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ALTERNATIVE TOTAL SYNTHESIS OF (±)-β-SANTALENE, (±)-EPI-β-SANTALENE, (±)-α-SANTALENE, (±)-COPACAMPHOR AND (±)-YLANGOCAMPHOR

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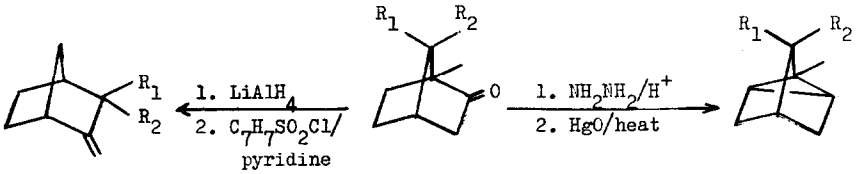
As indicated in a previous communication[1] we have been investigating the possibility of using campherenone (1) as a key intermediate in a general synthetic approach to a group of structurally-related polycyclic sesquiterpenes. The latter compounds can be divided into several groups whose members are sesquiterpene analogs of camphor, borneol, camphene and tricyclene and we considered that the key to the synthesis of each group of compounds involved the formation of the "parent" ketones: campherenone (1), epicampherenone (2), copacamphor (3), ylangocamphor (4) and longicamphor (5). The conversion of these compounds to others of the same group would involve known reactions or reactions for which there is ample analogy. A further synthetic generalisation was considered, namely, that campherenone (1) could serve as the synthetic precursor of the tricyclic ketones (3)-(5). Thus we were attracted by the promise of a general synthetic scheme[2] whose essential feature was a sequential synthetic relationship between appropriate monocyclic, bicyclic and tricyclic ketones.

Campherenone (1) occupies a key position in the general scheme and our recent total synthesis[1] of this compound and epicampherenone (2) from an appropriate monocyclic ketone has enabled us to study the validity of these synthetic proposals. Reduction of (±)-campherenone (1) with lithium aluminium hydride yielded (±)-isocampherenol,[1,3] which, on heating with pyridine and p-toluenesulfonyl chloride, provided (±)-β-santalene (6)[4] in 80% overall yield.[3] The same sequence of reactions starting with (±)-epicampherenone (2)[1] proceeded smoothly to yield (±)-epi-β-santalene (7)[4]. The synthesis of (±)-α-santalene (8)[4] was accomplished in 65% overall yield when a methanolic solution of hydrazones from (1) and (2) was heated with mercuric oxide.[10] The synthetic samples of α-, β- and epi-β-santalene exhibited the same spectral and g.l.c. characteristics as authentic specimens of these compounds isolated from sandalwood oil.[11]

Our attention was then directed towards the construction of the tricyclic systems represented by copacamphor (3), ylangocamphor (4) and longicamphor (5). Treatment of



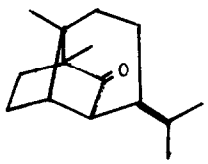
6; $R_1 = CH_2CH_2CH=C(CH_3)_2$, $R_2 = CH_3$

7; $R_1 = CH_3$, $R_2 = CH_2CH_2CH=C(CH_3)_2$

1; $R_1 = CH_3$, $R_2 = CH_2CH_2CH=C(CH_3)_2$

2; $R_1 = CH_2CH_2CH=C(CH_3)_2$, $R_2 = CH_3$

8; $R_1 = CH_3$, $R_2 = CH_2CH_2CH=C(CH_3)_2$



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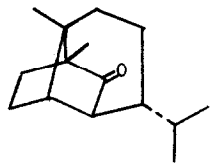

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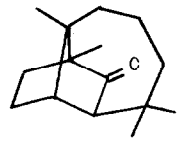

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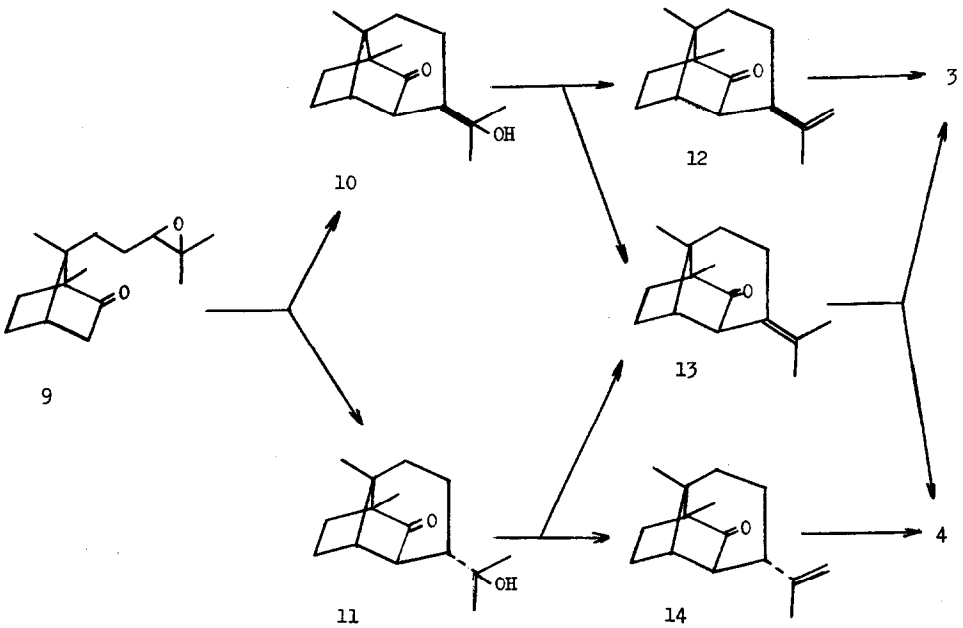

(±)-campherenone (1) with n-butyllithium followed by acetic anhydride[12] provided the corresponding enol acetate in 85% yield but unfortunately our attempts to cyclise this compound under a variety of conditions have failed to produce a reasonable yield of tricyclic material. In an alternative approach to the tricyclic systems, campherenone (1) was treated with m-chloroperbenzoic acid in benzene and converted to the corresponding epoxide (9). Subsequent cyclisation of (9) with potassium t-butoxide in refluxing t-butanol provided a good yield (> 80%) of tricyclic alcohols (10) and (11) which were separated by preparative g.l.c. Dehydration of (10) with thionyl chloride/pyridine yielded a mixture (7:3) of tricyclic alkenes (12) and (13) which were separated by preparative g.l.c. Catalytic reduction (Pt/H_2) of (12) yielded (±)-copacamphor (3) while reduction of (13) gave a mixture (5:1) of ylangocamphor (4) and copacamphor (3). In the isomeric series an identical sequence of reactions yielded the terminal alkene (14) which was subsequently reduced (Pt/H_2) to (±)-ylangocamphor (4). The g.l.c. and spectral characteristics of our synthetic copacamphor (3) were identical to those of authentic copacamphor[13,14] while the spectral characteristics of synthetic ylangocamphor (4) were identical to those of ylangocamphor prepared by an alternative synthetic route.[14]

The results outlined above demonstrate that key transformations in our general synthetic scheme can be accomplished in a simple and efficient manner and remaining aspects of our general proposals are being investigated.

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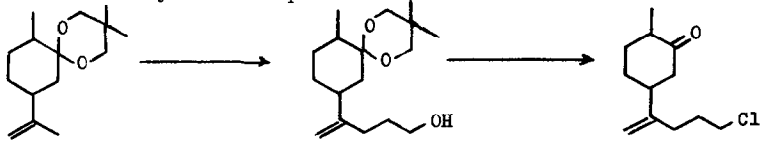

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2. This scheme reflects the framework of biogenetic proposals (devoid of absolute configurational considerations) which were presented at the C.I.C.-A.C.S. Conference in Toronto, May, 1970; cf. also T. Money, "Biogenetic-Type Synthesis of Terpenes", Progress in Organic Chemistry, Vol. 8, in press.

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