Total Synthesis of (±)-Solavetivone; *X*-Ray Crystal Structure of 2-Hydroxy-6,10-dimethylspiro[4.5]dec-6-en-8-one

By C. Iwata,* T. Fusaka, T. Fujiwara, K. Tomita, and M. Yamada
(*Faculty of Pharmaceutical Sciences, Osaka University*, 133-1 *Yamada-Kami, Suita, Osaka* 565, *Japan*)

Summary (±)-Solavetivone (**1**) was synthesized by a new spiro-annelation reaction and a unique regio- and stereo-selective reduction of the spiro-dienone (**4**) to give (**5**), the structure of which has been determined by *X*-ray crystallography.

(−)-Solavetivone (**1**), which has a vetispirane skeleton, has been isolated as a stress metabolite from potato tubers infected with the blight fungus *Phytophoria infestans.*[1] Recently, Fujimori *et al.*[2] have reported its isolation from air-cured Burley tobacco (*Nicotiana tabacum* cv. Burley), and its total synthesis and stereostructure have been reported by Yamada *et al.*[3] We now describe an alternative synthesis of this natural product by a process utilizing a new spiro-annelation reaction[4] and a unique regio- and stereo-selective reduction of a spiro-dienone.[5]

β-(2,6-Dimethyl-4-hydroxyphenyl)ethyl diazomethyl ketone (**2**) was prepared quantitatively from β-(2,6-dimethyl-4-hydroxyphenyl)propanoic acid[6] by the following sequence: protection of the phenolic hydroxy-group as the acetate (acetic anhydride in 1N aqueous NaOH); reaction with thionyl chloride in refluxing benzene for 1 h followed by treatment with diazomethane; deprotection[7] with sodium carbonate and sodium hydrogen carbonate in 30% aqueous methanol at 20 °C. Decomposition of the diazoketone (**2**) in the presence of copper(II) chloride in refluxing benzene gave the spiro-dienone (**3**) in 56% yield[4] [m.p. 114—115 °C; λ_{max} (EtOH) 247 (ϵ 17,100) nm; ν_{max} ($CHCl_3$) 1747, 1668, and 1626 cm^{-1}; δ($CDCl_3$) 1·8—2·4 (8H, m, with s at 2·03), 2·4—2·8 (4H, m), and 6·07 (2H, s); *m/e* 190 (M^+)]. Selective reduction with lithium tri-t-butoxyaluminium hydride in tetrahydrofuran (THF) at 5 °C afforded the alcohol (**4**)† in 80% yield, Birch reduction (lithium in ammonia–THF–toluene) of which afforded the enone-alcohol (**5**) regio- and stereo-selectively[5]‡ (78%): m.p. 85—86 °C; λ_{max}(Et_2O) 233 (ϵ 15,400) nm; ν_{max} ($CHCl_3$) 3608, 3450, 1665, and 1618 cm^{-1}; δ($CDCl_3$) 1·03 (3H, d, *J* 6·2 Hz), 1·5—2·8 (12H, m, with s at 1·89), 3·27 (1H, br s), 4·42 (1H, br s), and 5·71 (1H, s); *m/e* 194 (M^+). The stereostructure of (**5**) was confirmed by single-crystal *X*-ray analysis of (−)-(**5**); m.p.

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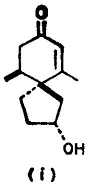
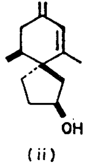
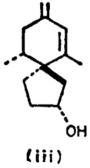
† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ Compound (5) and its isomers (i)—(iii) were obtained in a ratio of *ca.* 91 : 7 : 1 : 1 [(5) : i : ii : iii] in 78% yield, estimated from the n.m.r. spectrum of the crude product.

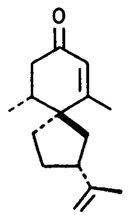

(i)

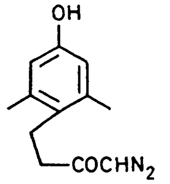

(ii)

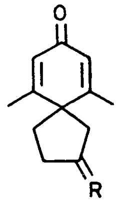

(iii)

78—80 °C (Et_2O–light petroleum), $[\alpha]_D^{18}$ $-57°$ (*c* 0·14, $CHCl_3$).§

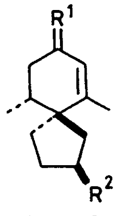
Crystal data: $C_{12}H_{18}O_2$, $M = 194{\cdot}67$, orthorhombic, space group $P2_12_12_1$, $a = 7{\cdot}640(1)$, $b = 22{\cdot}861(3)$, $c = 6{\cdot}126(1)$ Å, $Z = 4$, $U = 1069{\cdot}96$ Å^3, $D_c = 1{\cdot}209$, $D_m = 1{\cdot}209$ g cm^{-3}. A total of 1073 non-zero independent reflections up to $2\theta = 120°$ were measured on an automated diffractometer using the 2θ–ω scan technique with graphite-monochromatized Cu-K_α radiation. The structure was solved by direct methods using MULTAN 78.[8] Block-diagonal least-squares refinement with anisotropic temperature factors for non-hydrogen atoms and isotropic ones for hydrogen atoms reduced *R* to 0·061.¶ The absolute configuration has not been determined; an ORTEP view of one of its enantiomers is shown in the Figure.


(1)


(2)

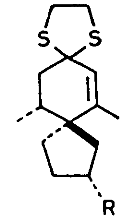

(3); R = O

(4); R = $<^{OH}_{H}$


(5); R^1 = O, R^2 = OH

(6); R^1 = $\langle^S_S]$, R^2 = OH

(7); R^1 = $\langle^S_S]$, R^2 = OSO_2Me


(8); R = $CH(CO_2Et)_2$

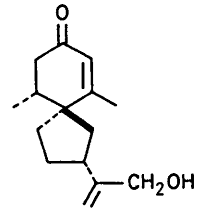
(9); R = $CHCO_2H(CO_2Et)$

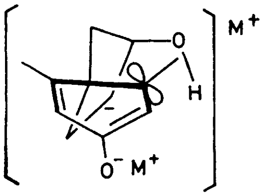
(10); R = $-\!-\!\langle^{CO_2Et}$

(11); R = $-\!-\!\langle^{CH_2OH}$

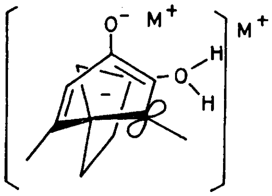
(12); R = $-\!-\!\langle^{CH_2Cl}$

(13); R = $-\!-\!\langle^{Me}$


(14)



(A)



(B)

M = metal

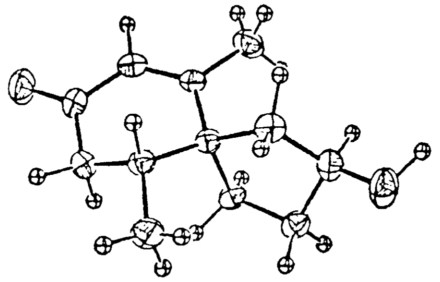


FIGURE. ORTEP view of (5).

The unusual stereoselectivity in the preparation of (**5**) might be explained as follows. Molecular models representing the reduction process *via* intramolecular protonation[5] show two possible epimeric dianion (or radical anion) transition states:[9] (**A**) (chair form) and (**B**) (boat or half-chair form). There is a strong interaction between the alcohol oxygen atom and the methyl group in (**A**), but not in (**B**), and so the reduction will proceed predominantly *via* (**B**).

Protection of (**5**) with ethylenedithiol in the presence of boron trifluoride–ether in methanol at room temperature to give (**6**) followed by methanesulphonation gave the methanesulphonate (**7**) quantitatively, m.p. 129—131 °C. A solution of (**7**) in 1,2-dimethoxyethane (DME) was added to a stirred solution of diethyl sodiomalonate in DME at 0 °C, and the mixture was refluxed for 17 h to give the product (**8**) (67%).** Compound (**8**) was hydrolysed (KOH, EtOH) to give (**9**), which was heated with diethylamine and 35% aqueous formaldehyde for 30 min. Addition of sodium acetate and glacial acetic acid and further heating for 15 min[10] led to a 92% yield of (**10**); λ_{max} (EtOH)207 (ϵ 16,900) nm; $\nu_{max}(CCl_4)$ 1722 and 1631 cm^{-1}; δ (CCl_4) 1·05 (3H, d, *J* 6·0 Hz), 1·3—2·3 (15H, m, with t, *J* 7·0 Hz, at 1·30 and d, *J* 1·6 Hz, at 1·71), 2·6—3·4 (5H, m), 4·15 (2H, q, *J* 7·0 Hz), 5·38 (1H, br s), 5·46 (1H, t, *J* 1·4 Hz), and 6·02 (1H, d, *J* 1·4 Hz); *m/e* 352 (M^+). Reduction of (**10**) in

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§ The racemic enone (**5**) was resolved by conversion into a mixture of diasteroisomers of the carbamate formed with (*S*)-(−)-phenethyl isocyanate in the presence of triethylamine in benzene at 50 °C, which could be separated by t.l.c. on alumina, the R_f values of the diastereoisomers being 0·40 and 0·32, with CH_2Cl_2–AcOEt–light petroleum (80 : 2·5 : 17·5) as eluant. Treatment of the carbamate with the lower R_f value with trichlorosilane in the presence of triethylamine in CH_2Cl_2 (W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, 1977, **42**, 2781) afforded the optically active enone-alcohol (**5**).

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

** Assignment of structure (**8**) was confirmed by synthesis from this compound of solavetivone and (**14**); compound (**8**): ν_{max} (CCl_4) 1762, 1743, and 1644 cm^{-1}; $\delta(CCl_4)$ 1·01 (3H, d, *J* 6·0 Hz), 1·1—2·2 (18H, m, with t, *J* 7·0 Hz, at 1·23 and s at 1·68), 2·2—2·8 (1H, m), 2·9—3·5 (5H, m), 4·10 (4H, q, *J* 7·0 Hz), and 5·34 (1H, br s); *m/e* 412 (M^+).

toluene at $-70\,^{\circ}C$ with di-isobutylaluminium hydride (3 equiv.) afforded (**11**) which was converted into the allyl chloride (**12**) by reaction with hexachloroacetone and triphenylphosphine in THF at 20 °C for 30 min.[11] Immediate treatment of (**12**) with zinc powder suspended in AcOH–benzene–EtOH at 80 °C for 10 min afforded (**13**) [67% overall yield from (**11**)]. Finally, deprotection of (**13**) with methyl iodide[12] afforded (±)-solavetivone (**1**) in good yield, the identity of which was confirmed by comparing its i.r., n.m.r., and mass spectra with those of an authentic sample.[13] Further, dethioacetalation of (**11**) gave the enone derivative (**14**), which was identical with the aglycone of a glucoside isolated from flue-cured Virginia tobacco.[13]

We thank Dr. Fujimori for kindly supplying the i.r., n.m.r. and mass spectral data for solavetivone, Dr. J. S. Roberts for spectra of the natural sample of (**14**), and Prof. M. Inoue, Osaka College of Pharmacy, for the use of a diffractometer.

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