Total synthesis of (±)-aristolone[1]

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Received August 28, 1968

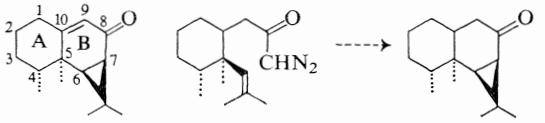
A novel and efficient total synthesis of the racemic form of the sesquiterpene (−)-aristolone (**1**) is presented. The key step involves the cupric sulfate catalyzed intramolecular cyclization of the diazoketone **27**, which produces a mixture of products, the major component of which is (±)-aristolone.

Canadian Journal of Chemistry, **47**, 831 (1969)

The sesquiterpene (−)-aristolone was initially isolated from *Aristolochia debilis* Sieb. *et* Zucc. in 1955 (1). The structure determination of this interesting natural product was reported (2) some six years later and, in 1962, Büchi and co-workers (3), on the basis of an indirect correlation with maaliol (4), of known absolute configuration, established the absolute configuration of (−)-aristolone as depicted in **1**. We previously carried out, and reported in preliminary form (5), a model study involving the synthesis of (±)-4-demethylaristolone. In this paper we describe the total synthesis of (±)-aristolone.

In any consideration of possible approaches to the total synthesis of (±)-aristolone, it is obvious that the most difficult and complex part of the synthesis would involve the construction of ring B, containing the olefinic double bond and the *gem* dimethylcyclopropyl moiety conjugated to the carbonyl. Of the number of possible routes which might be employed in the construction of these functionalities, we chose the scheme which can be illustrated, in general terms, by the hypothetical conversion of **2** into **3**. This conversion, involving an intramolecular cyclization of an olefinic diazoketone, appeared at first sight to be a potentially efficient method for the synthesis of the required substituted bicyclo[4·1·0]heptanone system. The use of olefinic diazoketones in intramolecular cyclizations was already well documented (6), and success of the above proposed conversion (**2** into **3**) appeared, in our opinion, quite likely.

The starting material which was chosen for the synthesis of the required crucial intermediate of type **2** was the readily available 2,3-dimethylcyclohexanone (7). Conversion of the latter into



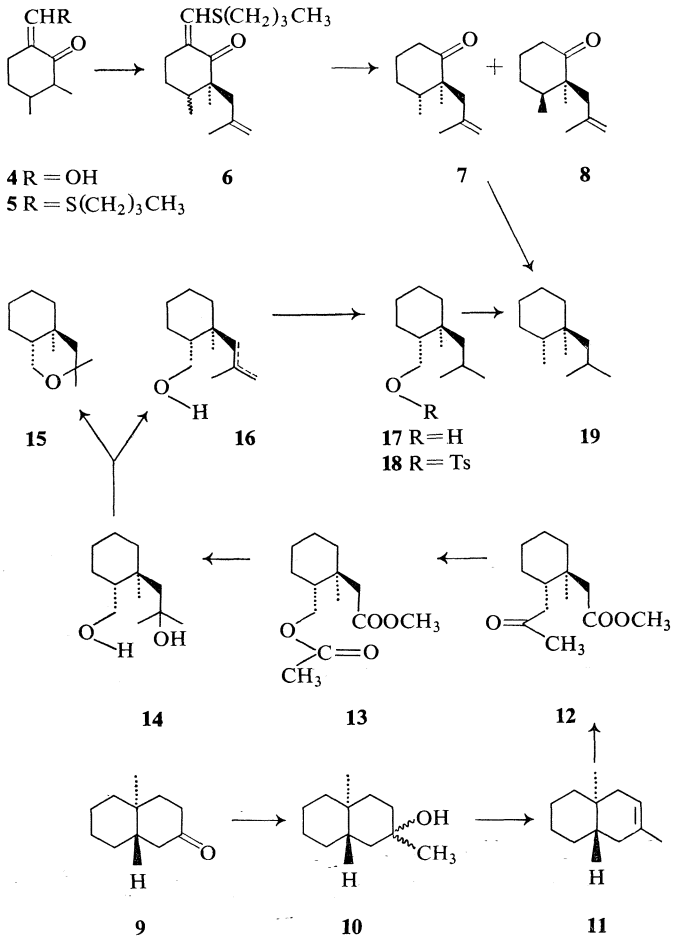
1 **2** **3**

its 6-*n*-butylthiomethylene derivative **5**, *via* the corresponding hydroxymethylene compound **4**, was readily accomplished by standard procedures (8). Alkylation of **5** with methallyl chloride in *t*-butyl alcohol in the presence of potassium *t*-butoxide (8) gave, in 87% yield, a mixture of the corresponding alkylated products (**6**). Removal of the *n*-butylthiomethylene blocking group by treatment of **6** with potassium hydroxide in refluxing aqueous diethylene glycol (8) provided, in 90% yield, a mixture of *cis*-(**7**) and *trans*-2,3-dimethyl-2-methallylcyclohexanone (**8**). Analysis of this mixture by gas–liquid chromatography (g.l.c.) indicated that these two compounds were present in a ratio of approximately 4:1, respectively. An analytical sample of each epimer was obtained by preparative g.l.c. and each exhibited spectral data which were fully in accord with the assigned structure.

Since the factors which affect the stereochemical outcome of the alkylation of cyclohexanone derivatives are not well understood in detail and were, in fact, the subject of very recent discussion (9), it was rather difficult to predict with certainty the stereochemistry of the alkylation products **7** and **8**. We therefore felt it necessary to obtain unambiguous proof concerning this point and showed that the major alkylation product was, in fact, the desired *cis* compound **7**.

Reaction of the well known and readily available (10) *trans*-10-methyl-2-decalone (**9**) with excess methyllithium in refluxing ether provided a high yield of a semicrystalline material,

[1]Presented at the 51st Annual Conference and Exhibition of the Chemical Institute of Canada, Vancouver, British Columbia, June 3–6, 1968.



consisting of a mixture of the epimeric tertiary alcohols **10**. Dehydration of this material with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene produced 2,10-dimethyl-*trans*-2-octalin (**11**) (see ref. 11). The latter was obtained as a clear, colorless oil and was shown by g.l.c. analysis to be greater than 95% pure. Furthermore, the nuclear magnetic resonance (n.m.r.) spectrum exhibited only one olefinic proton signal, an unresolved multiplet at τ 4.72, with a half-height width of 8 Hz. This was clearly in accord with the octalin structure having the olefinic double bond at the 2-position.

The octalin **11** was subjected to a modified ozonolysis reaction (12) and the resulting crude keto-aldehyde was immediately oxidized with Jones reagent (13). The keto-acid thus obtained was esterified with ethereal diazomethane, affording an overall 68% yield (from the octalin **11**) of the keto ester **12**.

In order to obtain, from the keto-ester **12**, a compound suitable for appropriate comparison with the alkylation products (**7** and/or **8**), it can readily be seen that the acetic ester side chain of **12** required conversion to an *iso*butyl-type group, while the keto containing side chain required degradation to a methyl group. This was accomplished as follows.

Baeyer–Villiger oxidation of the keto-ester **12** with trifluoroperacetic acid in dichloromethane in the presence of disodium hydrogen phosphate (see ref. 14) gave, in 83% yield, the diester **13**. Interestingly, the n.m.r. spectrum of this compound exhibited, in addition to the expected signals, a pair of quartets (AB of ABX system) between τ 5.65 and τ 6.32, readily attributable to

the methylene protons on the carbon bearing the acetate group. However, the magnetic non-equivalence of methylene protons found in an asymmetric environment is a well-established phenomenon (15), and this therefore deserves no further comment.

Reaction of the diester **13** with excess refluxing ethereal methyllithium afforded the diol **14** in 97% yield. Treatment of the latter with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene, followed by careful distillation of the crude product, gave, in addition to the cyclic ether **15** (44%, b.p. 64–66° at 0.1 mm), a mixture of the olefinic alcohols **16** (46%, b.p. 104–108° at 0.1 mm). Hydrogenation of the latter over Adam's catalyst in ethanol at room temperature and atmospheric pressure provided the primary alcohol **17**. This material was converted, by treatment with *p*-toluenesulfonyl chloride in pyridine at 0°, into the corresponding tosylate (**18**) and the crude material thus obtained was subjected to lithium aluminium hydride reduction in refluxing tetrahydrofuran. The product, *cis*-1,2-dimethyl-1-*iso*butylcyclohexane (**19**) was obtained in 66% overall yield from the alcohol **17**.

When the major alkylation product (**7**) was subjected to successive catalytic hydrogenation (ethanol, Adam's catalyst) and Huang–Minlon reduction (16), the corresponding hydrocarbon was obtained in high yield. The latter was shown to be identical (refractive index, infrared and n.m.r. spectra, g.l.c. retention time) with *cis*-1,2-dimethyl-1-*iso*butylcyclohexane (**19**) obtained from alcohol **17** as described above. This comparison unambiguously proved that the major alkylation product was, in fact, the desired *cis*-2,3-dimethyl-2-methallylcyclohexanone (**7**).

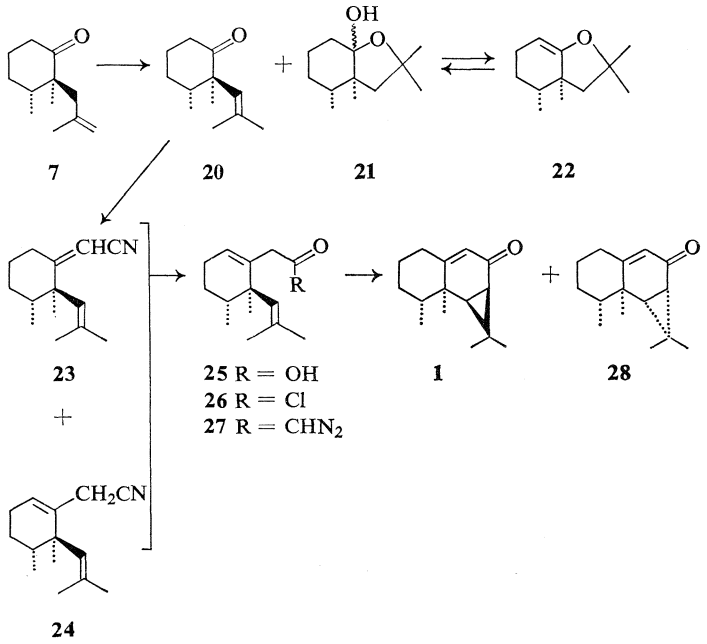
Having obtained a suitable synthetic intermediate with appropriate stereochemistry, it became necessary at this point, bearing in mind the initially proposed synthetic approach, to convert the methallyl group of **7** into the methylpropenyl moiety. In this connection, we had found in a model study (5) that 2-methyl-2-methallylcyclohexanone was smoothly converted, by treatment with *p*-toluenesulfonic acid in refluxing benzene, into a mixture consisting mainly of the starting material and 2-methyl-2-methylpropenylcyclohexanone in a ratio of approximately 1:3, respectively. This procedure was therefore adopted in the present work.

A solution of compound **7** in benzene containing *p*-toluenesulfonic acid was refluxed for three days and the reaction mixture was then subjected to aqueous work-up. Gas–liquid chromatographic analysis of the crude product showed that it consisted of a mixture, containing the starting material **7** (approximately 12%), the desired cyclohexanone derivative **20** (46%), the cyclic hemiketal **21** (37%) and an unidentified compound (5%). Distillation of this material (b.p. 66–68° at 2.8 mm) allowed the isolation (see Experimental) of a small amount of the crystalline hemiketal **21**, m.p. 74–74.5°. The spectral data of this compound was in full accord with the assigned structure. It should be noted that the hemiketal **21**, when heated at temperatures greater than 120° readily dihydrated to afford the corresponding cyclic enol-ether **22** (see below).

When the bulk of the material obtained from the above distillation was redistilled, at 53 mm pressure, through a spinning band column, the initial fractions consisted of a mixture of water and the enol ether **22** (the dehydration product of hemiketal **21**). The structure assigned to compound **22**, b.p. 128° at 53 mm, was fully substantiated by spectral data. It should be noted that this compound was extremely sensitive to moisture and, even upon exposure to the atmosphere, readily hydrated to re-form the crystalline hemiketal **21**.

A later fraction from the above spinning-band distillation consisted of nearly pure desired *cis*-2,-3-dimethyl-2-methylpropenylcyclohexanone **20**, b.p. 143–144° at 53 mm. The isolated yield of this compound was approximately 22% and thus, in contrast to the equivalent reaction in the model study (5), the direct acid-catalyzed conversion of compound **7** into compound **20** was not particularly efficient.[2] The n.m.r. spectrum of compound **20**, particularly when compared with that of the starting material **7**, clearly showed that the carbon–carbon double bond had undergone the desired migration. Thus, while **7**

[2]We were subsequently able to show (E. Piers and W. de Waal, unpublished results) that the conversion of **7** into **20** could be carried out more efficiently by use of a modified sequence in which the keto group of **7** was first protected by formation of the corresponding ethylene ketal. Subsequent acid-catalyzed isomerization of the carbon–carbon double bond, followed by removal of the ketal protecting group (*p*-toluenesulfonic acid in refluxing dry acetone) and separation of isomers allowed the isolation of cyclohexanone **20** in 50% overall yield (from **7**).



exhibited signals for two olefinic protons (τ 5.17 and τ 5.27) and one vinyl methyl group (τ 8.38), the isomerized material **20** showed signals for only one olefinic proton (τ 4.59) and two vinyl methyl groups (τ 8.27 and τ 8.57).

Having obtained in sufficient quantity a cyclohexanone derivative with the desired functionality and stereochemistry, we planned to use the keto group of **20** as a "handle" for the introduction of the required diazoketone-containing side chain. We initially considered for this purpose the reaction of **20** with the modified Wittig reagent, triethyl phosphonoacetate (17). However, this reaction proved very sluggish and even when carried out at elevated temperatures, produced no useful result. Since we felt that the failure of this reaction was due, at least in part, to the sterically hindered nature of the carbonyl group in **20**, we decided to attempt the use of a reagent which was sterically less demanding, namely, diethyl cyanomethylphosphonate (17). This approach proved successful. Thus, reaction of cyclohexanone **20** with diethyl cyanomethylphosphonate in the presence of methylsulfinyl carbanion in dimethyl sulfoxide (18) at 100° for 1 h, produced, in 87% yield, a mixture of the α,β-unsaturated nitrile **23** and the β,γ-unsaturated nitrile **24**, in a ratio of approximately 2:1, respectively.[3] The fact that these compounds were isomeric was clearly shown by the spectral data. The α,β-unsaturated isomer **23** exhibited a strong ultraviolet absorption at 220.5 mμ (ε = 12 300) and, in the n.m.r. spectrum, showed a one-proton singlet at τ 4.75 (=CHCN). The β,γ-unsaturated isomer **24**, on the other hand, gave no strong ultraviolet absorption and, in the n.m.r. spectrum, exhibited a broad one-proton signal at τ 4.07 (γ-vinyl H) and a two-proton multiplet at τ 7.01 (—CH_2CN).

Hydrolysis of the mixture of nitriles (**23** and **24**) with potassium hydroxide in refluxing aqueous ethanol afforded, in 82% yield, the β,γ-unsaturated carboxylic acid **25**. That the double bond had now completely isomerized into the β,γ-position was again clearly shown by the lack of an appropriate absorption in the ultraviolet and by the n.m.r. spectrum which showed, in addition to a two-proton multiplet at τ 7.07 (—CH_2COOH), the γ-vinyl proton as a poorly resolved triplet at τ 4.35. Although the

[3]The relative amounts of these two isomers in the product depended somewhat on the reaction conditions and reaction time.

base-promoted equilibration of α,β- and β,γ-unsaturated carboxylic acids is a well-known process (19), it is interesting that in the present case the equilibrium lies completely on the side of the β,γ-unsaturated isomer. One of the major factors contributing to this phenomenon may well be the $A^{(1,3)}$ strain (20) which would be associated with the exocyclic double bond in the α,β-unsaturated isomer.

The carboxylic acid **25** was converted into its sodium salt and the latter was reacted with oxalyl chloride in benzene at 0°. The crude acid chloride **26** (λ_{max} 5.62 μ) thus obtained was, due to its instability, immediately converted, by reaction with dry ethereal diazomethane, into the corresponding diazoketone **27** (λ_{max} 4.79, 6.15 μ). The n.m.r. spectrum of the crude diazoketone indicated that during the sequence **25** → **26** → **27**, the olefinic double bond had remained in the β,γ-position with respect to the carbonyl group. This was of some importance since any migration of the double bond into conjugation with the carbonyl would undoubtedly have resulted in a large predominance of the geometric isomer having the diazoketone moiety *trans* to the ring carbon bearing the methylpropenyl substituent, thus making the subsequent intramolecular cyclization (see below) of the diazoketone impossible.

When the crude diazoketone **27** was refluxed in cyclohexane in the presence of cupric sulfate (6) and the crude product distilled under reduced pressure, a clear oil (70%, based on the carboxylic acid **25**) was obtained. This material was shown by g.l.c. analysis to consist of approximately 42% (±)-aristolone (**1**), 20% (±)-6,7-epi-aristolone (**28**) and a number of minor unidentified components. Purification of this mixture by a combination of preparative thin-layer chromatography and preparative g.l.c. allowed the isolation of both of the major products. Thus, (±)-aristolone (**1**) was obtained as a crystalline solid which, upon recrystallization from petroleum ether, exhibited m.p. 62–63°. This material was shown to be identical (m.p., mixed m.p., infrared, and n.m.r.[4] spectra) with a recrystallized (petroleum ether) 1:1 mixture of (−)-aristolone and α-ferulone [(+)-aristolone] (22).

[4]For an analysis of the n.m.r. spectrum of (−)-aristolone, see ref. 21.

(±)-6,7-Epi-aristolone (**28**) was obtained as an oil. It was shown to be isomeric with (±)-aristolone by high resolution mass spectrometry, and gave spectral data in complete accord with the assigned structure.

It should be noted that very recently another synthesis of (±)-aristolone by a sequence completely different from that described above, was reported (23).

Experimental

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Ultraviolet spectra were, unless otherwise noted, measured in methanol solution on either a Cary, model 14, or a Unicam, model SP. 800, spectrophotometer. Routine infrared spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer, while all comparison spectra were recorded on a Perkin–Elmer model 421 spectrophotometer. Nuclear magnetic resonance spectra were taken in dueteriochloroform solution on Varian Associates spectrometers, model A-60 and/or model HA-100. Line positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Gas–liquid chromatography (g.l.c.) was carried out on an Aerograph Autoprep, model 700. The following columns (10 ft × 1/4 in., unless otherwise noted) were employed, with the inert, supporting material being 60/80 mesh Chromosorb W in each case: column A, 20% FFAP; column B (10 ft × 3/8 in.), 30% FFAP; column C, 15% QF-1; column D, 3% SE-30; column E, 20% SE-30; column F (10 ft × 3/8 in.), 30% Apiezon J; column G, 10% Apiezon J; column H, 10% FFAP; column I (20 ft × 3/8 in.), 30% SE-30. The specific column used, along with column temperature and carrier gas (helium) flow-rate (in ml/min), are indicated in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

*6-Hydroxymethylene-2,3-dimethylcyclohexanone (**4**)*

To an ice-cooled, stirred suspension of powdered sodium methoxide 78 g, 1.44 moles) in 800 ml of dry benzene, kept under an atmosphere of dry nitrogen, was added 71 g (0.564 mole) of 2,3-dimethylcyclohexanone. The resulting mixture was stirred for 10 min, and then 70 g (0.945 mole) of ethyl formate was added. The mixture was warmed to room temperature and allowed to stand overnight. Water was added, the mixture was thoroughly shaken, and the layers separated. The organic layer was extracted with two portions of 10% aqueous sodium hydroxide. The combined aqueous layer and alkaline extracts were cooled, acidified with 6 *N* hydrochloric acid, and thoroughly extracted with ether. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure, gave 77.5 g (90%) of the hydroxymethylene derivative **4** as a pale-yellow oil, b.p. 60–63° at 2 mm,

n_D^{20} 1.5135. Ultraviolet, λ_{max} 281 mμ, λ_{max} (NaOH added) 316 mμ; infrared (film), λ_{max} 6.05, 6.25 μ. The instability of this compound precluded the acquisition of satisfactory analytical data.

6-n-Butylthiomethylene-2,3-dimethylcyclohexanone (5)

A solution of the hydroxymethylene derivative (**4**) (77.5 g, 0.504 mole), *n*-butyl mercaptan (55.5 g, 0.615 mole), and *p*-toluenesulfonic acid (50 mg) in 500 ml of dry benzene was refluxed in a nitrogen atmosphere under a Dean–Stark water separator for 6 h, at which time 6 ml of water had been collected. The cooled solution was washed with saturated aqueous sodium bicarbonate, then with water and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which, upon distillation under reduced pressure, afforded 99.4 g (87%) of the *n*-butylthiomethylene derivative (**5**), b.p. 116–118° at 0.3 mm, n_D^{20} 1.5368; ultraviolet, λ_{max} 309 mμ (ε = 15 400); infrared (film), λ_{max} 6.01, 6.48 μ.

Anal. Calcd. for $C_{13}H_{22}OS$: C, 68.97; H, 9.79. Found: C, 68.59; H, 9.71.

2,3-Dimethyl-2-methallyl-6-n-butylthiomethylenecyclohexanone (6)

The *n*-butylthiomethylene derivative **5** (99.4 g, 0.440 mole) was added to 1800 ml of dry *t*-butanol containing 144 g (1.40 moles) potassium *t*-butoxide and the resulting solution was stirred at room temperature for 10 min and then cooled to 0°. Freshly distilled methallyl chloride (255 g, 2.82 moles) was added slowly and the reaction mixture was refluxed under an atmosphere of dry nitrogen for 2 h. Most of the solvent was removed under reduced pressure and the residue was diluted with water. The resulting mixture was extracted thrice with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which, upon distillation under reduced pressure, afforded 107 g (87%) of 2,3-dimethyl-2-methallyl-6-*n*-butylthiomethylenecyclohexanone (**6**) (mixture of epimers), b.p. 106–109° at 0.25 mm, n_D^{20} 1.5043; ultraviolet, λ_{max} 281 mμ (ε = 14 700); infrared (film), λ_{max} 6.00, 6.32, 11.10 μ.

Anal. Calcd. for $C_{17}H_{28}OS$: C, 72.80; H, 10.06. Found: C, 73.09; H, 10.11.

cis- and trans-2,3-Dimethyl-2-methallylcyclohexanone (7 and 8)

To a solution of the above alkylated material (**6**) (107 g) in 700 ml of diethylene glycol was added 650 ml of 25% aqueous potassium hydroxide and the resulting solution was refluxed under nitrogen for 18 h. The reaction mixture was steam distilled until the distillate was clear. The distillate was saturated with salt and extracted thrice with ether. The combined ether extracts were washed with water, dried (anhydrous magnesium sulfate), and evaporated. The residual oil, upon distillation under reduced pressure, gave 66 g (96%) of a mixture of *cis*- and *trans*-2,3-dimethyl-2-methallyl cyclohexanone, (**7** and **8**), b.p. 76–80° at 3.6 mm. Analysis of this mixture by g.l.c. (column A, 140°, 85) indicated that the ratio of the *cis* compound (**7**) to the *trans* compound (**8**) was approximately 4:1. An analytical sample of each epimer was obtained by preparative g.l.c. (column B, 250°, 120). The desired *cis* epimer **7** exhibited n_D^{20} 1.4809. Infrared (film), λ_{max} 5.89, 6.13, 11.25 mμ; n.m.r., τ 5.17, 5.27 (unresolved multiplets, 2H, $=CH_2$), 7.33, 7.84 (broadened AB-type pair of doublets, 2H, vinyl $—CH_2$, J = 14 Hz), 8.38 (broad singlet, 3H, vinyl methyl), 9.13 (singlet, 3H, tertiary methyl), 9.28 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Anal. Calcd. for $C_{12}H_{20}O$: C, 80.01; H, 11.11. Found: C, 79.78; H, 11.31.

The *trans* epimer (**8**) exhibited n_D^{20} 1.4812; infrared (film), λ_{max} 5.88, 6.11, 11.28 μ; n.m.r., τ 5.22, 5.32 (unresolved multiplets, 2H $=CH_2$), 7.62, 8.04 (broadened AB-type pair of doublets, 2H, vinyl $—CH_2$, J = 14 Hz), 8.42 (broad singlet, 3H, vinyl methyl), 8.84 (singlet, 3H, tertiary methyl), 9.27 (doublet, 3H, secondary methyl, J = 5.8 Hz).

Anal. Calcd. for $C_{12}H_{20}O$: C, 80.01; H, 11.11. Found: C, 79.78; H, 11.27.

2,10-Dimethyl-trans-2-octalin (11)

To a solution of *trans*-10-methyl-2-decalone (10) (**9**, 44.5 g, 0.236 mole) in 1 l of dry ether was added 9 g (0.41 mole) of methyllithium in 200 ml of ether. The solution was refluxed for 8 h, cooled, and the excess methyllithium was destroyed by careful addition of dilute hydrochloric acid. The ether layer was washed with water, dried (anhydrous magnesium sulfate), and evaporated. Distillation of the residual material under reduced pressure gave 42.7 g (88%) of a mixture of epimeric alcohols (**10**) as a semi-crystalline mass, b.p. 62–67° at 0.2 mm. This material was not further purified, but was used directly for the next step.

A solution of the above mixture of alcohols (**10**) (2.0 g) and *p*-toluenesulfonic acid (25 mg) in 25 ml of dry benzene was refluxed under a Dean–Stark water separator until the required amount of water had been collected. The solution was cooled, washed with dilute aqueous sodium hydroxide, and evaporated. Distillation of the residual oil afforded 1.15 g (70%) of 2,10-dimethyl-*trans*-2-octalin (**11**) as a clear colorless oil, b.p. 91–93° at 11 mm. Gas–liquid chromatographic analysis (column C, 170°, 85) indicated that this material was greater than 95% pure. An analytical sample, collected by preparative g.l.c. (column C, 150°, 85) exhibited n_D^{20} 1.4873. Infrared (film), λ_{max} 6.94, 7.33, 12.73 μ; n.m.r., τ 4.72 (unresolved multiplet, 1H, olefinic proton, width at half-height = 8 Hz), 8.37 (broad singlet, 3H, vinyl methyl), 9.23 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.58; H, 12.40.

Preparation of Keto-ester 12

A solution of the octalin **11** (19.6 g, 0.12 mole) in 1 l of dry methanol was cooled by means of a dry ice – acetone bath. Ozone was bubbled through the solution until a permanent blue color persisted, and then continued for an additional 15 min. Dimethyl sulfide (11.9 ml, 0.162 mole) was added and the solution was allowed to warm to room temperature. The methanol and excess dimethyl sulfide were removed under reduced pressure and the residue was taken up in ether. The ether solution was washed with water, dried (anhydrous magnesium sulfate), and evaporated. The residual crude keto-aldehyde was immediately oxidized with Jones reagent (13) (30 ml) and, after

the normal work-up, afforded 22.7 g of the corresponding keto-acid. Treatment of the latter crude material with excess ethereal diazomethane, followed by removal of the ether and distillation of the residual oil, gave 18.2 g (68%) of the desired keto-ester (**12**), b.p. 85–85.5° at 0.1 mm. An analytical sample isolated by preparative g.l.c. (column D, 160°, 80), showed n_D^{20} 1.4712. Infrared (film), λ_{max} 5.83, 6.97, 9.83 μ; n.m.r., τ 6.34 (singlet, 3H, —$COOCH_3$), 7.73 (singlet, 2H, —CH_2COOCH_3), 7.85 (singlet, 3H, —$COCH_3$), 9.07 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.79. Found: C, 69.30; H, 10.01.

The 2,4-dinitrophenylhydrazone derivative of the keto-ester **12** exhibited m.p. 111–112°.

Anal. Calcd. for $C_{19}H_{26}N_4O_6$: C, 56.15; H, 6.44; N, 13.78. Found: C, 55.85; H, 6.65; N, 13.61.

*Preparation of Diester **13***

To a solution of the keto-ester **12** (18.2 g, 85 mmoles) in 1.7 l of dichloromethane was added 220 g of anhydrous disodium hydrogen phosphate. The resulting mixture was stirred vigorously and a solution of trifluoroperacetic acid (prepared by adding 13.5 ml of 90% hydrogen peroxide to 86.5 ml of trifluoroacetic anhydride in 42 ml of dichloromethane) was added. The mixture was stirred at room temperature for 1.5 h and then at reflux for 3.5 h. Ethyl acetate (500 ml) was added and the mixture was washed with saturated aqueous sodium bicarbonate, water, saturated brine, and then dried over anhydrous magnesium sulfate. Removal of the solvents, followed by distillation of the residual oil afforded 16.2 g (83%) of the diester **13**, b.p. 96–102° at 0.1 mm. An analytical sample, collected by preparative g.l.c. (column D, 190°, 90), exhibited n_D^{20} 1.4658; infrared (film), λ_{max} 5.77, 6.97, 9.71 μ; n.m.r., τ 5.65–6.32 (pair of quartets, 2H, —CH_2—OAc, AB of ABX system), 6.35 (singlet, 3H, —$COOCH_3$), 7.64 (singlet, 2H, CH_2COOCH_3), 7.96 (singlet, 3H, —$OCOCH_3$), 9.03 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.43; H, 9.14. Found: C, 64.28; H, 9.23.

*Preparation of Diol **14***

To a solution of the diester **13** (15.8 g, 65.5 mmoles) in 250 ml of dry ether was added 300 ml of 1.7 *M* methyllithium in ether. The solution was refluxed overnight, cooled, and quenched by careful addition of water. The ether solution was dried over anhydrous magnesium sulfate. Removal of the ether and distillation of the residual oil provided 12.6 g (97%) of the diol **14**, b.p. 109–110° at 0.15 mm; infrared (film), λ_{max} 3.08, 6.89, 9.80 μ; n.m.r., τ 6.17–6.83 (pair of quartets, 2H, —CH_2OH, AB of ABX system), 6.65 (singlet, 2H, 2—O—H), 8.15, 8.54 (doublets, 2H, —CH_2—$C(CH_3)_2$, AB system, J = 15 Hz), 8.64, 8.76 (singlets, 6H, —$C(CH_3)_2$), 9.12 (singlet, 3H, tertiary methyl). Due to the ease with which this compound dehydrated, it was virtually impossible to obtain pure diol which was not contaminated with small amounts of its dehydration products. Satisfactory analytical data was therefore not obtained.

*Dehydration of Diol **14***

A solution of the diol **14** (5.0 g) in 250 ml of dry benzene containing 50 mg of *p*-toluenesulfonic acid was refluxed under a Dean–Stark water separator for 4 h, at which time the required amount of water had been collected. The solution was cooled, washed with dilute aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Removal of the benzene gave an oil, which, upon distillation gave two distinct fractions. The first fraction (2.0 g, 44%, b.p. 64–66° at 0.1 mm) was shown by g.l.c. analysis (column E, 135°, 100) to consist of nearly pure cyclic ether **15**. An analytical sample was collected by preparative g.l.c. (column F, 230°, 150), and exhibited n_D^{20} 1.4747; infrared (film), λ_{max} 6.97, 7.30, 9.40, 9.57 μ; n.m.r., τ 6.25–6.80 (diffuse, 2H, —CH_2—O—, overlapped AB of ABX system), 8.71, 8.81, 8.97 (singlets, 9H, tertiary methyls).

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.07; H, 12.15. Found: C, 79.19; H, 12.17.

The second fraction (2.1 g, 46%) was a mixture of the two olefinic alcohols **16**, b.p. 104–108° at 0.1 mm, n_D^{20} 1.4919; infrared (film), λ_{max} 3.05, 6.12, 6.98, 9.80, 10.19, 11.28 μ.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.07; H, 12.15. Found: C, 79.17; H, 12.35.

*Preparation of Alcohol **17***

The hydrogenation of the mixture of the olefinic alcohols **16** was carried out in ethanol at room temperature and atmospheric pressure using platinum as the catalyst. From 1.85 g of **16** there was obtained 1.23 g (71%) of pure saturated alcohol **17**, b.p. 110–115° (bath temperature) at 0.15 mm, n_D^{20} 1.4749. Infrared (film), λ_{max} 6.04, 6.90, 9.83 μ; n.m.r., τ 6.12–6.88 (pair of quartets, 2H, —CH_2OH, AB of ABX system), 9.07 (doublet, 6H, —$CH(CH_3)_2$, J = 6.2 Hz), 9.22 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.19; H, 13.12. Found: C, 78.33; H, 13.20.

*cis-1,2-Dimethyl-1-isobutylcyclohexane (**19**)*

*(a) From Alcohol **17***

A solution of alcohol **17** (1 g, 5.4 mmoles) in 5 ml of dry pyridine was cooled to 0° and 1.09 g (5.75 mmoles) of *p*-toluenesulfonyl chloride was added. The solution was stirred at 0° for 1.5 h and then diluted with ice-cold water. The mixture was extracted with ether and the ether solution was washed with saturated aqueous sodium bicarbonate, water, saturated brine, and then dried over anhydrous magnesium sulfate. Removal of the ether gave 1.77 g of the crude tosylate **18** as a pale-yellow oil. The latter was dissolved in 32 ml of dry tetrahydrofuran and 380 mg (10 mmoles) of lithium aluminium hydride was added. The mixture was refluxed, with stirring, for 22 h, cooled, and the excess hydride was destroyed by careful addition of ice-cold water. Ether was added and the organic layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvents, followed by distillation of the residual oil, afforded 500 mg (66%) of *cis*-1,2-dimethyl-1-*iso*butylcyclohexane (**19**), b.p. 110° at 10 mm. An analytical sample was collected by preparative g.l.c. (column G, 165°, 85) and exhibited n_D^{20} 1.4544. The n.m.r. spectrum of this compound showed signals only in the expected region, between τ 8.0 and τ 9.3.

Anal. Calcd. for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.73; H, 14.41.

(b) From cis-2,3-Dimethyl-2-methallylcyclohexanone (7)

Hydrogenation of 202 mg of *cis*-2,3-dimethyl-2-methallylcyclohexanone (**7**) in ethanol at room temperature and atmospheric pressure, using platinum as the catalyst, gave 195 mg of undistilled *cis*-2,3-dimethyl-2-*iso*butylcyclohexanone, which exhibited one component by g.l.c. (column G, 200°, 80). The latter was not further purified, but was directly subjected to Huang–Minlon reduction (16). Thus, a solution of the cyclohexanone (190 mg) in diethylene glycol (1.5 ml) containing 0.5 g of potassium hydroxide and 0.2 ml of hydrazine hydrate was refluxed for 2 h. The reflux condensor was removed and replaced by a distillation head, and the temperature of the reaction mixture was slowly raised to 195° and kept at this temperature for 1 h. The distillate and the cooled reaction mixture were combined, diluted with water, and thoroughly extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid, water, saturated brine, and dried over anhydrous magnesium sulfate. Careful removal of the ether afforded 176 mg (94%) of a pale-yellow oil which exhibited one component by g.l.c. (column G, 155°, 80). An analytical sample, collected by preparative g.l.c. (column G, 155°, 80), exhibited refractive index, infrared and n.m.r. spectra, and g.l.c. retention time identical with those of *cis*-1,2-dimethyl-1-*iso*butylcyclohexanone (**19**) obtained from the alcohol **17**, as described above.

Acid-catalyzed Isomerization of cis-2,3-Dimethyl-2-methallylcyclohexanone (7)

A solution of compound **7** (62 g, containing approximately 5% of its epimer **8**) in 1 l of dry benzene containing 1 g of *p*-toluenesulfonic acid was refluxed under an atmosphere of nitrogen for 3 days. The cooled solution was extracted twice with saturated aqueous sodium bicarbonate, then with water, and finally with saturated brine. After drying (anhydrous magnesium sulfate) the benzene was removed, yielding a yellow oil, which was shown by g.l.c. analysis (column H, 140°, 85) to consist of approximately 46% of the desired cyclohexanone **20**, 12% of the starting material, 37% of the cyclic hemiketal **21**,[5] and 5% of an unidentified compound. Distillation of the oil under reduced pressure (2.8 mm) gave the following fractions: fraction 1, b.p. 66–66.5°, 7 g; fraction 2, b.p. 66.5°, 7 g; fraction 3, b.p. 66.5–67.5°, 37.5 g; fraction 4, b.p. 67.5–68°, 3.5 g. Fraction 3 contained a small amount of crystalline material, while fraction 4 was nearly entirely crystalline. Isolation of this material, followed by recrystallization from petroleum ether (b.p. 60–80°) gave pure hemiketal **21** (3.2 g), m.p. 74–74.5°. Infrared (Nujol), λ_{max} 2.92, 6.92, 7.28, 9.16, 9.85, 10.08 μ; n.m.r., τ 7.69 (broad singlet, 1H, —O—H, D_2O exchange), 8.14 (singlet, 2H, —C—CH_2—C—), 8.58, 8.65, 9.06 (singlets, 9H, 3 tertiary methyls), 9.13 (doublet, 3H, secondary methyl J = 6.2 Hz).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 73.00; H, 11.00.

Fraction 2 and the oil of fraction 3 from the above distillation were combined and subjected to careful fractional distillation through a spinning band column (stainless steel, 8 mm × 24 in.). The distillation was carried out at a pressure of 53 mm, and the various fractions were subjected to g.l.c. analysis (column H, 140°, 85). The initial three fractions (5.5 g) consisted mainly of a mixture of the cyclic enol-ether **22** and water (due to dehydration of the hemiketal **21**). Fraction 4 (11.1 g, b.p. 128°) was nearly pure enol-ether **22**, fraction 7 (13.7 g, b.p. 143–144°) was shown to be greater than 90% pure ketone **20**, while fractions 5 and 6 (6.4 g, b.p. 128–143°) consisted of a mixture of compounds **20** and **22**. Fractions 8 and 9 (5 g, b.p. 144–147°) contained ketone **20** and starting material **7** in a ratio of approximately 5:2, respectively.

An analytical sample of the cyclic enol ether **22** was obtained from fraction 4 by preparative g.l.c. (column B, 200°, 110). This compound was extremely sensitive to moisture and, even upon exposure to the atmosphere, readily hydrated to afford the crystalline hemiketal **21**. The pure enol-ether exhibited n_D^{20} 1.4760. Ultraviolet (cyclohexane) λ_{max} 200 mμ (ε = 8 760); infrared (film), λ_{max} 5.92 μ; n.m.r., τ 5.36 (triplet, 1H, olefinic H, J = 3.5 Hz), 8.57, 8.74, 8.90 (singlets, 9H, tertiary methyls), 9.10 (doublet, 3H, secondary methyl, J = 6 Hz).

Anal. Calcd. for $C_{12}H_{20}O$: C, 80.01; H, 11.11. Found: C, 80.19; H, 11.10.

An analytical sample of *cis*-2,3-dimethyl-2-methylpropenylcyclohexanone (**20**) was obtained from fraction 7 by preparative g.l.c. (column B, 200°, 110) and exhibited n_D^{20} 1.4822. Infrared (film), λ_{max} 5.85 μ; n.m.r., τ 4.59 (multiplet, 1H, vinyl H), 8.27, 8.57 (doublets, 6H, vinyl methyls, J = 1.5, 1.3 Hz, respectively), 8.91 (singlet, 3H, tertiary methyl), 9.17 (doublet, 3H, secondary methyl, J = 7 Hz).

Anal. Calcd. for $C_{12}H_{20}O$: C, 80.01; H, 11.11. Found: C, 80.08; H, 11.02.

Reaction of Ketone 20 with Diethyl Cyanomethylphosphonate

A stirred suspension of sodium hydride (9.3 g, 0.387 mole) in dry dimethyl sulfoxide (200 ml) was slowly heated under an atmosphere of nitrogen, to 75° and kept at this temperature until frothing had ceased (approximately 45 min). The solution was cooled to room temperature and a solution of diethyl cyanomethylphosphonate (72.6 g, 0.387 mole) in 125 ml of dimethyl sulfoxide was added. The solution was stirred for 10 min and then a solution of compound **20** (13 g, 64.2 mmoles) in 125 ml of dimethyl sulfoxide was added. The reaction mixture was heated at 100° for 1 h, cooled, diluted with water, and then thoroughly extracted with petroleum ether (b.p. 30–60°). The combined extracts were washed twice with water, once with saturated brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced

[5]It should be noted that the hemiketal **21** was not stable to the high temperatures used in the g.l.c. analysis, but, in fact, dehydrated to the enol-ether **22**. Thus, both authentic hemiketal and enol-ether exhibited identical g.l.c. retention times. However, distillation of the crude reaction product under reduced pressure at a relatively low temperature clearly showed that none of the relatively low boiling enol-ether was present in the initially obtained mixture.

pressure yielded 12.7 g (89%) of a pale-yellow oil, b.p. 86–91° at 0.25 mm. This material was shown, by g.l.c. analysis (column C, 190°, 100), to consist of a mixture of the α,β-unsaturated nitrile **23** and the β,γ-unsaturated nitrile **24**, in a ratio of approximately 2:1, respectively. An analytical sample of each of these compounds was isolated by preparative g.l.c. (column F, 230°, 120). The α,β-unsaturated nitrile **23** exhibited n_D^{20} 1.5109. Ultraviolet, λ_{max} 220.5 mμ (ε = 12 300); infrared (film), λ_{max} 4.53, 6.20 μ; n.m.r., τ 4.75 (singlet, 1H, =CHCN), 4.82 (unresolved multiplet, 1H, vinyl H), 8.25, 8.44 (doublets, 6H, vinyl methyls, J = 1.4, 1.6 Hz, respectively), 8.84 (singlet, 3H, tertiary methyl), 9.13 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.85; H, 10.25.

The β,γ-unsaturated nitrile **24** exhibited n_D^{20} 1.4981. Infrared (film), λ_{max} 4.48, 6.06 μ; n.m.r., τ 4.07 (unresolved multiplet, 1H, γ-vinyl H), 4.94 (unresolved multiplet, 1H, vinyl H), 7.01 (unresolved multiplet, 2H, —CH_2CN) 8.31, 8.40 (doublets, 6H, vinyl methyls, J = 1.5, 1.7 Hz respectively), 9.00 (singlet, 3H, tertiary methyl), 9.11 (doublet, 3H, secondary methyl).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.71; H, 10.45.

Preparation of Carboxylic Acid ***25***

Potassium hydroxide (77 g) was dissolved in a mixture of ethanol (380 ml) and water (20 ml), and a mixture of the two nitriles (**23** and **24**) (13.2 g) was added. The solution was refluxed under an atmosphere of nitrogen for 3 days and then most of the solvent was removed under reduced pressure. The residual material was diluted with water and the resulting solution was washed with ether. The aqueous layer was acidified with 6 *N* hydrochloric acid and extracted thoroughly with ether. The combined extracts were washed with water, saturated brine, and then dried over anhydrous sodium sulfate. Removal of the solvent gave a viscous yellow oil which, upon distillation under reduced pressure, yielded 12 g (82%) of the β,γ-unsaturated carboxylic acid **25** as a clear viscous oil, b.p. 130–134° at 0.25 mm, n_D^{20} 1.5040; infrared ($CHCl_3$), λ_{max} 2.9–4.2 (broad), 5.88 μ; n.m.r., τ 4.35 (poorly resolved triplet, 1H, γ-vinyl H), 4.93 (unresolved multiplet, 1H, vinyl H), 7.07 (unresolved multiplet, 2H,—CH_2C-OOH), 8.32, 8.38 (doublets, 6H, vinyl methyls, J = 1.5, 1.3 Hz, respectively), 8.99 (singlet, 3H, tertiary methyl), 9.11 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.61; H, 10.00.

*(±)-Aristolone (**1**) and (±)-6,7-Epi-aristolone (**28**)*

The β,γ-unsaturated carboxylic acid **25** (5.0 g, 22.4 mmoles) was dissolved in aqueous sodium hydroxide (25.0 mmoles), the water was evaporated under reduced pressure, and the residue was dried in a vacuum oven at 70°. A stirred suspension of the resulting dry sodium salt in 140 ml of dry benzene containing 0.5 ml of pyridine was cooled to 0° and 56 g (0.44 mole) of oxalyl chloride was added. The reaction mixture was stirred at 0° for 15 min, filtered, and evaporated under reduced pressure (vacuum pump). The solution was kept at 0° during this process. The crude acid chloride **26** [infrared (film), λ_{max} 5.62 μ; n.m.r., very similar to that of the carboxylic acid] thus obtained was taken up in 250 ml of dry ether and the resulting solution was added to excess alcohol free ethereal diazomethane which had been dried over potassium hydroxide. The solution was stirred for 15 min and evaporated under reduced pressure affording the crude diazoketone **27**. Infrared (film), λ_{max} 4.79, 6.15 μ. The crude diazoketone **27** was dissolved in 600 ml of cyclohexane and cupric sulfate (15 g) was added. The resulting suspension was refluxed, with stirring, until the infrared absorption at 4.79 μ had disappeared (approximately 4 h). The cooled mixture was filtered and the filtrate was washed with saturated aqueous sodium bicarbonate, water, saturated brine, and then dried over anhydrous sodium sulfate. Removal of the solvent, followed by distillation of the residual material under reduced pressure, yielded 3.5 g (approximately 70%, based on the acid **25**) of a clear oil, b.p. 100–110° (bath temperature) at 0.1 mm. This material was shown by g.l.c. analysis (column G, 220°, 110) to consist of approximately 42% of (±)-aristolone (**1**), 20% of (±)-6,7-epi-aristolone (**28**) and a number of minor unidentified components. This mixture was partially purified by preparative thin-layer chromatography. Neutral alumina plates (20 × 60 cm, 0.5 mm thick) were used, with 3:2 *n*-hexane – ether being employed as developing solvent. Approximately 150 mg of the distilled material was applied per plate and the appropriate band of each plate, containing (±)-aristolone (**1**) and its isomer **28**, was eluted with ether. From 3.5 g of distilled material there was thus obtained 2.1 g of a clear oil which consisted mainly of (±)-aristolone (**1**) and its isomer **28**, in a ratio of approximately 2.4:1, respectively. Final purification was effected by preparative g.l.c. (column I, 240°, 110). Crystalline (±)-aristolone (**1**), thus obtained was recrystallized from petroleum ether (b.p. 60–80°), and exhibited m.p. 62–63°. Ultraviolet, λ_{max} 236 mμ (ε = 10 300); infrared ($CHCl_3$), λ_{max} 6.09 μ; n.m.r., τ 4.28 (unresolved multiplet, 1H, —C^9H, width at half-height = 3.5 Hz), 8.28 (pair of doublets, 1H, —C^7H, J = 8 and 1.2 Hz), 8.61 (doublet, 1H, —C^6H, J = 8 Hz), 8.74, 8.80, 8.81 (singlets, 9H, tertiary methyls), 8.93 (doublet, 3H, secondary methyl, J = 6.5 Hz). This material was found to be identical (m.p., mixed m.p., infrared, n.m.r., g.l.c. retention time) with authentic (±)-aristolone, prepared by recrystallizing, from petroleum ether (b.p. 60–80°), a 1:1 mixture of (−)-aristolone and α-ferulone [(+)-aristolone] (23).

Mol. Wt. Calcd. for $C_{15}H_{22}O$: 218.167. Found (high resolution mass spectrometry): 218.166.

Pure (±)-6,7-epi-aristolone (**28**) was obtained as a colorless oil. Ultraviolet, λ_{max} 233 (ε = 10 000); infrared ($CHCl_3$), λ_{max} 6.08 μ; n.m.r., τ 4.24 (unresolved multiplet, 1H, —C^9H, width at half-height = 2.5 Hz), 8.38 (pair of doublets, 1H, —C^7H, J = 8 and 1.1 Hz), 8.45 (doublet, 1H, —C^6H, J = 8 Hz), 8.80, 8.81, 8.84 (singlets, 9H, tertiary methyls), 9.02 (doublet, 3H, secondary methyl, J = 6.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{22}O$: 218.167. Found (high resolution mass spectrometry): 218.167.

Acknowledgments

We are very grateful to Professor A. Marsili for generous samples of (−)-aristolone and

α-ferulone, and to Professor F. Sorm for a generous quantity of (−)-aristolone. Financial support from the National Research Council of Canada, and a National Research Council of Canada Studentship (to W. de W.) are gratefully acknowledged.

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