# Stereospecific Total Synthesis of (±)-α-Amorphene

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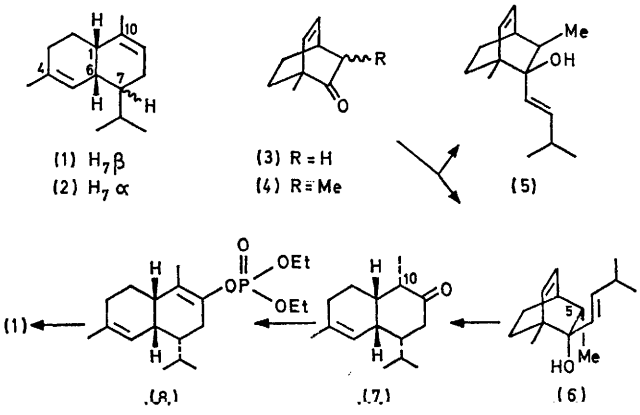
*Summary* The total synthesis of (±)-α-amorphene (zizanene) (**1**) has been achieved stereospecifically in six steps from the known ketone, 1-methylbicyclo[2,2,2]oct-2-en-6-one (**3**).

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**).

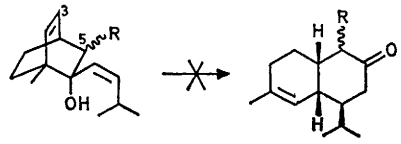
Our starting material was the known[5] 1-methylbicyclo-[2,2,2]oct-2-en-6-one (**3**), which we prepared in 60% yield from 1-methylcyclohexa-1,3-diene,[6] by Diels–Alder reaction with α-chloroacrylonitrile, followed by treatment of the 9:1 mixture of epimeric chloronitriles† with ethanolic sodium sulphide.[7]

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† ($\nu_{max}$ 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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[1] (+)-α-Amorphene (**1**) = Zizanene: M. Romanuk and V. Herout, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2540; N. H. Andersen, *Tetrahedron Letters*, 1970, 4651. (−)-α-Amorphene is the enantiomer of (**1**): Y. Ohta, K. Ohara, and Y. Hirose, *Tetrahedron Letters*, 1968, 4181; Y. Ohta and Y. Hirose, *ibid.*, 1969, 1601.
[2] A. Zabza, M. Romanuk, and V. Herout, *Coll. Czech. Chem. Comm.*, 1966, **31**, 3373; L. Westfelt, *Acta Chem. Scand.*, 1966, **20**, 2852.
[3] J. A. Berson and M. Jones, *J. Amer. Chem. Soc.*, 1964, **86**, 5017, 5019; J. A. Berson and E. J. Walsh, *ibid.*, 1968, **90**, 4729, 4730, 4732.
[4] D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Letters*, 1972, 137.
[5] K. L. Rabone and N. A. J. Rogers, *Chem. and Ind.*, 1965, 1838.
[6] A. J. Birch and G. S. R. Subba Rao, *Austral. J. Chem.*, 1970, **23**, 1641.
[7] D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Letters*, 1972, 121.
[8] C. Ainsworth, *Org. Synth.*, 1959, **39**, 28.
[9] C. Rappe, *Acta Chem. Scand.*, 1963, **17**, 2766; *Arkiv Kemi*, 1964, **21**, 503.
[10] G. B. Bachman, *J. Amer. Chem. Soc.*, 1933, **55**, 4279; J. K. Farrell and G. B. Bachman, *ibid.*, 1935, **57**, 1281.
[11] E. J. Corey and E. W. Cantrall, *J. Amer. Chem. Soc.*, 1959, **81**, 1745; R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, 1972, **37**, 2877.
[12] G. M. Steinberg, *J. Org. Chem.*, 1950, **15**, 637.
[13] R. E. Ireland and G. Pfister, *Tetrahedron Letters*, 1969, 2145.
[14] M. Fetizon, M. Jurion, and N. T. Anh, *Chem. Comm.*, 1969, 112.