Synthesis of Phytuberin from Elemol

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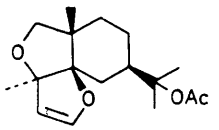
Summary Phytuberin lactone, the known synthetic progenitor of phytuberin, has been stereoselectively synthesised from elemol.

PHYTUBERIN (**1**), an antifungal sesquiterpene, is produced by bacterially inoculated potato tubers[1] 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.



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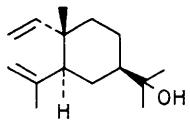


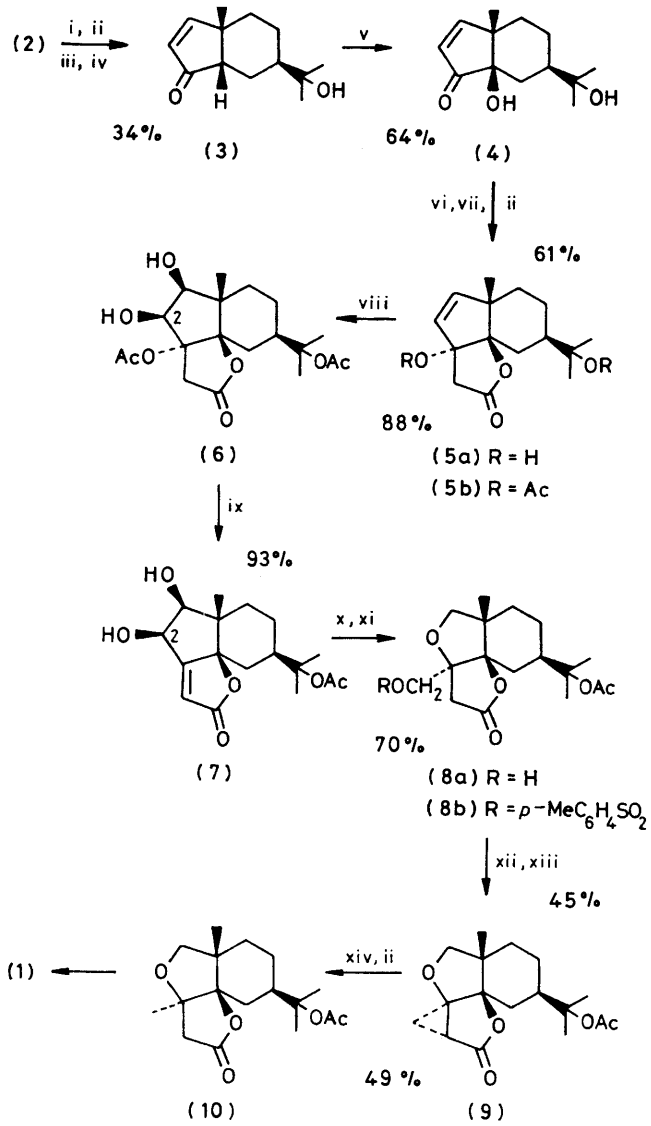
(2)

oxidised with Lemieux–Johnson reagent, and then treated with alkali to afford the cyclopentenone (**3**).[5] The stereoselective introduction of a hydroxy-group onto the angular position in (**3**) was achieved by autoxidation 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**). OsO_4 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 OsO_4. The elimination product (**7**) was subjected to $Pb(OAc)_4$ oxidation and the resulting dialdehyde was, without purification, reduced with $NaBH_4$ 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 $NaBH_3CN$, the cyclopropane derivative (**9**) in moderate yield (70%, based on the consumed toluene-*p*-sulphonate), whereas the use of conventional bases (lithium di-isopropylamide, Et_3N, *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 NH_3 followed by acetylation gave the lactone (**10**), $[\alpha]_D^{20}$ +44·3° (*c.* 0·7, EtOH), which was identified as phytuberin lactone[1] 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, O_3, Me_2S; ii, MeCOCl, $PhNEt_2$; iii, $NaIO_4$, OsO_4 (catalytic); iv, NaOH, MeOH; v, O_2, NaH, $(MeO)_3P$, *NN*-dimethylformamide, Bu^tOH; vi, $LiCH_2CO_2Li$, HMPT, $MeOCH_2OCH_2OMe$; vii, H_3O^+; viii, OsO_4, pyridine; ix, DBU, PhH; x, $Pb(OAc)_4$,PhH; xi, $NaBH_4$, EtOH; xii, *p*-$MeC_6H_4SO_2Cl$, pyridine; xiii, $NaBH_3CN$, HMPT; xiv, Li, liquid NH_3, Bu^tOH.

Transformation of (**10**) into (**1**) may be effected by the known procedure ($LiAlH_4$ reduction[1] followed by pyrolysis of the acetylated reduction product[4]).

We thank Dr. D. T. Coxon (Food Research Institute) for providing us with a sample and the spectra of (**10**) and Ogawa Perfumery Co. for supplying an elemol-rich fraction of citronella oil. Thanks are also due to Jeol Ltd. for measurements of the field-desorption mass spectra.

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[1] D. T. Coxon, K. R. Price, B. Howard, and R. F. Curtis, *J. Chem. Soc., Perkin Trans.* 1, 1977, 53, and references therein.
[2] A. Murai, M. Ono, A. Abiko, and T. Masamune, *J. Am. Chem. Soc.*, 1978, **100**, 7751.
[3] D. Caine and T. L. Smith, Jr., *J. Am. Chem. Soc.*, 1980, **102**, 7568.
[4] J. A. Findlay, D. N. Desai, G. C. Lonergan, and P. S. White, *Can. J. Chem.*, 1980, **58**, 2827.
[5] A. F. Thomas, C. Vial, M. Ozainne, and G. Ohloff, *Helv. Chim. Acta*, 1973, **56**, 2270.
[6] J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, 1968, **33**, 3294.
[7] H. J. Ringold, T. A. Wittstruck, S. K. Malhotra, and A. D. Cross, *J. Am. Chem. Soc.*, 1963, **85**, 1699.