Cyclization of the 1,3-Dimethyl-3-vinylcyclohexyl Carbonium Ion: a Model for Tetracyclic Diterpene Biosynthesis

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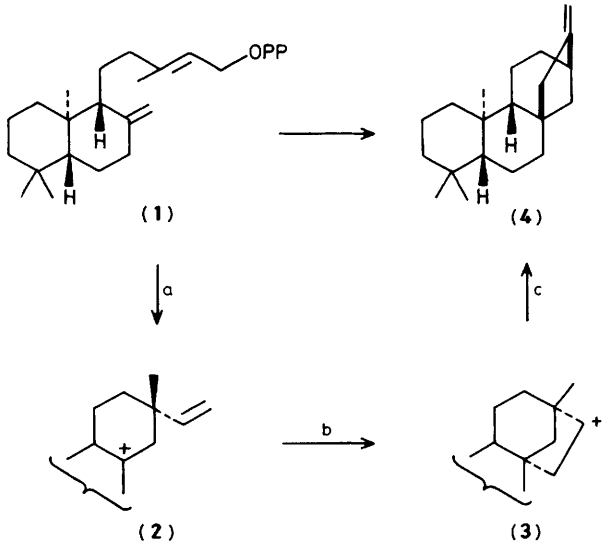
Extraction of 3-methyl-3-vinylmethylenecyclohexane (**5**) into fluorosulphonic acid–fluorosulphonyl chloride at 100 °C followed by quenching with water afforded 2,4-dimethylbicyclo[2.2.2]octan-2-ol (**6**); the initial vinyl group cyclization (**9**) → (**10**) mimics the pimarenyl → beyeranyl cyclization step (**2**)→(**3**) postulated in the biosynthesis of the beyerane–kaurane diterpenes.

The biosynthesis of the tetracyclic diterpenes of the beyerane–kaurane class [*e.g.* kaurene (**4**)] from copalyl pyrophosphate (**1**) is thought to occur *via* the Wenkert biogenetic scheme (Scheme 1) which consists of (a) S_N' cyclization to the pimarenyl carbonium ion (**2**), (b) vinyl group cyclization to the beyeranyl carbonium ion (**3**), and (c) Wagner–Meerwein rearrangement followed by proton elimination.[1,2] Although steps (a) and (c) have been shown to occur readily in acid-catalysed and/or solvolytic reactions,[3] attempts to achieve the pimarenyl → beyeranyl cyclization (b) with diterpene substrates have been uniformly unsuccessful.[3–7] Indeed, the failure of these model reactions has raised questions regarding the validity of this route to tetracyclic diterpenes.[4,5] We now report that a vinyl group cyclization analogous to step (b) in Scheme 1 can be achieved with a monocyclic model compound under super-acid conditions.

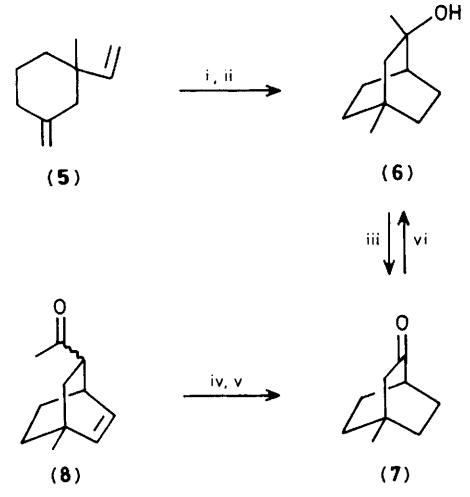
The monocyclic model substrate, 3-methyl-3-vinylmethylenecyclohexane (**5**),† was prepared in 54% yield by Wittig methylenation [$Ph_3P{=}CH_2$, dimethyl sulphoxide (DMSO)] of 3-vinyl-3-methylcyclohexanone.[8] Although treatment of (**5**) or either of the corresponding tertiary alcohols with various protic and Lewis acids failed to effect vinyl group cyclization, extraction of a dichloromethane solution of (**5**) with fluorosulphonic acid–fluorosulphonyl chloride at −100 °C for 2.5—5 min followed by rapid transfer into a suspension of frozen aqueous sodium carbonate in tetrahydrofuran (THF) at −78 °C provided tertiary alcohol (**6**) (7—14%): i.r. (CCl_4), 3607, 3484 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.74, 1.26 (2s, 2Me); ^{13}C n.m.r. ($CDCl_3$) δ 72.2 (C–OH); h.r.m.s., 154.1337 ($C_{10}H_{18}O$). Quenching of the super-acid solution with sodium methoxide in methanol at −78 °C afforded the corresponding methyl ether (5—10%) of (**6**) which exhibited similar spectral properties.

Dehydration of (**6**) with phosphorus oxychloride in pyridine gave a 52 : 48 mixture of two olefins (g.c. analysis), ozonolysis of which, in the presence of tetracyanoethylene (TCNE),[9] afforded the known[10] bicyclic ketone (**7**): i.r. (CCl_4) 1725 cm^{-1}. The structures of (**6**) and (**7**) were confirmed by independent synthesis. A 70:30 mixture of the isomeric unsaturated methyl ketones (**8**)[10a]‡ was converted into (**7**) by the four-step reaction sequence shown in Scheme 2 (29% overall yield). Reaction of (**7**) with methyl-lithium in ether gave tertiary alcohol (**6**). The identity of (**6**) and (**7**) from both sources was established by comparisons of i.r., ^1H n.m.r., and mass spectra as well as capillary g.c. retention times.

The bicyclo[2.2.2]octanyl carbonium ion precursor (**12**) to (**6**) and its methyl ether is evidently formed by the following steps (Scheme 3): protonation of the exocyclic methylene of (**5**), vinyl group cyclization, 4,6-hydride shift, and Wagner–Meerwein rearrangement. The 4,6-hydride shift that interconverts the 6- and 2-bicyclo[3.2.1]octanyl carbonium ions is to be expected since this rearrangement occurs readily in competition with nucleophilic capture by acetate ion under solvolysis conditions,[11] and in super-acid at low temperature.[12] Tertiary carbonium ion (**12**) is apparently more stable than the isomeric



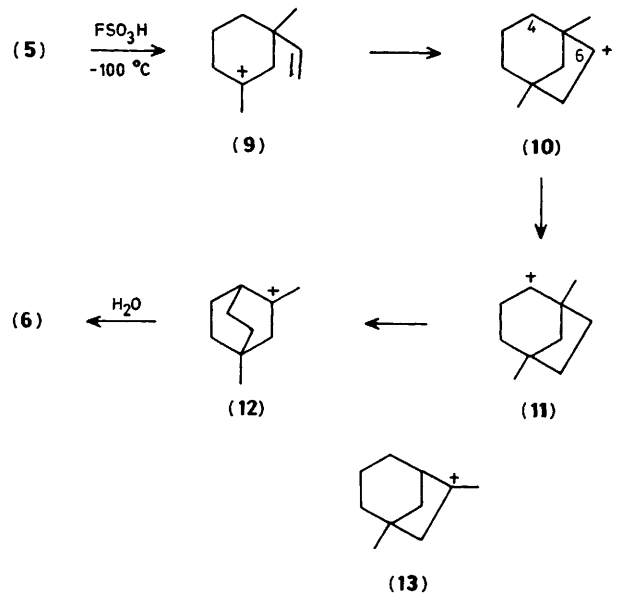
Scheme 1. Proposed mechanism for the enzymatic cyclization of copalyl pyrophosphate (**1**) to kaurene (**4**).



Scheme 2. *Reagents and conditions:* i, FSO_3H–FSO_2Cl, CH_2Cl_2, −100 °C, 2.5—5 min; ii, Na_2CO_3, H_2O, THF, −78 °C; iii, $POCl_3$, pyridine; O_3, TCNE, MeOAc, −78 °C; iv, H_2, Pd/C, MeOH; *m*-$ClC_6H_4CO_3H$, $CHCl_3$, reflux; v, $LiAlH_4$, ether; pyridinium chlorochromate, CH_2Cl_2; vi, MeLi, ether, 0 °C.

† Compounds (**5**)—(**7**) and the acetate intermediate in the conversion of (**8**) into (**7**) have been fully characterized by satisfactory i.r., ^1H n.m.r., and mass spectra. Elemental compositions were established by combustion analysis or high resolution mass spectroscopy (h.r.m.s.).

‡ We are grateful to Professor C. H. Heathcock, University of California–Berkeley, for a generous sample of ketones (**8**).



Scheme 3. Proposed mechanism for cyclization and rearrangement of diene (**5**) to 2,4-dimethylbicyclo[2.2.2]octan-2-ol (**6**).

1,6-dimethylbicyclo[3.2.1]octan-6-yl ion (**13**), with which (**12**) is presumably in equilibrium *via* Wagner–Meerwein rearrangement of (**10**). The lower thermodynamic stability of (**13**) is probably caused by angle strain around the trigonal carbon in the strongly puckered 5-membered ring. The greater thermodynamic stability of the 2-methylbicyclo[2.2.2]octan-2-yl carbonium ion over the related 2-methylbicyclo[3.2.1]-octan-2-yl ion in antimony pentafluoride–fluorosulphonyl chloride at −103 °C has been established.[13]

The vinyl group cyclization, (**9**) → (**10**), occurs readily at −100 °C despite the ostensibly unfavourable orbital overlap in the 5-*endo*-trig transition state[14] and the conversion of a tertiary into a secondary carbonium ion. With this precedent for the pimarenyl → beyeranyl cyclization, all steps of the Wenkert biogenetic pathway to the beyerane–kaurane family of diterpenes have been realized under appropriate chemical conditions in the absence of enzymatic control. It is noteworthy that the hydride shift and Wagner–Meerwein rearrangement sequence (**10**) → (**11**) → (**12**) parallels the biogenetic mechanism[3] for formation of atiserene,[15] a related diterpene having a bicyclo[2.2.2]octane structure for the C and D rings.

We thank the National Institutes of Health for a research grant which supported this work. The acquisition of g.c./m.s. analyses in the School of Chemical Sciences Mass Spectrometry Center was aided by a grant from the National Institutes of General Medical Sciences.

Received, 15th September 1986; Com. 1313

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