Annelation of 2,3-dimethylcyclohexanone. Synthetic proof for the stereochemistry of the sesquiterpene aristolone

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An efficient annelation of 2,3-dimethylcyclohexanone is described. The key step of this process involves the reaction of the enol lactone **16** with methyllithium, under carefully controlled conditions. The completely stereoselective conversion of the sesquiterpene (−)-aristolone (**1**) into the levorotatory decalone **22***b* is described. Comparison of the latter with the unambiguously synthesized racemic decalone **22***a* conclusively establishes the relative stereochemistry of aristolone (**1**).

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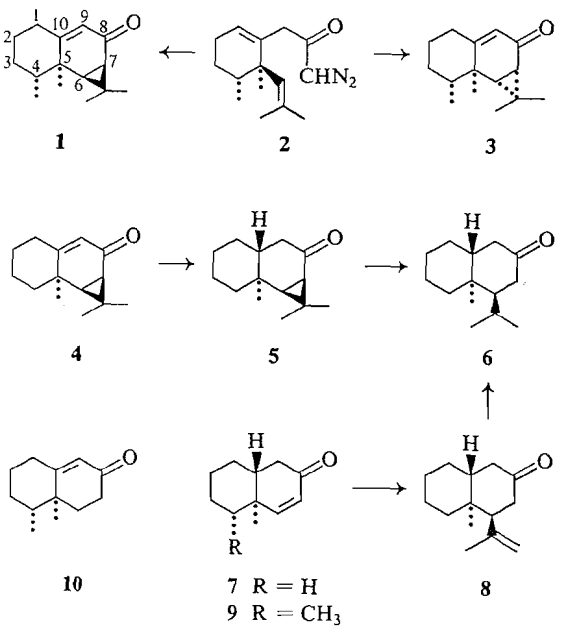
The relative and absolute stereochemistry of the sesquiterpene aristolone (1,2) has been proposed (3) as shown in formula **1**. However, even though two independent and entirely different total syntheses of the racemic form of this interesting natural product have recently been reported (4,5), the stereochemical proposal (3) has not as yet received synthetic verification, since both of the syntheses were stereochemically ambiguous. For example, in the synthesis reported by the present authors (5), the key step involved the cupric sulfate catalyzed intramolecular cyclization of the olefinic diazoketone **2**. This reaction was not completely stereoselective, since it produced not only (±)-aristolone (**1**), but also the isomeric (±)-6,7-epi-aristolone (**3**). Therefore, although the stereochemistry of the crucial synthetic intermediate **2** was clearly and unambiguously determined (5), the above synthesis did not unequivocally establish the total relative stereochemistry of aristolone (**1**). We have therefore obtained direct independent synthetic evidence which fully corroborates the stereochemical assignment (3) of this sesquiterpene.

Previously, in a model study (6,7) we had shown that (±)-4-demethylaristolone (**4**) gave, upon reduction with lithium in ammonia, a near quantitative yield of (±)-9,10-dihydro-4-demethylaristolone (**5**). The latter, when again subjected to lithium–ammonia reduction, afforded the substituted decalone **6**. Furthermore, we had also shown (6,7) that the cuprous chloride catalyzed conjugate addition of isopropenylmagnesium bromide to the octalone **7** gave, completely stereoselectively, the decalone **8** which, upon hydrogenation, produced compound **6**, identical with that obtained from the lithium–ammonia reduction of **5**.



1 **2** **3**
4 **5** **6**
10 **7** R = H, R = CH_3 **8**

From the foregoing, it was clearly apparent that a similar series of reactions involving aristolone (**1**) and the octalone **9** would provide unambiguous synthetic proof for the relative stereochemistry of the natural product. It appeared highly unlikely that the presence of an extra (equatorial) methyl group (**1** and **9** as compared with **4** and **7**, respectively) would alter the stereochemical outcome of either the lithium–ammonia reduction (of **1**) or the conjugate addition of isopropenylmagnesium bromide (to **9**).

The first synthetic objective, then, was the octalone **10**, which presumably could be readily converted by standard reactions into the required isomeric compound **9**. One obvious way

to prepare **10** would be to carry out the Robinson annelation (8) of 2,3-dimethylcyclohexanone with methyl vinyl ketone or its equivalent. In fact, Ourisson and co-workers (4) had already reported this reaction, although no yield was given by these workers. We attempted the Robinson annelation of 2,3-dimethylcyclohexanone with both methyl vinyl ketone and 4-diethylamino-2-butanone methiodide under a variety of experimental conditions, but were unable to obtain the annelated material in yields exceeding approximately 15%. Furthermore, the octalone which was obtained consisted, in each case, of a mixture of two epimers in a ratio of approximately 3:2, making it extremely difficult to obtain a reasonable quantity of the desired octalone **10** in a pure state. Therefore, since the Robinson annelation did not appear to be a particularly efficient method for the preparation of **10**, we considered alternative routes to this compound.

During our work on the total synthesis of (±)-aristolone (5) we had observed that alkylation of 2,3-dimethyl-6-*n*-butylthiomethylenecyclohexanone (**11**) with methallyl chloride produced, in high yield, a mixture of *cis*- (**12**) and *trans* - 2,3 - dimethyl - 2 - methallyl - 6 - *n* - butylthiomethylenecyclohexanone (**13**), in a ratio of approximately 4:1, respectively. The fairly high stereoselectivity of this process encouraged us to consider a preparation of **10** which was based upon alkylation of **11**. This approach proved to be very satisfactory.

Alkylation of compound **11** with ethyl 3-bromopropionate in the presence of potassium-*t*-butoxide in *t*-butyl alcohol (9) proved to be a very facile reaction and produced, in 86% yield, a mixture of the keto esters **14**. Removal of the *n*-butylthiomethylene blocking group from the latter was accomplished in the normal way (9) (potassium hydroxide in hot aqueous diethylene glycol) and was accompanied by hydrolysis of the ester group. The product, a mixture of keto acids **15**, was obtained in 90% yield.

When the mixture of keto acids **15** was refluxed in acetic anhydride containing sodium acetate (see ref. 10), there was produced, in 85% yield, a crystalline material which consisted of a mixture of the two epimeric enol lactones **16** and **17**. The ratio of the two epimers, as judged by the nuclear magnetic resonance (n.m.r.) spectrum of the mixture, was approximately 9:1, respectively. The major, desired epimer **16** could readily be obtained in 80% yield from the mixture by careful recrystallization of the latter from *n*-hexane. An analytical sample of **17** was obtained from the mother liquors of recrystallization by means of preparative gas–liquid chromatography (g.l.c.). Both **16** and **17** exhibited spectral data which was in complete accord with the assigned structures.

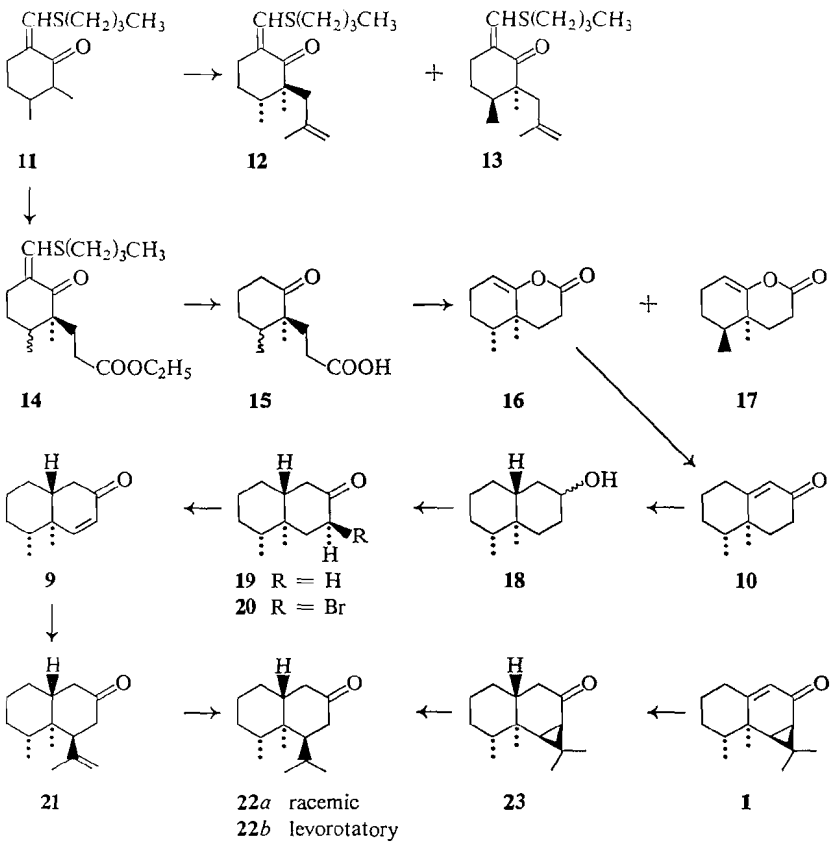
Although, in order to convert the enol lactone **16** into the required octalone **10**, we investigated the use of a number of different reagents,[1] it was eventually found that methyllithium was the most convenient and gave the most consistent results. Thus, reaction of **16** with methyllithium in dry ether at −25° for 1.75 h, followed by successive acidic hydrolysis and base-catalyzed aldol cyclization afforded, in addition to a small amount (10%) of starting material (in the form of the keto acid **15**, *cis* epimer) a 70% yield of the desired octalone. The overall yield of pure octalone **10**, based on 2,3-dimethylcyclohexanone, was, therefore, approximately 30%, obviously a considerable improvement over the Robinson annelation method.

It should be noted that the success of the reaction of the enol lactone **16** with methyllithium depended, to a large extent, upon a judicious choice of the reaction temperature and reaction time. That is, use of reaction temperatures greater than −25°, or use of longer reaction times, resulted in the formation of a considerable amount of alcohol-containing product, presumably due to "di-addition" of methyllithium to the enol lactone. On the other hand, milder reaction conditions (lower temperatures, shorter reaction times) resulted in the recovery of fairly copious amounts of starting material, in the form of the corresponding keto acid (**15**, *cis* epimer).

Reduction of the octalone **10** with lithium in ammonia in the presence of ethanol (see ref. 16) gave, in 75% yield, the decalol **18** which, upon oxidation with Jones reagent (17) gave the decalone **19**. The latter exhibited infrared (i.r.) spectrum and gas–liquid chromatographic retention times identical with those of the (+)-antipode of **19**, which had previously been prepared, via a lengthy synthetic sequence, by Djerassi and coworkers (18).[2] This comparison conclusively showed that the initial alkylation of compound

[1]For previous examples of annelation via enol lactones, see refs. 11–15, inclusive.

[2]We are very grateful to Professor Djerassi for a small sample of this compound.



11 with β-bromopropionate had been stereoselective in the desired sense and that, therefore, our synthetic intermediates indeed possessed a *cis* stereochemistry with respect to the two methyl groups.

Bromination of the decalone **19** with bromine in acetic acid (19) afforded the known (4) bromo ketone **20**. Dehydrobromination of the latter with a mixture of lithium bromide and lithium carbonate in hot dimethylformamide (20) gave, in 86% yield, a mixture of compounds which contained, in addition to a number of minor components, the desired octalone **9** as the major (80%) constituent. This material was isolated from the mixture by means of preparative g.l.c., and showed the expected spectral properties. Of particular pertinence was the ultraviolet (u.v.) spectrum, which exhibited a maximum at 230 mμ, and the n.m.r. spectrum, which showed the vinyl protons as an AB pair of doublets (J = 10 Hz) at τ 2.88 and 4.11.

When the octalone **9** was reacted with isopropenylmagnesium bromide in the presence of cuprous chloride in tetrahydrofuran (7), the decalone **21** was produced as the only conjugate addition product.[3] Hydrogenation of **21** over Adams catalyst afforded the racemic decalone **22*a***.

Lithium–ammonia reduction of (−)-aristolone (**1**)[4] gave, in high yield, (+)-9,10-dihydroaristolone (**23**). The latter gave an u.v. absorption maximum at 213 mμ (see ref. 21) and, in the n.m.r. spectrum, showed no signal due to a vinyl proton, thus clearly demonstrating that only the olefinic double bond had reduced. When compound **23** was again reduced with lithium in ammonia, the expected (22) levorotatory decalone **22*b*** was obtained in virtually quantitative yield. This compound gave spectra (i.r., n.m.r.)

[3]For a discussion regarding the stereochemical outcome of the conversion of **9** into **21**, see ref. 7.

[4]We are very grateful to Professor A. Marsili and to Professor F. Sorm for generous samples of authentic (−)-aristolone.

and gas–liquid chromatographic retention times identical with those of the racemic decalone **22***a* obtained as outlined above. Since, by analogy with previous work (7), the stereochemistry of **22***a* was completely defined, this comparison provided unambiguous synthetic evidence for the stereochemistry of aristolone (**1**).

Experimental[5]

*Alkylation of 2,3-Dimethyl-6-n-butylthiomethylene-cyclohexanone (**11**) with Ethyl 3-Bromopropionate*

The *n*-butylthiomethylene derivative **11** (5) (100 g, 0.44 mole) was added to 1800 ml of dry *t*-butyl alcohol containing 144 g (1.4 moles) of potassium *t*-butoxide and the resulting solution was stirred at room temperature for 10 min. Ethyl 3-bromopropionate (250 g, 1.38 mole) was added slowly from a dropping funnel. The alkylation was exothermic and, after the addition was complete, the reaction mixture was stirred for an additional 15 min. Most of the solvent was removed under reduced pressure and the residue was diluted with water. Isolation of the product with ether gave an oil which, upon distillation under reduced pressure, afforded 124 g (86%) of the keto ester **14** (mixture of epimers); b.p. 190–195° at 0.2 mm; n_D^{20} 1.5261; u.v., λ_{max} 311 mμ (ε = 14 900); i.r. (film), λ_{max} 5.79, 6.03, 6.52 μ.

Anal. Calcd. for $C_{18}H_{30}O_3S$: C, 66.22; H, 9.26. Found: C, 66.14; H, 9.33.

*Preparation of Keto Acid **15***

To a solution of the above alkylated material (**14**) (124 g, 0.38 mole) in 600 ml of diethylene glycol was added 600 ml of 25% aqueous potassium hydroxide, and the resulting solution was refluxed, under an atmosphere of nitrogen, for 18 h. The solution was cooled, diluted with water, and extracted twice with ether. The ether extracts were discarded. The aqueous layer was acidified with 6 *N* hydrochloric acid, and the product was extracted with ether. Distillation of the crude material afforded 67.5 g (90%) of the keto acid **15** (mixture of epimers) as a clear viscous oil; b.p. 142–147° at 0.15 mm; n_D^{20} 1.4868; i.r. (film), λ_{max} 2.7–4.2 (very broad), 5.78, 5.85 μ.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.83; H, 9.07.

*Preparation of Enol Lactones **16** and **17***

A solution of the mixture of keto acids **15** (64 g, 0.32 mole) in 1400 ml of acetic anhydride containing 14 g of anhydrous sodium acetate was refluxed under an atmosphere of nitrogen for 2 h. The acetic anhydride was removed under reduced pressure, and the residual material was diluted with water. Isolation of the product with ether, followed by distillation, gave 49 g (85%) of crystalline material; b.p. 90–94° at 0.15 mm. This material, as judged by its n.m.r. spectrum, consisted of a mixture of the enol lactones **16** and **17**, in a ratio of approximately 9:1, respectively. Recrystallization of this mixture from *n*-hexane produced pure **16** (40 g). An analytical sample of **16** was obtained by vacuum sublimation and exhibited m.p. 51–51.5°; i.r. (CS_2), λ_{max} 5.72, 5.98 μ; n.m.r., τ 4.72 (triplet, 1H, vinyl H, J = 3.5 Hz), 8.97 (singlet, 3H, tertiary methyl), 9.04 (doublet, 3H, secondary methyl, J = 6.0 Hz).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.60; H, 8.93.

An analytical sample of the minor epimer **17**, an oil, was obtained from the mother liquors of the above recrystallization by means of preparative g.l.c. (column E, 225°, 200) and exhibited n_D^{20} 1.4910; i.r. (film) λ_{max} 5.71, 5.98 μ; n.m.r., τ 4.68 (triplet, 1H, vinyl H, J = 4.0 Hz), 8.79 (singlet, 3H, tertiary methyl), 9.04 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Mol. Wt. Calcd. for $C_{11}H_{16}O_2$: 180.115. Found (high resolution mass spectrometry): 180.113.

*Preparation of Octalone **10***

A solution of the crystalline enol lactone **16** (19.6 g, 0.11 mole) in 200 ml of dry ether was cooled to −25° by means of an external carbon tetrachloride–dry ice slush bath. An ethereal solution of methyllithium (75 ml, 2.35 M) was added over a period of 3 min, and the resulting solution was stirred at −25°, under an atmosphere of dry nitrogen, for 1.75 h. The reaction mixture was poured into dilute hydrochloric acid and the product was extracted with ether. To the crude, oily product thus obtained was added a solution of potassium hydroxide (16 g) in 120 ml of water and 1000 ml of methanol, and the solution was refluxed under an atmosphere of nitrogen for 2 h. The methanol was removed under reduced pressure, the residue was diluted with water, and the neutral product was isolated by extraction with ether. Distillation of the crude yellow oil thus obtained gave 13.5 g (70%) of the octalone **10**; b.p. 96–99° at 0.2 mm; n_D^{20} 1.5155; u.v., λ_{max} 240 mμ (ε = 12 100); i.r. (film), λ_{max} 5.98, 6.19 μ; n.m.r., τ 4.33 (broad singlet, 1H, vinyl H), 8.90 (singlet, 3H, tertiary methyl), 9.09 (unresolved multiplet,[6] 3H, secondary methyl).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.96; H, 10.29.

The basic aqueous layer from the above extraction was acidified with concentrated hydrochloric acid and the acidic product was isolated by extraction with ether. Distillation of the crude product provided 2.1 g (10%) of a carboxylic acid (**15**, *cis* epimer) which, upon treatment with sodium acetate in refluxing acetic anhydride, as described above, gave the enol lactone **16**.

*Preparation of Decalol **18***

To a solution of 6 g of lithium metal in 1500 ml of liquid ammonia was slowly added, from a dropping funnel, a solution of the octalone **10** (15 g, 0.084 mole) in 100 ml of anhydrous ether. After 1 h, 16 ml of anhydrous ethanol was added and the reaction mixture was allowed to stir for an additional 1.5 h. The reaction was then quenched by careful addition of excess ethanol, and the ammonia was allowed to evaporate. The residual

[5]For general information, see preceding paper (ref. 7).

[6]In the n.m.r. spectrum of each of the compounds **9**, **10**, **18**, **19**, and **20**, the signal due to the secondary methyl group appeared as a broad band, with very little resolution. Presumably, this was due to virtual coupling (see ref. 23).

material was diluted with saturated brine and the product was isolated by extraction of the mixture with ether. Distillation of the crude product afforded 11.5 g (75%) of the decalol **18**, b.p. 86–90° at 0.2 mm, as a clear, viscous oil which resisted crystallization. An analytical sample, collected by preparative g.l.c. (column F, 250°, 200), exhibited n_D^{20} 1.4944; i.r. (film), λ_{max} 3.01, 9.54 μ; n.m.r., τ 6.40 (broad signal, 1H, —C*H*OH), 9.24 (unresolved multiplet, 3H, secondary methyl), 9.29 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.03; H, 11.97.

Preparation of Decalone ***19***

Standard chromic acid solution (17) was added to a solution of the decalol **18** (8.7 g, 0.048 mole) in acetone (200 ml) at 0° until the orange color persisted. Isopropyl alcohol was added to destroy the excess oxidizing reagent, and the solution was evaporated under reduced pressure. The residual material was diluted with water and the product was extracted with ether. Distillation of the crude oil gave 7 g (81%) of the decalone **19**; b.p. 83–86° at 1.0 mm; n_D^{20} 1.4943; i.r. (film), λ_{max} 5.84 μ; n.m.r., τ 9.08 (singlet, 3H, tertiary methyl), 9.13 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.21; H, 11.24.

This compound exhibited i.r. spectrum and gas–liquid chromatographic retention time (column G, 245°, 190) identical with those of the (+)-antipode of **19**, which had been previously prepared by Djerassi and co-workers (18).

Preparation of the Bromo Ketone ***20***

A solution of bromine (4.7 g, 29.5 mmoles) in glacial acetic acid (40 ml) was added slowly, at room temperature, to a stirred glacial acetic acid (40 ml) solution of the decalone **19** (5.3 g, 29.5 mmoles). After the addition was complete, the solution was stirred for an additional 30 min and then poured into ice-cold water. The resultant mixture was extracted with ether. The combined ether extracts were washed twice with water, then with saturated aqueous sodium bicarbonate until free of acid, and finally with saturated brine. Recrystallization of the crude crystalline product from ether afforded 5.6 g (72%) of the bromo ketone **20**. An analytical sample was obtained by vacuum sublimation and exhibited m.p. 132–133° [lit. m.p. 132–133° (4)]; i.r. ($CHCl_3$), λ_{max} 5.80 μ; n.m.r., τ 5.22 (pair of doublets, 1H, —CHBr, J = 6.5 Hz and 13.5 Hz), 8.98 (singlet, 3H, tertiary methyl), 9.10 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for $C_{12}H_{19}OBr$: C, 55.61; H, 7.37; Br, 30.83. Found: C, 55.68; H, 7.48; Br, 31.02.

Preparation of Octalone ***9***

A stirred suspension of lithium bromide (0.3 g) and lithium carbonate (0.4 g) in 6 ml of dry dimethylformamide was heated to 120°, under an atmosphere of nitrogen. The bromo ketone **20** (0.57 g, 2.2 mmoles) was added and the reaction mixture was stirred at 120° for 75 min. The suspension was cooled and filtered. The filtrate was diluted with water and the product was isolated with *n*-heptane. Distillation of the crude oil gave 0.34 g (86%) of a clear, colorless oil, b.p. 100° (bath temperature) at 0.4 mm. Analysis of this material by g.l.c. (column F, 250°, 240) showed that it was a mixture consisting of approximately 80% of the desired octalone **9**, 5% of the isomeric octalone **10** (on the basis of g.l.c. retention time only), and some minor unidentified components. The desired compound **9** was isolated by preparative g.l.c. (column F, 250°, 240) and exhibited n_D^{20} 1.5122; u.v., λ_{max} 230 mμ (ε ≈ 9400); i.r. (film), λ_{max} 5.97, 6.15 μ; n.m.r., τ 2.88 (doublet, 1H, β-vinyl H, J = 10 Hz), 4.11 (doublet, 1H, α-vinyl H, J = 10 Hz), 9.03 (unresolved multiplet, 3H, secondary methyl), 9.07 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.83; H, 10.16.

Preparation of Decalone ***21***

To a stirred solution of isopropenylmagnesium bromide (0.29 g, 2 mmoles) in 2 ml of dry tetrahydrofuran was added approximately 6 mg of anhydrous cuprous chloride and the resulting mixture was cooled to 0°. A solution of the octalone **9** (0.1 g, 0.56 mmoles) in tetrahydrofuran (4 ml) was added by means of a syringe, and the reaction mixture was stirred, under an atmosphere of nitrogen, at 0° for 15 min and then refluxed for 1 h. The cooled reaction mixture was poured slowly into rapidly stirred, ice-cold dilute hydrochloric acid, and the product was isolated by extraction with ether. Distillation of the crude product gave 110 mg (89%) of a clear oil, b.p. 100° (bath temperature) at 0.4 mm. Gas–liquid chromatographic analysis (column G, 245°, 190) of this material showed that it contained, in addition to a number of minor components, approximately 80–85% of the desired decalone **21**. The latter was isolated by preparative g.l.c. (column G, 245°, 190) and showed n_D^{20} 1.5147; i.r. (film), λ_{max} 5.87, 6.15, 11.22 μ; n.m.r., τ 5.10, 5.36 (unresolved multiplets, 2H, $=CH_2$, width at half-height ≃ 4.5 and 3.5 Hz, respectively), 8.24 (unresolved multiplet, 3H, vinyl methyl, width at half-height ≃ 3 Hz), 9.00 (singlet, 3H, tertiary methyl), 9.12 (poorly resolved doublet, 3H, secondary methyl).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.99; H, 11.08.

Preparation of Decalone ***22a***

Hydrogenation of the decalone **21** was carried out in ethanol, at atmospheric pressure and room temperature, over Adams catalyst. From 50 mg of **21** there was obtained a quantitative yield of decalone ***22a*** as a crystalline solid. Recrystallization from *n*-hexane afforded an analytical sample; m.p. 49–51°; i.r. (CS_2), λ_{max} 5.87 μ; n.m.r., τ 9.02 (singlet, 3H, tertiary methyl), 9.06, 9.17 (doublets, 3H and 6H, respectively, secondary methyls, J = 6.8 Hz).

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.198.

*(+)-9,10-Dihydroaristolone (****23****)*

Small pieces of freshly cut lithium metal (210 mg) were added to 150 ml of liquid ammonia which had been distilled from sodium metal. The resulting solution was stirred for 30 min. A solution of (−)-aristolone (**1**) (300 mg) in 25 ml of dry ether was added and the reaction mixture was stirred for 45 min. After the reaction had been quenched by careful addition of excess dry ammonium chloride, the ammonia was allowed to evaporate under a stream of nitrogen. The residual material was

diluted with saturated brine and the product was isolated by extraction with ether. Distillation of the crude product gave 275 mg (92%) of (+)-9,10-dihydroaristolone (**23**) as a clear colorless oil; b.p. 100° (bath temperature) at 0.1 mm; $[\alpha]_D^{24}$ + 7° (*c*, 0.76 in methanol); u.v., λ_{max} 213 mμ (ε = 4300); i.r. (film), λ_{max} 5.98 μ; n.m.r., τ 8.36 (doublet, 1H, —C^7H, *J* = 8 Hz), 8.70 (doublet, 1H, —C^6H, *J* = 8 Hz), 8.59, 8.83, 9.08 (singlet, 9H, tertiary methyls), 8.99 (doublet, 3H, secondary methyl, *J* = 6 Hz).

Mol. Wt. Calcd. for $C_{15}H_{24}O$: 220.183. Found (high resolution mass spectrometry): 220.182.

Preparation of (−)-Decalone 22b

The lithium–ammonia reduction of (+)-9,10-dihydroaristolone (**23**) was carried out by a procedure identical with that described above for the reduction of (−)-aristolone. From 120 mg of **23**, there was obtained 110 mg (91%) of the crystalline (−)-decalone **22***b*. Recrystallization from *n*-hexane provided an analytical sample; m.p. 80–82°; $[\alpha]_D^{24}$ −30° (*c*, 0.59 in methanol). This material gave spectra (i.r., n.m.r.) and gas–liquid chromatographic retention times (column H, 210°, 90; column I, 260°, 200) identical with those of the racemic decalone **22***a*, prepared as described previously.

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.197.

Acknowledgments

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