The Mechanism of the Acid-catalysed Cyclization of Labdadienols

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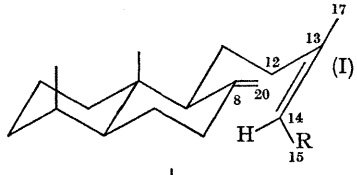
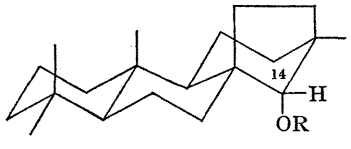
Summary The mechanism of the formic acid-catalysed cyclization of the allylic isomer (Ia) of manool to 14α-hibol formate is determined using deuterium labelling.

WE have shown that the bicyclic alcohol (Ia) is cyclized in formic acid *via* a cyclo-octenyl route to 14α-hibol formate (IIa). Thus, in agreement with previous reports,[1–4] treatment of manool with formic acid for 1 hr. gave, after chromatography (SiO_2–$AgNO_3$), a mixture of olefins (77%) and formates (19%). The olefin fraction consisted principally (g.l.c.) of isopimaradiene (1·4% from manool), Δ^8-pimaradiene (19%), and Δ^8-sandracopimaradiene (25% (as well as at least four other tricyclic dienes as yet unidentified. The formate fraction consisted of the allylic ester (Ib) (11%) and 14α-hibol formate (IIa) (8%). The latter compound was identified by basic hydrolysis to the known[3,4] 14α-hibol (IIb), m.p. 114—115°, and by its n.m.r., i.r., and mass spectra.

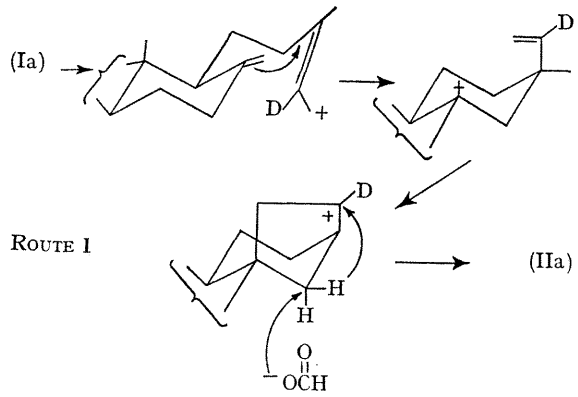


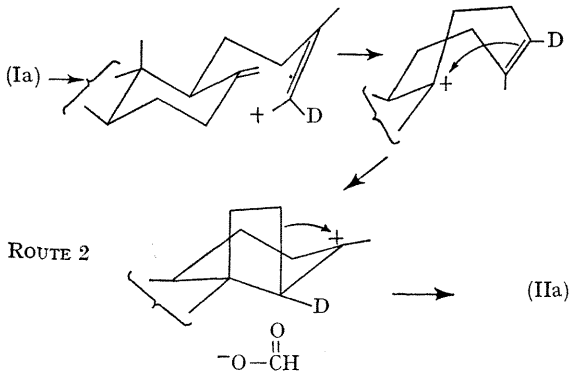
(I) a; R=CH_2OH
b; R=CH_2OCHO
c; R=CHO
d; R=CO_2Me



(II) a; R=CHO
b; R=H

Reduction of the allylic ester (Ib) with $LiAlH_4$ and subsequent oxidation with chromic anhydride and pyridine gave (84%) the aldehyde (Ic). Oxidation of (Ic) according to the method of Corey[5] with NaCN, HOAc, and active MnO_2 in methanol yielded (79%) *enantio*-methyl copalate[6]





(Id). Beas-catalysed deuterium exchange, followed by $LiAlH_4$ reduction afforded (57%) the allylic alcohol (Ia)

deuteriated at C-12, C-17, and C-14. The extent of deuteriation at C-14 in (Ia) was easily ascertained to be 50% by n.m.r. comparison of the intensity of the pair of signals (δ 4·47, 4·80) due to the C-20 hydrogens with the triplet (δ 5·26) due to that attached to C-14.

The deuteriated alcohol (Ia) was treated with formic acid and, after chromatography, 14α-hibol formate (IIa) was isolated in low yield. Careful integration of the n.m.r. signal due to the formate hydrogen (δ 9·20) and comparison with that due to the 14β-hydrogen (δ 4·44) in this 14α-hibol formate revealed that within experimental error (±3%) all of the deuterium originally at C-14 in (Ia) was located at C-14 in (IIa). Furthermore, mass spectral analysis of the deuteriated (Ia) and the 14α-hibol formate (IIa) produced from it indicated that the deuterium at C-12 and C-17 in the former were not lost in the reaction.

The final stages of the biogenesis of the tetracarbocyclic diterpenes related to the gibberellins have recently been shown[7] to proceed *in vivo via* a labdadienol→pimaradiene→hibaene route (Route 1).

Two mechanisms (Routes 1 and 2) have been suggested[1,3,4] for the *in vitro* conversion of (Ia) into (IIa). The complete transfer of the C-14 deuterium in (Ia) to the 14β-position in (IIa) not only rules out Route 1 for this transformation,[4] but firmly establishes the cyclo-octenyl pathway (Route 2) as the mode of reaction.

The complete transfer of all deuterium atoms in the starting alcohol (Ia) to (IIa) is noteworthy in that it eliminates biformene or sclarene intermediates in this transformation. These bicyclic trienes are major products of the acetic acid-catalysed reaction of manool or (Ia).

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† The allylic cation generated from the *trans*-alcohol (Ia) is undoubtedly capable of *cis–trans*-isomerization under the reaction conditions. This *cis*-form is required for this transformation.

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