Synthesis of (−)-Shyobunone and its Epimers[1]

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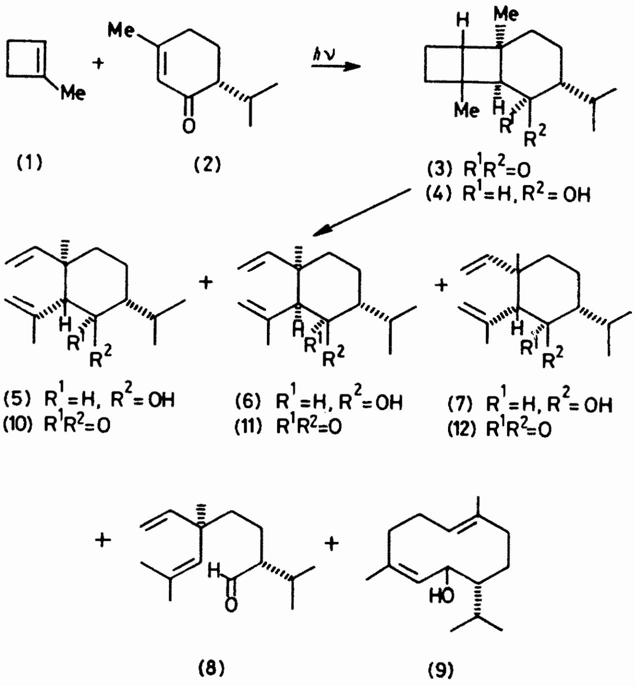
Summary (−)-Shyobunone (**10**) and its epimers were synthesized from methylcyclobutene (**1**) and L-piperitone (**2**) in *ca.* 24% overall yield *via* irradiation followed by thermolysis of the reduced intermediate photoadduct (**4**).

(+)-Shyobunone, whose structure is the mirror image of (**10**), was initially isolated from *Acorus calamus L.*[2] and belongs to the elemene class of sesquiterpenes.[3] It has been the topic of a number of recent syntheses.[4] We here report a concise synthesis of (−)-shyobunone (**10**) and its C-2 and C-3 epimers, (**11**) and (**12**), respectively.

It occurred to us[5] and to others[6] that photochemical cycloaddition of cyclobutenes to cyclohexenones, followed by thermolysis of these photoadducts affords a convenient method for the synthesis of the germacrene and *cis*-1,2-divinylcyclohexane ring systems. Therefore, by starting with an isoprene synthon, methylcyclobutene (**1**), and a commercially available chiral monoterpenoid, L-piperitone (**2**), $[\alpha]_D$ −6·9° [enantiomeric excess (e.e.) 14%],[7] shyobunone and its epimers could be synthesized as shown in the Scheme.



(1) (2)
(3) R^1R^2=O
(4) R^1=H, R^2=OH
(5) R^1=H, R^2=OH
(10) R^1R^2=O
(6) R^1=H, R^2=OH
(11) R^1R^2=O
(7) R^1=H, R^2=OH
(12) R^1R^2=O
(8) (9)

Scheme

Methylcyclobutene (**1**), which was obtained by the catalytic isomerization of methylenecyclobutane,[8] and L-piperitone (**2**) were irradiated at −78 °C† until all (**2**) had disappeared.‡ The photoadduct (**3**)§ was formed in 71% yield; i.r. (neat) 1688 cm^{-1}; n.m.r. ($CDCl_3$) δ 2·76 (s, 1H), 1·16 (s, 3H), 1·10 (s, 3H), 0·95 (d, 3H, *J* 7·6 Hz), and 0·80 (d, 3H, *J* 7·6 Hz). The photoadduct exhibited a positive Cotton effect, $[\theta]_{311}$ +5660, which supports the structure (**3**). Thermolysis of (**3**) yielded a substituted cadinene.[9] However, if the ketone group in (**3**) was first reduced, this intramolecular reaction was avoided.

Reduction of (**3**) ($NaBH_4$, MeOH) afforded the alcohol (**4**) in 71% isolated yield; m.p. 72—72·5 °C; i.r. (KBr) 3313 cm^{-1}; n.m.r. ($CDCl_3$) δ 3·71 (dd, 1H, *J* 8, 12 Hz), 2·77 (d, 1H, *J* 8 Hz), 1·38 (s, 3H), 1·01 (s, 3H), 0·97 (d, 3H, *J* 8 Hz), and 0·78 (d, 3H, *J* 8 Hz). Thermolysis of (**4**) in a sealed tube (250 °C; xylene) yielded three major structural isomers: a mixture of the elemene alcohols (**5**), (**6**), and (**7**) (relative

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† Quartz apparatus, 450 W Hanovia Lamp, −78 °C (dry ice–propan-2-ol).

‡ Monitored by ^1H n.m.r. spectroscopy on an R-32 Perkin-Elmer 90 MHz n.m.r. spectrometer.

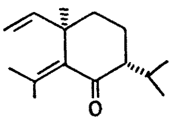
§ All new compounds have given satisfactory analytical and spectral data.

ratios 21:26:54, 48% yield); an aldehyde (**8**, 43%); and a germacrenol (with the probable structure (**9**, 6%). The relative stereochemistry of the elemene alcohols (**5**)—(**7**) was elucidated by their spectral data and by their conversion (Jones oxidation) into the known ketones (**10**)—(**12**).[2,4,10] A comparison of the Cotton effects exhibited in the c.d. spectra of the ketones with that exhibited in the o.r.d. of the naturally occurring compounds[10] established the absolute stereochemistry of the products as (−)-shyobunone (**10**), $[\alpha]_D$ −16° (e.e. 14%),[4] $[\theta]_{296\cdot 5}$ −1510; 2-*epi*-(−)-shyobunone (**11**), $[\theta]_{301\cdot 5}$ +3040; and 3-*epi*-(−)-shyobunone (**12**), $[\theta]_{297\cdot 5}$ −1830.

The aldehyde (**8**) was successfully converted into the alcohol (**5**) with $SnCl_4$,[11] thereby establishing the general structure of (**8**). This was confirmed by the following data: i.r. (neat) 1729 and 1630 cm^{-1}; n.m.r. ($CDCl_3$) δ 9·56 (d, 1H, *J* 2·4 Hz), 5·66—6·05 (m, 1H), 5·10 (br s, 1H), 4·8—5·1 (m, 2H), 1·68 (d, 3H, *J* 1 Hz), 1·60 (d, 3H, *J* 1 Hz), 1·13 (s, 3H) and 0·97 (d, 6H, *J* 7·6 Hz). The alcohol (**5**) was converted into (−)-shyobunone (**10**), $[\theta]_{296\cdot 5}$ −1429, to establish the absolute stereochemistry of the aldehyde as that of (**8**).

The intermediate photoadduct (**4**) probably is cleaved by a radical process[12] and may form the elemenes directly or, more probably, yields an intermediate germacrenol skeleton[5,6] which undergoes a Cope rearrangement to yield the observed elemene alcohols. The elemene alcohols (**5**)—(**7**) rearrange on further heating to the aldehyde (**8**).

Since treatment of shyobunone with base causes the isopropenyl double bond to move into conjugation with the ketone, this also constitutes a synthesis of isoshyobunone (**13**).[2,4,10]



(**13**)

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