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

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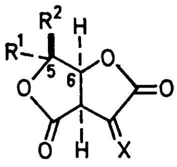
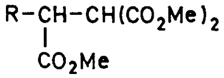
Summary (±)-Canadensolide (Ib) and its C-5 epimer (Ia) have been synthesised stereoselectively; the stereochemistry previously assigned to the former is shown to be incorrect.

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

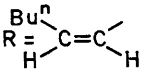


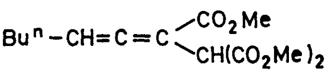
$$\underset{CO_2Me}{R-CH}-CH(CO_2Me)_2$$

(II)

a; R = Bu^n-C≡C-

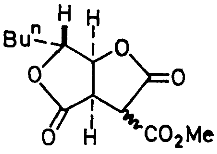
b; R =





$$Bu^n-CH=C=C\genfrac{}{}{0pt}{}{CO_2Me}{CH(CO_2Me)_2}$$

(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), ν_{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^{t}OH[5]) (IIb) gave rise to the *cis*-fused dilactonic ester (IV; 30% yield†), m.p. 126·5—128°,‡ ν_{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°, ν_{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°, ν_{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°, ν_{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°, ν_{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).

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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.

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[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.

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