

## Total Synthesis of ( $\pm$ )-Eremophilolide

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**Summary** The total synthesis of the racemic modification of the sesquiterpenoid eremophilolide confirms the structure and stereochemistry assigned to it.

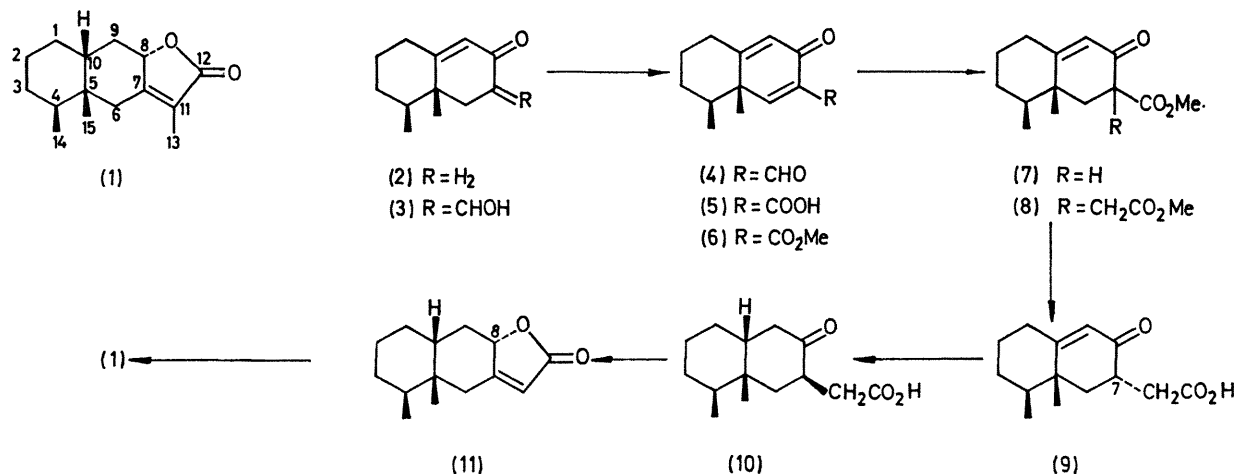
THE structure and absolute stereochemistry of eremophilolide, an eremophilane-type sesquiterpenoid isolated<sup>1</sup> from *Petasites officinalis* Moench., have been assigned<sup>2</sup> as depicted in (1).‡ We report the total synthesis of ( $\pm$ )-eremophilolide *via* a route which fully confirms the structural and stereochemical assignments. This represents the first total synthesis of an eremophilane sesquiterpenoid containing the  $\alpha\beta$ -unsaturated  $\gamma$ -lactone functionality.

Conversion of the dimethyloctalone (2)<sup>3</sup> into the corresponding hydroxymethylene derivative (3), followed by dehydrogenation of the latter with 2,3-dichloro-5,6-dicyanobenzoquinone<sup>4</sup> in dioxan, afforded in 83% yield the cross-conjugated keto-aldehyde (4), m.p. 64.5–66°. Oxidation

127.5–128°. The stereochemistry of the latter was undoubtedly as indicated, since the epimeric (at C-7) compound would contain a 1,3-diaxial interaction between the angular methyl group and the acetic acid side chain.

Hydrogenation of keto-acid (9) with ethanolic sodium hydroxide and Pd/C gave a quantitative yield of a mixture (*ca.* 1:1) of the desired decalone (10) and the corresponding *trans*-fused decalone.§ The two keto-acids were separated by fractional crystallization. The pure, desired *cis*-fused decalone (10) had m.p. 114–115°, while the *trans*-fused compound had m.p. 134–135°.¶

Treatment of keto-acid (10) with toluene-*p*-sulphonic acid in refluxing toluene gave a good yield of ( $\pm$ )-11-demethyl-eremophilolide (11), m.p. 112–112.5°. Since the latter is formed under equilibrating conditions, this compound undoubtedly possessed the stereochemistry shown in (11). The lactone (11) would be considerably more stable than the corresponding epimeric (at C-8) compound.<sup>2</sup>



of compound (4) with silver oxide<sup>5</sup> and esterification of the resultant carboxylic acid (5) (m.p. 105°) with silver oxide and methyl iodide, gave the keto-ester (6) in 86% overall yield. Reduction of (6) with sodium borohydride in pyridine<sup>6</sup> gave, in 87% yield, the  $\beta$ -keto-ester (7), m.p. 108–108.5°.

Alkylation (NaH–C<sub>6</sub>H<sub>6</sub>) of compound (7) with methyl bromoacetate gave a quantitative yield of the keto-diester (8), which upon hydrolysis (ethanolic NaOH) and decarboxylation, yielded (82% overall) the keto-acid (9), m.p.

Alkylation (trityl sodium in ether–tetrahydrofuran) of compound (11) with methyl iodide afforded ( $\pm$ )-eremophilolide (1), m.p. 110.5–111.5°. This material exhibited i.r. and n.m.r. spectra and g.l.c. retention times identical with those of authentic eremophilolide.

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‡ The numbering shown in (1) is that normally employed for eremophilane-type sesquiterpenes.

§ Subsequent investigations have shown that hydrogenation of (9) with rhodium on charcoal produces a greater proportion of the desired *cis*-fused decalone system.

¶ The stereochemistry of (10) and the corresponding *trans*-fused decalone were established by spectral data and by an independent, unambiguous synthesis of the latter compound. Details will be given in the full paper.

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<sup>3</sup> E. Piers, R. W. Britton, and W. de Waal, *Canad. J. Chem.*, 1969, 47, 4307.

<sup>4</sup> D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, 67, 153.

<sup>5</sup> Cf. K. J. Clark, G. I. Gray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, 1959, 6, 217.

<sup>6</sup> S. B. Kadin, *J. Org. Chem.*, 1966, 31, 620.