

## Synthesis of Isoshyobunone

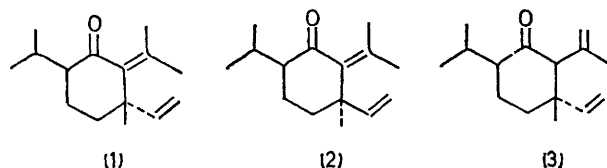
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**Summary** Isoshyobunone was synthesised *via* two pathways which involved the 1,4-addition of a vinyl reagent; in both cases, isoshyobunone was contaminated with its epimer.

In order to study the thermal behaviour of sesquiterpene ketones having an elemene skeleton, we have synthesised isoshyobunone (1)<sup>1</sup> and its epimer (2) from readily available

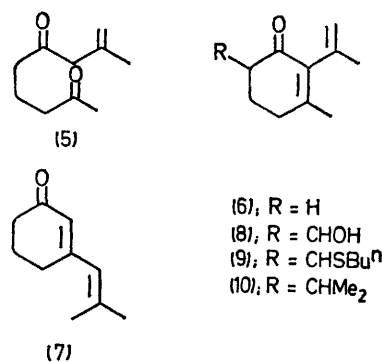
cyclohexenones (6) and (7),<sup>5</sup> easily separated by distillation. Compound (6) (b.p. 44–46 °C, 0.1 mmHg) was converted<sup>6</sup> into the hydroxymethylene derivative (8) (75%) then into



compounds. Previously only very small quantities of (1) or of shyobunone (3) have been obtained from costunolide<sup>2</sup> or santonin.<sup>3</sup>

δ-Cetocapronitrile (4)<sup>4</sup> was prepared by the condensation of acrylonitrile and ethylacetoacetate. The ketal of (4) (ethyleneglycol, TsOH) gave, after addition of methallylmagnesium chloride, and hydrolysis (6N-HCl, acetone, 0 °C, 20 min) the δ-diketone (5).†

The intramolecular aldol condensation of (5) (3% NaOH, EtOH, 0–5 °C 2h) gave a 3:2 mixture in 80% yield of two



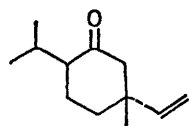
the thioether (9) (100%) (b.p. 142–144 °C, 0.01 mmHg using n-butylmercaptan. Reaction of (9) with Me<sub>2</sub>CuLi in THF gave (10) (72%) (b.p. 66–68 °C, 0.1 mm Hg).

Finally, conjugate addition using 1 equivalent of a reagent made from vinyl magnesium bromide, and a catalytic amount of cuprous iodide in diisopropylsulphide and THF<sup>7</sup> (0–3 °C, 3 h) provided (1) and its epimer (2) in a 4:1 ratio (90% yield).‡

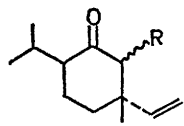
† All new compounds gave satisfactory physical data.

‡ I.r. and n.m.r. data of (1) agree with ref. 1 and n.m.r. of (2) shows the position of a methyl singlet at δ = 1.28 p.p.m. instead of 1.36 p.p.m. in (1).

A second approach to isoshyobunone was carried out from piperitone<sup>8</sup> as starting material.



(11)

(12); R = CO<sub>2</sub>Me(13); R = C(OH)Me<sub>2</sub>

formed into a mixture of (1) and (2) (1:1 ratio) by the following sequence (36% overall yield).

The  $\beta$ -ketoesters (12), from (11) [OC(OMe)<sub>2</sub>, NaH, benzene] were easily transformed<sup>9</sup> (MeLi, ether, in the presence of NaH), into the  $\beta$ -hydroxyketones (13) which, by dehydration (HCl 1%, MeOH, b.p., 2 h) led to (1) and (2).

Thus our synthesis demonstrates the possibility of carrying out conjugate addition with the copper reagent derived from vinylbromide on sterically hindered cyclic enones.<sup>¶</sup>

Conjugate addition with the same organocopper reagent<sup>6</sup> on this enone led to (11)<sup>7</sup>§ (82% yield) which was trans-

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§ A model of piperitone would indicate that there would be no stereospecificity in its reaction with the organocuprate reagent, but we found that only one isomer was formed. (Analyses were carried out on a Gas Chromatograph with stationary phase SE 30, and by t.l.c. and completed by solvent effects in n.m.r.),

¶ 1,4-additions to 3-methylcyclohexenones using vinylmetallic reagents have never been reported so far probably because divinyl copperlithium is unstable above -10°C.<sup>7</sup>

<sup>1</sup> M. Iguchi, A. Nishiyama, H. Koyama, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1968, 5315; 1969, 3729; M. Iguchi, A. Nishiyama, S. Yamamura, and Y. Hirata, *ibid.*, 1969, 4295; M. Iguchi, M. Niwa, A. Nishimaya, and S. Yamamura, *ibid.*, 1973, 2759.

<sup>2</sup> G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 1964, 20, 1301.

<sup>3</sup> K. Kato, Y. Hirata, and S. Yamamura, *Chem. Comm.*, 1970, 1324.

<sup>4</sup> C. W. Yoho and R. Levine, *J. Amer. Chem. Soc.*, 1952, 74, 5597.

<sup>5</sup> The formation of a mixture [(6) + (7)] by internal aldolization may be rationalized, according to arguments developed by P. M. McCurry Jr. and R. K. Singh, *J. Org. Chem.*, 1974, 39, 2316.

<sup>6</sup> For this sequence to introduce an isopropyl group, see R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, 1971, 93, 1027.

<sup>7</sup> C. Alexandre and F. Rouessac, *Bull. Soc. chim. belges*, 1974, 83, 393.

<sup>8</sup> S. Lawesson, E. Larsen, H. Jakobson, and C. Frisell, *Rec. Trav. Chim.*, 1964, 83, 464.

<sup>9</sup> Cf. K. Yamakawa, I. Izuta, H. Oka, and R. Sakaguchi, *Tetrahedron Letters*, 1974, 2187.