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TOTAL SYNTHESIS OF COPACAMPHENE

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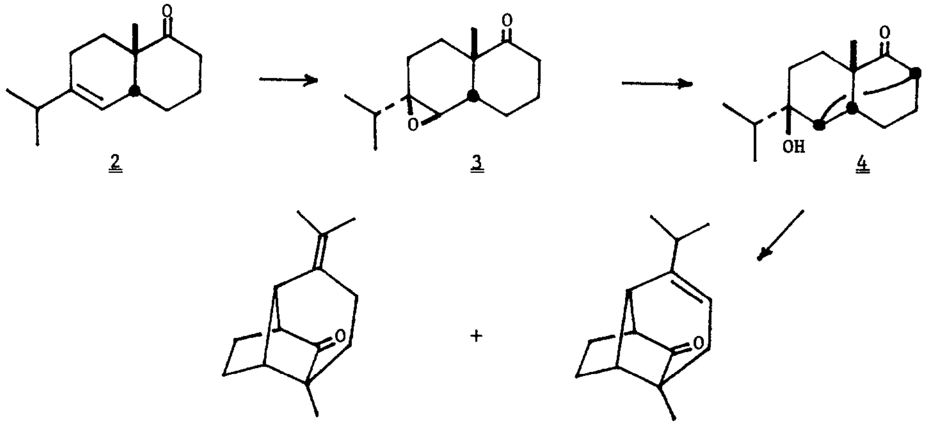
In connection with the isomerization study described in the accompanying communication, we needed to obtain a sample of copacamphene, 1. This sesquiterpene, although not yet found to be naturally occuring[2] has been prepared by rearrangement of copaborneol, but its structure proof was not definitive[3]. We therefore undertook a total synthesis of this material, both to obtain a sample and to verify the proposed structure.

Our starting material was the keto-olefin 2 described previously as an intermediate in our synthesis of sativene[4]. When 2 was treated with 1 equiv. *m*-chloroperbenzoic acid in chloroform, the oily epoxide 3 [ir, (film) 1710, 1240, 755 cm^{-1}; nmr (CCl_4), τ 7.50 (s, 1 H), 8.90 (s, 3 H), 8.98 and 9.02 (two doublets, J = J' = 6 Hz, total 6 H)] was formed in 95% yield. On treatment with either dimsyl sodium in DMSO for 2 days at 65° or with refluxing KO*t*Bu/ *t*BuOH for 7 days, 3 underwent intramolecular epoxide opening in 95% yield to generate the tricyclic tertiary alcohol 4 [ir (film), 3500, 1750 cm^{-1}; nmr (CCl_4), τ 7.68 (s, 1 H, bridgehead C-H next to the carbonyl), 9.05 (s, 3 H), 9.11 (d, J = 7 Hz, 6 H); mass spectrum, (80 ev), m/e (relative intensity), 222 (3, M^+), 204 (3), 179 (100), 161 (25).] This alcohol was dehydrated in quantitative yield to a 31:69 mixture of the two olefins 5 [nmr (CCl_4) τ 8.32 and 8.40 (two broad singlets, 6 H), 9.01 (s, 3 H)] and 6 [ir (film) 1750 cm^{-1}; nmr (CCl_4), τ 4.88 (t, J = 3 Hz, 1 H), 7.40 (broad singlet, 1 H), 8.98 (s, 3 H), 9.02 (d, J = 7 Hz, 6 H); mass spectrum (80 ev) m/e 204 (M^+)] by brief treatment in hexane with

50% aqueous sulfuric acid.

Although it is not essential for synthetic purposes, the two olefins could be readily separated by column chromatography on alumina or by preparative vpc. We chose to carry out our further work on the major isomer 6 rather than deal with a mixture. After separation, 5 could of course be re-equilibrated with 6 thus making it possible to obtain 6 in high overall yield.

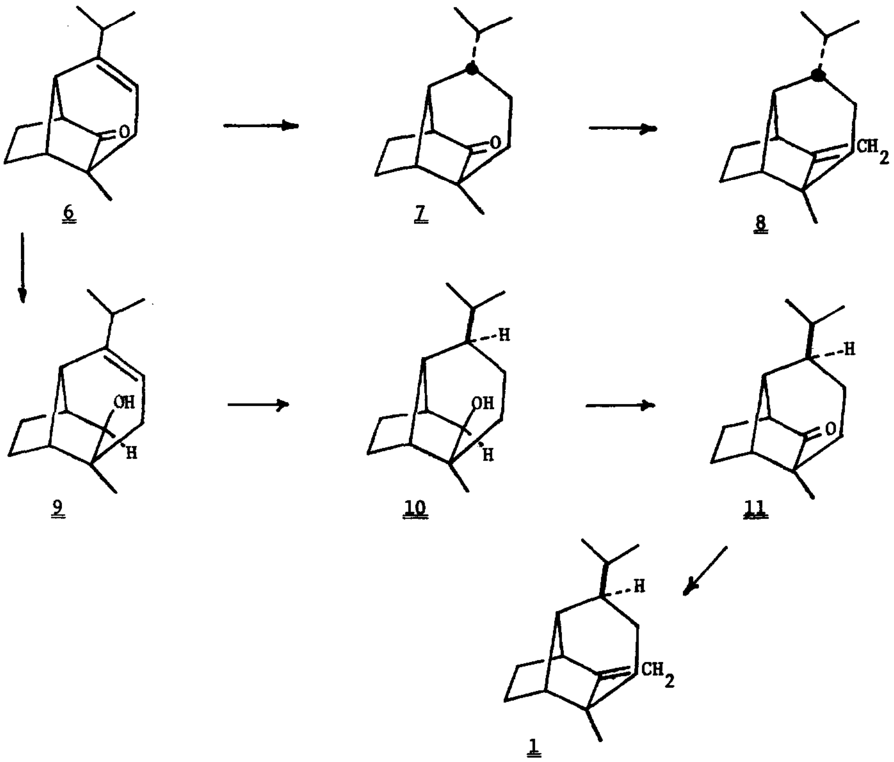


2 3 4

5 + 6

Hydrogenation of 6 over Adam's catalyst in acetic acid gave a single saturated compound which was pure by spectral and vpc criteria, and which had ir and nmr identical[4] to authentic 7. Treatment of 7 with methyllithium followed by dehydration of the resultant alcohol with thionyl chloride in pyridine gave pure (±)sativene, 8, (82% overall from 2) identical with an authentic sample[4] by ir, nmr, vpc, and mass spectral comparison.

From an insepction of models, it is evident that 7 is formed by delivery of hydrogen to 6 from the less hindered side, but we had been hopeful that a mixture would be formed and were dismayed at the (wrong) stereospecificity of the reaction. We therefore sought a means of delivering hydrogen from the more hindered side of the double bond. Reduction of 6 with $LiAlH_4$ in ether gave an oily alcohol [ir (film) 3500 cm^{-1}] which, assuming reduction from the less hindered side, should have structure 9. The hydroxyl in 9 is in close proximity to the double bond, and we thought that if the hydrogenation were carried out in a non-polar solvent the catalyst might bond to the hydroxyl and deliver hydrogen to the double bond from the more hindered side[5]. Reduction of 9 in hexane solution at atmospheric pressure over a palladium on charcoal catalyst proceeded slowly but reached completion after 5 days. Collins oxidation[6] of the product gave a mixture of saturated ketones which could not be separated by vpc. Treatment of the mixture with methyllithium followed by dehydration with thionyl chloride in pyridine gave a product mixture which, although again homogeneous on a variety of vpc columns, was found by nmr to be a 55:45 mixture of copacamphene and sativene.



It did prove possible however to separate the copacamphene/sativene product mixture by careful column chromatography on silver nitrate impregnated silica gel. The (±)copacamphene thus obtained [ir (CCl_4) 3090, 1655, 872 cm^{-1}; nmr (CCl_4) τ 5.21 and 5.50 (two singlets, 2 H), 7.55 (broad singlet, 1 H), 9.00 (s, 3 H), 9.10 (d, J = 6 Hz, 6 H); mass spectrum (80 ev), m/e (relative intensity, 204 (19 M^+), 189 (21), 161 (78), 108 (100)] was identical to the natural material[7] by spectral (ir, nmr, and m.s.) and vpc comparison, thus confirming the proposed structure.

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References

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7. We thank Dr. Westfelt for providing us with a generous sample of copaborneol, the precursor to copacamphene.