# Synthesis of (±)-Canadensolide and Its C-5 Epimer. Revision of the Stereochemistry

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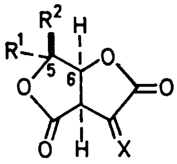
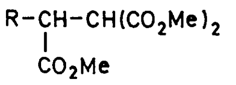
*Summary* (±)-Canadensolide (Ib) and its C-5 epimer (Ia) have been synthesised stereoselectively; the stereochemistry previously assigned to the former is shown to be incorrect.

Canadensolide is a mould metabolite produced by *Penicillium canadense* which shows antigerminative activity against fungi. Its relative stereochemistry has been determined as (Ia) on the basis of n.m.r. evidence,[1] and the coupling constant between 5-H and 6-H (4·5 Hz) has been ascribed to the *trans*-disposition of these hydrogens.



(I)

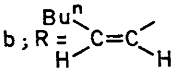
a; $R^1 = Bu^n, R^2 = H, X = CH_2$
b; $R^1 = H, R^2 = Bu^n, X = CH_2$
c; $R^1 = Bu^n, R^2 = H, X = H_2$
d; $R^1 = H, R^2 = Bu^n, X = H_2$

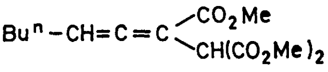


$R{-}\underset{\displaystyle CO_2Me}{CH}{-}CH(CO_2Me)_2$

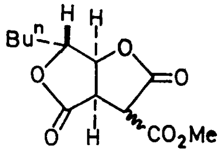
(II)

a; $R = Bu^n{-}C{\equiv}C{-}$





(III)



(IV)

We report that the compound (Ia) and its epimer (Ib) have been synthesised stereoselectively from hex-1-yne, and that the relative stereochemistry of canadensolide should be revised to (Ib).[2]

The Grignard reagent, prepared from hex-1-yne[3] and ethylmagnesium bromide, was allowed to react with trimethyl ethylenetricarboxylate[4] in the presence of cuprous chloride in tetrahydrofuran, giving the adduct (IIa; 60—70% yield) contaminated by a trace of the allenic ester (III). Hydrogenation of (IIa) on palladium–barium carbonate in methanol containing quinoline led to the *cis*-ethylenic ester (IIb), $\nu_{max}$ 1745 cm⁻¹, δ 5·25 and 5·72 (*J* 10·5 Hz), in quantitative yield. Upon Milas oxidation ($OsO_4$–$H_2O_2$–$Bu^tOH$[5]) (IIb) gave rise to the *cis*-fused dilactonic ester (IV; 30% yield†), m.p. 126·5—128°,‡ $\nu_{max}$ 1778 and 1742 cm⁻¹. Judging from the known stereoselective course of the oxidation, the stereochemistry shown may be assigned to the dilactonic ester.

Compound (IV) was hydrolysed and decarboxylated by heating with 6N-hydrochloric acid at 100° for 1·5 h, affording the dilactone (Ic), m.p. 85—86°, $\nu_{max}$ (KBr) 1780 cm⁻¹, δ 4·70 (5-H, t, *J* 6 Hz) and 4·90 (6-H, d, *J* 6 Hz; $J_{5,6}$ 0 Hz), quantitatively. This compound has been synthesised by an alternative route[6] and was identified by direct comparison with an authentic specimen.

Compound (IV) was heated with 6N-hydrochloric acid under milder conditions (55°, 2·5 h), and the resulting acidic product was treated with formalin in acetic acid containing diethylamine and sodium acetate,[7] yielding 5-epi-canadensolide [(Ia); 59% from (IV)], m.p. 47·5—48·5°, $\nu_{max}$ (KBr) 1780 and 1665 cm⁻¹. The i.r. and n.m.r. spectra of (Ia) were not identical with those of the natural product; in particular, the coupling constant between protons on C-5 and C-6 (1·5 Hz) was smaller than the value reported for the natural product. These results threw doubt upon the relative stereochemistry assigned to canadensolide.

The *cis*-ethylenic ester (IIb) was submitted to *trans*-oxidation with performic acid. The oxidation gave a complex mixture, from which lactonic products were separated on a silica gel column. The combined lactonic fractions were heated with 50% sulphuric acid at 120° for 2 h, and gave the dilactone (Id), m.p. 81—82·5°, $\nu_{max}$ (KBr) 1770 cm⁻¹, δ 4·70 (5-H, dt) and 5·09 (6-H, dd, $J_{5,6}$ 4 Hz), as colourless needles. On the other hand, the above-mentioned lactonic product obtained on oxidation was heated with 6N-hydrochloric acid at 60° for 5 h, and the product was treated with formalin in acetic acid containing diethylamine and sodium acetate giving (±)-canadensolide (Ib), m.p. 92·5—93·5°, $\nu_{max}$ (KBr) 1765 and 1666 cm⁻¹, which was identified by i.r. and n.m.r.

It was thus found that the relative stereochemistry suggested for canadensolide should be revised to (Ib).

We thank Dr. McCorkindale for identification of canadensolide and Professor Mukaiyama for providing a sample of the dilactone (Ic).

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† The yield does not exceed 50%, because a pair of diastereomers would be expected to be formed, in equal amounts. One of the diastereomers is capable of forming the dilactonic ester (IV).

‡ Despite the narrow melting range, n.m.r. indicated the compound to be a mixture of compounds epimeric at the methoxycarbonyl group.

[1] N. J. McCorkindale, J. L. C. Wright, P. W. Brian, S. M. Clarke, and S. A. Hutchinson, *Tetrahedron Letters*, **1968**, 727.

[2] Recently, Dr. McCorkindale has determined the absolute configurations at C-5 and C-6 of canadensolide and has established a *cis*-relationship of the hydrogens at these centres. (Personal communication.)

[3] K. N. Campbell and B. K. Campbell, *Org. Synth., Coll. Vol.* **4**, p. 117 (1963).

[4] H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, **1968**, **33**, 957.

[5] N. A. Milas and S. Sussman, *J. Amer. Chem. Soc.*, **1936**, **18**, 1302.

[6] T. Mukaiyama, K. Hagio, H. Takei, and K. Saigo, *Bull. Chem. Soc. Japan*, **1971**, **44**, 161.

[7] W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **1969**, **91**, 7208.