Total Synthesis and Stereostructure of (±)-Solavetivone, a Stress Metabolite from Infected Potato Tubers; *X*-Ray Crystal and Molecular Structure of an Intermediate in the Synthesis

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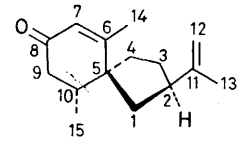
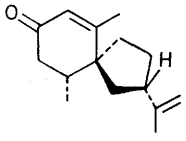
Summary A total synthesis of (±)-solavetivone (**1**) has been performed starting from the spiro compound (**3**), and the stereostructure of solavetivone (**1**) was unambiguously established by *X*-ray analysis of the synthetic intermediate (**5a**).

SOLAVETIVONE (**1**) is a stress metabolite produced by infected potato tubers, and the planar structure was established as spirovetiva-6(7),11-dien-8-one;[1] although the absolute configuration of C-2 was shown to be *R*, no stereochemical relation between the three asymmetric centres (C-2, C-5, and C-10) was determined.[1] Later, Coxon suggested two possible stereostructures, (**1**) and the enantiomer of (**2**), for (−)-solavetivone.[2]

We have attempted to synthesize solavetivone in racemic form, establishing the whole stereochemistry at the same time. The suggested two possible stereostructures, (**1**) and the enantiomer of (**2**), are epimers of each other at C-2, considering each in racemic form. For this reason, a synthetic route was devised which could lead to both racemic compounds, (**1**) and (**2**), using two intermediates epimeric at C-2. We here describe the total synthesis in racemic form and the stereostructure of solavetivone. The spiro ketone (**3**)[3] (racemic mixture) was converted into the conjugated ketone (**4**),†‡ m.p. 95—96 °C, in 77% yield by the following sequence: i, $LiNPr^i_2$, tetrahydrofuran (THF), −78 °C, then PhSSPh, room temp., 1·5 h; ii, *m*-chloroperbenzoic acid, CH_2Cl_2, −40 °C, 15 min; iii, $NaHCO_3$, toluene, reflux, 3 h. Conjugate addition of an isopropenyl group to the αβ-unsaturated ketone (**4**) [CH_2=C(Me)MgBr, CuI, THF, 0 °C, 2 h] afforded a diastereomeric mixture, which was separated by preparative t.l.c. on silica gel to give (**5a**),†‡ m.p. 134—135 °C (44%) and (**5b**),†‡ m.p. 94—96 °C (51%).§ Considering the steric course of the conjugate addition of the Grignard reagent to (**4**), the stereostructure (**5a**) was assigned to the minor isomer, m.p. 134—135 °C; this assignment was unambiguously substantiated by *X*-ray crystallographic analysis. *Crystal data:* $C_{17}H_{24}O_4$, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 9{\cdot}519(6)$, $b = 17{\cdot}379(7)$, $c = 10{\cdot}089(6)$ Å, $\beta = 100{\cdot}24°$-(7); $D_c = 1{\cdot}24$ g cm^{-3}. Unit cell parameters and intensity data were obtained with a Syntex P21 diffractometer using


(1)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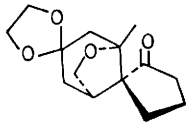
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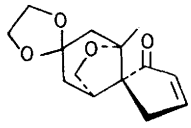
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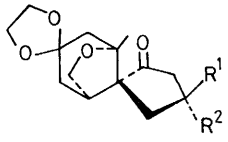
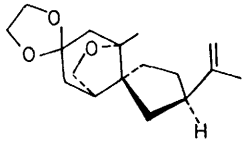
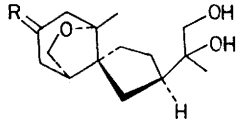
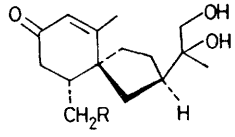
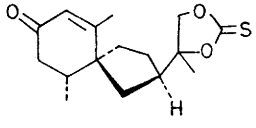

(5a) R^1 = C(=CH_2)Me, R^2 = H
(5b) R^1 = H, R^2 = C(=CH_2)Me


(6)


(7) R = O-CH_2 / O-CH_2


(9) R = I
(10) R = H

(8) R = O


(11)

† This racemic compound had i.r., n.m.r., and mass spectra, in agreement with the structure assigned. Only the structure of one enantiomer is shown.

‡ Satisfactory elemental analyses or exact mass spectral data were obtained for this compound.

§ Two compounds, (**1**) and (**2**), in racemic form can be synthesized using the diastereomers (**5a**) and (**5b**), respectively.

monochromatized Cu-K_α radiation; 2242 observed reflections were measured using the ω-scan technique. The structure was solved by direct methods and refined by full-matrix least-squares to a final R value of 0·044.¶

Wolff–Kishner reduction of (**5a**) ($NH_2NH_2 \cdot H_2O$, KOH, diethylene glycol, reflux, 2 h) yielded (**6**)†‡ (85%). Since the double bond in (**6**) readily underwent extensive migration under the conditions in the later stages of the synthesis, protection of the double bond was necessary: (**6**) was converted (OsO_4, THF, pyridine, room temp., 3 h) into the 1,2-diol (**7**),†‡ which was deacetalized [aqueous methanolic $(COOH)_2$, room temp., 2 h], affording the ketone (**8**)†‡ [69% from (**6**)]. The ketone (**8**) was transformed [$(PhO)_3PMe \cdot I$, $BF_3 \cdot OEt_2$, MeCN, room temp., 1 h] to the iodoketone (**9**),† which on treatment with zinc (NH_4Cl, aq. EtOH, room temp., 30 min) provided the enone (**10**)†‡ [49% from (**8**)]. Conversion of the 1,2-diol part of (**10**) into a double bond was effected by treatment of (**10**) with di-imidazol-1-yl thioketone (MeCOEt, reflux, 5 h) and subsequent heating of the resulting thiocarbonate (**11**)† [$(MeO)_3P$, reflux, 63 h], affording a liquid, which was purified by preparative t.l.c. on silica gel and g.l.c. (SE-30 5% on Celite 545, 175 °C) to give pure (±)-solavetivone (**1**)†‡ [24% from (**10**)]. The i.r., u.v., n.m.r., and mass spectral, as well as chromatographic properties of the synthetic compound, were identical with those of natural solavetivone. This synthetic result coupled with the known absolute configuration (*R*) of C-2 establishes that the absolute stereochemistry of (−)-solavetivone is represented by (**1**), which is in agreement with that obtained very recently by Gunn and his co-workers.[4]

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¶ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[1] D. T. Coxon, K. R. Price, B. Howard, S. F. Osman, E. B. Kalan, and R. M. Zacharius, *Tetrahedron Letters*, 1974, 2921.
[2] D. T. Coxon, personal communication; *cf.* D. L. Hughes and D. T. Coxon, *J.C.S. Chem. Comm.*, 1974, 822.
[3] K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, *Tetrahedron Letters*, 1973, 4963.
[4] The structures and absolute stereochemistry of four spirovetivane sesquiterpene glucosides from flue-cured Virginia tobacco have been determined, and the derived aglycones were correlated with (−)-solavetivone, establishing the absolute configuration of (−)-solavetivone: R. C. Anderson, D. M. Gunn, J. Murray-Rust, P. Murray-Rust, and J. S. Roberts, *J.C.S. Chem. Comm.*, 1977, 27.