1047 cm^{-1}; nmr 4.20 (m, 1 H) and 1.11 (d, 3 H, J = 7 Hz). The estimated positions for the protons α to the carbonyl carbon are 2.15 for H_A and 2.35 for H_B.

The nmr spectrum in the presence of $Eu(DPM)_3$ (0.22 equiv) shows 8.32 (2 H; symmetrical 7 line pattern, the AB part of an ABX system; J_{AB} = 16.5 Hz, $J_{AX} = J_{BX}$ = 5 Hz, $\nu_A - \nu_B$ = 13.8 Hz, δH_A = 8.42 and δH_B = 8.19),[28] 7.51 (br d, 1 H, J = 7 Hz), and 2.18 (d, 3 H, J = 7 Hz). The Δδ values are H_A, 6.27; H_B, 5.84; H_M, 3.31; CH_3, 1.70.

1-(1′β-methyl-3′-phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl Acetate (17b). Crystalline alcohol **17a** (16.00 g, 6.5 mmol) was converted to the acetate (**17b**) by treatment with acetic anhydride in pyridine as described above. The colorless liquid (18.86 g, ~100%) so obtained was used in the ozonolysis without further purification.

An 0.30-g portion of this material was chromatographed on 15 g of silica gel. Elution with benzene gave 0.25 g of an analytical sample: ir (film) 1725, 1602, 1447, 1450 cm^{-1} (fingerprint region slightly different from **18b**); nmr 7.10 (s, 5 H), 4.67 (br d, 1 H, J = 7 Hz), 2.84–2.28 (m, 2 H), 2.15 (br s, 1 H), 1.89 (s, 3 H), and 0.88 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.46; H, 9.15.

4β-Methyl-4-(*exo*-2′-acetoxybicyclo[2.2.1]hept-1′-yl)butanoic Acid (19a) and Keto Acetate 15. Acetate **17b** (18.0 g, 62.8 mmol) was treated with ozone and then Jones reagent as above to give 22.47 g of a tan oil. This material was chromatographed on 1100 g of silica gel. Elution with 20% ethyl acetate in cyclohexane gave 2.88 g (15%) of ketone **15**: ir (film) 1730, 1690, 1601, 1580, and 1450 cm^{-1} (fingerprint region slightly different from ketone **16**); nmr 8.10–7.80 (m, 2 H), 7.58–7.27 (m, 3 H), 4.70 (br d, 1 H, J = 7 Hz), 3.10–2.40 (m, 2 H), 2.18 (br s, 1 H), 1.97 (s, 3 H), and 0.87 (d, 3 H, J = 7 Hz); 2,4-dinitrophenylhydrazone, mp 193–194. Preparative glpc (column C at 210°) gave an analytical sample.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.06; H, 7.92.

Elution with 50% ethyl acetate in cyclohexane containing 1% acetic acid gave 8.10 g of crude acid **19a**: ir (film) 3300 (v br), 1725, and 1700 cm^{-1}; nmr ($CDCl_3$) 11.45 (s, 1 H), 4.72 (d, 1 H, J = 7 Hz), 2.01 (s, 3 H), and 0.85 (d, 3 H, J = 6.5 Hz). The bulk of this material was used in the next step without further purification; however, a portion was esterified by treatment with excess ethereal diazomethane at 0°. After stirring for 2 hr at room temperature the ether was evaporated to give a yellow oil. Glpc (column A at 211°) analysis showed four major components in the ratio of 1:2:2:8 (in order of increasing retention time). The four components were separated by preparative glpc (column B, 212°) and identified as follows: methyl benzoate (ir comparison); lower homolog ii (see footnote 30), ir (film) 1730 cm^{-1}, *m/e* 180 (M − 60); lower homolog i (see footnote 30), ir (film) 1730 cm^{-1}, *m/e* 193 (M − 60); and ester **19b**, ir (film) 1730 cm^{-1}, *m/e* 208 (M − 60). The yield of acid **19a**, when corrected for the three contaminants present, is 30–35%.

3β-Methyl-3-(*exo*-2′-hydroxybicyclo[2.2.1]hept-1′-yl)propionic Acid Lactone (22). Baeyer–Villiger oxidation of 0.30 g (1.0 mmol) of ketone **15**, hydrolysis, and purification as described above for the epimeric ketone **16** gave 0.10 g (52% from **15**) of lactone **22**; ir (film) 1730 cm^{-1}; nmr 4.10 (m, 1 H) and 1.02 (d, 3 H, J = 7 Hz). The estimated position for the protons α to the carbonyl are 3.1 for H_A and 2.35 for H_B. An analytical sample was obtained by preparative glpc (column C at 205°).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.17; H, 8.79.

The nmr spectrum in the presence of $Eu(DPM)_3$ (0.20 equiv) shows 6.75–5.75 (3 H; 2 H make up eight-line pattern, the AB part of an ABX system; J_{AB} = 17.5 Hz, J_{AX} = 6 Hz, J_{BX} = 10 Hz, $\nu_A - \nu_B$ 29.2 Hz; δH_A = 6.52 and δH_B = 6.02; 1 H is a doublet at about 6.25),[28] 4.25–3.64 (m, 1 H), and 1.80 (d, 3 H, J = 7 Hz). The Δδ values are H_A, 4.37; H_B, 3.67; H_M, 2.15; methyl, 0.78.

4β-Methyl-4-(*exo*-2′-acetoxybicyclo[2.2.1]hept-1′-yl)butanamide (25). To a stirred solution of impure acid **19a** (7.00 g, ~27.5 mmol) in 55 ml of benzene under nitrogen at room temperature was added oxalyl chloride (8.74 g, 68.8 mmol) over 5 min. This solution was then stirred an additional 2 hr at room temperature. The benzene and excess oxalyl chloride were evaporated at reduced pressure. Additional benzene was added and the solution again evaporated to give the acid chloride (9.48 g) as a light brown oil: ir (film) 1800 and 1725 cm^{-1}.

Ammonia was bubbled into a cooled (ice–water bath) solution of the acid chloride in ether (110 ml) for 20 min. The white precipitate which had separated was removed by filtration and washed with tetrahydrofuran. The filtrate was evaporated leaving a light brown, viscous oil (6.06 g). This was chromatographed on 300 g of silica gel. Elution with 5% methanol in ethyl acetate gave 5.10 g (>73%) of impure amide (**25**) as a light yellow glass: ir (film) 3350, 1725, and 1660 cm^{-1}; nmr ($CDCl_3$) 6.04 (br s, 2 H), 4.78 (br d, 1 H, J = 7 Hz), 2.02 (s, 3 H), and 0.84 (d, 3 H, J = 6.5 Hz).

1-(4′-Amino-1β′-methylbutyl)bicyclo[2.2.1]heptan-*exo*-2-ol (26). To a stirred mixture of lithium aluminum hydride (4.42 g, 0.117 mol) in 65 ml of ether under a nitrogen atmosphere was added a solution of amide **25** (4.92 g, ~19.4 mmol) in 65 ml of ether at a rate so as to maintain a gentle reflux. After spontaneous reflux ceased, the mixture was heated under reflux for 24 hr. The mixture was cooled in an ice-bath and 8.84 ml of 1:1 aqueous tetrahydrofuran was slowly added. This was followed by 4.42 ml of 15% sodium hydroxide and then 13.26 ml of water. The resulting white precipitate was removed by filtration and washed with tetrahydrofuran. The filtrate was evaporated to give 3.98 g (>95%) of amine alcohol **26** as a white semisolid. Three recrystallizations from benzene gave 0.90 g (~22%) of **26** (~90% pure). Two additional recrystallizations afforded a sample of analytical purity: mp 101–104°; ir (Nujol) 3300, 1600, and 1455 cm^{-1}; nmr ($CDCl_3$) 3.68 (br d, 1 H, J = 7 Hz), 2.70 (m, 2 H), 2.13 (br s, 1 H), and 0.90 (d, 3 A, J = 6.7 Hz).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.76; H, 11.70; N, 7.00.

1-(*N*-Acetyl-4′-amino-1′β-methylbutyl)bicyclo[2.2.1]heptan-*exo*-2-ol (27). Amine alcohol **26** (0.85 g, 4.3 mmol) was converted to the

(53) A. S. Narula and S. Dev, *Tetrahedron Lett.*, 1733 (1969).

diacetyl derivative by treatment with acetic anhydride in pyridine as described above (methylene chloride used in place of ether). The pale yellow oil so obtained was purified by chromatography on silica gel (75 g). Elution with 10% methanol in ethyl acetate gave 1.17 g (~96%) of **27**; ir (film) 3250 and 1725 cm^{-1}; nmr ($CDCl_3$) 6.19 (br s, 1 H), 4.70 (br d, 1 H, J = 7 Hz), 3.24 (br quartet, 2 H, J = 6 H), 2.20 (br s, 1 H), 2.00 (s, 3 H), 1.96 (s, 3 H), and 0.82 (d, 3 H, J = 6.5 Hz).

A solution of the diacetyl derivative (1.00 g, 3.56 mmol) in 12.5 ml of 1% (w/v) potassium hydroxide in methanol was stirred at room temperature for 24 hr. The solution was then diluted with chloroform, washed with saturated ammonium chloride and saturated salt solutions, dried ($MgSO_4$), and evaporated to give 0.99 g of a viscous pale yellow oil. Trituration with ether afforded white, solid monoacetyl derivative **27** (0.77 g, ~90%). Recrystallization from ethyl acetate gave an analytical sample, mp 104–106°; ir (Nujol) 3220 and 1650 cm^{-1}; nmr ($CDCl_3$) 6.18 (br s, 1 H), 3.68 (br s, 1 H), 1.97 (s, 3 H), and 0.89 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{11}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.32; H, 10.66; N, 5.62.

1-(*N*-Acetyl-4′-amino-1′β-methylbutyl)bicyclo[2.2.1]heptan-2-one (28). To a stirred solution of pyridine (2.30 g, 29.10 mmol) in 37 ml of dry methylene chloride was added chromium trioxide (1.46 g, 14.55 mmol) and the resulting mixture stirred for 20 min at room temperature.[54] *N*-Acetyl alcohol **27** (0.56 g, 2.34 mmol) in 2 ml of methylene chloride was added and the resulting mixture was stirred for 30 min at room temperature. The supernatant was then decanted into methylene chloride, and this solution was washed with 5% sodium hydroxide, 5% hydrochloric acid, saturated sodium bicarbonate and saturated salt solutions, dried ($MgSO_4$), and evaporated to give a light brown oil (0.60 g) which was chromatographed on 30 g of silica gel. Elution with 10% methanol in ethyl acetate gave 0.50 g (85%) of keto amide **28** as a pale yellow oil: ir (film) 3270, 1740, 1660, and 1550 cm^{-1}; nmr ($CDCl_3$) 6.56 (br s, 1 H), 3.27 (m, 2 H), 2.60 (br s, 1 H), 1.99 (s, 3 H), and 0.96 (d, 3 H, J = 6.5 Hz).

3β-Methyl-1,2,3,3a,4,5,6,8aα-octahydro-3aβ,6β-methanoazulen-8(7*H*)-one (4a). To a stirred mixture of dinitrogen tetroxide (1.68 g, 18.30 mmol) and sodium acetate (2.95 g, 36.6 mmol) in 15 ml of methylene chloride cooled to −30° was added keto amide **28** (2.65 g, ~11.16 mmol)[55] in 9 ml of methylene chloride by syringe.[21a,31] The temperature was allowed to rise to between −10 and 0° and held there for 35 min. During this time the color changed from green to yellow. The mixture was then washed with cold 10% potassium carbonate and cold water and dried (K_2CO_3), and the solvent evaporated to give 2.67 g (90%) of the *N*-nitroso amide as a dark yellow oil: ir (film) 1735, 1500, 1370, 1115, and 945 cm^{-1}.

To 5 ml of refluxing methylene chloride was simultaneously added by syringe 1.75 ml of 0.1 *N* sodium methoxide and the *N*-nitroso amide (2.66 g, ~10 mmol) in 5 ml of methylene chloride over 10 min.[21b] The solution was refluxed an additional 15 min, cooled, diluted with additional methylene chloride, washed with saturated salt solution, dried ($MgSO_4$), and evaporated to give 1.78 g of a yellow liquid: ir (film) 1705 and 1740 (shoulder) cm^{-1}. This material was chromatographed on 100 g of silica gel. Elution with 15% ether in pentane gave two major components, the less polar of which was identified as epoxide iii (0.35 g):[32] ir (film) 1550, 1530, 953, 858, and 829 cm^{-1}; nmr 3.05 (d, 1 H, J = 1.5 Hz), 2.43 (m, 1 H), and 0.93 (d, 3 H, J = 7 Hz); *m/e* 165 (M^+). Preparative glpc (column B at 123°) gave an analytical sample.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.53; H, 9.79.

The more polar component (0.95 g, 67% when corrected for homolog impurity) was identified as tricyclic ketone **4a**: ir (film) 1705 cm^{-1}; nmr 2.8–2.4 (m, 2 H), 2.4–2.1 (m, 2 H), and 0.97 (d, 3 H, J = 7 Hz); *m/e* 178 (M^+). Preparative glpc (column B at 150°) gave an analytical sample.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.09.

Equilibration of Ketone 4a. A solution of 0.15 g of ketone **4a** and 200 mg of NaOMe in 10 ml of methanol was stirred at room temperature for 25 hr. Ammonium chloride was added and the methanol evaporated. The residue was taken up in a water–ether mixture, and the separated aqueous layer was extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give a mixture of ketones **4a** and **4b** (0.12 g) as a yellow liquid: nmr methyl doublets at 0.97 (J = 7 Hz) and 0.94 (J = 6.5 Hz) (30:70 ratio). The 30:70 distribution of ketones **4a**:**4b** is assumed to represent the thermodynamic equilibrium since the conditions employed are sufficient to equilibrate the more hindered norzizanone epimers (**31** and **32**).

3β-Methyl-3aβ,6β-methanohexahydroindan-1-one (iv).[32] To a stirred solution of epoxide iii (0.25 g, 1.5 mmol)[32] in 10 ml of benzene at room temperature was added boron trifluoride etherate (0.1 ml, 0.75 mmol).[56] After 30 min the solution was poured into water. The organic layer was washed with additional water, dried ($MgSO_4$), and evaporated to yield 0.26 g of ketone iv[32] as a yellow liquid which was purified by preparative glpc (column B at 152°): ir (film) 1740 cm^{-1}; nmr 1.11 (d, 3 H, J = 6.5 Hz); *m/e* 164 (M^+).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.16; H, 9.76.

7-*n*-Butylthiomethylene-3β-methyl-1,2,3,3a,4,5,6,8aα-octahydro-3aβ,6β-methanoazulen-8(7*H*)-one (30b). To a stirred mixture of 57% sodium hydride dispersion (0.22 g, 5.27 mmol) in 15 ml of ether under nitrogen at room temperature were added a drop of ethanol and then a solution of ketone **4a** (0.94 g, 5.27 mmol) and ethyl formate (0.59, g, 7.9 mmol) in 5 ml ether over 30 min.[57] This mixture was stirred at room temperature for 18 hr. Ethanol (0.1 ml) was added and the brown suspension was stirred for another 1 hr. Water (5 ml) was added, the layers were separated, and the ether portion was extracted with water and 1 *N* NaOH. The aqueous extracts were washed with ether, acidified with 3 *N* hydrochloric acid, saturated with salt, and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give a brown oil which was chromatographed on 50 g of silica gel. Elution with 15% ether in pentane gave 0.79 g (73%) of hydroxymethylene derivative **30a** as a tan liquid: ir (film) 1640, 1580 and 1170 cm^{-1}; nmr 13.85 (br s, 1 H), 7.98 (s, 1 H), 2.87 (m, 1 H), and 0.91 (d, 3 H, J = 6 Hz).

A solution of **30a** (0.78 g, 3.79 mmol), *n*-butanethiol (0.36 g, 4.00 mmol), and a crystal of *p*-toluenesulfonic acid hydrate in 10 ml of dry benzene was heated under reflux for 7 hr with azeotropic removal of water.[36a] The resulting tan solution was washed with 10% potassium carbonate and water, dried ($MgSO_4$), and evaporated to give 0.92 g of a tan oil. Chromatography on 50 g of silica gel (eluting with 15% ether in pentane) gave the *n*-butylthiomethylene derivative **30b** (0.87 g, 82%) as a yellow oil: ir (film) 1665 and 1550 cm^{-1}; nmr (CCl_4) 7.02 (s, 1 H), 2.25–2.68 (m, 3 H), and 0.89 (d, 3 H, J = 5.5 Hz).

Anal. Calcd for $C_{17}H_{26}OS$: C, 73.33; H, 9.41; S, 11.51. Found: C, 73.32; H, 9.46; S, 11.64.

(±)-13-Nor-5α-zizan-6-one ((±)-31). To a refluxing solution of lithium (0.12 g, 17.3 mmol) in 100 ml of liquid ammonia swept with nitrogen were added a solution of *n*-butylthiomethylene derivative **30b** (0.75 g, 2.50 mmol) and *tert*-butyl alcohol (0.37 g, 5.00 mmol) in 25 ml of ether over a 30 min period.[36b] After stirring an additional 30 min more ether (50 ml) was added, followed by a solution of methyl iodide (4.25 g, 30.0 mmol) in 25 ml of ether (20 min period). This mixture was stirred an additional 40 min, the ammonia was evaporated and 80 ml of water was added. The aqueous portion was saturated with salt and extracted with ether. The ether extracts were washed with 5% hydrochloric acid and water, dried ($MgSO_4$), and evaporated to yield 0.70 g of a tan liquid which was purified by chromatography on 50 g of silica gel. Elution with 5% ether in pentane gave 0.36 g (69%) of a yellow liquid. The ir and nmr spectra are identical with those of natural 5α-norzizanone (see below).

(±)-13-Norzizan-6-one (32). (±)-5-α-Norzizanone (**31**) was equilibrated as described above for ketone **4a**. The two isomers (0.37 g) were separated by chromatography on 50 g of silica gel. Elution with 5% ether in pentane gave 0.14 g of pure **31** (R_f value 0.4) and 0.22 g of (±)-norzizanone (**32**) (R_f value 0.3) containing a small amount of **31**. Two more equilibrations and chromatographies gave an additional 0.09 g of **32** (64% total yield). The ir and nmr spectra of this synthetic (±)-norzizanone are superimposable upon the corresponding spectra of authentic (+)-32 (see below).

(54) R. Ratcliffe and R. R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(55) This quantity was obtained by combining the above 0.50 g of pure keto amide with less pure material carried separately along from the *N*-acetylamine alcohol stage (**27**). The principal impurity introduced was evidently the lower homolog derived originally from the ester i (see footnote 30).

(56) D. J. Reif and H. O. House, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 375.

(57) C. Ainsworth, *ibid.*, p 536.

Methyl Zizanonate (1, R = CO_2CH_3). An ether solution of 388 g of vetiver oil (Haiti)[58] was extracted with 1 *N* sodium hydroxide and the acid regenerated in the usual manner to give 11.22 g (~48 mmol) of crude zizanoic acid (**2**). This was dissolved in ether and treated with an excess of ethereal diazomethane at 0°. This solution was allowed to come to room temperature and stir over night. Removal of a white precipitate and evaporation of the solvent gave 11.38 g of a brown oil which was purified by chromatography on silica gel (550 g). Elution with benzene gave 7.64 g of a pale yellow liquid: ir (film) 1730, 1635, 1165, and 893 cm^{-1}; nmr 4.71 and 4.57 (t, 1 H each, J = 2 Hz), 6.61 (s, 3 H), 2.85–1.15 (m, 13 H), and 1.07 and 1.04 (s, 3 H each). The spectral data are in good agreement with those reported for methyl zizanoate.[7a]

Khusimol (Zizan-12-ol; R = CH_2OH). A solution of methyl zizanoate (7.64 g, 30.8 mmol) in ether was slowly added to a stirred mixture of lithium aluminum hydride (6.42 g, 0.167 mol) in ether under nitrogen and this mixture refluxed for 1.5 hr. After cooling and work-up as described above for amine alcohol **26**, 6.64 g (98%) of khusimol was obtained: ir (film) 3330 and 895 cm^{-1}.[7a]

(+)-Zizaene (1). To a stirred solution of khusimol (6.64 g, 30.2 mmol) in 70 ml of pyridine under nitrogen was added a solution of tosyl chloride (11.48 g, 60.3 mmol) in 75 ml of pyridine. After the mixture was stirred for 6 hr at room temperature, ether was added. The solution was washed with 6 *N* hydrochloric acid, saturated sodium bicarbonate and saturated salt solutions, dried ($MgSO_4$), and evaporated to give a tan oil which was chromatographed on 600 g of silica gel. Elution with benzene gave 9.19 g (89%) of the tosylate as a light yellow oil: ir (film) 1640, 1600, and 1365 cm^{-1}.

To a stirred refluxing mixture of lithium aluminum hydride (5.08 g, 0.134 mol) in 350 ml of tetrahydrofuran under nitrogen was added a solution of the tosylate (9.19 g, 26.8 mmol) in 350 ml of tetrahydrofuran over 1 hr. Reflux was continued for an additional 20 hr, and then the product was isolated as above for amine alcohol **26**. The tan oil so obtained was chromatographed on 275 g of silica gel. Elution with petroleum ether (bp 30–60°) gave 4.30 g (68% from methyl zizanoate) of zizaene (**1**): ir (film) 1640, 1480, 1375 and 895 cm^{-1}; nmr 4.71 and 4.56 (t, 1 H each, J = 2 Hz), 1.08 (s, 3 H), 1.06 (s, 3 H), and 0.96 (d, 3 H, J = 7 Hz). These spectral data correspond well with the literature values.[7a]

(+)-Norzizanone (32). Ruthenium dioxide dihydrate (0.84 g, 5.0 mmol) was dissolved in a solution of sodium periodate (47.2 g, 0.22 mol) in 940 ml of water with stirring (yellow ruthenium tetroxide formed).[37] Zizaene (3.00 g, 14.7 mmol) in carbon tetrachloride (60 ml) was added, and the mixture was rapidly stirred for 17 hr. The carbon tetrachloride phase turned brown immediately upon addition. Isopropyl alcohol (30 ml) was added, and after stirring for 30 min, the mixture was diluted with ether, the aqueous layer was saturated with salt, and the layers were separated. The aqueous layer was extracted with ether, and the organic extracts were washed with saturated salt solution, dried ($MgSO_4$), and evaporated to give a brown oil (3.34 g) which was chromatographed on 165 g of silica gel. Elution with benzene gave 1.62 g (53%) of (+)-norzizanone ((+)-**32**): ir (film) 1705, 1460, 1380, 1360, and 1150 cm^{-1}; nmr 2.85 (br t, 1 H, J = 8 Hz), 1.18 (s, 3 H), 1.01 (s, 3 H), and 0.98 (d, 3 H, J = 7 Hz); (C_6H_6) 1.09 (s, 3 H), 1.01 (s, 3 H), and 9.82 (d, 3 H J = 7 Hz); $[\alpha]^{25}D$ +211° (*c* 1.00, EtOH). Preparative glpc (column A at 145°) gave an analytical sample; however the nmr spectrum of this collected material indicated some equilibration to **31**.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.78.

5-Bromo-13-norzizan-6-one (36). To a stirred solution of (+)-norzizanone (0.30 g, 1.46 mmol) in 2 ml of acetic acid at 15° was added a solution of bromine (0.24 g, 1.50 mmol) in 2 ml of acetic acid over a 10-min period. After an additional 20 min at 15°, the solution was poured into water and extracted twice with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and saturated salt solution, dried ($MgSO_4$), and evaporated to give a tan oil (0.43 g) which was purified by chromatography on silica gel (25 g). Elution with benzene gave 0.31 g (76%) of bromo ketone **36** as a tan liquid which solidified upon standing, mp 33–36°: ir (film) 1705 cm^{-1}. Recrystallization from pentane (−78°) afforded an analytical sample, mp 38–41°; nmr 1.19 (s, 6 H) and 0.97 (d, 3 H, J = 6.5 Hz); $[\alpha]^{25}D$ +55.2 (*c* 0.54, EtOH).

Anal. Calcd for $C_{14}H_{21}OBr$: C, 58.95; H, 7.42; Br, 28.02. Found: C, 58.84; H, 7.45; Br, 27.77.

13-Nor-5α-zizan-6-one (31). To a stirred solution of bromo ketone **36** (0.25 g, 0.9 mmol) in 10 ml of acetic acid at room temperature was added 3 g of zinc in portions over 30 min.[41] This mixture was stirred an additional 3 hr and poured into 500 ml of water; the zinc was removed by filtration. The aqueous mixture was extracted with ether and the ether extracts were washed with water, saturated sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to yield 0.17 g (94%) of 5α-norzizanone (**31**) as a colorless liquid: ir (film) 1705, 1470, 1460, 1380, and 1120 cm^{-1}; nmr 1.10 (s, 3 H), 1.02 (s, 3 H), and 0.92 (d, 3 H, J = 6.5 Hz); (C_6H_6) 1.07 (br s, 6 H) and 0.81 (d, 3 H, J = 6.5 Hz).

Equilibration of (+)-Norzizanone ((+)-32) and 5α-Norzizanone (31). (+)-Norzizanone ((+)-**32**, 0.2 g) was equilibrated with sodium methoxide in methanol as described above for tricyclic ketone **4a**, except that the solution was heated under reflux for 18 hr. The nmr spectrum of the recovered ketone mixture shows two new methyl singlets at δ 1.10 and 1.02 and a new methyl doublet at δ 0.94 (J = 6.5 Hz) in addition to signals for remaining (+)-norzizanone. The ratio of **32**:**31** is estimated as 40:60.

5α-Norzizanone (**31**) was equilibrated in like manner but with a 12-hr reflux period. The nmr spectrum of the resulting ketone mixture (after purification by filtration over silica gel in benzene) was identical with that obtained from (+)-norzizanone.

Zizan-6-ol (39). To a stirred solution of 3.73 ml of 1.95 *M* methyllithium in 6.27 ml of ether blanketed with nitrogen at 0° was added a solution of (+)-norzizanone ((+)-**32**, 0.50 g, 2.44 mmol) in 5 ml of ether over 10 min. After an additional 1 hr, the product was isolated by a standard extractive work-up and chromatographed on 25 g of silica gel. Elution with benzene gave 0.47 g (87%) of alcohol **39**: ir (film) 3500 cm^{-1}; nmr 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.88 (d, 3 H, J = 7 Hz), and 0.73 (s, 1 H, disappears upon addition of D_2O).

Dehydration of Zizan-6-ol (39). To a solution of alcohol **39** (0.30 g, 1.35 mmol) and 1 ml of pyridine in 24 ml of benzene at room temperature (nitrogen atmosphere) was added a solution of thionyl chloride (0.17 ml) in 2.9 ml of benzene.[46] This mixture was stirred for 10 min and then poured into 20 ml of cold 1 *N* hydrochloric acid. The layers were separated; the aqueous portion was extracted with ether. The organic extracts were washed with saturated sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to yield 0.29 g of a pale yellow liquid. Tlc analysis (benzene elution) showed only one nonpolar spot and only a trace of starting material. Glpc analysis (column A at 109°) showed two major components (3:2 ratio) which were collected by preparative glpc (column G at 125°). The major component (shorter retention time) was isozizaene (**40**); ir (film) 1455, 1370, 1075, and 812 cm^{-1} (weak); nmr, 1.43 (vinyl methyl), 1.00 (s, 3 H), 0.97 (s, 3 H), and 0.83 (d, 3 H, J = 7 Hz). The minor olefin was identified as (+)-zizaene (**1**) by ir, nmr, and glpc comparisons.

(±)-13-Thiophenylzizan-6-yl Benzoate (41b). A solution of phenylthiomethyllithium (~0.5 *M*) was prepared by reaction of thioanisole (6.22 g, 50 mmol) in dry tetrahydrofuran (72 ml) with phenyllithium (22.0 ml of 2.3 *M* solution) for 15 hr at room temperature under nitrogen.[47] (±)-Norzizanone (**32**, 0.22 g, 1.07 mmol) in tetrahydrofuran (5 ml) was added to a 6.4 ml (~3.2 mmol) portion of the phenylthiomethyllithium solution with cooling (ice–water bath). After 24 hr at room temperature the solution was poured into saturated salt solution and extracted with ether. The combined ether extracts were washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The resulting brown liquid was further purified by column chromatography on silica gel (75 g). Elution with 1:2 benzene–hexane gave a pale yellow liquid (0.32 g) which according to nmr analysis was a mixture of thioanisole (5 parts) and phenylthiomethyl adduct **41a** (7 parts, 0.24 g, 71%): ir (film) 3400, 1585, 1480 and 1440 cm^{-1}; nmr 7.2 (m, 5 H), 3.08 (AB quartet, J = 14.5, $\Delta\nu$ = 7.8 Hz), 2.52 (s, 1 H), 1.07 (s, 3 H), 0.92 (s, 3 H), and 0.87 (d, 3 H, J = 7 Hz).

n-Butyllithium (0.49 ml of a 1.54 *M* solution, 0.76 mmol) was added to the above mixture of **41a** (0.24 g, 0.76 mmol) and thioanisole in ether (6 ml) under a nitrogen atmosphere at ice bath temperature. After 1 hr at room temperature a solution of benzoyl chloride (0.12 ml, 1.0 mmol) in 2 ml of ether was added to the cloudy solution with cooling (ice bath). This mixture was then stirred for 3 hr at room temperature. The mixture (white precipitate formed) was diluted with additional ether, washed with water, saturated sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The resulting light yellow oil (0.65 g) was chromatographed on 50 g of silicage l. Elution with 1:2 benzene–hexane gave 0.09 g of

(58) Source of vetiver oil was Fritzsche Dodge and Oleott, Inc., N. Y.

an 8:5 mixture of unreacted **41a** (29%) and thioanisole (nmr analysis). Increasing the benzene concentration gave 0.23 g (71%) of benzoate **41b** as a yellow oil which solidified upon standing, mp 82–85°; ir (film) 1720 and 1580 cm^{-1}; nmr 8.15–7.90 (m, 2 H), 7.70–7.05 (m, 8 H), 3.98 (AB quartet, J = 12.5 Hz, $\Delta\nu$ = 28.3 Hz), 1.29 (s, 3 H), 1.18 (s, 3 H), and 0.90 (d, 3 H, J = 6.5 Hz).

(±)-Zizaene. To a refluxing solution of lithium (0.04 g, 5.8 mmol) in liquid ammonia (15 ml) under nitrogen was added a solution of benzoate **41b** (0.23 g, 0.54 mmol) in 5 ml of ether over a 30-min period. After an additional 30 min at reflux with stirring, the blue color was quenched by addition of ammonium chloride in small portions. The ammonia was then slowly evaporated. Pentane was added in small portions during the evaporation. The resulting mixture was added to water, the layers were separated, and the aqueous portion was extracted with additional pentane. The pentane extracts were washed with 1 N NaOH and water, dried ($MgSO_4$), and evaporated. The pale yellow liquid (0.11 g) obtained was chromatographed on 10 g of silica gel. Elution with pentane gave 0.07 g (64%) of (±)-zizaene ((±)-**1**) as a clear, colorless liquid. This material has the same glpc retention time (column A at 118°) and ir and nmr spectra as zizaene (see above).

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Synthesis of 8α-Histidyl-3,8-dimethyl-10-ethylisoalloxazine and Related Isoalloxazines[1]

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Abstract: The new 10-ethylisoalloxazines, 6-hydroxymethyl-, 7-methyl-, 8-hydroxymethyl-3-methyl-, 9-hydroxymethyl-, and 8α-histidyl-3,8-dimethyl-10-ethylisoalloxazine, have been synthesized, the 8α-histidyl-3,8-dimethyl-10-ethylisoalloxazine being a model for 8α-histidylriboflavin, the succinate dehydrogenase flavin. Synthesis was achieved, except for the histidyl compound, by condensation of the appropriately substituted 2-amino-*N*-ethylaniline with alloxan or *N*-methylalloxan, the substituted diaminobenzenes being obtained from carboxy-substituted 2-nitroacetanilides by consecutive reduction with diborane and Raney nickel–hydrogen. Conversion of 8-hydroxymethyl-3-methyl-10-ethylisoalloxazine to the corresponding bromomethyl derivative and condensation of the bromo derivative with N^{α}-benzoylhistidine followed by hydrolysis yielded the 8α-histidyl-3,8-dimethyl-10-ethylisoalloxazine. The new isoalloxazines exhibit, as expected, the spectral properties and fluorescence behavior of flavins and, in particular, 8α-histidyl-3,8-dimethyl-10-ethylisoalloxazine closely resembles 8α-histidylriboflavin. Visible and near uv absorbance band shifts of flavins resulting from protonation and from substituents on the benzene ring are interpreted on the basis of resonance interactions, visible maxima being assigned to resonance forms involving N^{10} lone electron pair interaction while near uv maxima are assigned to resonance forms involving electron release from the benzene ring.

In connection with the structure and mode of attachment of riboflavin covalently linked to the peptide chain of succinate dehydrogenase,[2,3] this laboratory several years ago undertook the synthesis of flavin models substituted at the 8α-methyl position with a nucleophilic function appropriate to an amino acid side chain, the choice of 8α-substituted flavins as models for the succinate dehydrogenase flavin being made on the basis of the following considerations. The ribityl side chain and the pyrimidine ring having been ruled out by previous investigations[2,3] as the flavin site of attachment, chemical considerations,[4–6] in particular the ease of substitution of 8α-methyl hydrogen by deuterium under mild conditions,[5] and biosynthetic possibilities suggested the 8α-methyl position as the site of attachment to the protein, the biosynthetic possibilities suggesting that ionization from the 8α-methyl group provides a pair of electrons for oxidation to the oxidation level requisite for substitution by a nucleophilic function of an amino acid residue such as the ε amino of a lysine residue or a nitrogen atom of the imidazole ring of a histidine residue, etc. Subsequent to our undertaking the synthesis of 8α-methyl-substituted flavins, the 8α position was identified[7] as the site of attachment, the 8-methyl group being substituted[8,9] by a ring nitrogen of a histidine residue.

To provide 8α-methyl-substituted flavins models, as well as other methyl-substituted flavins, a general synthetic approach to N^{10}-alkylisoalloxazines substituted in the benzene ring with hydroxymethyl groups was utilized (Scheme I) and in this paper we report on the synthesis of 3-methyl-8-hydroxymethyl-10-ethylisoalloxazine, 6- and 9-hydroxymethyl-10-ethylisoalloxazines, 7-methyl-10-ethylisoalloxazine, and 8α-histidyl-3,8-dimethyl-10-ethylisoalloxazine.

Synthesis of the above compounds starts (Scheme I) with the corresponding carboxy-substituted *o*-nitroanilines (the four acids, Ia, Ib, Ic, and Id, being syn-

(1) Abstracted in part from the Ph.D. Thesis of P. Johnson, Sept 1971.
(2) E. B. Kearney, *J. Biol. Chem.*, **235**, 865 (1960).
(3) T. Y. Wang, C. L. Tsou, and Y. L. Wang, *Sci. Sinica*, **14**, 1193 (1965).
(4) P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **42**, 2164 (1959).
(5) E. Y. Bullock and O. Jardetzky, *J Org. Chem.*, **30**, 2056 (1965).
(6) F. Muller and P. Hemmerich, *Helv. Chim. Acta*, **49**, 2352 (1966).
(7) P. Hemmerich, A. Ehrenberg, W. H. Walker, L. E. G. Eriksson, J. Salach, P. Bader, and T. P. Singer, FEBS (*Fed. Eur. Biochem. Soc.*) *Lett.*, **3**, 37 (1969).
(8) H. W. Walker and T. P. Singer, *J. Biol. Chem.*, 245, 4224 (1970).
(9) S. Ghisla, U. Hartmann, and P. Hemmerich, *Angew. Chem., Int. Ed. Engl.*, **9**, 642 (1970).