

The Total Synthesis of (±)-Guaiol

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Summary (±)-Guaiol has been synthesised from 2-methylcyclopentanone and 4-oxovaleric acid *via* a bicyclo[3,2,1]-octanone intermediate.

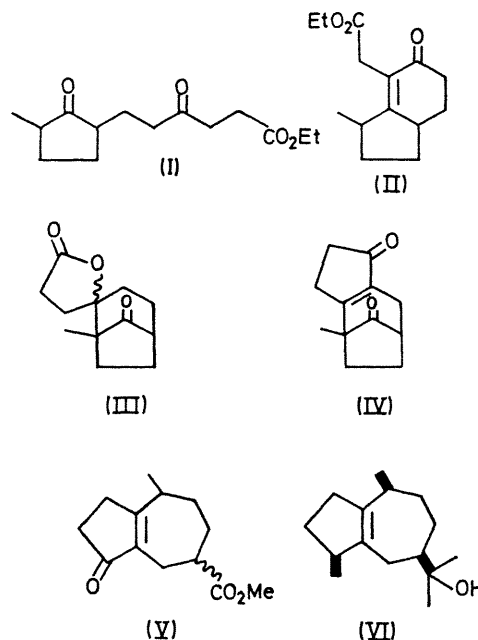
BRIDGE scission of bridged bicyclic compounds provides a useful route to particularly substituted medium-sized rings,¹ although the reaction has been little used as a synthetic method. We report here its application to the total synthesis of (±)-guaiol.†

The Mannich base of 4-oxovaleric ester² condensed with 2-methylcyclopentanone under thermal Michael conditions³ to give (I) (68%), free from the 2,2-disubstituted isomer. Under a variety of conditions (NaOMe; BF₃; toluene-*p*-sulphonic acid), cyclisation of this diketone afforded the αβ-enone (II) [λ_{max} 243 nm (ε 12,100), ν_{max} (CCl₄) 1732 and 1664 (C=O) cm⁻¹]. However, stirring at room temperature with 10N-HCl brought about ester hydrolysis and aldol cyclisation, the product being trapped by lactonisation to (III) (80%) as a mixture of two isomers [ν_{max} (CCl₄) 1780 and 1750 (C=O) cm⁻¹ and 1772 and 1758 (C=O) cm⁻¹].

The principal factor governing the cyclisation of 1,5-diketones of this type to bridged rather than fused bicycles appears to be the presence of substituents at the developing ring-junction.⁴ However, the foregoing results indicate that the bridged product is the *first* formed in a rapid reversible step and justifies our tentative suggestion⁵ that the bridged bicycles are kinetically favoured whereas the fused αβ-enones are the products of thermodynamic control.

The spiro-lactones (III), separately or as a mixture, were converted into (IV) [λ_{max} 247 nm (ε 9000), ν_{max} (CCl₄) 1760 and 1705 (C=O) cm⁻¹] and then (V) [λ_{max} 237 nm (ε 11,900), ν_{max} (CCl₄) 1735 and 1704 (C=O) cm⁻¹] by successive treatment with polyphosphoric acid and NaOMe. The

final product was a 1:1 mixture of stereoisomers, inseparable by t.l.c. or g.l.c., but discernible by n.m.r. This mixture was treated with methyl-lithium and on mild dehydration followed by reduction (H₂/5% Pd-C) of the crude product yielded a mixture of isomers, separable by g.l.c. One of these was identical (g.l.c. and mass spectrum) with natural guaiol (VI).



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† Since this manuscript was submitted, a more stereoselective but more arduous synthesis has been published (J. A. Marshall, A. E. Greene, and R. Ruden, *Tetrahedron Letters*, 1971, 855; J. A. Marshall and A. E. Greene, *ibid.*, p. 859).

¹ For a review see G. L. Buchanan, "Topics in Carbocyclic Chemistry", ed. D. Lloyd, Logos Press, London, 1969, p. 227.

² G. L. Buchanan, A. C. W. Curran, and R. T. Wall, *Tetrahedron*, 1969, 25, 5503.

³ H. L. Brown, G. L. Buchanan, A. C. W. Curran, and G. W. McLay, *Tetrahedron*, 1968, 24, 4565; E. M. Austin, H. L. Brown, and G. L. Buchanan, *Tetrahedron*, 1969, 25, 5509; E. M. Austin, H. L. Brown, G. L. Buchanan, and R. A. Raphael, jun., *Tetrahedron*, 1969, 25, 5517.

⁴ W. G. Dauben and J. W. McFarland, *J. Amer. Chem. Soc.*, 1960, 82, 4245; S. A. Julia, *Bull. Soc. chim. France*, 1954, 780; J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, 1965, 30, 3642; R. D. Sands, *J. Org. Chem.*, 1963, 28, 1710.

⁵ Ref. 1, p. 207.