# Acid-Catalyzed Cyclization of (*E*)- and (*Z*)-4,8-Dimethylnona-3,7-dien-2-one

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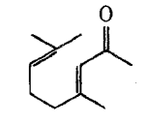
Cyclization of (*E*)- and (*Z*)-4,8-dimethylnona-3,7-dien-2-one (**1**) with 75% aqueous sulfuric acid gave 1,3,5-trimethyl-2-oxabicyclo[3.3.1]non-3-ene (**2**), the tertiary alcohol **4**, and only minor amounts of 1,1,3-trimethyl-2-acetylcyclohex-3-ene (**3**). The major product **2** results from a hypothetical dienone **10** formed prior to cyclization. The mechanism of these cyclizations is discussed briefly.

Both the overall structural and stereochemical course of acid-catalyzed polyene cyclizations are fairly well known today.[1] These reactions are of great importance, not only because of their close relationship with enzymic cyclizations leading to polycyclic terpenes and steroids in nature but also because of their synthetic value in the *in vitro* synthesis of such substances. In the vast majority of cases the products of cyclization result directly from the starting polyolefin and there is no need to consider movements of double bonds prior to cyclization. In the course of a study aimed at preparing ketones related to damascenone[2] we found that acid-catalyzed cyclization of the dienone **1** leads to a



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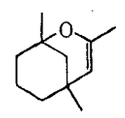

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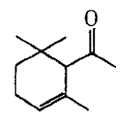

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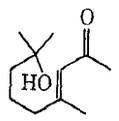

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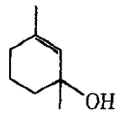

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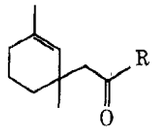


**6**, R = $OC_2H_5$
**7**, R = OH
**8**, R = $CH_3$

major product not derived from the starting material directly.

Cyclization of 4,8-dimethylnona-3,7-dien-2-one (**1**) (mixture of *E* and *Z* isomers) prepared from citral as described[3] with cold aqueous sulfuric acid gave three principal products separable by vapor phase or column chromatography. Examination of the spectral properties of the major product led to the conclusion that it is the vinyl ether **2** rather than a ketone. Further evidence in favor of structure **2** was provided by synthesis. Condensation of 1,3-dimethyl-2-cyclohexen-1-ol (**5**) with triethyl orthoacetate[4] followed by saponification of the ester **6** and condensation of the resulting acid **7** with methyllithium afforded the monocyclic ketone **8**. As anticipated, when submitted to the action of sulfuric acid the unsaturated ketone **8** was cyclized to the bicyclic vinyl ether **2**.

(1) For summaries see W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968); A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Connor, Ed., J. and A. Churchill, London, 1959.

(2) E. Demole, P. Enggist, U. Säuberli, M. Stoll, and E. sz. Kováts, *Helv. Chim. Acta*, **53**, 541 (1970).

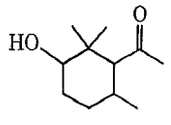
(3) C. Aguilar, M. Salmón, and F. Walls, *Bol. Inst. Quim. Univ. Nacl. Autón. Méx.*, **21**, 226 (1969).

(4) Method of W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

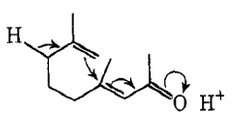
Spectral properties and elemental composition of the second product indicated that it had structure **4** resulting from hydration of the nonconjugated double bond. This was verified by an alternative synthesis from **1** using the oxymercuration–demercuration sequence[5] and by cyclization to a 4:1 mixture of **2** and **3** in the presence of sulfuric acid.

The least abundant product formed in the acid-catalyzed cyclization of the dienone **1** was the anticipated monocyclic ketone **3** identical with the product prepared from α-cyclogeranic acid and methyllithium.

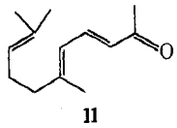
The sulfuric acid catalyzed cyclization of dienone **1** was explored previously by Walls and coworkers.[3] They did not investigate the "nonpolar" fraction of the reaction mixture and consequently did not identify the three major products **2**, **3**, and **4**. The only product reported was isolated from the "polar" fraction in 2.5% yield and assigned structure **9**. After receiving an



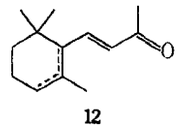
**9**



**10**



**11**



**12**

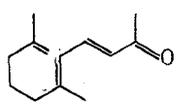
authentic sample of the hydroxy ketone **9** from Professor Walls[6] we were able to detect it in trace amounts in our crude reaction mixtures but did not accumulate enough material to substantiate its structure.

A few comments on the mechanism of these cyclizations seem justified. In analogy with the highly efficient cyclization of ψ-ionone (**11**) to the ionones **12** in the presence of acid (*e.g.*, sulfuric or formic acid) the formation of **3** is initiated by Markovnikov protonation of the nucleophilic isopropylidene double bond. Cyclization within the carbonium ion followed by loss of a proton affords the thermodynamically more stable β,γ-unsaturated ketone **3**. The major product **2**, on the other hand, originates from cyclization of the isomeric diene **10**. Protonation of the carbonyl oxygen atom, cyclization (arrows in **10**), deprotonation, and proton transfer leads to the monocyclic ketone **8**. Molecular models reveal the transition state for this cyclization to be much less crowded than that leading from **1** to the monocyclic ketone **3**. In support of the intermediacy of the hypo-

(5) H. C. Brown and P. Geoghean, *ibid.*, **89**, 1522 (1967).

(6) We wish to thank Professor F. Walls, University of Mexico, for a sample of his hydroxy ketone. He has verified his earlier experiments but reported in a letter of August 25, 1970, that the actual yield of this compound is in the order of 1%.

thetical compound **10** we cite the formic acid catalyzed cyclization of 6,10-dimethyl-3,5,10-undecatrien-2-one (**13**) to a mixture of ketones **14**.[7] Interestingly, cycliza-



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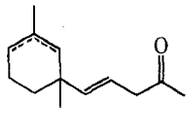

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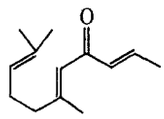

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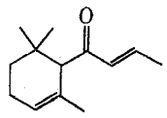

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tion of **13** in concentrated sulfuric acid is set off by protonation of the weakly basic isopropenyl double bond and gives $\beta$-ionone (**12**) in 85% yield.[7] Finally, the behavior of dienone **1** in aqueous sulfuric acid should be contrasted with that of the structurally related $\psi$-damascone (**15**) in benzene containing stannic chloride. No double-bond isomerization prior to cyclization was observed in the latter case and $\alpha$-damascone (**16**) was formed in good yield.[8] We attribute the difference to the catalyst and the medium. Proton transfers leading to double-bond isomerizations are faster in protic solvents than in hydrocarbon solvents containing a Lewis acid.

## Experimental Section

Microanalyses were performed by the M. I. T. Microanalytical Laboratory. Infrared (ir) spectra were taken in chloroform solution on a Perkin-Elmer Model 247 grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associates T-60 instrument and chemical shifts are reported in parts per million ($\delta$) downfield from an internal tetramethylsilane standard. The abbreviations s, t, q, and m refer to singlet, triplet, quartet, and multiplet, respectively. Vpc analyses were carried out on a F & M gas chromatograph Model 720 on columns having silicon rubber as the liquid phase. Merck silica gel, 0.2–0.05 mm, was used for column chromatography. All solutions were dried over anhydrous sodium sulfate.

**Cyclization of (*E*)- and (*Z*)-4,8-Dimethylnona-3,7-dien-2-one (1).**—To a solution of 20 ml of 75% aqueous sulfuric acid which was kept below 0° with an ice–salt bath was added 4.6 g of **1**. After the addition was complete (10 min) the mixture was stirred for 4 hr at −5 to 0°, poured into 50 g of ice, and extracted four times with 50 ml of ether. The combined ether extracts were washed with sodium bicarbonate and sodium chloride solutions, dried, and concentrated *in vacuo* to yield 4.5 g of a yellow oil which was shown by vpc analysis to consist of three compounds. Four grams of the mixture was chromatographed on 150 g of silica gel. Elution with hexane–ethyl acetate (8:2) gave 1.500 g of **2**: ir ($CHCl_3$) 1670 $cm^{-1}$ (sharp); nmr ($CCl_4$) $\delta$ 0.95 (s, 3 H), 1.18 (s, 3 H), 1.68 (s, 3 H), 4.0 (s, 1 H), broad pattern of signals from 1.35 to 1.80 (8 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (40), 151 (55), 123 (100), 108 (33), 93 (34), 83 (45), 43 (81).

*Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.42; H, 11.15.

Further elution gave 0.35 g of **3**: ir ($CHCl_3$) 1705 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.90 (s, 6 H), 2.06 (s, 3 H), 2.60 (broad s, 1 H), 5.45 (s, 1 H), broad pattern of signals from 1.02 to 2.10 (7 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (25), 123 (100), 81 (62), 32 (45).

*Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.46; H, 11.21.

The last fractions of the chromatogram contained 1.040 g of **4**: ir ($CHCl_3$) 3640, 3470, 1685, 1615 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.15 (s, 6 H), 1.35–1.45 (m, 3 H), 1.85 (s, 1 H), 1.90 (s, 1 H) (OH), 2.08 (s, 6 H), 2.30–2.55 (m, 2 H), 5.95 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 169 (6.5), 166 (7), 151 (13), 123 (30), 109 (53), 95 (37), 83 (43), 43 (100).

**Ethyl 1,3-Dimethylcyclohex-2-en-1-ylacetate (6).**—A solution of 1.26 g (0.01 mol) of **5**, 11 g (0.07 mol) of triethyl orthoacetate, and 0.045 ml of propionic acid was stirred for 5 hr at 138° until no more starting alcohol was detectable by thin layer chromatography. After excess triethyl orthoacetate was distilled off at 50° (20 mm), the residue was washed with sodium bicarbonate and sodium chloride solutions, dried, and distilled to give 0.38 g (20%) of a colorless oil: bp 45–48° (1 mm); ir ($CHCl_3$) 1720 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.02 (s, 3 H), 1.12 (t, $J$ = 8 Hz, 3 H), 1.60 (s, 3 H), 1.50–1.85 (m, 6 H), 2.12 (s, 2 H), 4.05 (q, $J$ = 8 Hz, 2 H), 5.16 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 196 (4), 181 (1.7), 150 (5), 109 (100), 108 (54), 107 (17), 93 (26), 81 (9), 79 (10), 77 (9), 67 (20), 55 (10), 43 (8), 41 (16), 29 (16).

*Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.10; H, 10.52.

**1,3-Dimethylcyclohex-2-en-1-ylacetic Acid (7).**—A solution of 0.090 g (0.54 mmol) of **6** in 2 ml of 1.2% sodium hydroxide in methanol was refluxed for 40 min. After the methanol was removed *in vacuo*, the residue was poured into 3 ml of water and was washed three times with ether. The aqueous phase was acidified with 2 *N* hydrochloric acid and extracted four times with ether. The combined ether solutions were dried and the solvent was removed *in vacuo* to yield a brown oil which was distilled at 1 mm (bath 140°) to give 0.061 g (75%) of a colorless, viscous oil: ir ($CHCl_3$) 2950 (broad), 1700 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.12 (s, 3 H), 1.62 (s, 3 H), 1.40–1.90 (m, 6 H), 2.12 (s, 2 H), 5.15 (s, 1 H), 11.60 (broad s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (7), 153 (5), 122 (4), 109 (100), 108 (36), 93 (37), 77 (17), 67 (28), 55 (12), 41 (22).

*Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.81.

**1,3-Dimethylcyclohex-2-en-1-ylacetone (8).**—A solution of 0.62 g (0.0037 mol) of **7** and 10 ml of anhydrous ether was added dropwise to 5.2 ml of 1.6 *M* methyllithium in ether at −78°. After the addition was complete (20 min) the reaction mixture was stirred for 1 hr at this temperature and was then poured into 5 g of ice and extracted four times with ether. The combined ether solutions were washed with sodium chloride solution and dried, and the solvent was removed *in vacuo*. The residue was distilled at 28 mm (130° bath temperature) to give 0.565 g of a colorless liquid which showed two peaks in the vpc in the ratio of 88:12. The compounds were chromatographed on 15 g of silica gel with hexane–ethyl acetate (95:5) to give after distillation 0.402 g of pure **8**: ir ($CHCl_3$) 1700 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.02 (s, 3 H), 1.62 (s, 3 H), 1.40–1.92 (m, 6 H), 2.00 (s, 3 H), 2.30 (s, 2 H), 5.20 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (0.7), 151 (1.3), 123 (3.5), 109 (100), 108 (70), 93 (30), 81 (17), 67 (30), 55 (14), 43 (67), 41 (19).

*Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.37; H, 11.08.

**1,3,5-Trimethyl-2-oxabicyclo[3.3.1]non-3-ene (2).**—To 1.0 ml of 75% aqueous sulfuric acid at 0° was added dropwise 0.180 g of **8**. After stirring for 4 hr in an ice bath, the mixture was poured onto 3 g of ice and extracted four times with ether. The organic phase was washed with sodium bicarbonate and sodium chloride solutions and dried, and the solvent was removed *in vacuo*. The residue was distilled at 25 mm (bath 90°) to give 0.146 g (81%) of a colorless liquid which had ir, nmr, mass spectrum, and vpc retention time identical with those of an authentic sample of **2**.

**1,1,3-Trimethyl-2-acetylcyclohex-3-ene (3).**—To 10 ml of 1.6 *M* methyllithium solution in ether was added 0.100 g (0.55 mmol) of $\alpha$-cyclogeranic acid methyl ester and the mixture was heated at reflux for 12 hr. The reaction mixture was poured onto 5 g of ice and extracted five times with ether, the combined organic extract was washed with sodium chloride solution and dried, and the solvent was evaporated *in vacuo*. The residue was distilled at 20 mm (bath 120°) to give 0.060 g (66%) of a colorless liquid, which had ir, nmr, mass spectrum, and vpc retention time identical with those of an authentic sample of **3**.

**Hydration of 4,8-Dimethylnona-3,7-dien-2-one (1).**—To a suspension of 3.5 g of mercuric acetate in 22 ml of water–tetrahydrofuran (1:1) was added 1.66 g (0.01 mol) of **1**. The temperature was kept below 20° with an ice bath. The yellow precipitate disappeared after 20 sec and the clear solution was stirred for 10 min at 25°. After cooling in an ice bath, 11 ml of 3 *N* sodium hydroxide and 11 ml of 0.5 *M* sodium borohydride in 3 *N* sodium

(7) W. Hoffmann, H. Pasedach, H. Pommer, and W. Reif, *Justus Liebigs Ann. Chem.*, **747**, 60 (1971).

(8) K. H. Schulte-Elte, H. Strickler, and G. Ohloff, *Helv. Chim. Acta*, in preparation.

hydroxide were added. The liquid phase was decanted from the precipitated mercury and extracted with ether. The organic extract was washed with sodium chloride solution and dried, and the solvent was removed *in vacuo* to yield 1.80 g of a yellow liquid which showed four spots on tlc. Chromatography on 30 g of silica gel eluting with hexane–ethyl acetate (2:1) gave 0.300 g of a compound which had ir, nmr, mass spectrum, and tlc identical with those of **4**.

**Cyclization of 4.**—To a solution of 0.40 ml of 75% aqueous sulfuric acid was added 0.10 g of **4**. After stirring for 4 hr at 10°, the mixture was poured onto 2 g of ice and extracted four times with ether. The organic phases were washed with sodium bicarbonate and sodium chloride solutions and dried. The residue, after evaporation of the solvent *in vacuo*, showed by vpc analysis **2** and **3** in the ratio of 81:19 as the only reaction products.

**Registry No.**—(*E*)-**1**, 27539-94-2; (*Z*)-**1**, 27575-61-7; **2**, 37709-65-2; **3**, 37709-66-3; **4**, 27243-05-6; **5**, 29481-98-9; **6**, 37709-69-6; **7**, 37709-70-9; **8**, 37709-71-0.

**Acknowledgment.**—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

# Synthesis of *C*-Methyl Derivatives of 1-Phenyl-1,3,5-hexanetrione[1]

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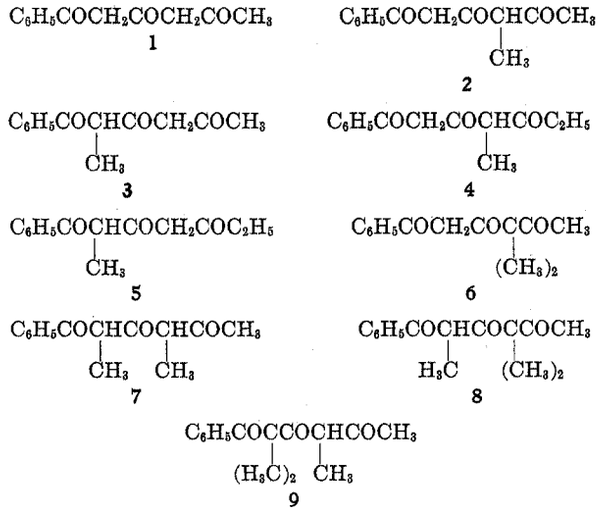
Eight *C*-methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**) have been prepared using two basic techniques: acylation of substituted diketones with esters using lithium amide or sodium hydride as the base, and alkylation of triketone **1** with methyl iodide using sodium hydride or potassium carbonate as the base. The lithium amide method compliments the sodium hydride method in the acylation of diketones, since the former gives good yields when aliphatic esters are employed and the latter is convenient for, but limited to, aromatic esters. The reaction of triketone **1** with sodium hydride and methyl iodide gave the 2- and 4-mono- and 2,2- and 4,4-dimethylation products, the 4 position being the preferred site of reaction. Proton transfer reactions played a major role in the formation of the dialkylation products. Under conditions suppressing proton transfer reaction, the disodium salt of triketone **1** reacted with methyl iodide to give the 2,4-dimethyl derivative. The 2,2,4- and 2,4,4-trimethyl derivatives were prepared by treatment of **1** with excess methyl iodide and potassium carbonate in acetone; both of the trimethylation products cyclized spontaneously to give cyclic hemiketals.

The cyclization reactions of 3,5,7-triketo acids have been studied intensively because they are possible models of the pathways by which resorcylic acids, acylphloroglucinols, and related compounds are formed in nature.[2] Often these metabolites are found having methyl or other alkyl groups present at one or more of the unsubstituted positions, and it has been proposed[3] and, in some cases, demonstrated[4] that these substituents can be introduced prior to cyclization of the triketo acids. For this reason we sought to study the cyclization reactions of 2-, 4-, and 6-*C*-methyl derivatives of 7-phenyl-3,5,7-trioxoheptanoic acid, the synthesis of which required the corresponding methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**). Numerous triketones have been prepared previously, but most of those required for this study have not. This paper, therefore, describes synthetic approaches to methyl derivatives **2**–**9**, employing either acylation reactions of $\beta$ diketones or methylation reactions of anions of **1**. Although the alkylation reactions of $\beta$-dicarbonyl compounds have been studied extensively,[5] the reactions of $\beta$ triketones have received only limited attention.[6,7]




## Results

**Acylation Reactions.**—Hauser and coworkers developed several closely related procedures for the preparation of 1,3,5 triketones by acylation of $\beta$ diketones with esters in the presence of strong bases. The use of sodium amide or potassium amide in liquid ammonia gave satisfactory results with aromatic esters, but aliphatic esters required the use of lithium amide.[8] These reactions involve formation and acylation of 1,3 dianions of the $\beta$ diketones; the metallic cation effect results from rapid proton abstraction from aliphatic esters by disodio and dipotassio diketones but relatively slow abstraction by the dilithium derivatives. With aromatic esters, an attractive alternative to the amide methods is the use of sodium hy-

(1) We gratefully acknowledge the generous support by the U. S. Public Health Service through Research Grant GM-12848 and Career Development Grant (to T. M. H.) GM-27013.

(2) T. T. Howarth and T. M. Harris, *J. Amer. Chem. Soc.*, **93**, 2506 (1971), and references cited therein.

(3) A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

(4) For example, see A. I. Scott, H. Guilford, and E. Lee, *J. Amer. Chem. Soc.*, **93**, 3534 (1971).

(5) See H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(6) K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).

(7) J. Carnduff, J. A. Miller, B. R. Stockdale, J. Larkin, D. C. Nonhebel, and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 692 (1972).

(8) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960); S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963); F. B. Kirby, T. M. Harris, and C. R. Hauser, *ibid.*, **28**, 2266 (1963).