Stereospecific Total Synthesis of (±)-α-Amorphene

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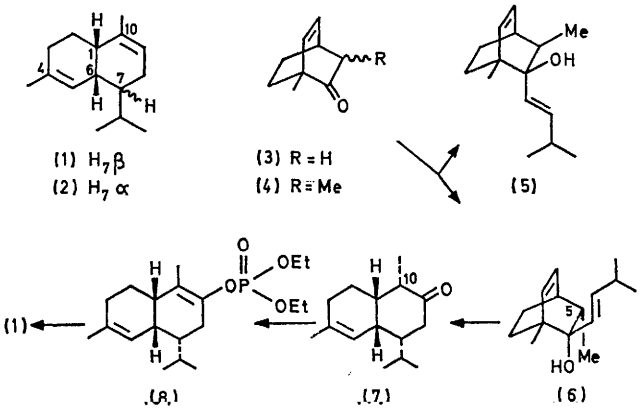
Summary The total synthesis of (±)-α-amorphene (zizanene) (**1**) has been achieved stereospecifically in six steps from the known ketone, 1-methylbicyclo[2,2,2]oct-2-en-6-one (**3**).

A GREAT deal of interest in recent years has centred on bicyclic sesquiterpenes with a cadinane skeleton whose carbocyclic rings are *cis*-fused. These compounds are classified into two groups, according to the configuration of the isopropyl group relative to the ring junction, and are exemplified by α-amorphene (**1**)[1] and α-muurolene (**2**)[2]. The oxy-Cope rearrangement has previously been applied to the synthesis of *cis*-octalones from vinyl-[3] and isopropenyl-[4] bicyclo[2,2,2]octenols. We now describe the total synthesis of (±)-α-amorphene by a route whose key step was the stereospecific introduction of all three chiral centres in one step by an oxy-Cope rearrangement of (**6**).

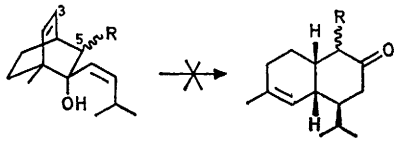
Our starting material was the known[5] 1-methylbicyclo-[2,2,2]oct-2-en-6-one (**3**), which we prepared in 60% yield from 1-methylcyclohexa-1,3-diene,[6] by Diels–Alder reaction with α-chloroacrylonitrile, followed by treatment of the 9:1 mixture of epimeric chloronitriles† with ethanolic sodium sulphide.[7]

The hydroxymethylene derivative of (**3**) was prepared by a standard method[8] and converted into the epimers (**4**)† (3:1, *endo*:*exo*) with methyl iodide in a methanolic solution of sodium methoxide followed by hydrolysis. A Grignard reaction between (**4**) and four equivalents of *trans*-3-methylbut-1-enyl bromide (prepared from *cis*-4-methylpent-2-enoic acid[9] by successive bromination and decarboxylation–dehydrobromination[10]) in tetrahydrofuran afforded in 85% yield a 3:1 mixture† of the allylic alcohols (**5**) and (**6**). Chromatography of this mixture on basic alumina gave fractions greatly enriched in (**6**) which, when heated at 300° *in vacuo* for 1 h, underwent the expected suprafacial [3,3] sigmatropic reaction to give ketone (**7**) as an oil† (ν_{max} 1715 cm^{-1}) in 60% yield from (**6**). The configuration of the C(10)-methyl in (**7**) is uncertain, although it had no bearing on the successful outcome of the synthesis. The relative configuration at C(5) in (**6**) should have been retained during the oxy-Cope rearrangement and have given rise to an axial C(10)-methyl in (**7**) as depicted, but (**7**) was recovered unchanged after treatment with methanolic sodium methoxide.



† This product gave correct microanalysis for carbon and hydrogen.

Titration of a solution of (**7**) in glyme with a solution of potassium triphenylmethide[11] in the same solvent, followed by addition of diethyl phosphorochloridate,[12,13] gave the enol phosphate (**8**) which was purified by chromatography on silica gel. Reduction of (**8**) in ether–t-butyl alcohol (1 : 1)



(**9**) R = Me
(**10**) R = H

(**11**)

with an excess of lithium in liquid ammonia[14] afforded (±)-α-amorphene (**1**)† whose i.r., ^{1}H n.m.r., and mass spectra, and g.l.c. behaviour, were identical with those of a natural sample of (+)-α-amorphene.

The carbinol (**9**) with a *cis* side-chain might have been expected to furnish (±)-α-muurolene (**2**) by a similar sequence. However, preliminary experiments with the oxy-Cope rearrangement of the demethyl analogue (**10**) gave only aromatic compounds and no trace of octalone (**11**) (R=H) under a variety of thermolytic conditions. It is noteworthy that there is considerable steric crowding between the olefinic bridge and the isopropyl group when the side-chain of (**10**) [but not of (**6**)] is forced to adopt a conformation favourable for a concerted rearrangement.

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