A New Route to Functionalised Hydroazulenes. Synthesis of (±)-Confertin

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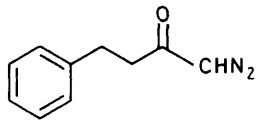
The advanced confertin intermediate (**13**) has been synthesised in 20% yield from a simple dihydrocinnamic acid precursor, the hydroazulene skeleton having been constructed by rhodium(II) mandelate-catalysed cyclisation–ring expansion of an α-diazoketone.

α-Diazoketones derived from dihydrocinnamic acids cyclise to bicyclo[5.3.0] decatrienones very efficiently in the presence of certain rhodium(II) catalysts, (**1**), the parent member of the series furnishing (**2**) in >95% yield with rhodium(II) acetate.[1] This cyclisation–ring expansion offers an unusually direct route to molecules possessing the azulene skeleton and our interest in it extends to its application to the synthesis of perhydroazulene sesquiterpenes, *e.g.*, the guaianolides and pseudoguaianolides, from readily available aromatic precursors. These natural series, of which confertin (**3**) is a member,



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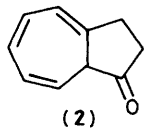

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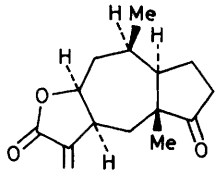

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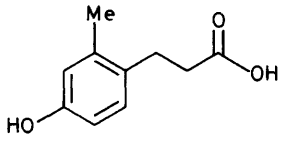

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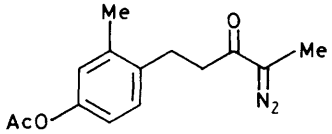

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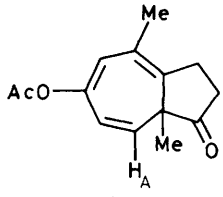

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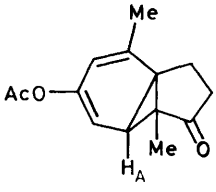
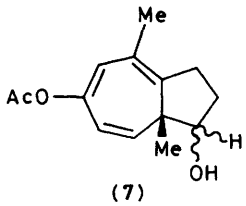


(6b)



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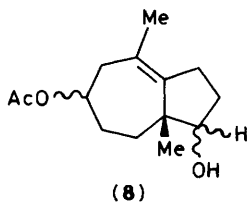

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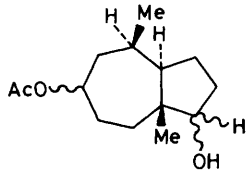

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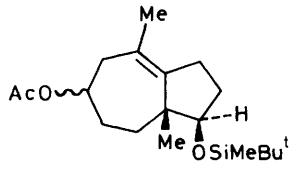

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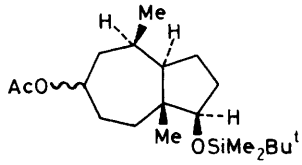

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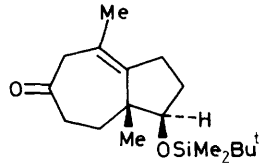

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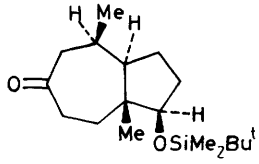

(13)

have attracted much interest synthetically because of their broad array of biological activity.[2] Several basic strategies have been developed for synthesising hydroazulenes from alicyclic precursors[2] and we now show that cyclisation–ring expansion of an aromatic ring represents a particularly effective approach to the problem, furnishing an advanced confertin intermediate in a short sequence of simple reactions.

3-(4-Hydroxy-2-methyl)phenylpropionic acid (**4**) was acetylated (acetic anhydride/potassium acetate), and the resulting ester was transformed into diazoketone (**5**) in 75% yield by sequential treatment with oxaloyl chloride in hot benzene and ethereal diazoethane. When (**5**) was exposed to catalytic amounts of rhodium(II) mandelate[3] in hot dichloromethane it underwent cyclisation–ring expansion quantitatively affording a single product (**6**) which initially appeared to be the expected bicyclic trienone (**6a**), but which on closer inspection of its spectral data is probably better represented as existing in rapid equilibrium with its tricyclic norcaradiene-like valence tautomer (**6b**), the n.m.r. chemical shift data† suggesting that (**6b**) is the dominant component of the equilibrium. As far as we are aware this is the first example of the use of rhodium(II) mandelate as a catalyst for diazoketone decomposition; its efficacy in this type of diazoketone cyclisation is significantly greater than that of rhodium(II) acetate.

Reduction of (**6**) with lithium tri-t-butoxyaluminohydride in ether at 0 °C caused the tricyclic form to disappear, affording a mixture of epimeric alcohols (**7**) (72%) which was shown by tris(trifluoroacetylcamphorato)europium(III) [Eu(tfc)$_3$]-expanded n.m.r. analysis to contain a preponderance (3 : 1 ratio) of the isomer with the hydroxy group *cis* to the bridgehead substituent. Hydrogenation of (**7**) over 10% palladium on carbon gave the tetrahydro derivative (**8**) as the major product together with a small amount of the perhydro derivative (**9**) (total yield 93%). The (**8**) + (**9**) mixture was next treated with an excess of t-butyldimethylsilyl chloride and imidazole in dimethylformamide at 70 °C to afford (**10**) and (**11**) (the minor constituent) in 53% yield from (**7**). As with the (**8**) + (**9**) mixture (**10**) and (**11**) were not separated since they were both destined for the same target molecule. The acetate functionality was now disposed of by treatment of (**10**) + (**11**) with aqueous alcoholic potassium hydroxide followed by (without purification) pyridinium chlorochromate in dichloromethane whereupon ketones (**12**) (62%) and (**13**) (21%) were obtained. To complete the synthesis (**12**) was hydrogenated (4.5 bar, 20 °C) over 5% rhodium on alumina according to Quinkert's procedure, and the crude product treated with pyridinium chlorochromate in dichloromethane to re-oxidise the traces of alcohol co-product, to afford (**13**) (41%) (68% yield based on recovered alkene); about 10% of the *cis*-fused hydroazulene was also produced. The n.m.r. and i.r. spectral data for (**13**) were identical with those of (+)-(**13**) kindly provided by Professor Quinkert.[4] Thus an advanced confertin

† ^{1}H N.m.r. (60 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.97 (s, 3H), 2.18 (s, 3H), 2.30 (m, 4H), 3.54 (d, 1H, *J* 7.5 Hz), 5.66 (d, 1H, *J* 7.5 Hz), 5.88 (s, 1H). In particular proton H_A appears as a doublet at δ 3.54, a resonance more consistent with a preponderance of the norcaradiene form (**6b**). The value of the ^{13}C resonance for the carbon atom carrying proton H_A (δ 69.2) corroborates this interpretation. This conclusion is also supported by the recent n.m.r. analysis of the cycloheptatriene ⇌ norcaradiene equilibrium reported by K. Hanneman.[6]

intermediate has been obtained from a simple benzenoid precursor (**5**) in 6 stages and 20% overall yield. Since (**13**) has been converted into confertin,[4,5] this work constitutes a total synthesis of this member of the pseudoguaianolide series. Diazoketone cyclisations of the type employed here should also be applicable to other members of the pseuodoguaianolide and guaianolide series.

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References

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2 For a summary of pseudoguaianolide syntheses up to 1983, see C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White in 'The Total Synthesis of Natural Products', ed. J. ApSimon, John Wiley and Sons Inc., New York, 1983, vol. 5, pp. 347—377; two further syntheses have been completed since then; see reference 4 and M. C. Welch and T. A. Bryson, *Tetrahedron Lett.*, 1988, **29**, 521.

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4 G. Quinkert, H.-G. Schmalz, E. Walzer, T. Kowalczyk-Przewloka, G. Durner, and J. W. Bats, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 61.

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