# Five-membered Ring Annelation *via* Thermal Rearrangement of β-Cyclopropyl-αβ-unsaturated Ketones: a New Total Synthesis of (±)-Zizaene

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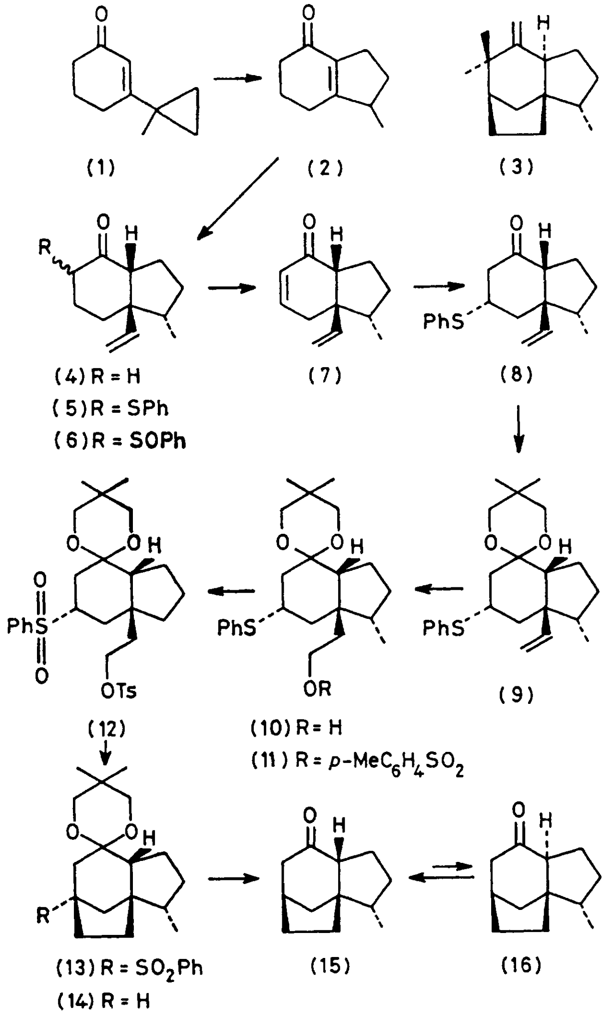
*Summary* The bicyclic αβ-unsaturated ketone (**2**), conveniently prepared by thermal rearrangement of (**1**), is converted, *via* an 11-step sequence, into the tricyclic ketone (**15**), thus formally completing a new total synthesis of (±)-zizaene (**3**).

Recently, we reported a new method for five-membered ring annelation based on the thermal rearrangement of β-cyclopropyl-αβ-unsaturated ketones.[1] For example, thermolysis of 3-(1-methylcyclopropyl)cyclohex-2-enone (**1**) at 450 °C, followed by base treatment of the initially formed product, afforded the annelated ketone (**2**) (87%).[2] We report herein that compound (**2**) can serve as a convenient starting material for a new, efficient total synthesis of the racemic modification of (+)-zizaene (**3**) (also named as tricyclovetivene, khusinene, and khusene), the parent hydrocarbon of the small ziza-ane family of structurally interesting sesquiterpenoids isolated from vetiver oil.[3]



Scheme.

Treatment of the bicyclic enone (**2**) with 1·1 equiv. of lithium divinylcuprate in ether–dimethyl sulphide (−50 °C, 20 min; room temperature, 1 h) afforded, after suitable work-up, the conjugate addition product (**4**)† (72%). The stereochemical relationship between the methyl group and the newly introduced vinyl functionality was assigned as shown (Scheme) since, for steric reasons, the cuprate reagent would be expected to approach the enone system in (**2**) from the side opposite the methyl group.‡ When the keto olefin (**4**) was treated with lithium di-isopropylamide (3 equiv.) in tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA), and the resultant enolate anion was trapped with diphenyl disulphide,[4] the α-sulphenylated ketone (**5**) (mixture of epimers) was obtained in 91% yield. Oxidation (NaIO$_4$, MeOH–H$_2$O) of (**5**), followed by thermolysis [direct distillation (120 °C, 0·3 Torr) from a small amount of CaCO$_3$] of the resultant sulphoxide (**6**), gave the αβ-unsaturated ketone (**7**) (64%).

Conjugate addition of benzenethiol (PhSH, Bu$^n_4$NF, acetone, room temperature)[5] to the enone (**7**), followed by treatment of the resultant product (**8**)§ with 2,2-dimethylpropane-1,3-diol in the presence of toluene-*p*-sulphonic acid in refluxing benzene, afforded the acetal sulphide (**9**) (94% overall). Appropriate functionalisation of the angular vinyl group was accomplished by hydroboration of (**9**) (H$_3$B:SMe$_2$, THF; H$_2$O$_2$, NaOH),[6] followed immediately by tosylation (toluene-*p*-sulphonyl chloride, pyridine) of the resultant alcohol (**10**). Treatment of the tosylate (**11**) with *m*-chloroperbenzoic acid in dichloromethane at 0 °C provided [86% from (**9**)] the sulphone tosylate (**12**), m.p. 145—146 °C, thus making possible the formation of the final carbocyclic ring.

When freshly prepared, dry KOBu$^t$ was added to a solution of compound (**12**) in HMPA, and the resultant solution was stirred at room temperature for 1·5 h, the crystalline (m.p. 168—169 °C) tricyclic product (**13**) was produced in 85% yield. Reduction (sodium amalgam, Na$_2$HPO$_4$, MeOH–PhH)[7] of this material gave, in 90% yield, the tricyclic acetal (**14**). Removal of the acetal functionality under conditions (HO$_2$C–CO$_2$H, MeOH–H$_2$O–THF) which did not cause epimerisation of the resultant product afforded the pure tricyclic ketone (**15**) (93%). Treatment of this compound with NaOMe in MeOH produced a 2 : 1 mixture of (**15**) and its epimer (**16**). This mixture was spectrally identical¶ with the 2 : 1 mixture of the same two compounds which had been prepared previously by Coates and Sowerby[3d] and which had been

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† All compounds reported herein exhibited spectral properties in accord with assigned structures, and gave satisfactory elemental analyses and/or molecular weight determinations (high resolution mass spectrometry).

‡ Examination of molecular models, along with the knowledge that *cis*-hydrindan-4-one is more stable than the corresponding *trans*-isomer (C. S. Foote and R. B. Woodward, *Tetrahedron*, 1964, **20**, 687), led to the conclusion that compound (**4**) possessed a *cis*-fused ring system. This assignment, although not crucial in terms of the overall synthesis, was later shown to be correct (*vide infra*).

§ This material consisted of a single isomer. On the basis of conformational and steric considerations, along with the $^1$H n.m.r. spectrum of the product, the stereochemistry was assigned as shown in (**8**). Details will be presented in a full paper.

¶ We are very grateful to Professor R. M. Coates for his assistance in making this comparison possible.

converted by these workers into (±)-zizaene (**3**). Thus, the acquisition of this material completed, in a formal sense, a new total synthesis of the racemic sesquiterpenoid.

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[2] For another recent synthesis of this compound, see G. Stork and P. G. Williard, *J. Amer. Chem. Soc.*, 1977, **99**, 7067.

[3] For previous synthetic work in this area and for literature citations regarding the isolation and structural elucidation of ziza-ane-type sesquiterpenoids, see (a) F. Kido, H. Uda, and A. Yoshikoshi, *J.C.S. Perkin I*, 1972, 1755; (b) D. F. MacSweeney and R. Ramage, *Tetrahedron*, 1971, **27**, 1481; (c) A. Deljac, W. D. MacKay, C. S. J. Pan, K. J. Wiesner, and K. Wiesner, *Canad. J. Chem.*, 1972, **50**, 726; (d) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, 1972, **94**, 5386; (e) N. Hanayama, F. Kido, R. Tanaka, H. Uda, and A. Yoshikoshi, *Tetrahedron*, 1973, **29**, 945; (f) G. Büchi, A. Hauser, and J. Limacher, *J. Org. Chem.*, 1977, **42**, 3324; (g) H. J. Liu and W. H. Chan, *Canad. J. Chem.*, 1979, **57** 708.

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