Total synthesis, stereochemistry, and lithium–ammonia reduction of (±)-4-demethylaristolone and (±)-5-epi-4-demethylaristolone

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The total synthesis of (±)-4-demethylaristolone (**14**) and its epimer, (±)-5-epi-4-demethylaristolone (**15**) is described. The key step of this synthesis involves the intramolecular cyclization of the olefinic diazoketone **12**, which produces the two epimers, **14** and **15**, in a ratio of approximately 2:1, respectively. The stereochemistry of the two epimers is unambiguously determined. It is observed that the lithium–ammonia reduction of **14** gives a dihydro derivative **16** containing *trans*-fused six-membered rings, while, interestingly, a similar reduction of **15** affords the corresponding *cis*-fused decalone system **26**.

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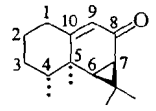
Very recently, we reported (1) the total synthesis of the racemic form of the sesquiterpenoid aristolone (**1**) (2–4). This synthesis, in which the key step involved the cupric sulfate catalyzed intramolecular cyclization of the diazoketone **2**, was based on a model study involving the preparation of (±)-4-demethylaristolone. The model study, which has already been reported in preliminary form (5), was undertaken primarily with the aim of determining whether or not the crucial cyclization of the type **2** → **1** would take place. That is, in order to initially avoid some of the stereochemical problems involved in the synthesis of aristolone itself, we first decided to prepare a diazoketone of the type **3**. Successful intramolecular cyclization of the latter would then eventually lead to aristolone-type compounds lacking the C-4 secondary methyl group. We report here the details of this model study which, in addition to demonstrating the feasibility of the proposed synthetic approach, also produced some interesting results regarding the lithium–ammonia reduction of the final products, (±)-4-demethylaristolone and (±)-5-epi-4-demethylaristolone.



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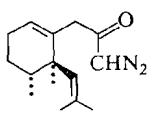

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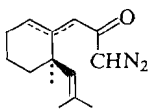

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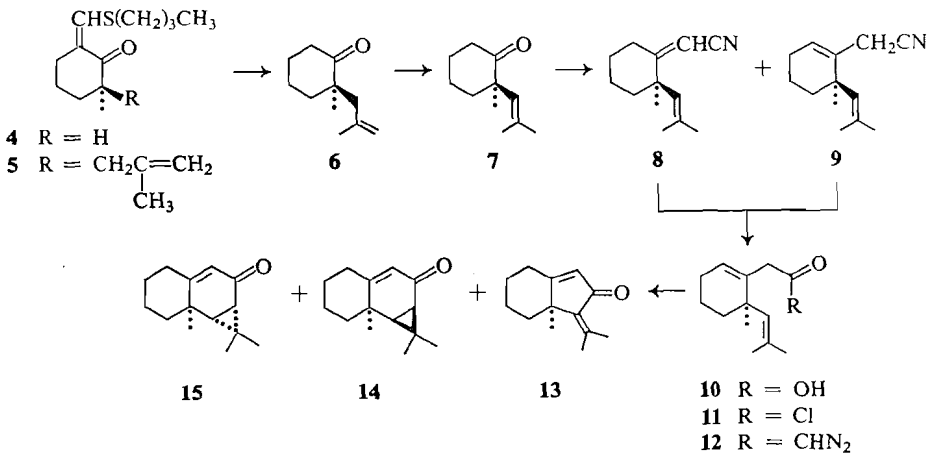
Alkylation of 2-methyl-6-*n*-butylthiomethylenecyclohexanone (**4**) (6) with methallyl chloride in *t*-butyl alcohol in the presence of potassium *t*-butoxide gave, after removal (6) of the *n*-butylthiomethylene blocking group from the product **5**, a 56% overall yield of 2-methyl-2-methallylcyclohexanone (**6**). Conversion of the latter into the desired 2-methyl-2-methylpropenylcyclohexanone (**7**) required isomerization of the olefinic double bond from the terminal position to the more highly substituted internal position. Although a number of different methods were attempted in order to carry out this transformation, it was eventually found that simple acid catalyzed isomerization was the most convenient. Thus, treatment of the methallyl compound **6** with *p*-toluenesulfonic acid in refluxing benzene for 3 days produced, in 77% yield, a mixture of compounds which, by gas–liquid chromatographic analysis, was shown to consist of approximately 80% of the desired isomerized ketone **7**, 17% of the starting material **6**, and 3% of an unidentified component. Careful fractionation of this mixture through a spinning band column allowed the isolation of nearly pure desired ketone **7**. The fact that simple double bond isomerization had taken place was shown clearly by the nuclear magnetic resonance (n.m.r.) spectra of compounds **6** and **7**. Thus, although the starting material **6** exhibited signals for two olefinic protons (τ 5.18 and 5.33) and one vinyl methyl group (τ 8.33), the product **7** showed signals for one olefinic proton (τ 4.74) and two vinyl methyl groups (τ 8.31 and 8.57).

In order to obtain, from ketone **7**, the diazoketone required to test the feasibility of the proposed intramolecular cyclization, the reaction of **7** with the modified Wittig reagent, triethyl phosphonoacetate (7), was attempted. This reaction proved very sluggish and even when high



reaction temperatures were used, none of the desired product could be isolated. However, use of the sterically less demanding reagent, diethyl cyanomethylphosphonate (7), proved successful. Thus, reaction of the cyclohexanone **7** with this reagent in the presence of methylsulfinyl carbanion in dimethyl sulfoxide (8) at 100° for 15 h gave, in 95% yield, a mixture of the α,β-unsaturated nitrile **8** and the β,γ-unsaturated nitrile **9**, in a ratio of approximately 4:1, respectively. An analytical sample of the major compound (**8**) was obtained by preparative gas–liquid chromatography (g.l.c.) and gave spectral data in complete accord with the assigned structure. Furthermore, the n.m.r. spectrum of the mixture clearly showed that the other component of the mixture was indeed the β,γ-unsaturated isomer **9**.

Hydrolysis of the mixture of nitriles with potassium hydroxide in ethanol produced, in good yield, the β,γ-unsaturated carboxylic acid **10**. The fact that the double bond had now completely isomerized into the β,γ-position was clearly shown by the spectral data. The acid **10** exhibited no strong absorption in the ultraviolet (u.v.) spectrum and, in the n.m.r. spectrum, exhibited, in addition to the expected signals due to the angular methyl group and the methylpropenyl side chain, a two-proton multiplet at τ 7.09 (—CH_2COOH) and a one-proton triplet at τ 4.38 due to the γ-vinyl hydrogen. Although it is well known that equilibration of α,β- and β,γ-unsaturated carboxylic acids occurs in the presence of base (9), it is of interest to note 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 (10) which would be associated with the exocyclic double bond in the α,β-unsaturated isomer. Presumably this is more severe than the $A^{(1,2)}$ strain (10) which is inherently present in the β,γ-unsaturated compound.

Treatment of the sodium salt of the carboxylic acid **10** with oxalyl chloride in benzene at room temperature gave the acid chloride **11**. The latter was quite unstable and readily cyclized to the cross-conjugated dienone **13**. In fact, when the acid chloride was allowed to stand at room temperature, or if it was gently warmed, a nearly quantitative yield of the dienone **13** was obtained. Therefore, even though special precautions were taken during the isolation of the crude acid chloride and even though the latter was reacted immediately with excess diazomethane, the resulting crude diazoketone **12** contained a considerable quantity of the bicyclic dienone **13**. Since no separation was affected at this stage, compound **13** was eventually isolated along with the demethylaristolones (*vide infra*). It is important to note that the n.m.r. spectrum of the crude diazoketone clearly showed that the olefinic double bond of this compound had remained in the β,γ-position with respect to the carbonyl group.

When the crude diazoketone **12** was heated with cupric sulfate in refluxing cyclohexane (11) for 2 h, a mixture of products was obtained. Analysis of the mixture by g.l.c. showed that it contained, in addition to a number of minor components, three major products, the cross-

conjugated dienone **13**, (±)-4-demethylaristolone (**14**), and (±)-5-epi-4-demethylaristolone (**15**), in a ratio of approximately 2:2:1, respectively. Treatment of this mixture with sodium hydroxide in hot aqueous ethanol for 10 min removed the minor components and gave a neutral product containing only the three compounds **13**, **14**, and **15**. Purification of this latter mixture by means of successive column chromatography on alumina and preparative g.l.c. allowed the isolation of all three components. The fact that the crucial cyclization had indeed taken place was clearly shown by the spectral data of the two cyclization products **14** and **15**. The major cyclization product, (±)-4-demethylaristolone (**14**), gave an u.v. maximum at 235 mμ and a strong carbonyl absorption at 6.10 μ in the infrared (i.r.). The n.m.r. spectrum, which was particularly instructive, exhibited a broad singlet at τ 4.32, due to the olefinic proton, and three sharp singlets at τ 8.70, 8.77, and 8.83 due to the three tertiary methyl groups. The minor cyclization product (±)-5-epi-4-demethylaristolone (**15**) was shown to be isomeric with **14** by means of a high resolution mass spectrometric measurement and gave spectral data very similar to that of compound **14**.

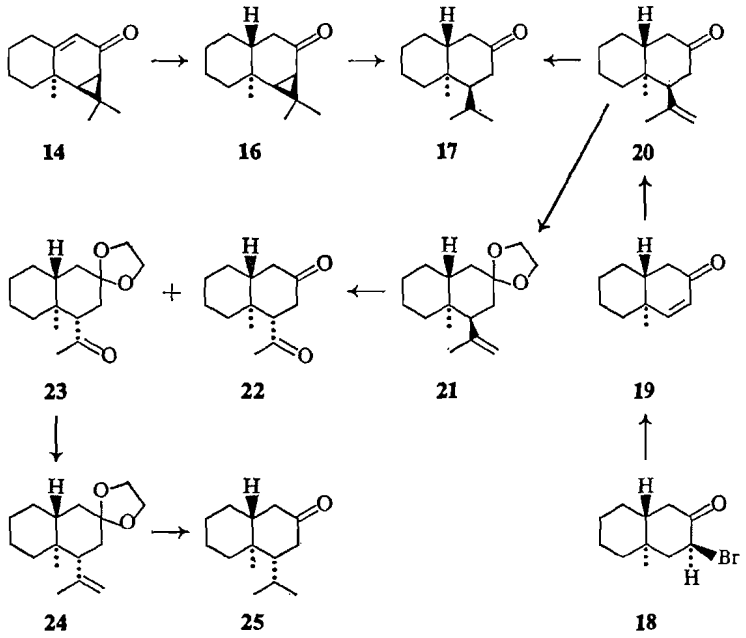
Having clearly shown that the initially proposed intramolecular cyclization of a diazoketone of the type **3** was a feasible process, we wished to unequivocally determine the stereochemistry of the two cyclization products, **14** and **15**. In order to accomplish this objective, we planned to convert the demethylaristolones into relatively simple decalone derivatives which, hopefully, could then be synthesized unambiguously.

Lithium–ammonia reduction of (±)-4-demethylaristolone (**14**) gave, in quantitative yield, (±)-9,10-dihydro-4-demethylaristolone (**16**). The fact that only the olefinic double bond had reduced and that the *gem* dimethylcyclopropyl moiety had been retained was clearly shown by the spectral data of the product **16**. The latter gave an u.v. absorption maximum at 212.5 mμ (see reference 12) and, in the n.m.r. spectrum, showed three sharp singlets due to the tertiary methyl groups, but gave no signal due to a vinyl proton. When compound **16** was again subjected to reduction with lithium in ammonia, the expected (13) substituted decalone **17** was obtained, again in virtually quantitative yield.

An unambiguous synthesis of the decalone **17** and subsequent correlation with the above reduction product would, of course, provide unequivocal proof for the stereochemistry of (±)-4-demethylaristolone (**14**). This synthesis was carried out as follows. Dehydrobromination of the known bromo ketone **18** (14) with a mixture of lithium bromide and lithium carbonate in hot dimethylformamide (15) afforded, in 90% yield, the octalone **19** (16). When the latter was reacted with isopropenylmagnesium bromide in the presence of cuprous chloride in tetrahydrofuran (17, 18), a mixture of products was obtained. Column chromatography of this mixture gave, in addition to a number of minor uncharacterized non-ketonic materials (presumably resulting from 1,2-addition of the Grignard reagent to the carbonyl of **19**), a 50% yield of the conjugate addition product **20**. It is noteworthy that the conjugate addition reaction was completely stereoselective, since a careful examination of the crude product of the reaction revealed that only one of the two possible epimeric 1,4-addition products was formed. Hydrogenation of the olefinic ketone **20** over Adams catalyst produced the decalone **17**, which was shown to be identical (m.p., mixed m.p., i.r.) with the decalone **17** obtained from the lithium–ammonia reduction of (±)-9,10-dihydro-4-demethylaristolone (**16**).

The stereochemical outcome of the above conjugate addition reaction requires comment. It has been proposed (19) that the conjugate introduction of a Grignard reagent to octalones of the type **19** must, for stereoelectronic reasons, take place via one (or both) of the two transition states **A** and **B**. Molecular models show that if stereoelectronic control is to be maintained in the boat-like transition state **B**, then the incoming Grignard reagent must approach the molecule in such a way that it is nearly eclipsed with the angular methyl group. The resulting torsional strain (20, 21) should override the steric hindrance (between the incoming isopropenyl group and the *syn*-axial hydrogens) present in transition state **A** and should ensure that the latter is favored over transition state **B**. Therefore, we fully expected that the cuprous chloride catalyzed 1,4-addition of isopropenylmagnesium bromide to octalone **19** would be highly stereoselective and, furthermore, predicted that the product should possess the stereochemistry depicted in **20**.

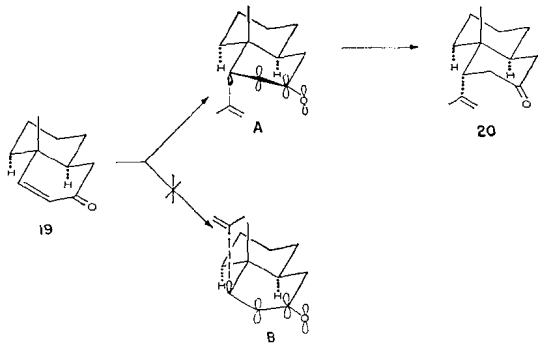
That the above prediction regarding the stereochemistry of **20** was correct was shown unambiguously as follows. Ketalization of **20** with



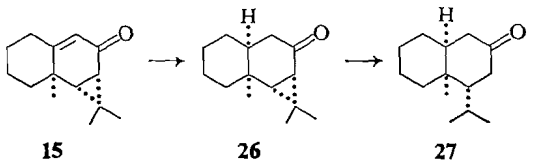
ethylene glycol afforded the crystalline ketal **21**, in 88% yield. Ozonolysis of this material, followed by column chromatography of the crude product, gave, in addition to the diketone **22**, the desired keto ketal **23**. The latter, upon reaction with methylenetriphenylphosphorane in dimethyl sulfoxide (8), gave a high yield of the olefinic ketal **24** which, on the basis of m.p., gas–liquid chromatographic retention time, and spectral data, was clearly different from, and therefore epimeric with, the olefinic ketal **21**. Successive hydrolysis and hydrogenation of compound **24** produced the decalone **25** which again was different from the decalone **17** obtained previously.

Obviously, the overall epimerization involved in the conversion of **21** into **24** required that the isopropenyl group was axial in the starting material **21**, and equatorial in the product **24**. The above stereochemical prediction was therefore correct and the stereochemistry of **20** was completely defined. This, in turn, unambiguously established the stereochemistry of (±)-4-demethylaristolone (**14**).

The lithium–ammonia reduction of (±)-5-epi-4-demethylaristolone (**15**) was also carried out. As in the case of the epimeric (±)-4-demethylaristolone (**14**), reduction of **15** was completely stereoselective and cleanly produced, in high yield, only one dihydro derivative (**26**). Lithium–



ammonia reduction of the latter afforded the substituted decalone **27**. Somewhat surprisingly, this decalone proved to be different from decalone **25**, the structure of which was unambiguously defined. This observation could only lead to the interesting conclusion that the lithium–ammonia reduction of (±)-5-epi-4-demethylaristolone (**15**) had produced a dihydro derivative with *cis*-fused six-membered rings. In contrast to the normal stereochemical outcome of reductions of this type (10, 22, 23) this is, to our knowledge, the



first recorded example of a lithium–ammonia reduction of a substituted $\Delta^{1(9)}$-octal-2-one which stereoselectively gave the corresponding *cis*-fused decalone derivative.

Experimental

General[1]

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Ultraviolet spectra were measured in methanol solution on either a Cary, model 14, or a Unicam, model SP.800, spectrophotometer. Routine i.r. 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 deuterochloroform solution on Varian Associates spectrometers, model A-60 and/or model HA-100. Signal 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. High resolution mass spectra were recorded on an AEI, type MS9, mass spectrometer. Gas–liquid chromatography was carried out on an Aerograph Autoprep, model 700. The following columns (10 ft × 1/4 in., unless otherwise stated) were employed, with the inert, supporting material being 60/80 mesh Chromosorb W in each case: Column A, 20% FFAP; Column B, 15% QF-1; Column C, 20% Apiezon J., Column D, 10% Apiezon J; Column E (10 ft × 3/8 in.), 30% FFAP; Column F (10 ft × 3/8 in.), 30% Carbowax 20 M; Column G (10 ft × 3/8 in.), 30% SE 30; Column H, 20% SE-30; Column I (10 ft × 3/8 in.), 30% Apiezon J. The specific column used, along with the 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.

The procedure employed for isolation of reaction products consisted of thorough extraction with the specified solvent, washing the combined extracts first with water, then with saturated brine, and drying over either anhydrous magnesium sulfate or sodium sulfate. The solvent was removed from the filtered extracts by means of a rotary evaporator, under reduced pressure.

2-Methyl-2-methallyl-6-n-butylthiomethylene-cyclohexanone (5)

To a stirred solution of potassium-*t*-butoxide (140 g, 1.23 moles) in 1200 ml of dry *t*-butyl alcohol was added 77 g (0.363 mole) of 2-methyl-6-*n*-butylthiomethylenecyclohexanone (**4**) (6) and the resulting solution was stirred at room temperature for 10 min and then cooled to 0°. Freshly distilled methallyl chloride (174 g, 1.92 moles) was added and the reaction mixture was refluxed under an atmosphere of dry nitrogen for 2 h. After most of the solvent had been removed under reduced pressure, the residue was diluted with water and the product was isolated with ether. Distillation under reduced pressure afforded 78 g (70%) of the alkylated ketone **5**, b.p. 101–103° at 0.08 mm; n_D^{20} 1.4965; u.v. λ_{max} 280 mμ (ε = 12 100); i.r. (film), λ_{max} 5.98, 6.31, 10.92 μ.

Anal. Calcd. for $C_{16}H_{22}OS$: C, 72.12; H, 9.84; S, 12.03. Found: C, 72.07; H, 9.77; S, 11.94.

2-Methyl-2-methallylcyclohexanone (6)

A stirred solution of compound **5** (65.8 g, 0.25 mole) in 150 ml of 25% aqueous potassium hydroxide and 150 ml of ethylene glycol was refluxed, under an atmosphere of nitrogen, for 18 h. The reaction mixture was steam distilled until the distillate was clear. The distillate was saturated with salt and the product was extracted with ether. Distillation of the crude oil gave 33.3 g (80%) of the desired ketone **6**, b.p. 54–58° at 0.6 mm; n_D^{20} 1.4772; i.r. (film), λ_{max} 5.86, 6.10, 11.16 μ; n.m.r., τ 5.18, 5.33 (two multiplets, 2H, $=CH_2$), 8.33 (broad singlet, 3H, vinyl methyl), 8.92 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.67; H, 10.79.

2-Methyl-2-methylpropenylcyclohexanone (7)

A solution of the ketone **6** (36 g) and *p*-toluenesulfonic acid (460 mg) in 700 ml of dry benzene was refluxed under nitrogen for 3 days. The solution was cooled, washed with saturated aqueous sodium bicarbonate, washed with saturated brine, and the product was isolated in the normal manner. Distillation of the crude product gave 27.7 g (77%) of a clear oil, b.p. 59–62° at 0.8 mm. Gas–liquid chromatographic analysis (column A, 170°, 75) of this material indicated that it was a mixture, consisting of approximately 80% of the desired ketone **7**, 17% starting material **6**, and 3% of an unidentified compound. This mixture was subjected to fractional distillation through a spinning band column (stainless steel, 8 mm × 24 in.). The distillation was carried out at a pressure of 28 mm, and each fraction was submitted to gas–liquid chromatographic analysis (column A, 170°, 75). The initial, small fractions (1 and 2), b.p. 105–112°, consisted mainly of the unidentified impurity. Fractions 3, 4, and 5 (15.1 g, b.p. 112–116°) contained the desired ketone **7**, greater than 97% pure. Fraction 6 (3.3 g, b.p. 116–118°) contained approximately 80% of the desired product **7**, and 20% starting material **6**. The still-pot residue (6.4 g) consisted of a mixture of compounds **6** (85%) and **7** (15%). An analytical sample of 2-methyl-2-methylpropenylcyclohexanone (**7**) was collected by preparative g.l.c. (column A, 170°, 75) and exhibited n_D^{20} 1.4767; i.r. (film), 5.88 μ; n.m.r., τ 4.74 (multiplet, 1H, vinyl H), 8.31, 8.57 (doublets, 6H, vinyl methyls, J = 1.5, 1.2 Hz, respectively), 8.91 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.56; H, 11.10.

Reaction of Ketone 7 with Diethyl Cyanomethylphosphonate

A stirred suspension of sodium hydride (10.9 g, 0.454 mole) in dry dimethyl sulfoxide (220 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 (80.5 g, 0.455 mole) in 150 ml of dimethyl sulfoxide was added. After stirring the reaction mixture for 10 min, a solution of ketone **7** (15.1 g, 0.091 mole) in 40 ml of dimethyl sulfoxide was added. The reaction was heated at 100° overnight, cooled, diluted with water,

[1]This general section is applicable to both the present paper and the succeeding paper (24).

and the product was isolated with petroleum ether (b.p. 30–60°). Distillation of the crude product gave 16.3 g (95%) of a clear oil, b.p. 84–87° at 0.15 mm. Analysis by g.l.c. (column B, 200°, 100) showed that this material was a mixture, containing approximately 80% of the α,β-unsaturated nitrile **8** and 20% of the β,γ-unsaturated nitrile **9**. An analytical sample of the major product was obtained by preparative g.l.c. (column B, 170°, 100) and exhibited n_D^{20} 1.5069; u.v., λ_{max} 219 mμ (ε = 10 900); i.r, (film), 4.55, 6.20 μ; n.m.r. τ 4.75 (singlet, 1H, =CHCN), 4.81 (multiplet, 1H, vinyl H), 8.28, 8.49 (doublets, 6H, vinyl methyls, J = 1.4, 1.3 Hz, respectively), 8.80 (singlet, 3H, tertiary methyl).

Mol. Wt. Calcd. for $C_{13}H_{19}N$: 189.152. Found (high resolution mass spectrometry): 189.150.

Although the minor product **9** was not isolated in pure form, the n.m.r. spectrum of the mixture of **8** and **9** clearly showed that the minor constituent was indeed the β,γ-unsaturated nitrile **9**. The mixture also gave satisfactory analytical data.

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.13. Found: C, 82.25; H, 10.35.

Preparation of Carboxylic Acid ***10***

To a solution of potassium hydroxide (75 g) in 390 ml of 95% ethanol was added 15.1 g (0.08 mole) of the mixture of nitriles **8** and **9**. The solution was refluxed under an atmosphere of nitrogen for 3 days. Most of the solvent was removed under reduced pressure, and the residue was diluted with water. The mixture was washed with ether and then acidified with dilute hydrochloric acid. The product was isolated in the normal manner with ether. Distillation of the crude product gave 10.9 g (65%) of the β,γ-unsaturated carboxylic acid **10**, b.p. 118–122° at 0.05 mm; n_D^{20} 1.5035; i.r. ($CHCl_3$), λ_{max} 2.9–4.1 (broad), 5.85 μ; n.m.r., τ 4.38 (triplet, 1H, γ-vinyl H), 4.95 (multiplet, 1H, vinyl H), 7.09 (multiplet, 2H, $-CH_2COOH$), 8.36, 8.40 (doublets, 6H, vinyl methyls, J = 1.5, 1.2 Hz, respectively), 8.87 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{13}H_{26}O_2$: C, 74.96; H, 9.68. Found: C, 74.80; H, 9.91.

Dienone ***13****, (±)-4-Demethylaristolone (****14****), and (±)-5-Epi-4-demethylaristolone (****15****)*

The β,γ-unsaturated carboxylic acid **10** (4.0 g, 20.6 mmoles) was dissolved in 0.1 *N* aqueous sodium hydroxide (22.6 mmoles), the water was removed under reduced pressure, and the residue was dried in a vacuum oven at 70°. To a stirred suspension of the resulting acid salt in 80 ml of cold (0°), dry benzene was added 6 drops of pyridine, followed by 28 ml of oxalyl chloride. The solution was stirred at room temperature for 30 min, filtered, and concentrated, under reduced pressure, at 40°. The crude acid chloride **11** [i.r. (film), λ_{max} 5.60 μ] thus obtained was immediately dissolved in 40 ml of dry ether and an excess of dry, alcohol-free ethereal diazomethane was added. After 30 min the solvent was removed under reduced pressure, affording the crude diazoketone **12**. The i.r. (film) spectrum showed λ_{max} 4.80, 6.16 μ. The n.m.r. spectrum of this crude material indicated that the olefinic double bond had remained in the β,γ-position relative to the carbonyl group. Furthermore, it was clear from the spectrum that the crude material contained a significant amount of the cross-conjugated dienone **13**.

The crude diazoketone was dissolved in 400 ml of cyclohexane and 8 g of anhydrous cupric sulfate was added. The resulting suspension was stirred vigorously and refluxed under an atmosphere of nitrogen for 2 h, at which time the i.r. absorption at 4.80 μ had disappeared. The suspension was cooled, filtered, washed with saturated aqueous sodium bicarbonate and with saturated brine, dried, and concentrated. Gas–liquid chromatographic analysis (column C, 200°, 85) of the resulting crude product (3.77 g) showed that it contained, in addition to a number of minor components of short retention time, three major components, **13**, **14**, and **15**, in a ratio of 2:2:1, respectively. The crude product was refluxed for 10 min in a mixture of ethanol (280 ml) and water (25 ml) containing 10 g of sodium hydroxide. The solution was concentrated under reduced pressure, the residue was diluted with water, and the neutral product was isolated with ether. Analysis of this crude product (2.32 g) by g.l.c. showed that all the minor components had been removed by this treatment, leaving only a mixture of the three major components **13**, **14**, and **15**. After partial separation of these compounds had been effected by column chromatography on Woelm neutral alumina, activity 1, an analytical sample of each compound was obtained by preparative g.l.c. (column C, 200°, 85).

The cross-conjugated dienone **13**, an oil, exhibited n_D^{20} 1.5408; u.v. λ_{max} 255 mμ (ε = 17 200); i.r. ($CHCl_3$), λ_{max} 5.98, 6.18 μ; n.m.r., τ 4.13 (broad singlet, 1H, vinyl H, width at half-height = 2 Hz), 7.68, 8.06 (singlets, 6H, vinyl methyls), 8.66 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.05; H, 9.54. Found: C, 81.94; H, 9.72.

This compound could also be prepared by allowing the acid chloride **11** to stand at room temperature for 24 h, followed by distillation, b.p. 75° (bath temperature) at 0.2 mm. This product was identical with **13**, described above.

(±)-4-Demethylaristolone (**14**), an oil, exhibited the following spectral properties: u.v., λ_{max} 235 mμ (ε = 11 600); i.r. ($CHCl_3$), λ_{max} 6.10 μ; n.m.r., τ 4.32 (broad singlet, 1H, vinyl H), 8.70, 8.77, 8.83 (singlets, 9H, tertiary methyls).

Mol. Wt. Calcd. for $C_{14}H_{20}O$: 204.151. Found (high resolution mass spectrometry): 204.151.

The crystalline (±)-5-epi-4-demethylaristolone (**15**) was recrystallized from petroleum ether (b.p. 60–80°) and exhibited m.p. 86.5–87.5°; u.v. λ_{max} 232 mμ (ε = 11 700); i.r. ($CHCl_3$), λ_{max} 6.11 μ; n.m.r. τ 4.28 (singlet, 1H, vinyl H), 8.62, 8.65, 8.70 (singlets, 9H, tertiary methyls).

Mol. Wt. Calcd. for $C_{14}H_{20}O$: 204.151. Found (high resolution mass spectrometry): 204.150.

Preparation of Octalone ***19***

A stirred suspension of lithium bromide (1.1 g) and lithium carbonate (1.6 g) in 30 ml of dry dimethylformamide was heated, under an atmosphere of nitrogen, to 120°. A solution of the bromo ketone **18** (14) (1.5 g, 6.1 mmoles) in 30 ml of dry dimethylformamide was added and the mixture was heated at 120° for 1.75 h. The reaction mixture was cooled, filtered, diluted with water, and the product was isolated with *n*-heptane. Distillation

of the crude product gave 0.91 g (90%) of octalone **19** as a clear, colorless oil, b.p. 100° at 0.35 mm; n_D^{20} 1.5088 (lit. b.p. 69° at 0.1 mm; n_D^{26} 1.5006 (16)). Gas–liquid chromatographic analysis (column D, 200°, 85) of this material showed that it consisted of only one component; u.v. λ_{max} 229 mμ (ε = 9200); i.r. (film), λ_{max} 5.95, 6.16 μ; n.m.r., τ 3.33, 4.24 (pair of doublets, 2H, (O=C)CH=C*H* and (O=C)C*H*=CH, respectively, J = 9.8 Hz), 8.96 (singlet, 3H, tertiary methyl).

Preparation of Decalone ***20***

To a stirred, ice-cold 1 *M* solution (120 ml) of isopropenylmagnesium bromide in tetrahydrofuran was added 0.65 g of anhydrous cuprous chloride. A solution of octalone **19** (10.0 g, 0.061 mole) in 40 ml of tetrahydrofuran was added dropwise, over a period of 20 min. The reaction mixture was stirred for 2 h at 0° and then poured into 350 ml of aqueous ammonium chloride–ammonium hydroxide buffer (p*H* ≃ 8). The product was isolated by extraction with ether. Analysis by g.l.c. (column D, 180°, 80) revealed that the crude product (10.7 g, b.p. 99–103° at 0.5 mm) contained, in addition to a number of minor components, one major product (approximately 60% of the mixture). Chromatography of this mixture on Woelm neutral alumina (300 g) afforded, in the fractions eluted with 4:1 benzene–ether, 5.2 g (50%) of decalone **20**, as pale yellow crystals. A careful examination of the various chromatography fractions showed that **20** was the only carbonyl-containing compound present in the product. Recrystallization of **20** from hexane–ether afforded clear, colorless plates, m.p. 83–84°; i.r. (KBr), λ_{max} 5.88, 6.14, 11.25 μ; n.m.r., τ 5.08, 5.45 (multiplets, 2H, =CH_2), 8.23 (multiplet, 3H, vinyl methyl), 8.84 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.33; H, 10.69.

Lithium–ammonia Reduction of
*(±)-4-Demethylaristolone (**14**)*

To 50 ml of ammonia, which had been distilled from sodium metal, was added 70 mg of lithium metal, and the resulting blue solution was stirred, under an atmosphere of dry nitrogen, for 15 min. A solution of (±)-4-demethylaristolone (**14**) (100 mg) in 8 ml of anhydrous ether was added dropwise and the resulting solution was stirred for 1 h. After the reaction had been quenched with ammonium chloride, the ammonia was allowed to evaporate and the residual material was diluted with water. Isolation of the product with ether gave 90 mg (90%) of a clear, colorless oil. Gas–liquid chromatographic analysis (column C, 200°, 85) showed that this material consisted of nearly pure (±)-9,10-dihydro-4-demethylaristolone (**16**), the only impurity being a small amount of starting material (**14**). An analytical sample of compound **16**, an oil, was obtained by preparative g.l.c. (column C, 200°, 85); u.v., λ_{max} 212.5 mμ (ε = 5200); i.r. ($CHCl_3$), λ_{max} 6.00 μ; n.m.r., τ 8.35, 8.94 (pair of doublets, 2H, cyclopropyl protons, J = 8.0 Hz), 8.59, 8.87, 8.97 (singlets, 9H, tertiary methyls).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.166.

Preparation of Decalone ***17***

(a) By Hydrogenation of Decalone ***20***

Hydrogenation (platinum oxide, ethanol) of compound **20** was carried out at atmospheric pressure and room temperature. From 200 mg of **20**, there was obtained 182 mg (91%) of the crystalline decalone **17**. Recrystallization from *n*-hexane gave an analytical sample, m.p. 49–50°; i.r. ($CHCl_3$), λ_{max} 5.85 μ; n.m.r., τ 8.89 (singlet, 3H, tertiary methyl), 9.08, 9.17 (doublets, 6H, secondary methyls, J = 6.8 Hz).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.95; H, 11.51.

(b) By Lithium–ammonia Reduction of
*(±)-9,10-Dihydro-4-demethylaristolone (**16**)*

The lithium–ammonia reduction of compound **16** was carried out by a procedure identical with that used for the reduction of (±)-4-demethylaristolone (**14**) (see above). From 60 mg of **16** there was obtained 58 mg of the crude crystalline decalone **17**. Recrystallization from *n*-hexane gave an analytical sample, m.p. 49–50°. This material was shown to be identical (m.p., mixed m.p., g.l.c. retention time, i.r. spectrum) with compound **17** obtained as described above.

Preparation of Ketal ***21***

A solution of the decalone **20** (3.1 g, 15 mmoles), ethylene glycol (3.72 g, 60 mmoles), and *p*-toluenesulfonic acid (50 mg) in 50 ml of dry benzene was refluxed under a Dean–Stark water separator for 20 h. The cooled solution was diluted with 50 ml of ether and washed with 50 ml of aqueous sodium bicarbonate. The organic layer was dried and concentrated, affording 3.93 g of colorless crystals. Recrystallization from *n*-hexane gave 3.31 g (88%) of the ketal **21** as colorless plates, m.p. 80–81°; i.r. ($CHCl_3$), λ_{max} 6.15, 9.07, 9.28, 11.18 μ; n.m.r., τ 5.01, 5.20 (multiplets, 2H, =CH_2), 6.10 (multiplet, 4H, —OCH_2CH_2O—), 8.13 (multiplet, 3H, vinyl methyl), 9.02 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.46. Found: C, 76.69; H, 10.39.

Ozonolysis of Ketal ***21***

A solution of 3.0 g (12 mmoles) of ketal **21** was dissolved in 150 ml of ethyl acetate and the solution was cooled in a dry ice–acetone bath. Ozone was bubbled through the solution until a blue color began to appear (approximately 15 min) and continued for a further 15 min. Platinum oxide (400 mg) was added and the reaction mixture was subjected to hydrogenation at room temperature and atmospheric pressure. After hydrogen uptake had ceased, the mixture was filtered and the filtrate was concentrated under reduced pressure. Gas–liquid chromatographic analysis (column B, 200°, 85) showed that the residual oil (2.63 g) consisted of three components. This material was subjected to column chromatography on Woelm neutral alumina (120 g). The first fraction (500 mg) showed no carbonyl absorption in its i.r. spectrum, and was not investigated further. The fractions eluted with 9:1 to 4:1 benzene–ether gave a total of 620 mg (21%) of the crystalline keto ketal **23** which, upon recrystallization from *n*-hexane, exhibited m.p. 74–74.5°; i.r. ($CHCl_3$), λ_{max} 5.88, 9.08, 9.28 μ; n.m.r., τ 6.06 (singlet, 4H, —OCH_2CH_2O—), 7.84 (singlet, 3H, —$COCH_3$), 9.09 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.38; H, 9.59. Found: C, 71.15; H, 9.47.

The fractions from the above chromatography which were eluted with 4:1 to 7:3 benzene–ether afforded 1.0 g of oily crystals which were recrystallized from *n*-hexane to afford 840 mg (33%) of the diketone **22**, m.p. 95–95.5°; i.r. ($CHCl_3$), λ_{max} 5.85 μ; n.m.r., τ 7.80 (singlet, 3H, $-COCH_3$), 8.83 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.95; H, 9.67. Found: C, 74.98; H, 9.89.

Preparation of Ketal ***24***

To a solution of methylenetriphenylphosphorane (1.27 g, 4.5 mmoles) in 6 ml of dimethyl sulfoxide was added a solution of the keto ketal **23** (225 mg, 0.9 mmole) in 10 ml of dimethyl sulfoxide. The resulting solution was heated at 100° for 6 h, cooled, and poured into 25 ml of cold water. Isolation of the product with pentane gave 203 mg (91%) of the crystalline ketal **24** which, upon recrystallization from *n*-hexane, exhibited m.p. 76–77°; i.r. ($CHCl_3$), λ_{max} 6.14, 9.08, 9.28, 11.18 μ; n.m.r., τ 5.05, 5.34 (multiplets, 2H, $=CH_2$), 6.04 (singlet, 4H, $-OCH_2-CH_2O-$), 8.26 (multiplet, 3H, vinyl methyl), 9.17 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.46. Found: C, 77.00; H, 10.45.

Preparation of Decalone ***25***

A solution of the ketal **24** (186 mg, 0.75 mmole) in a mixture of acetone (5 ml) and 10% hydrochloric acid (5 ml) was heated on a steam bath until most of the acetone had distilled. The product was isolated from the cooled reaction mixture by extraction with ether. The crude product [156 mg; i.r. (film), λ_{max} 5.85, 6.14, 11.20 μ] thus obtained was not purified further, but was subjected directly to hydrogenation (platinum oxide, ethanol) at atmospheric pressure and room temperature. Distillation of the crude hydrogenation product gave 110 mg of pure decalone **25** as a clear, colorless oil, b.p. 95° at 0.1 mm; n_D^{20} 1.4965; i.r. (film), λ_{max} 5.85 μ; n.m.r., τ 9.01 (singlet, 3H, tertiary methyl), 9.12, 9.18 (doublets, 6H, secondary methyls, $J = 6.5$ Hz).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.63; H, 11.49.

*Lithium–ammonia Reduction of (±)-5-Epi-4-demethylaristolone (**15**)*

The lithium–ammonia reduction of **15** was carried out in a manner identical with that described previously for the reduction of (±)-4-demethylaristolone (**14**). From 100 mg of compound **15** there was obtained 90 mg of crude product, consisting nearly entirely of the dihydro derivative **26**. An analytical sample of the latter, an oil, was obtained by preparative g.l.c. (column C, 200°, 85); u.v., λ_{max} 210 mμ (ε = 4800); i.r. ($CHCl_3$), λ_{max} 5.99 μ; n.m.r., τ 8.43, 9.04 (pair of doublets, 2H, cyclopropyl protons, $J = 8$ Hz), 8.71, 8.74, 8.87 (singlets, 9H, tertiary methyls).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.167.

Lithium–ammonia Reduction of Compound ***26***

Reduction of 60 mg of compound **26**, *via* a procedure identical with that described previously for the reduction of **14**, gave 55 mg of crude crystalline material. Recrystallization from *n*-hexane afforded an analytical sample of the decalone **27**, m.p. 50.5–51°; i.r. ($CHCl_3$), λ_{max} 5.88 μ; n.m.r., τ 8.87 (singlet, 3H, tertiary methyl), 9.08, 9.16 (doublets, 6H, secondary methyls, $J = 6.5$ Hz).

Mol. Wt. Calcd. for $C_{14}H_{24}O$: 208.183. Found (high resolution mass spectrometry): 208.182.

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