

Synthesis of Phytuberin from Elemol

By FUSAO KIDO, HARUO KITAHARA, and AKIRA YOSHIKOSHI*

(*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan*)

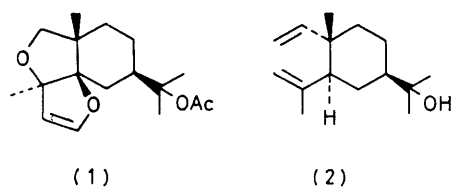
Summary Phytuberin lactone, the known synthetic progenitor of phytuberin, has been stereoselectively synthesised from elemol.

PHYTUBERIN (**1**), an antifungal sesquiterpene, is produced by bacterially inoculated potato tubers¹ and characterised by its unique tetrahydrofuranofuran structure. This intriguing structure has aroused the attention of synthetic

chemists and (**1**) has very recently been synthesised from α -santonin,² (–)-carone,³ and (–)-carvone.⁴ This paper deals with the synthesis of (**1**) from elemol (**2**), which is a conveniently functionalised starting material and is readily available from commercial essential oils such as citronella oil.

Compound (**2**) (Scheme) could not be ozonised completely even with an excess of ozone,[†] so the ozonisation product, after reductive work-up, was successively acetylated,

[†] The vinyl group in elemol was remarkably resistant to ozonisation, see ref. 5.

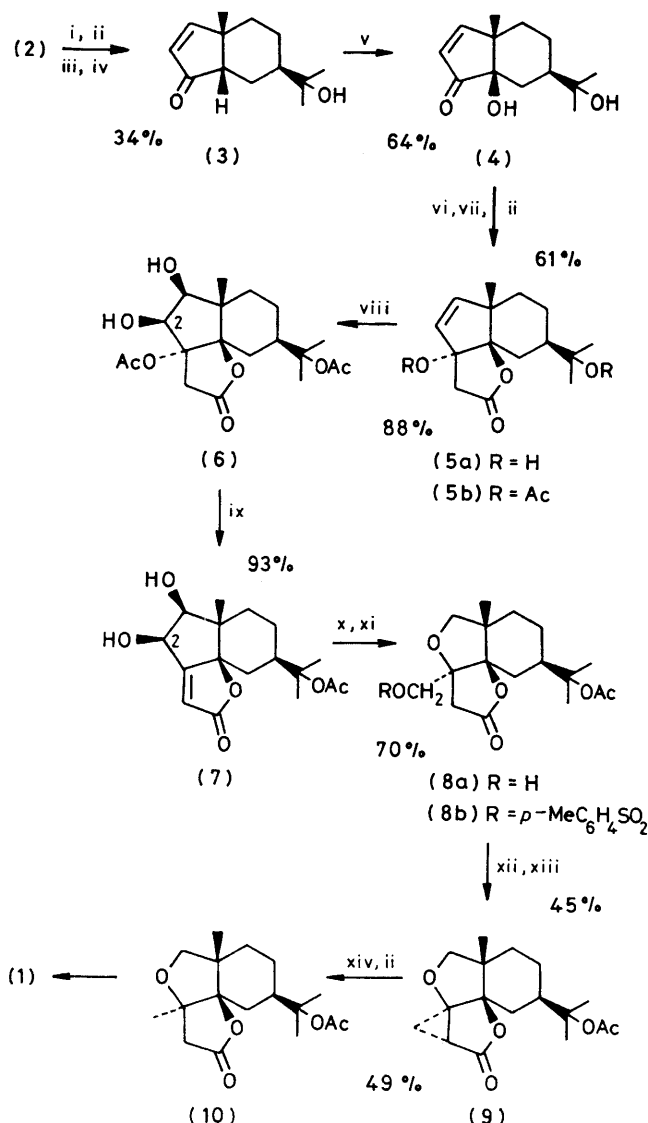


oxidised with Lemieux–Johnson reagent, and then treated with alkali to afford the cyclopentenone (2).⁵ The stereo-selective introduction of a hydroxy-group onto the angular position in (3) was achieved by autooxidation according to Gardner *et al.*,⁶ affording the α -hydroxy-ketone (4), m.p. 147 °C, in good yield. The orientation of the hydroxy-group introduced was eventually proved by conversion of (4) into (10) as follows.

In the reaction of (4) and the dianion of acetic acid, a reproducible yield of the hydroxy-acid corresponding to the lactone (5a) was obtained on addition of hexamethylphosphoric triamide (HMPT) to the reaction mixture. The crude product was worked up under acidic conditions to effect lactonisation to (5a), which was then acetylated to yield (5b). OsO₄ oxidation of (5b) afforded the diol (6), m.p. 169 °C, stereoselectively. The stereochemistry of the hydroxy-group in (6) was assigned on the basis of a 'W' spin-spin coupling (1 Hz) which was observed between the C-2 proton (δ 4.40) (data at 100 MHz) and one (δ 2.48) of the methylene protons on the lactone ring and confirmed by decoupling experiments.

Treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) effected the elimination of acetic acid from (6) giving the diol (7). In the ¹H n.m.r. spectrum of (7), an allylic coupling (2 Hz)⁷ was observed between the vinyl proton (δ 6.00) (data at 100 MHz) on the butenolide ring and the C-2 proton (δ 4.91), also supporting the aforementioned selective β -face oxidation of (5b) with OsO₄. The elimination product (7) was subjected to Pb(OAc)₄ oxidation and the resulting dialdehyde was, without purification, reduced with NaBH₄ to yield the lactone (8a) in good yield *via* intramolecular conjugate addition of the reduction product.

After some unsuccessful attempts at reduction of the hydroxymethylene group in (8a) to a methyl group, we found that the toluene-*p*-sulphonate (8b) afforded, on treatment with NaBH₃CN, the cyclopropane derivative (9) in moderate yield (70%, based on the consumed toluene-*p*-sulphonate), whereas the use of conventional bases (lithium di-isopropylamide, Et₃N, *etc.*) proved disappointing. The i.r. spectrum of (9) showed a cyclopropane methylene stretch at 3060 cm⁻¹. Although the electron impact mass spectrum of this compound showed no molecular ion, its pseudomolecular ion was observed at *m/e* 309 in field-desorption mass spectrometry. Reduction of (9) with Li in liquid NH₃ followed by acetylation gave the lactone (10), [α]_D²⁰ + 44.3° (*c.* 0.7, EtOH), which was identified as phytuberin lactone¹ by comparison of its spectra (i.r. and ¹H n.m.r.) and chromatographic behaviour (t.l.c.) with those of the authentic compound.



SCHEME. Reagents: i, O₃, Me₂S; ii, MeCOCl, PhNEt₂; iii, NaIO₄, OsO₄ (catalytic); iv, NaOH, MeOH; v, O₂, NaH, (MeO)₃P, *NN*-dimethylformamide, Bu^tOH; vi, LiCH₂CO₂Li, HMPT, MeOCH₂OCH₂OMe; vii, H₃O⁺; viii, OsO₄, pyridine; ix, DBU, PhH; x, Pb(OAc)₄, PhH; xi, NaBH₄, EtOH; xii, *p*-MeC₆H₄SO₂Cl, pyridine; xiii, NaBH₃CN, HMPT; xiv, Li, liquid NH₃, Bu^tOH.

Transformation of (10) into (1) may be effected by the known procedure (LiAlH₄ reduction¹ followed by pyrolysis of the acetylated reduction product⁴).

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