Seven-membered Ring Annelation *via* Cope Rearrangement of β-(2-Vinylcyclopropyl)-αβ-unsaturated Ketones: a New Synthesis of (±)-β-Himachalene

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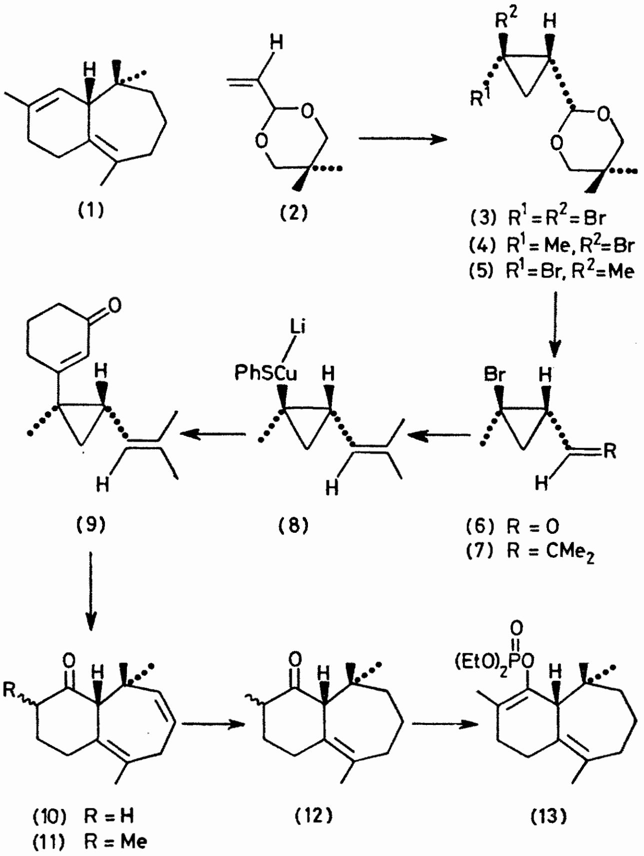
Summary A total synthesis of (±)-β-himachalene (**1**), involving the Cope rearrangement of the substituted β-(2-vinylcyclopropyl) enone (**9**) as a key step, is described.



RECENTLY, we reported a new method for cycloheptane-type annelation based on the synthesis and thermal rearrangement of β-(2-vinylcyclopropyl)-αβ-unsaturated ketones.[1] We report herein the application of this type of methodology to a total synthesis of the racemic modification of the bicyclic sesquiterpenoid (+)-β-himachalene (**1**). The compound (**1**), one of the major components of the essential oil of Himalayan deodar (*Cedrus deodara* Loud.), was shown to possess the structure[2a] and absolute stereochemistry[2b] as shown in (**1**).[3]

The acetal (**2**)† obtained (2,2-dimethylpropane-1,3-diol, $MeC_6H_4SO_3H$-*p*, $MgSO_4$, CH_2Cl_2) from acrolein, was converted by standard methodology ($CHBr_3$, NaOH–H_2O, EtOH, $PhCH_2N^+Et_3Cl^-$)[4] into the dibromocyclopropane derivative (**3**), m.p. 75—77 °C. When a cold (−95 °C) solution of (**3**) in 5 : 1 tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA) containing 2 equiv. of MeI was treated (dropwise) with 1 equiv. of Bu^{n}Li (hexane solution) and the resultant solution was warmed to 23 °C,[5] a mixture of the diastereomeric methylated derivatives (**4**) and (**5**) (ratio 87 : 13) was obtained (90%). These two compounds could be separated cleanly by means of column chromatography on silica gel [isolated yield of (**4**), m.p. 24·5—26 °C, 74%].‡

Although hydrolysis of (**4**) proved to be somewhat problematic, it was eventually achieved efficiently with 88% formic acid at room temperature. The derived aldehyde (**6**), obtained in 72% yield, was allowed to react

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† All compounds reported herein exhibited the expected spectral properties and gave satisfactory elemental analyses and/or molecular weight determinations (high resolution mass spectrometry).

‡ The stereochemical assignments for (**4**) and (**5**) were based on analogy (ref. 5) and on the ^{1}H n.m.r. spectra. Details will be given in a full paper.

with isopropylidenetriphenylphosphorane in THF at −78 °C to afford the corresponding olefin (**7**) (70%). Successive treatment of a solution of (**7**) in 1:1 ether–THF with 2 equiv. of Bu^tLi (−78 °C, 30 min) and 1 equiv. of PhSCu[6] (−20 °C, 30 min) afforded a solution of the cuprate reagent (**8**). When (**8**) was allowed to react (−78 °C to −20 °C, 15 min; 23 °C, 2 h) with 3-iodocyclohex-2-en-1-one[7] (0·67 equiv.), the substituted β-cyclopropyl enone (**9**) was obtained in quantitative yield.

The Cope rearrangement of (**9**) proceeded smoothly when a solution of this compound in xylene was heated to reflux for 3 h. Methylation [lithium di-isopropylamide (LDA), THF–HMPA; MeI] of the resultant product (**10**) afforded (**11**) [90% from (**9**)]. Hydrogenation [H_2,$(Ph_3P)_3RhCl$, PhH] of (**11**) gave (**12**) (95%) which was transformed [LDA, THF–TMEDA (tetramethylethylenediamine); $(EtO)_2$-POBr[8]§] into the enol phosphate (**13**). Reduction (Li, $EtNH_2$–Bu^tOH–THF)[9] of (**13**) afforded [38% from (**12**)] (±)-β-himachalene, which exhibited spectral properties identical with those of the natural product.

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§ The use of diethyl phosphorochloridate in this reaction failed to produce any of the corresponding enol phosphate.

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