

## Synthesis of (–)-Shyobunone and its Epimers<sup>1</sup>

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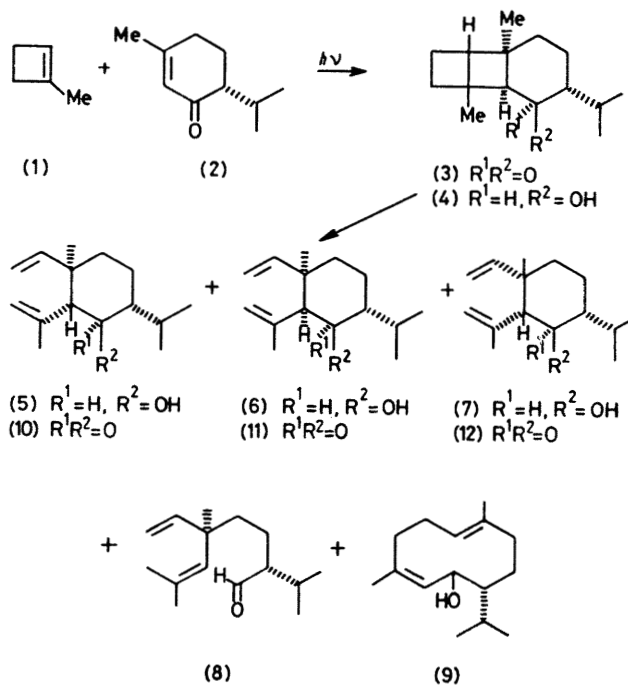
**Summary** (–)-Shyobunone (**10**) and its epimers were synthesized from methylcyclobutene (**1**) and L-piperitone (**2**) in *ca.* 24% overall yield *via* irradiation followed by thermolysis of the reduced intermediate photoadduct (**4**).

(+)-SHYOBUNONE, whose structure is the mirror image of (**10**), was initially isolated from *Acorus calamus* L.<sup>2</sup> and belongs to the elemene class of sesquiterpenes.<sup>3</sup> It has been the topic of a number of recent syntheses.<sup>4</sup> 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<sup>5</sup> and to others<sup>6</sup> 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**), [ $\alpha$ ]<sub>D</sub> –6.9° [enantiomeric excess (e.e.) 14%],<sup>7</sup> shyobunone and its epimers could be synthesized as shown in the Scheme.

Methylcyclobutene (**1**), which was obtained by the catalytic isomerization of methylenecyclobutane,<sup>8</sup> 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<sup>–1</sup>; n.m.r. (CDCl<sub>3</sub>)  $\delta$  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, [ $\theta$ ]<sub>311</sub> +5660, which supports the structure (**3**). Thermolysis of (**3**) yielded a substituted cadinene.<sup>9</sup> However, if the ketone group in (**3**) was first reduced, this intramolecular reaction was avoided.

Reduction of (**3**) (NaBH<sub>4</sub>, MeOH) afforded the alcohol (**4**) in 71% isolated yield; m.p. 72–72.5 °C; i.r. (KBr) 3313



SCHEME

cm<sup>–1</sup>; n.m.r. (CDCl<sub>3</sub>)  $\delta$  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

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

‡ Monitored by <sup>1</sup>H 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.

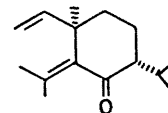
ratios 21:26:54, 48% yield); an aldehyde (**8**, 43%); and a germacrenol (with the probable structure (**9**, 6%). The relative stereochemistry of the elemene alcohols (**5**)—(**7**) was elucidated by their spectral data and by their conversion (Jones oxidation) into the known ketones (**10**)—(**12**).<sup>2,4,10</sup> 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<sup>10</sup> established the absolute stereochemistry of the products as (–)-shyobunone (**10**),  $[\alpha]_D -16^\circ$  (e.e. 14%),<sup>4</sup>  $[\theta]_{298.5} -1510$ ; 2-*epi*-(–)-shyobunone (**11**),  $[\theta]_{301.5} +3040$ ; and 3-*epi*-(–)-shyobunone (**12**),  $[\theta]_{297.5} -1830$ .

The aldehyde (**8**) was successfully converted into the alcohol (**5**) with  $\text{SnCl}_4$ ,<sup>11</sup> thereby establishing the general structure of (**8**). This was confirmed by the following data: i.r. (neat) 1729 and 1630  $\text{cm}^{-1}$ ; n.m.r. ( $\text{CDCl}_3$ )  $\delta$  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**),  $[\theta]_{298.5} -1429$ , to establish the absolute stereochemistry of the aldehyde as that of (**8**).

The intermediate photoadduct (**4**) probably is cleaved by a radical process<sup>12</sup> and may form the elemenes directly or,

more probably, yields an intermediate germacrenol skeleton<sup>5,6</sup> 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**).<sup>2,4,10</sup>



(13)

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