acetoxy), 7.68 (s, 3, acetoxy), 6.23 (q, 1, J = 11 and 9 Hz, one of $-CH_2O-$), 5.95 (q, 1, J = 11 and 5.5 Hz, one of $-CH_2O-$).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.36; H, 7.40.

Registry No.—**1a**, 2618-41-9; **2a**, 31582-01-1; **2b**, 32632-37-4; **2b** dimethyl ketal, 32632-38-5; **2c**, 31582-04-4; **3**, 32632-40-9; **4a**, 32670-67-0; **5**, 32670-68-1; **6**, 32632-41-0; **7**, 32632-42-1; **9a**, 32632-43-2; **9b**, 32632-44-3; **11b**, 32632-45-4; **12b**, 31582-00-0; **13**, 32670-69-2; **14a**, 32632-47-6; **14b**, 32632-48-7; **15a**, 31582-08-8; **15b**, 31582-09-9; **16**, 32632-51-2; **17a**, 32632-52-3; **18**, 32632-53-4; **19a**, 32632-54-5; **19b**, 32632-55-6; **20**, 32632-56-7; **21a**, 31582-11-3; **21b**, 32632-58-9; **22a**, 32632-59-0; **22b**, 32632-60-3; **22c**, 32632-61-4; **23**, 32632-62-5; **24**, 32632-63-6; **26**, 32632-64-7; **27**, 32632-65-8; **28a**, 32632-66-9; **28b**, 32670-70-5; **28c**, 32632-67-0; **30a**, 32632-68-1; **30b**, 32632-69-2.

Acknowledgments.—The authors thank Dr. Roy Bible, Jr., for his assistance in interpretation of the nmr spectra, and Mr. L. F. Johnson of Varian Associates for his assistance in running the nuclear Overhauser effect measurement. The authors gratefully acknowledge helpful discussion with Dr. F. B. Colton. The authors are indebted to Mr. R. H. Salzmann, Mr. J. Prahl, Mr. T. A. Bonnie, and Mr. H. Erisman for the preparation of the intermediates. Most of the column chromatographic separations were carried out by our Chromatography Department and thanks are due to Mr. R. T. Nicholson and Mr. R. Dahm. All of the spectral and elementary analyses were carried out by our Analytical Department.

Mirestrol. II.[1] A Synthesis of a New Tricyclic System

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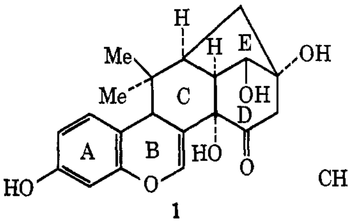
As a model experiment to construct the C,D,E ring system of mirestrol (**1**), the unequivocal synthesis of (±)-2β,4β-ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2α-ol-11-one (**2b**) from 2,2-dimethylcyclohexanone is described in Schemes I and II. This sequence involved elaboration of the starting material to the γ-keto ester **4b**, followed by introduction of an acetonyl side chain to obtain **6b**. The latter underwent an aldol condensation to the unsaturated bicyclic keto acid **7**, which was reduced catalytically to the *cis*-hydrindanone **18a**. Conversion of **18a** to the diketone **23a** and the subsequent intramolecular aldol ring closure gave the desired ketol **2b**.

As a part of our effort to synthesize mirestrol (**1**)[2] and related substances from the tricyclic ketone **2a**,[1] we explored an unambiguous synthesis of the new tricyclic ring system incorporated in the C,D,E rings of the natural product. To determine the feasibility of constructing such a ring system, we chose to convert a



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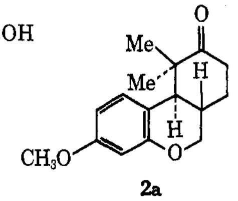
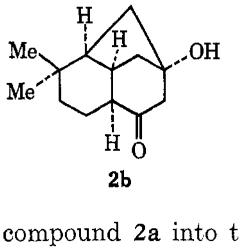


2a



2b

simple analog of compound **2a** into the ketol **2b**, and the successful synthesis of the latter compound is the subject of this paper. Although all synthetic compounds containing a chiral carbon atom are racemic, only one enantiomer is depicted for convenience.

2,2-Dimethylcyclohexanone, an obvious model for **2a**, was transformed by conventional methods (see Scheme I) into 6,6-dimethylcyclohexanone-3-carboxylic acid (**4a**), which was identical with the authentic specimen[3] prepared from camphoric anhydride by a series of known procedures.[3a]

Our next objective, the formation of the five-membered ring, was initiated by alkylation of the methyl ester **4b** with methallyl iodide[4] in the presence of potassium *tert*-butoxide to afford a mixture of *trans*- and *cis*-2-methallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (**5**) (see also **8a** and **9a**) in about a 3:1 ratio. Since further treatment of this mixture with sodium methoxide in refluxing methanol did not significantly alter the ratio of the isomers, the major product (lower boiling[5]) was suspected to be the more stable trans compound **8a**. This assumption was supported by conformational analysis, which indicated that **9a** is 0.55 kcal[6] less stable than **8a**. The mixture **5** was partially separated by distillation and more effective purification was achieved by preparative thin layer chromatography (see Experimental Section). The nmr spectrum of the more abundant isomer possessed a broad multiplet at τ 6.83 representing the hydrogen attached to C-2; the observed half-height width of 22 Hz is consistent with a diaxial coupling of H-2 and H-3, and the major epimer was designated trans as in **8a**. The cis isomer **9a** was obtained as a low-melting solid whose nmr displayed a

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(1) Part I: M. Miyano and C. R. Dorn, *J. Org. Chem.*, **36**, 259 (1971).

(2) (a) N. E. Taylor, D. C. Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960); (b) D. G. Bounds and G. S. Pope, *ibid.*, 3696 (1960).

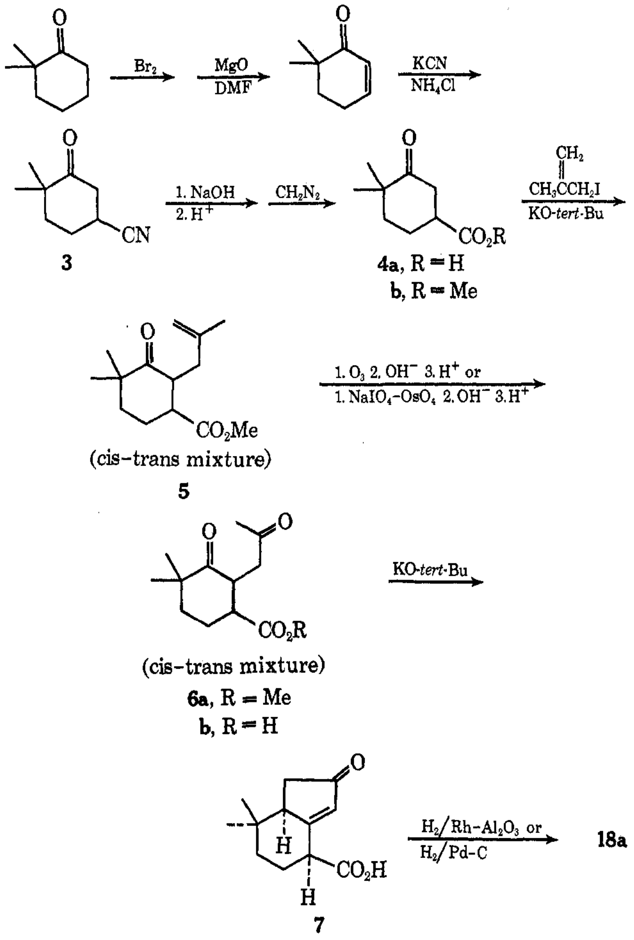
(3) (a) W. H. Perkin, *ibid.*, **73**, 796 (1898); (b) G. Blanc, *Bull. Soc. Chim. Fr.*, [3] **15**, 1193 (1896); [3] **21**, 835 (1899).

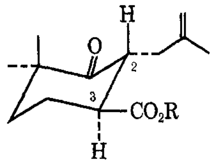
(4) For a similar procedure, see L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth, *J. Amer. Chem. Soc.*, **75**, 2112 (1953).

(5) The von Auwers-Skita rule suggests the trans isomer to boil lower than the cis. See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 216.

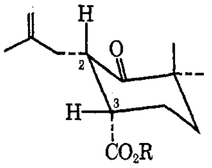
(6) The conformational energy (1.1 kcal) of the axial carbomethoxy group was divided by two. See E. L. Eliel, N. L. Allinger, J. S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 441.

Scheme I





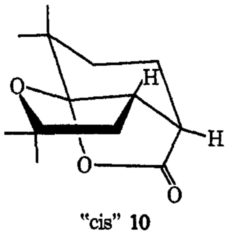
trans-**8a**, R = Me
b, R = H



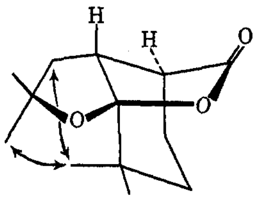
cis-**9a**, R = Me
b, R = H

broad signal at τ 6.85 with a width at half-height of only 7 Hz.

In contrast to the ester **4b**, alkylation of the free acid **4a** under similar conditions proceeded less efficiently and gave rise to the isomeric acids **8b** and **9b**, accompanied by appreciable amounts of starting material. The noncrystalline trans acid **8b** was again the predominant epimer and could be converted to **8a** by treatment with diazomethane. During chromatographic separation of the cis–trans mixture of γ-keto acids **8b** and **9b**, a neutral compound with spectral data (see Experimental Section) in agreement with **10** was isolated. The data were also consistent with **11**, although this "trans" lactone contains two significant nonbonded interactions and therefore is unlikely to be formed under such mild conditions.



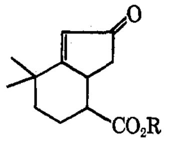
"cis" **10**



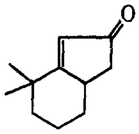
"trans" **11**

Periodate cleavage of **5** in the presence of osmium tetroxide[7] afforded **6a**, which was saponified to **6b**. The latter could also be obtained from **5** by ozonation and the subsequent alkaline work-up. Purification of the acetonyl derivatives **6a** and **6b** resulted in substantial loss of material and was not rigorously pursued, since the crude products gave acceptable results.

The cyclization of **6a** to **12a** was complicated by the hindered nature of the six-membered ketone. Even a simpler model, 2-acetonyl-6,6-dimethylcyclohexanone,[8] upon forced cyclization afforded a furan **14** along with the five-membered ketone **13**. Upon treatment with potassium *tert*-butoxide, the methyl ester **6a** gave rise to the triketone **15**, while on the other hand the acid **6b** yielded the cyclization–migration product **7**, rather than the expected unsaturated ketone **12b**. The nmr spectrum of **7** revealed a narrow triplet at τ 4.17 which can be rationalized by the weak coupling of the olefinic proton with the two allylic protons at C-4 and C-8 (see **16**). In addition, the hydrogen at C-4 (multiplet at τ 6.64) was slowly replaced by deuterium on treatment with deuterium oxide, thus collapsing the triplet at τ 4.17 to a narrow doublet ($J \cong 2$ Hz).



12a, R = Me
b, R = H



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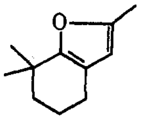
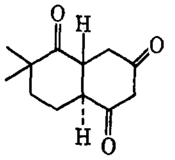


14



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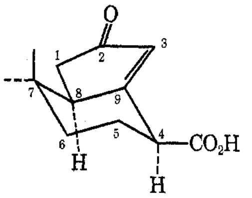

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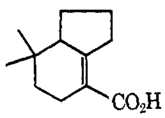

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Vigorous evolution of gas was noted as compound **7** was heated above its melting point, also suggesting the presence of a vinylogous β-keto acid. Considering the reaction conditions employed, the formation of **7** was apparently subject to thermodynamic control and the carboxyl group should be equatorial as in **16**.

Hydrindenones of type **7** generally yield cis-fused products upon catalytic hydrogenation[9] and presumably the catalyst would approach compound **7** predominantly from the side opposite of the β-oriented carboxyl group to afford the all-cis saturated acid **18a**. This was indeed the case, although the hindered nature of the

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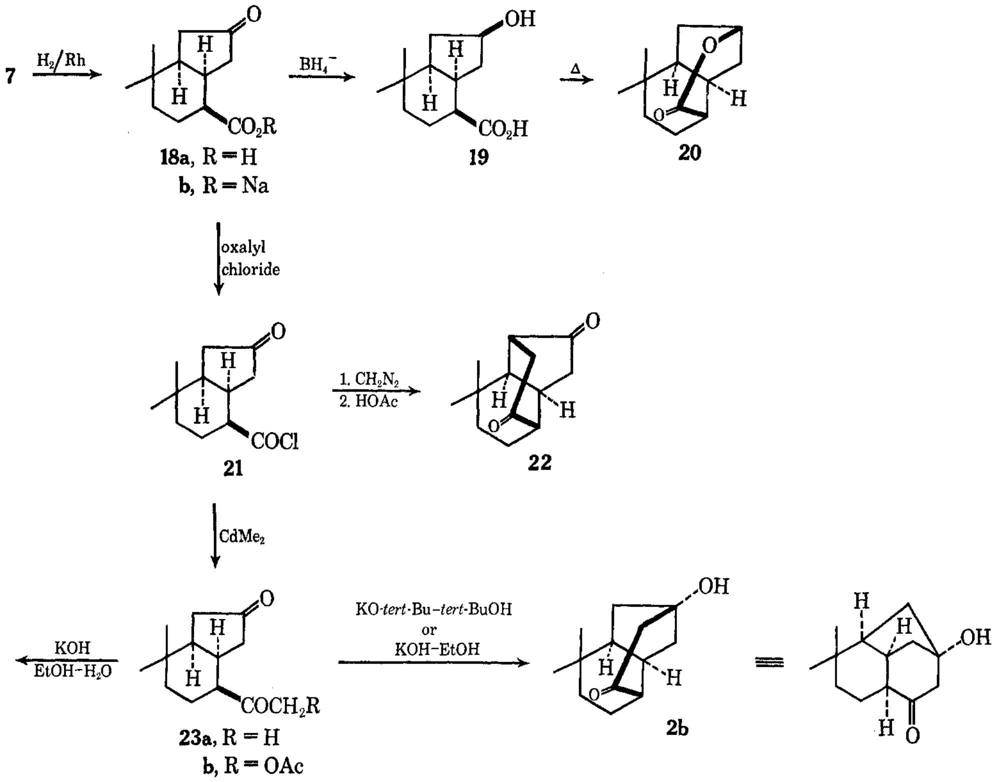
[7] For a general procedure, see R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 473 (1956).

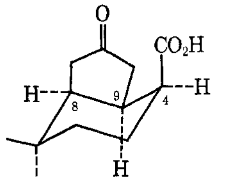
[8] Prepared by methallylation of 2,2-dimethylcyclohexanone followed by ozonation.

[9] R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

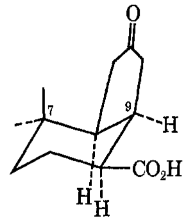
SCHEME II



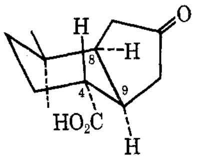
double bond caused some difficulty. For example, hydrogenation in the presence of 5% rhodium on alumina was sluggish and gave erratic results, while, if 10% palladium on carbon was employed as the catalyst, reduction of **7** gave reproducible yields of **18a** (about 50%) (Scheme II), but significant quantities of the hydrogenolysis product **17** resulted and some starting material was recovered. The nmr spectrum[10a] of **18a** could not be properly interpreted in terms of a single conformation like **26a**, **26b**, **27a**, **27b**,[10b] or **28**. It therefore seemed likely that **18a** is a conformational mixture of **26a** and **26b**. In agreement with the proposed stereochemistry, **18a** gave rise to the all-cis hydroxy acid **19**. A β orientation of the hydroxyl group is expected since the axial carboxyl group in **26a** and the axial methyl group in **26b** would hinder β-face attack of the reducing agent. Chemical evidence for the structure of **19** was demonstrated by its facile conversion (briefly heating above its melting point) to the tricyclic lactone **20**.



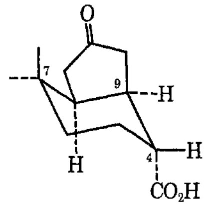
26a



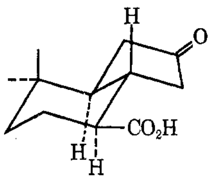
26b



27a



27b



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An attempted preparation of the methyl ketone **23a** from **18a** in the usual manner[11] was unsuccessful; that is, the sodium salt **18b** was converted into the acyl chloride **21**, which upon treatment with excess diazomethane followed by warm acetic acid failed to produce the acetoxymethyl ketone **23b**. Instead, the product was a tricyclic substance containing a five-membered ketone as well as a six-membered ketone (ir bands at 1748 and 1710 cm^{-1}). Taking into account the mechanism of formation (see **29**), compound **22** appeared to be the logical structure, thus providing additional evidence for the stereochemical assignment of **18a**.

The conversion of the carboxyl group in **18a** to an acetyl group in **23a** was effected in good yield by treat-

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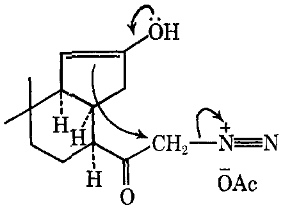
[10] (a) One of the methylene protons of the six-membered ring appeared as an irregular triplet (J = 4 Hz) in benzene solution, which may be compatible with rapidly equilibrating conformational isomers **26a** and **26b**, but not with conformers **27a** and **27b** (see footnote 10b) or the fixed structure **28**. For a similar situation, see protons a and b in N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "Nmr Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, No. 469. (b) Although **26a** contains a greater number of significant 1,3 nonbonded interactions than **26b**, this may be somewhat compensated by the more severe interaction of the C-7 axial methyl group and the C-9 methylene in **26b** as compared to the diaxial interaction of the C-4 carboxyl and the C-8 methylene in **26a**. Since the energies of **26a** and **26b** are roughly comparable, the prospect for equally populated species is reasonable. The situation for **27a** and its flipped form **27b** is different. Conformer **27b** possesses a very serious interaction between the axial methyl and the C-9 methylene which is not present in **27a**. The axial C-4 carboxyl group in **27b** also gives rise to significant 1,3 nonbonded interactions and one would predict that **27b** has a much higher energy content than **27a**. Conformational analysis indicates that at equilibrium the mixture contains at least 99% of **27a** at room temperature.

[11] G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961).



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ing the acid chloride **21** with dimethylcadmium in benzene. It is worth mentioning that the methyl ketone **23a** still retained the acetyl group in the configuration which was necessary for the subsequent cyclization. The fact that this was indeed the less stable configuration was demonstrated by the epimerization of **23a** to the more stable isomer **24** upon treatment with potassium hydroxide in aqueous ethanol.

Finally, the desired cyclization of **23a** to ketol **2b** was accomplished in modest yield by means of potassium hydroxide in ethanol, or more efficiently, by potassium *tert*-butoxide in 50% *tert*-butyl alcohol–benzene. Inspection of the spectral data of **2b** left no doubt concerning the structure of the intramolecular aldol condensation product; the signals of the methyl ketone at τ 7.83 (s, 3), the α-methylene protons of the five-membered ring at τ 7.23 (m, 4), and the five-membered ring ketone absorption at 1742 cm^{-1} present in **23a** all disappeared completely and were replaced by the signal of the newly formed six-membered ring α-methylene protons at τ 7.38 (broad s, 2) and a strong absorption of the newly formed hydroxyl group at 3610 cm^{-1}.

Experimental Section

Melting points were taken on a Fisher-Johns block and are uncorrected. Unless otherwise stated, infrared spectra were obtained as 3% solutions in chloroform. The nmr spectra were determined in deuteriochloroform (unless otherwise stated) on a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. The expression "worked up in the usual manner" involved the washing of an organic extract with dilute aqueous sodium chloride, drying the extract over anhydrous sodium sulfate, removal of the drying agent by filtration, and evaporation of the solvent under aspirator pressure. All reactions utilizing strongly basic reagents were conducted under nitrogen.

6,6-Dimethyl-2-cyclohexen-1-one.—A cold stirred solution of 63 g of 2,2-dimethylcyclohexanone[12] in 500 ml of tetrahydrofuran was treated with 80 g of bromine in 75 ml of methylene chloride over a period of 30 min, keeping the temperature of the reaction mixture below 10°. The yellow solution was stirred for an additional 10 min, then diluted with 650 ml of 10% aqueous sodium bicarbonate and poured into 2 l. of cold water. The mixture was extracted several times with methylene chloride and the combined organic extracts were washed with water, dried, and concentrated. The crude bromo ketone was dissolved in 75 ml of dimethylformamide and added to a hot (140°) suspension of 26 g of magnesium oxide in 750 ml of dimethylformamide. The mixture was stirred under a nitrogen atmosphere at 140° for 1 hr, then cooled in an ice bath as 1.5 l. of cold dilute hydrochloric acid was added. After all of the magnesium oxide dissolved, the mixture was diluted with about 1.5 l. of ice water and extracted several times with ether. The ether extracts were washed with aqueous sodium chloride, saturated sodium bicarbonate, and finally with saturated sodium chloride. After drying, the ether was distilled off at atmospheric pressure and the residue was fractionated (20 mm) through a 10-in. Vigreux column to yield 57 g of almost colorless unsaturated ketone, bp 55–60°. Spectral properties were consistent with the literature:[13] ir 1685, 1642, 1390 cm^{-1}; uv max (MeOH) 225 mμ (ϵ 9150); nmr τ 3.11 (sextet, 1), 4.07 (d, 2), 7.61 (m, 1), 8.15 (t, 2), 8.90 (s, 6).

3-Cyano-6,6-dimethylcyclohexanone (3).—To a solution of 56 g of potassium cyanide and 35 g of ammonium chloride in 300 ml of water was added 56 g of 6,6-dimethyl-2-cyclohexen-1-one dissolved in 600 ml of dimethylformamide. After stirring at 100° for 8 hr, the wine red reaction mixture was cooled, diluted with water, and extracted several times with ether. The combined organic solutions were washed with saturated sodium chloride, dried, and evaporated under reduced pressure. The residue was distilled at 20 mm to give 33 g of colorless nitrile boiling at 135–142°: ir 2250 (CN), 1725 cm^{-1}; nmr τ 8.81 (s, 3), 8.88 (s, 3).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67. Found: C, 71.35; H, 8.79.

6,6-Dimethylcyclohexanone-3-carboxylic Acid (4a).—A solution of 11 g of the nitrile **3** in 40 ml of dioxane and 220 ml of 10% aqueous sodium hydroxide was stirred and refluxed for 4.5 hr. The reaction mixture was cooled and diluted with water and ether. The aqueous layer was separated, washed with ether, acidified with dilute hydrochloric acid, and finally extracted with ether. The extract was worked up in the usual manner to produce a crystalline residue, which was recrystallized from ether–pentane to afford 8.5 g of colorless crystals, mp 82–85°. Recrystallization from the same solvent pair gave the pure sample: mp 87–89° (lit.[3a] mp 88–89°); ir 1710 cm^{-1}; nmr τ −0.93 (s, 1), 8.83 (s, 3), 8.91 (s, 3).

3-Carbomethoxy-6,6-dimethylcyclohexanone (4b).—A cold solution of 30 g of acid **4a** in 1.5 l. of ether was treated with a cold ethereal solution of diazomethane, prepared from 40 g of *N*-nitrosomethylurea. After a period of 30 min, a few milliliters of glacial acetic acid was carefully added to destroy excess diazomethane. The almost colorless solution was washed with water, aqueous sodium bicarbonate, and again with water, then dried and concentrated. The residue was distilled at 20 mm to give 28.8 g of pure, colorless ester: bp 120–124°; ir 1745, 1718, 1295, 1227, 1147 cm^{-1}; nmr τ 6.31 (s, 3), 8.83 (s, 3), 8.93 (s, 3).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.36; H, 8.92.

2-Methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (5).—A total of 7.3 g of potassium metal was dissolved in 220 ml of hot *tert*-butyl alcohol under an atmosphere of nitrogen. The solution was cooled to room temperature and diluted with 440 ml of benzene followed by 27.6 g of the ester **4b**. With rapid stirring, 45 g of methallyl iodide[4] was added in one portion; the temperature of the reaction mixture rose to 40° as potassium iodide was immediately precipitated. Stirring was continued for about an hour and then the reaction mixture was allowed to stand overnight at room temperature. Water was carefully added and the mixture was extracted several times with ether. The organic solutions were washed with water, dilute aqueous sodium thiosulfate, and again with water, dried and concentrated. The residue was distilled under reduced pressure (2 mm) through a 10-in. Vigreux column. After a small forerun, the main fraction amounted to 22.3 g of colorless **5** boiling at 122–126°. Gas chromatography (4-ft column packed with 8% SE-30 on Diatoport S) indicated that this material contained 73.4% of the trans isomer and 26.5% of the cis isomer (see below for separation). The oil **5** had the following spectral properties: ir 1736, 1712, 1650 cm^{-1}; nmr τ 5.25 (m, 1), 5.36 (m, 1), 6.32 and 6.34 (two singlets for a total of three protons, the signal at 6.32 being the major peak), 8.29 (s, 3), 8.73, 8.78, 8.85, and 8.92 (four singlets for a total of six protons with the signals at 8.73 and 8.92 having much greater intensities).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.76; H, 9.55.

Further distillation at 124–129° (2 mm) yielded an additional 5.1 g of colorless oil (56.2% trans and 43.8% cis by vpc). The ratio of isomers remained essentially the same after refluxing with sodium methoxide in methanol.

Separation of the epimers was effected by preparative tlc (silica gel; 95% benzene–5% ethyl acetate). The slightly less polar component was a colorless liquid identified as ***trans*-2-methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (8a)**: ir 1737, 1718, 1650, 898 cm^{-1}; nmr τ 5.30 (m, 1), 5.38 (m, 1), 6.32 (s, 3), 6.83 (m, 1, $W_{1/2}$ = 22 Hz), 8.30 (s, 3), 8.75 (s, 3), 8.92 (s, 3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.38. Found: C, 70.77; H, 9.63.

The minor isomer was isolated as an oil which slowly solidified to a crystalline mass. Recrystallization from a small amount of

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[12] Prepared by methylation of 2-methylanilinomethylene-6-methylcyclohexanone in the presence of potassium *tert*-butoxide followed by removal of the protecting group; see A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

[13] J. Warkentin and L. K. M. Lam, *Can. J. Chem.*, **42**, 1676 (1964).

pentane gave white crystals of ***cis*-2-methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (9a)**: mp 50–51°; ir 1732, 1710, 1650, 1174, 897 cm^{-1}; nmr τ 5.26 (m, 1), 5.43 (m, 1), 6.35 (s, 3), 6.85 (m, 1, $W_{1/2}$ = 8 Hz), 8.31 (s, 3), 8.80 (s, 3), 8.88 (s, 3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.38. Found: C, 70.59; H, 9.33.

Alkylation of 4a.—A stirred solution of potassium *tert*-butoxide (prepared from 3.4 g of potassium) in 110 ml of *tert*-butyl alcohol was treated with 5.8 g of **4a** in 200 ml of benzene, followed by 17 g of methallyl iodide. The temperature of the reaction mixture rose only slightly and after about 5 min potassium iodide began to slowly precipitate. Stirring was continued for 2 hr, and after standing overnight, the mixture was cooled, treated with 250 ml of cold water, and finally washed with ether. The aqueous solution was chilled, acidified with cold dilute hydrochloric acid, and extracted with ether. Washing of the organic extract with dilute aqueous sodium thiosulfate followed by the usual work-up yielded a yellow oil weighing about 8 g. The crude product was taken up in benzene and chromatographed on 800 g of silica. Elution of the column with 5% ethyl acetate produced 2.7 g of oil which crystallized slowly from pentane to give 315 mg of colorless cis acid (**9b**), mp 128–132°. Further elution with 10% ethyl acetate yielded 1.3 g of starting acid **4a**. Recrystallization of **9b** from ether–pentane gave analytically pure ***cis*-2-methallyl-6,6-dimethylcyclohexanone-3-carboxylic acid**: mp 133–134°; ir 1752, 1723, 1651, 900 cm^{-1}; nmr τ 5.20 (m, 1), 5.34 (m, 1), 6.82 (m, 1, $W_{1/2}$ = 6 Hz), 8.30 (s, 3), 8.81 (s, 3), 8.90 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.69; H, 9.06.

Upon prolonged refrigeration the pentane mother liquor from the crystallization of **9b** deposited 120 mg of hard, colorless prisms, mp 75–77°. Examination of the nmr spectrum revealed that this product did not contain a methallyl group (no signal near τ 5.30), but possessed four distinct methyl peaks in addition to a pair of isolated protons (bridgeheads) appearing in the τ 7.15–7.45 region. The infrared spectrum showed a single carbonyl absorption at 1776 cm^{-1} (five-membered lactone) and the substance was tentatively identified as **10**: ir 1776, 1272, 1185, 1120 cm^{-1}; nmr τ 8.58 (s, 3), 8.74 (s, 3), 8.88 (s, 3), 8.95 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.91; H, 9.16.

The filtrate obtained after the removal of **10** (see above) was examined by tlc (silica gel; benzene–ethyl acetate–acetic acid 30:10:1) and found to contain two spots with slightly different mobilities; the slower moving material (minor amount) had the same R_f value as the cis acid **9b**. Separation of the major isomer was eventually achieved by preparative tlc (SilicAR CC-4; 98.75% chloroform, 1% ethyl acetate, 0.25% acetic acid) affording ***trans*-2-methallyl-6,6-dimethylcyclohexanone-3-carboxylic acid (8b)** as a nonmobile oil: ir 1750, 1718, 1650, 898 cm^{-1}; nmr τ 5.27 (m, 1), 5.33 (m, 1), 6.85 (m, 1 $W_{1/2}$ = 20 Hz), 8.28 (s, 3), 8.75 (s, 3), 9.15 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.33; H, 8.98.

Esterification of **8b** and **9b** with diazomethane gave **8a** and **9a**, respectively.

2-Acetonyl-3-carbomethoxy-6,6-dimethylcyclohexanone (6a).—The methallyl compound **5** (10 g) was dissolved in 134 ml of dioxane and 40 ml of water and treated with 25.6 g of sodium metaperiodate followed by 3 ml of 4% osmium tetroxide in dioxane. The reaction flask was flushed with nitrogen, tightly stoppered, and stirred magnetically for 19 hr. The precipitated sodium iodate was filtered and washed well with ether. The resulting solution was washed with water, several times with dilute sodium thiosulfate, and twice more with water. The usual work-up left 7.5 g of brown oil which showed several spots on tlc (silica gel; benzene–ethyl acetate 5:1). Neither distillation nor chromatography separated all of the impurities, but it was found that the crude material was suitable for further modification. Partial purification could be achieved by chromatography on silica; elution with benzene containing 2% ethyl acetate gave **6a** as a yellow oil: ir 1732, 1715, 1382 cm^{-1}; nmr τ 6.30 and 6.32 (two singlets for a total of three protons), 7.75 and 7.77 (two singlets for a total of three protons), 8.85, 8.80, 8.90 and 8.93 (four singlets for six protons).

2-Acetonyl-6,6-dimethylcyclohexanone-3-carboxylic acid (6b). **A.**—The crude ester **6a** (3 g) was dissolved in 5 ml of dioxane and mixed with 10 ml of 30% aqueous sodium hydroxide. After standing overnight, the mixture was cooled in ice, acidified with 5 ml of concentrated hydrochloric acid, and extracted several times with chloroform. Washing of the extracts with saturated sodium chloride was followed by the usual work-up to give 2 g of dark brown oil. Although tlc (benzene–ethyl acetate–acetic acid 30:10:1) revealed that **6b** was impure, the crude product gave satisfactory results upon further transformation: ir 1718 cm^{-1}; nmr τ 6.55 (broad m, 1), 7.78 (s, 3), 8.74, 8.78, 8.93 (three singlets for a total of six protons).

B.—The methallyl ester **5** (24 g) in 200 ml of methanol and 100 ml of methylene chloride was cooled to −70° as a stream of ozonized oxygen was bubbled through the rapidly stirred solution for 105 min. At this point the initially colorless solution became blue. Excess ozone was removed under a stream of oxygen and the reaction mixture was poured into 2 l. of 2% aqueous sodium hydroxide and stirred for 1 hr at room temperature. About 500 ml of solvent was removed under aspirator pressure and the remaining aqueous solution was heated on the steam bath for 2 hr and finally allowed to stand overnight at room temperature. The orange reaction mixture was washed with ether, carefully acidified with cold dilute hydrochloric acid, saturated with sodium chloride, and then extracted with ether. The combined extracts were washed three times with saturated sodium chloride, dried, and concentrated to dryness. The residual oil amounted to 13 g and was comparable to **6b** prepared by saponification of **6a**.

6,6-Dimethyldecahydronaphthalene-1,3,5-trione (15).—A mixture of 4 g of crude **6a** in 25 ml of benzene was treated with a solution of 50 ml of *tert*-butyl alcohol containing 1.5 g of dissolved potassium. After stirring at room temperature for 2 days, the dark red solution was poured into 400 ml of ice water and 7 ml of concentrated hydrochloric acid. Ether extraction and the usual work-up produced about 3 g of dark green oil, which was triturated with ether to give 700 mg of tan crystals, mp 150–160°. Two recrystallizations from ethyl acetate gave material melting at 145–158°: ir (KBr) 1715 (C=O), 1613 (C=O of enol form[14]), 1563 (C=C of enol[14]), 1227 cm^{-1}; uv max (0.1 *N* HCl in MeOH) 251.5 mμ (ϵ 13,000); uv max (0.1 *N* NaOH in MeOH) 282 mμ (ϵ 23,000).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.72.

Chromatography of the mother liquors on silica yielded intractable mixtures.

4,5,6,7-Tetrahydro-8α(*H*)-7,7-dimethyl-2-oxo-$\Delta^{8(9)}$-indene-4β-carboxylic Acid (7).[15]—Crude diketone **6b** (30 g) in 300 ml of benzene was added to 600 ml of *tert*-butyl alcohol containing 20 g of dissolved potassium. The resulting mixture was stirred for 20 hr at room temperature, poured into about 2 l. of ice water, acidified with dilute hydrochloric acid, and extracted with ether. The usual work-up yielded a crystalline residue, which was triturated with ether to afford 15 g of slightly yellow crystals, mp 160–167° dec. The analytical sample was obtained by recrystallization from ethyl acetate: mp 170–172° dec; ir (KBr) 1736, 1667, 1603, 1410, 1190 cm^{-1}; uv max (MeOH) 232 mμ (ϵ 14,500); nmr (CD_3SOCD_3) τ 4.17 (t, 1, $J \approx$ 2 Hz), 6.64 (m, 1), 9.03 (s, 3), 9.37 (s, 3).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.49; H, 7.87.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2-oxoindan-4β-carboxylic Acid (18a). **A.**—The unsaturated ketone **7** (1 g) was dissolved in 150 ml of methanol and hydrogenated in the presence of 200 mg of 5% rhodium on alumina for 29 hr at atmospheric pressure and room temperature. After removal of the catalyst by filtration, the filtrate was evaporated to an oil which was dissolved in benzene and chromatographed on 150 g of SilicAR CC-4. The column was washed with increasing percentages of ethyl acetate and the fractions eluted with 10% ethyl acetate were concentrated and then crystallized from ether–pentane to give 290 mg of tan crystals, mp 97–102°. Two recrystallizations from the

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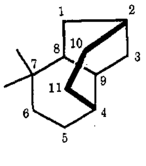
[14] For a discussion on the infrared spectra of cyclic β-diketones, see K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, San Francisco, Calif., 1962, p 65.

[15] For the sake of uniformity, all of the compounds depicted in Scheme II are designated by the following numbering system.



same solvent mixture furnished colorless **18a**: mp 110–112°; ir 1745, 1712 cm^{-1}; nmr τ −0.35 (s, 1), 9.07 (s, 3), 9.20 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.54.

B.—A solution of 10.4 g of **7** in 250 ml of isopropyl alcohol was shaken in an atmosphere of hydrogen with 6 g of 10% palladium on carbon for 18 hr. Removal of the catalyst followed by concentration gave about 11 g of orange oil, which was taken up in benzene and placed on 1000 g of SilicAR CC-4. Elution with 2% ethyl acetate yielded about 800 mg of solid, which was recrystallized from aqueous ethanol to give colorless crystals of **7,7-dimethyl-5,6,7,8-tetrahydroindan-4-carboxylic acid (17)**, mp 158–162°. The analytical sample of the hydrogenolysis product was obtained by recrystallization from aqueous ethanol: mp 162–163°; ir 1686 (conjugated acid), 1645, 1282 cm^{-1}; uv max (MeOH) 231.5 mμ (ϵ 11,250); nmr τ −1.79 (s, 1), 8.98 (s, 3), 9.28 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.36; H, 9.41.

The material obtained from the 15% ethyl acetate fractions was recrystallized from ether–pentane to yield 5 g of product, mp 108–110°, which was identical with **18a**. Continued elution of the above column with 50% ethyl acetate gave about 1 g of the starting ketone **7**.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2β-hydroxyindan-4β-carboxylic Acid (19).—A solution of 208 mg of keto acid **18a** was dissolved in 2 ml of ethanol and neutralized with 0.1 *N* aqueous sodium hydroxide to a phenolphthalein end point. The solution was cooled in an ice bath as 500 mg of solid sodium borohydride was added portionwise. The mixture was allowed to warm to room temperature and stand overnight, then cooled and carefully acidified with saturated aqueous citric acid. The precipitate was filtered, washed with water, and air dried to give 185 mg of solid, mp 185–188°. Recrystallization from methanol–ethyl acetate separated 157 mg of pure **19**: mp 187–189°; ir (KBr) 3450, 1710 cm^{-1}; nmr (CD_3SOCD_3) τ 5.80 (m, 1), 9.09 (s, 3), 9.18 (s, 3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.09; H, 9.58.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2β-hydroxyindan-4β-carboxylic Acid 4β → 2β-Lactone (20).—The hydroxy acid **19** (72 mg) was heated with an oil bath at 190–195° for 1 min. The product was cooled and taken up in ether, and the solution was washed with 3% aqueous sodium bicarbonate. Drying and removal of the solvent produced 63 mg of crystalline residue which gave a single spot on tlc (silica gel; 80% benzene–20% ethyl acetate). Recrystallization from pentane followed by sublimation (20 mm at a bath temperature of 120°) yielded colorless crystals: mp 61–62°; ir 1727, 1380, 1148, 992 cm^{-1}; nmr τ 5.22 (m, 1), 7.30 (m, 1), 8.98 (s, 3), 9.11 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.44.

1β,4β-Ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2,11-dione (22).—The saturated ketone **18a** (800 mg) was dissolved in 10 ml of 95% ethanol and slowly treated with 0.1 *N* aqueous sodium hydroxide to a phenolphthalein end point. The solution was allowed to evaporate at room temperature (or concentrated under high vacuum) and the solid residue was powdered and dried at 65° under high vacuum to a constant weight. The dried sodium salt **18b**, amounting to 770 mg, was suspended in 10 ml of dry benzene containing 3 drops of pyridine. The suspension was stirred and cooled in a cold water bath as 2.5 ml of oxalyl chloride was introduced. After the vigorous reaction subsided, the cooling bath was removed and the reaction mixture was stirred at room temperature for about 1 hr. The mixture was concentrated; 5 ml of benzene was added and the evaporation was repeated. The residue was mixed with 10 ml of benzene and filtered, and the solution of the acid chloride **21** was immediately added to a cold ethereal solution of excess diazomethane (prepared from *N*-nitrosomethylurea and dried over potassium hydroxide pellets). There was an immediate evolution of gas and the yellow solution was allowed to stand in an ice bath for 2 hr. At this point, glacial acetic acid was added dropwise and when gas evolution ceased, the mixture was gradually poured into 20 ml of warm (60°) glacial acetic acid. The solution was heated at 60° for 1 hr, then concentrated under a stream of nitrogen to a partially crystalline residue. An nmr spectrum of this crude material indicated that the acetoxy ketone **23b** was not formed (no signal in the τ 5.00 region). Preparative tlc (silica; 50% benzene–ethyl acetate) yielded a solid which was recrystallized from ether–pentane to give colorless crystals of **22**: mp 70–71°; ir 1748 (five-membered ketone), 1710 cm^{-1} (six-membered ketone); nmr τ 6.76 (d of m, 1), 7.12 (m, 1), 8.94 (s, 3), 9.26 (s, 3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.00; H, 8.94.

4β-Acetyl-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2-one (23a).—A mixture of dimethylcadmium[16] (prepared from 20 ml of 3.0 *M* methylmagnesium bromide in diethyl ether and 6.0 g of anhydrous cadmium chloride) in 35 ml of benzene was stirred and cooled in a cold water bath as a benzene solution of the crude acid chloride **21** (prepared from 3 g of **18a** as described above) was added rapidly. The cooling bath was removed and the mixture was refluxed for 30 min, cooled, and poured into ice-cold dilute hydrochloric acid. The product was isolated by ether extraction and recrystallized from ether–pentane to give 2.2 g of pure **23a**: mp 84–86°; ir 1742, 1711, 1150 cm^{-1}; nmr τ 7.23 (m, 1), 7.83 (s, 3), 9.08 (s, 3), 9.23 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.76.

4α-Acetyl-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2-one (24).—Diketone **23a** (82 mg), dissolved in 8 ml of methanol, was mixed with 8 ml of 1.0 *N* aqueous potassium hydroxide and the resulting solution was allowed to stand overnight at room temperature under nitrogen. The mixture was acidified with dilute acetic acid and extracted with ether. The organic extract was washed several times with aqueous sodium chloride, dried, and evaporated to an almost colorless oil weighing 75 mg. This product showed a single spot which migrated slightly faster than the starting ketone on tlc (silica gel; benzene–ethyl acetate–acetic acid 30:10:1): ir 1749, 1712, 1360, 1158 cm^{-1}; nmr τ 7.85 (s, 3), 8.93 (s, 3), 9.10 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.32; H, 9.59.

2β,4β-Ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2α-ol-11-one (2b). A.—A solution of 1.25 g of **23a** in 20 ml of benzene was added to 20 ml of *tert*-butyl alcohol containing 350 mg of dissolved potassium metal. After standing at room temperature for 3 hr, the deep red solution was poured into ice water, acidified with cold, dilute hydrochloric acid, and extracted twice with ether. The extract was treated in the usual manner to afford a partially crystalline residue, which upon recrystallization from ether–pentane yielded 510 mg of yellow crystals, mp 100–103°. Chromatography of the mother liquor on 60 g of SilicAR CC-4 gave an additional 150 mg of material upon elution with 30% ethyl acetate–benzene. The analytical sample of colorless **2b** was prepared by recrystallization from ether–pentane: mp 103–104°; ir 3610, 1709, 1086 cm^{-1}; nmr τ 7.38 (broad s, 2) 9.02 (s, 3), 9.20 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.46.

B.—The diketone **23a** (76 mg) was dissolved in 1 ml of anhydrous ethanol and mixed with 3.5 ml of 4.0 *N* ethanolic potassium hydroxide. The resulting solution was allowed to stand at room temperature for 2 days, then acidified with dilute aqueous acetic acid and extracted with ether. The usual work-up and recrystallization of the product from ether–pentane yielded 21 mg of tan crystals, mp 100–103°. This compound exhibited spectra data identical with those of **2b**.

Registry No.—**1**, 2618-41-9; **2b**, 32632-70-5; **3**, 32632-71-6; **4b**, 32632-72-7; *cis*-**6a**, 32632-73-8; *trans*-**6a**, 32640-74-7; *cis*-**6b**, 32632-74-9; *trans*-**6b**, 32640-75-8; **7**, 32632-75-0; **8a**, 32632-76-1; **8b**, 32632-77-2; **9a**, 32632-78-3; **9b**, 32632-79-4; **10**, 32632-80-7; **15**, 32640-65-6; **17**, 32640-66-7; **18a**, 32640-67-8; **19**, 32640-68-9; **20**, 32640-69-0; **22**, 32640-70-3; **23a**, 32640-71-4; **24**, 32640-72-5.

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[16] J. Cason and F. S. Prout, *J. Amer. Chem. Soc.*, **66**, 46 (1944).

and Mrs. Joyann Serauskas. Column chromatography and thin layer chromatography were accomplished under the direction of Mr. R. T. Nicholson and Mr. B. G. Smith, Mr. W. W. Aksamit and staff provided the vpc results. We are grateful to Dr. J. W. Ahlberg and staff for both spectral data and elemental analyses.

Badgerin, a New Germacranolide from *Artemisia arbuscula* ssp. *arbuscula*

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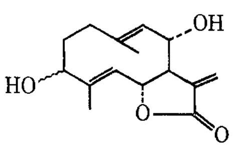
Samples of *Artemisia arbuscula* ssp. *arbuscula,* collected in Montana, contained tatridin-A (**1**) and a new germacranolide which was named badgerin. Structure **2** was assigned to the new lactone on the basis of its spectral properties and chemical reactions.

The sesquiterpene lactones of three subspecies of big sagebrush (*Artemisia tridentata*) were investigated[2] in this laboratory as a part of our program on chemical constitutents of sagebrush in Montana.[2-4] One of the subspecies, *A. tridentata* ssp. *vaseyana,* collected from several locations in this state gave the same sesquiterpene lactones that have been isolated from *A. arbuscula* Nutt. ssp. *arbuscula* collected in another location.[5] This prompted us to investigate the sesquiterpene lactones of a Montana plant known as *A. arbuscula* ssp. *arbuscula.*

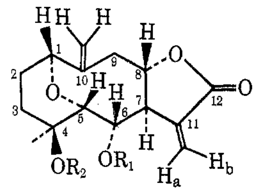
Results and Discussion

Different samples of this plant were collected from a 1 square mile area near Badger Pass and extracted with chloroform. Tlc analysis of the extracts gave a consistent pattern for the sesquiterpene lactone contents, which were quite different from those reported earlier for *A. arbuscula* ssp. *arbuscula.*[5]

Extensive chromatographic separation of the lactones from the combined chloroform extracts resulted in the isolation of two pure crystalline lactones along with some gummy fractions and a crystalline mixture. One of the two crystalline lactones was identified as tatridin-A[6] (**1**) by its physical constants, spectral properties and ultimately by tlc and mixture melting point with an authentic sample. The other crystalline lactone was an unknown compound. It was named badgerin and assigned the structure 2 on the basis of the following considerations.



1



2, $R_1 = R_2 = H$
3, $R_1 = R_2 = Si(Me)_3$
4, $R_1 = Ac$; $R_2 = H$
5, $R_1 = R_2 = Ac$

Composition and Functional Groups.—Mass spectroscopy and elemental analysis showed the molecular weight of 280 and the empirical formula of $C_{15}H_{20}O_5$. The compound had an α,β-unsaturated γ-lactone, as shown by uv end absorption, ir bands at 1766 and 1639 cm^{-1}, and the nmr spectrum discussed later (see Table I, 2). There were two hydroxyl groups, with an ir band at 3378 cm^{-1}, which formed a di(trimethylsilyl) ether derivative (**3**). One of these hydroxyl groups was readily acetylated to give a monoacetate compound (**4**) and was proved to be secondary (see Table I and the following nmr discussions). The monoacetate showed an ir band at 3510 cm^{-1} for a free hydroxyl group. However, it could not be oxidized by chromium trioxide–acetic acid[7,8] or by Jones[9] reagent, indicating the tertiary nature of the remaining hydroxyl group.

The lactone moiety and the hydroxyl groups account for four of the five oxygen atoms present. Since no other functional group could be detected it became evident that the fifth oxygen must form an oxide ring. The oxide ring could not be cleaved on treatment with acetic anhydride and *p*-toluenesulfonic acid,[10] or acetic anhydride and sulfuric acid,[11] indicating the presence of an unusually stable ring structure. This almost ruled out the possibility of a labile epoxide ring in favor of a more stable structure such as a pyran derivative. Under the employed drastic acetylating conditions, however, the free hydroxyl groups in badgerin were acetylated to give a crystalline diacetate (**5**).

Badgerin was not oxidized by sodium metaperiodate even after 48 hr, nor did it form a benzeneboronate derivative on treatment with benzeneboronic acid,[12] showing that the two hydroxyl groups are neither adjacent nor are likely to be 1,3-diaxially oriented.

Other than the methylene group conjugated to the lactone carbonyl function, badgerin had another double bond and on hydrogenation it absorbed 2 mol of hydrogen. The hydrogenation product, which lacked olefinic protons in its nmr spectrum, unfortunately proved

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(1) Established through a grant from Hoerner–Waldorf Corp. of Montana.

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(3) F. Shafizadeh and W. Bukwa, *ibid.,* **9**, 871 (1970).

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