Cyclisations involving Enol Acetates: Synthesis of (±)-Campherenone, (±)-Campherenol, and (±)-Epicampherenone

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Summary Preliminary investigations of a general synthetic route to a group of bicyclic, tricyclic, and tetracyclic sesquiterpenes have been made and the total synthesis of key intermediates (campherenone, epicampherenone, and the corresponding alcohols) is described.

A RECENT report from this laboratory described a new and potentially general route to [2,2,1]bicyclic ketones and this was illustrated by a simple and efficient synthesis of camphor.[1] The facility of this route to bicyclic ketones of the camphor type (and, by extension, to compounds corresponding to borneol, camphene, and tricyclene) prompted us to investigate the application of our synthetic process to sesquiterpene analogues. Our particular objective was to develop a general synthetic route† to a group of bicyclic, tricyclic, and tetracyclic sesquiterpenes using enol acetate intermediates and involving sequences which could be important in Nature. The key to the general synthetic scheme was the synthesis of campherenone (10)[2] and this report describes the first total synthesis of this compound and its C-7 epimer (11). In our initial studies the keto-diene (1) was synthesised and converted into the tetra-substituted enol acetate (2). Treatment of (2) with boron trifluoride in wet methylene chloride solution afforded a mixture of bicyclic and tricyclic ketones whose structures are still under investigation.‡ It was readily demonstrated, however, that campherenone (10) or its epimer (11) were not products of this reaction and that selective monocyclisation had not been achieved.

A variation in our general approach was therefore devised and a variety of enol acetates were synthesised and subjected to cyclisation conditions (BF_3/CH_2Cl_2). As a result of these studies the chloro-ketone (6) was shown to be convenient for our purpose and was synthesised as described below. Condensation of keto-acetal (4), derived from dihydrocarvone (3), with the Wittig reagent from 3-iodo-1-propyl tetrahydropyranyl ether yielded (5; R = C_5H_9O). Treatment of (5; R = C_5H_9O) in benzene with

† An outline of the general synthetic route and related biogenetic proposals was given at the C.I.C.–A.C.S. Conference in Toronto, May, 1970.

‡ A detailed account of the synthesis of (1) and the structure of the cyclisation products derived from (2) will be given in a later paper.

TABLE 1. *N.m.r. signals of bicyclic ketones*[a]

		C-8	C-9	C-10	C-12	C-14, C-15
Camphor	CCl_4	9·19	9·07	9·18	—	—
	C_6H_6	9·40	9·35	9·11	—	—
Campherenone	CCl_4	—	9·03(9·04)	9·14(9·15)	4·95(4·97)	8·35(8·36), 8·39(8·41)
	C_6H_6	—	9·30(9·33)	9·07(9·10)	4·97(5·02)	8·35(8·38), 8·48(8·51)
Epicampherenone	CCl_4	9·13	—	9·13	4·89	8·32, 8·38
	C_6H_6	9·35	—	9·06	4·83	8·28, 8·41

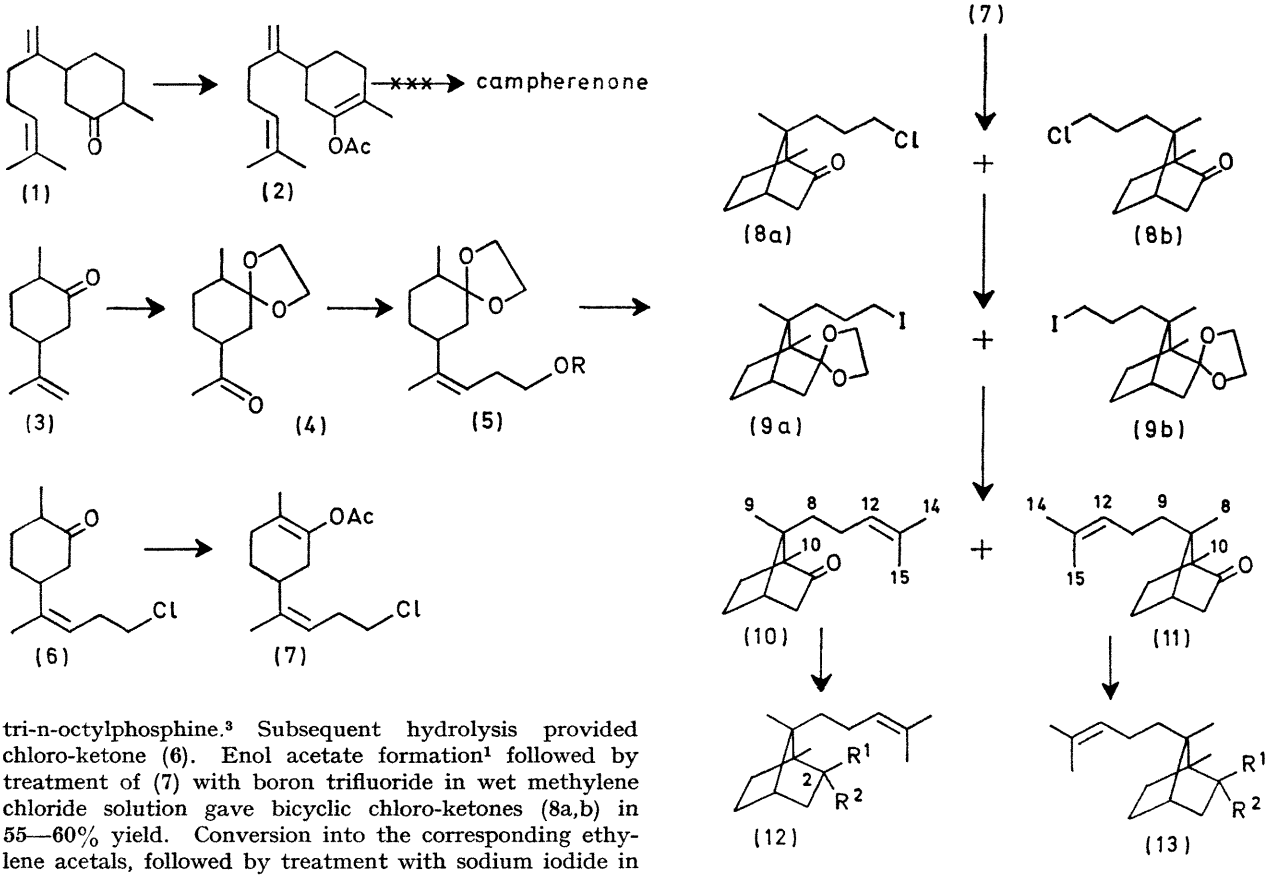
[a] Literature values[2] for campherenone are shown in parentheses.

TABLE 2. *N.m.r. signals of bicyclic alcohols* (CCl_4)[a]

		C-2	C-8	C-9	C-10	C-12	C-14, C-15
Borneol		6·08	9·14	9·14	9·17	—	—
Isoborneol		6·49	8·98	9·17	9·11	—	—
Campherenol	(12; R^1 = H, R^2 = OH)	6·00(6·03)	—	9·11	9·17	4·94	8·34, 8·41
Isocampherenol	(12; R^1 = OH, R^2 = H)	6·46(6·49)	—	9·18	9·12	4·92	8·36, 8·39
Epicampherenol	(13; R^1 = H, R^2 = OH)	6·06	9·13	—	9·18	4·92	8·33, 8·40
Isoepicamphereno	(13; R^1 = OH, R^2 = H)	6·47	8·96	—	9·12	4·93	8·33, 8·39

[a] Literature values[2] for campherenol and isocampherenol are shown in parentheses.

ethylene glycol and oxalic acid provided the hydroxy-acetal (5; R = H) which was converted into the corresponding chloride by reacting with carbon tetrachloride and tri-n-octylphosphine.[3] Subsequent hydrolysis provided chloro-ketone (6). Enol acetate formation[1] followed by treatment of (7) with boron trifluoride in wet methylene chloride solution gave bicyclic chloro-ketones (8a,b) in 55—60% yield. Conversion into the corresponding ethylene acetals, followed by treatment with sodium iodide in acetone yielded iodo-acetals (9a,b). The triphenylphosphonium salts derived from (9a) and (9b) reacted with acetone in the presence of dimsyl sodium to yield a mixture of campherenone and epicampherenone ethylene acetals which were separated by preparative g.l.c. Subsequent hydrolysis of the separated acetals provided (±)-campherenone (10) and (±)-epicampherenone (11) with spectral properties (i.r., n.m.r.) and elemental analysis in agreement with the assigned structures.§ A distinction between diastereoisomers (10) and (11) was made possible by consideration of their n.m.r. spectra in carbon tetrachloride and benzene[2,4] (Table 1).



§ We were unable to obtain an authentic sample of campherenone or campherenol.[2]

Further evidence for the structure of our synthetic product (10) was obtained when reduction with sodium/n-propanol[5] and with lithium aluminium hydride[2] yielded (±)-campherenol (12; $R^1 = H$, $R^2 = OH$)[2] and (±)-isocampherenol (12; $R^1 = OH$, $R^2 = H$),[2] respectively. In a similar fashion (±)-epicampherenone (11) was converted into the corresponding alcohols (13; $R^1 = H$, $R^2 = OH$) and (13; $R^1 = OH$, $R^2 = H$). N.m.r. data for (12), (13), borneol, and isoborneol are shown in Table 2. The synthesis of campherenone and campherenol, which co-occur[2] in *Cinnamomum camphora* Siebold (Lauraceae), provides independent confirmation for the structures assigned to these compounds and has enabled us to investigate other aspects of our general synthetic proposals.

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