Biogenetic-Type Synthesis of (±)-Camphor

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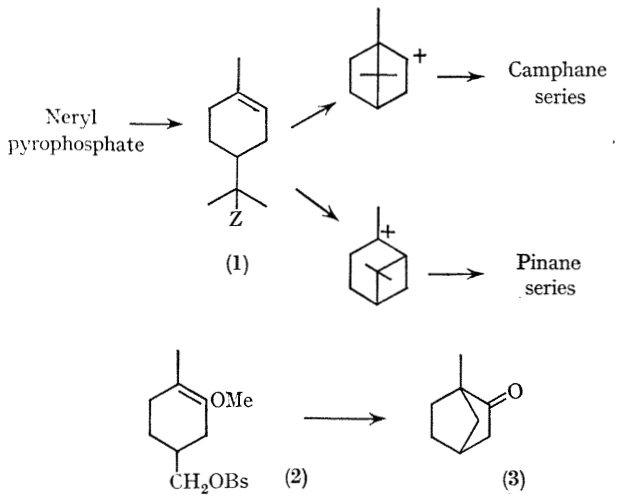
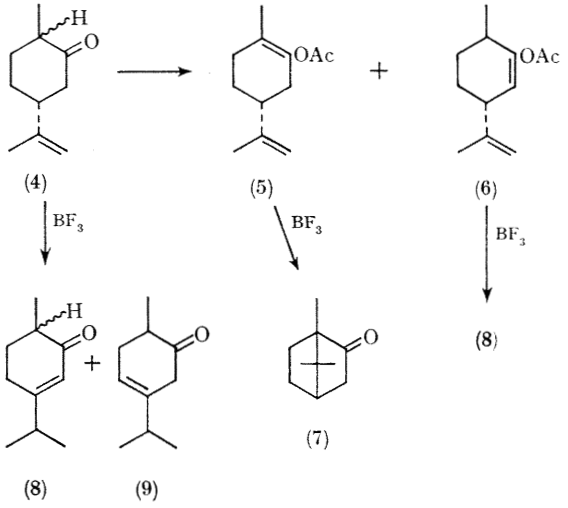
Summary A new route to bicyclo[2,2,1]heptane systems is illustrated by a two-step synthesis of (±)-camphor from dihydrocarvone.

RECENT studies[1,2] have provided fresh insight into the problems presented by the biosynthesis of bicyclic monoterpenes[3] but no evidence has been presented which demonstrates that monocyclic compounds *e.g.* (1; Z = cation or its enzymic or non-enzymic functional equivalent) are intermediates in this process. In addition various laboratory attempts to form bicyclo[2,2,1]- or [3,1,1]- heptane derivatives by solvolysis of Δ^3-cyclohexenyl carbinyl systems *e.g.* (1; Z = Cl, OH, *p*-nitrobenzoate, or phosphate) have failed.[4] A recent report, however, has shown that solvolytic cyclisation of the primary *p*-bromobenzenesulphonate (2) to bicyclic ketone (3) can be accomplished in 12% yield.[5]



We have recently been concerned with attempts to provide chemical analogy for the conversion of monocyclic into bicyclic monoterpenes and this report describes one approach to problems associated with the biogenetic-type synthesis of compounds of the camphane series. Suitably reactive enol derivatives (*e.g.*, ethers or esters) of the natural monoterpene dihydrocarvone (4) seemed to offer a potentially useful solution to these problems and some of our results are illustrated by the following sequence of reactions. Dihydrocarvone (4),[6] $[\alpha]_D^{24}$ + 12°, was treated with isopropenyl acetate in the presence of toluene-*p*-sulphonic acid and converted into a mixture of enol acetates (5) and (6) [relative yield, 4 : 1]. Separation and purification of the enol acetates by g.l.c. gave (5): $[\alpha]_D^{24}$ + 77°; τ(CCl_4) 5·27 (2H, s), 7·95 (3H, s), 8·26 (3H, s), and 8·51 (3H, s); ν_{max} 1750, 1215, and 890 cm.$^{-1}$; and (6) [τ (CCl_4) 4·83 (1H, s), 5·21 (2H, s), 7·93 (3H, s), 8·26 (3H, s), and 9·02 (3H, d, *J* 6·5 Hz.); ν_{max} 1750, 1215, and 893 cm.$^{-1}$] as colourless oils.

Treatment of (5) with boron trifluoride[7] in methylene chloride at room temperature for 10 min. gave a product which was shown by g.l.c. to be mainly one compound. Purification by preparative g.l.c. or sublimation afforded a white solid which was shown to be (±)-camphor (7): $[\alpha]_D$ 0°; retention time and i.r., n.m.r. (carbon tetrachloride and benzene[8]), and mass spectroscopic properties identical with those of authentic (±)-camphor. The yield, as estimated by g.l.c., was 90% and this was repeatedly obtained when the concentration of enol acetate (5) was 0·1% and the solvent was pre-saturated with boron trifluoride. Higher concentrations of (5) and other variations in reaction conditions resulted in lower yields of camphor and a corresponding increase in the yield of carvenone (8) [λ_{max} 234 nm. (ϵ 13,200) in MeOH; ν_{max} 1670 and 880 cm.$^{-1}$; τ (CCl_4) 4·27 (1H, s), 8·89 (6H, d, *J* 6·5 Hz.), and 8·95 (3H, d, 6·5 Hz.)]. Similar treatment of enol acetate (6) yielded carvenone (8) as the major product. In the



description provided above we have assumed that prior formation of the enol acetate (5) was essential for successful cyclisation. To provide some support for this, dihydrocarvone (4) was treated with boron trifluoride under conditions identical with those described above. The major reaction product, isolated by preparative g.l.c., was shown to be (+)-carvenone (8) ($[\alpha]_D^{24}$ + 67°) and a minor product was tentatively assigned structure (9) [ν_{max} 1710 cm.$^{-1}$; τ (CCl_4) 4·46 (1H, s), 7·26 (2H, s), and 8·96 (9H, d, *J* 6·5 Hz.); τ (benzene) 7·38 (2H, s), 9·01 (3H, d, *J* 5·0 Hz.), 9·18 (6H, *d*, *J* 5·0 Hz.].

The racemic nature of our synthetic product was unexpected since the enol acetate (5) was optically pure and (+)-camphor does not racemise under these conditions. One possible explanation is that prior migration of the disubstituted double bond in (5) to the tetrasubstituted position occurs. This would allow formation of enantiomeric boron trifluoride complexes and explain the formation of (±)-camphor. Other explanations are possible and we are currently investigating this aspect of the cyclisation reaction together with its application to the synthesis of

other bicyclic systems. The simple high-yield conversion of dihydrocarvone into camphor prompts us to suggest that a similar reaction (*e.g.*, *via* enol phosphate derivative) could occur in the natural system.

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[3] (a) L. Ruzicka, *Experientia*, 1953, **9**, 357; (b) alternative explanations for the biosynthesis of bicyclic monoterpenes are available. α- or β-pinene and derivatives could be formed directly by concerted cyclisation of neryl pyrophosphate. In addition there is ample chemical analogy for the postulate that pinene derivatives are precursors of the [2,2,1]-bicyclic monoterpenes. A monocyclic intermediate would seem necessary, however, to explain the formation of [4,1,0]-bicyclic monoterpenes.

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