

SYNTHESIS OF BRIDGED CARBOCYCLIC SYSTEMS RELATED TO DITERPENES INVOLVING INTRAMOLECULAR
 CYCLISATION OF DIAZOMETHYL KETONES

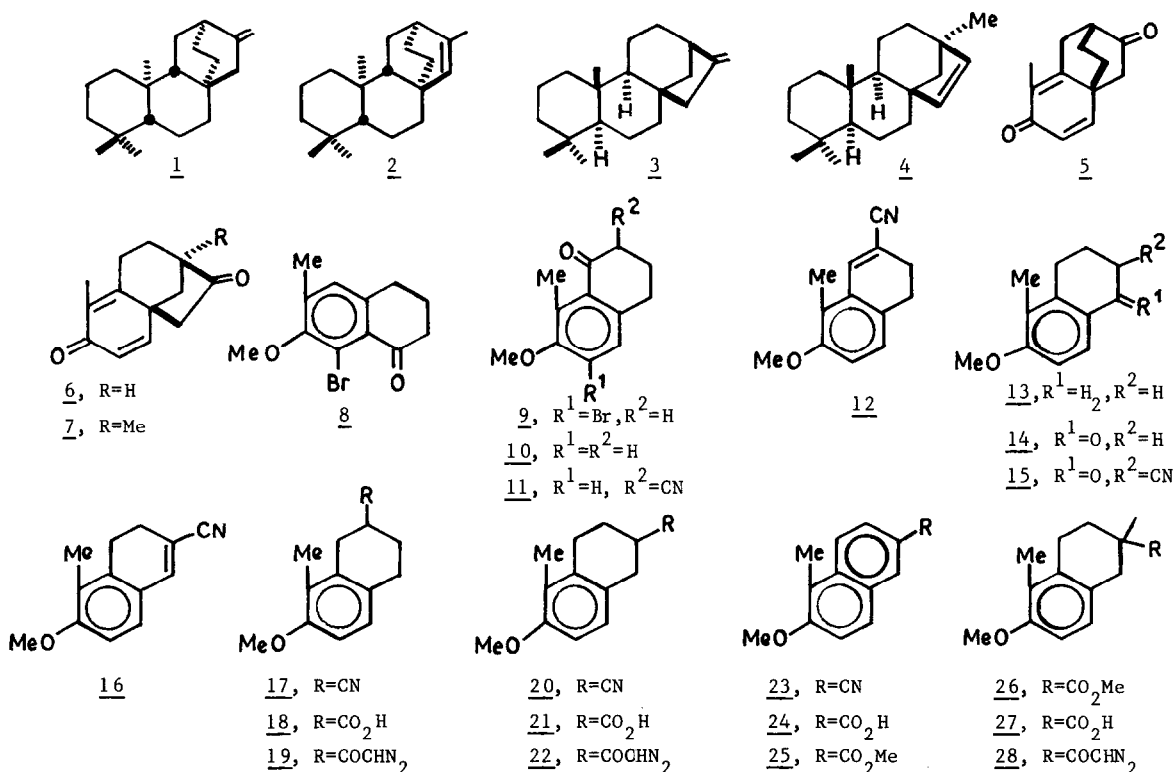
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Summary: The tricyclic dienones 5, 6 and 7 have been synthesised for entry into the ring systems of the tetracyclic diterpenes atisirene (1), phyllocladene (3) and hibaene (4) respectively.

Atisirene and isoatisirene are tetracyclic diterpenes isolated^{1a} from the wood of *Erythroxylon monogynum* Roxb. The structure and absolute stereochemistry of (-)-atisirene (1) and (-)-isoatisirene (2) have been unequivocally established through correlation^{1b} with compounds of known absolute stereochemistry. For synthetic entry into the bridged tetracyclic framework of the diterpenes 1 and 2, we have synthesised the tricyclic dienone 5 involving acid-induced intramolecular cyclisation of the diazomethyl ketone 19. Selective reduction² of the disubstituted double bond of 5 followed by Robinson annelation reaction of the resulting enone with ethyl vinyl ketone is expected³ to lead to the desired objective. From a common bicyclic starting material 10 we have also synthesised the dienones 6 and 7 which incorporate rings B/C/D of the tetracyclic diterpenes phyllocladene (3) and hibaene (4) respectively. The dienones 6 and 7 possess the potentiality of serving as useful intermediates for the synthesis of the diterpenes 3⁴ and 4⁵.



Bromination⁶ of γ -(3-methyl-4-methoxyphenyl)butyric acid in AcOH with 1 mole of Br₂ in the presence of catalytic amount of iron powder at 50° for 24 hr afforded a mixture of isomeric bromo-acids (78%) which without separation was directly cyclised with PPA. The resulting neutral product was chromatographed over alumina to furnish the bromo-ketones 8, m.p. 110° (lit.⁶ m.p. 110°) and 9, m.p. 61° (lit.⁶ m.p. 61-62°) in 40% and 48% yields respectively. Reductive debromination (H₂, 10% Pd-C) of the bromo-ketone 9 in the presence of Et₃N afforded the tetralone 10 in 95% yield, m.p. 46-47° (lit.⁶ m.p. 46-47°). Reduction of the ketone 10 with NaBH₄ followed by hydrogenolysis (H₂, 10% Pd-C) of the crude product in AcOH furnished the compound 13 which on oxidation with CrO₃ yielded the tetralone 14 in 70% overall yield, m.p. 114° (lit.⁷ m.p. 112-113°). The ketones 10 and 14 were converted into the corresponding β -ketonitriles 11 (78%), m.p. 153-154° and 15 (81%), m.p. 131-132° using the isoxazole procedure⁸ of Johnson *et al.* Reduction of 11 and 15 with NaBH₄ and subsequent dehydration of the crude hydroxynitriles with KHSO₄ at 170° furnished the unsaturated nitriles 12, m.p. 80° and 16, m.p. 68-69° in 82% and 84% yields respectively. Reduction of 12 and 16 with Mg and MeOH afforded the saturated nitriles 17 (85%), m.p. 88-89° and 20 (85%), m.p. 104-105° which on subsequent base hydrolysis yielded the corresponding acids 18 (88%), m.p. 179-180° and 21 (90%), m.p. 184°. The diazoketone 19, prepared from the acid chloride of 18 with CH₂N₂, was treated with trifluoroacetic acid (TFA) in CH₂Cl₂ at -20° to afford the dienone 5 (45%), m.p. 128-129°; IR (KBr): 1720, 1660, 1632, 1606 cm⁻¹; ¹H-NMR (CDCl₃): δ 1.84 (s, 3H), 1.47-2.95 (m, 9H), 6.23, 6.67 (AB_q, 2H, J=10 Hz). Similar treatment of the diazoketone 22 furnished the dienone 6 (58%), m.p. 149-150°; IR (KBr): 1735, 1658, 1624, 1606 cm⁻¹; ¹H-NMR (CDCl₃): δ 1.94 (s, 3H), 1.55-3.20 (m, 9H), 6.32, 6.76 (AB_q, 2H, J=10 Hz).

For the synthesis of the dienone 7, the unsaturated nitrile 16 was subjected to dehydrogenation with 10% Pd-C in refluxing p-cymene. The naphthonitrile 23 (81%) thus obtained, m.p. 105-106° was converted into the naphthoic ester 25, m.p. 112-113° *via* the acid 24 in 84% overall yield. Reductive methylation⁹ of 25 in anhydrous ammonia followed by catalytic hydrogenation of the crude product furnished the ester 26 (75%), ¹H-NMR (CCl₄): δ 1.20 (s, 3H), 2.03 (s, 3H), 1.53-3.32 (m, 6H), 3.60 (s, 3H), 3.75 (s, 3H), 6.53, 6.76 (AB_q, 2H, J=8.5 Hz). Base hydrolysis of 26 yielded the acid 27 (87%), m.p. 164-165° which was converted into the corresponding diazomethyl ketone 28. Treatment of 28 with TFA in CH₂Cl₂ at -20° furnished the dienone 7, m.p. 139° in 65% yield; IR (KBr): 1733, 1659, 1629, 1608 cm⁻¹; ¹H-NMR (CDCl₃): δ 1.15 (s, 3H), 1.90 (s, 3H), 1.41-3.18 (m, 8H), 6.28, 6.68 (AB_q, 2H, J=10 Hz). Further elaborations of the dienones 5-7 are in progress.

References:

- 1 (a) A.H. Kapadi, R. Soman, R.R. Sobti and Sukh Dev, *Indian J. Chem.*, **22B**, 964 (1983) and references therein; (b) R. Soman, A.H. Kapadi, R.R. Sobti and Sukh Dev, *ibid.*, **22B**, 989 (1983) and references therein.
- 2 R. Vitali, G. Caccia and R. Gardi, *J. Org. Chem.*, **37**, 3745 (1972).
- 3 D. Mukherjee, S.K. Mukhopadhyay, K.K. Mahalanabis, A. Dasgupta and P.C. Dutta, *J. Chem. Soc. Perkin I*, 2083 (1973).
- 4 A.S. Kende and P.J. Sanfilippo, *Synth. Commun.*, **13**, 715 (1983) and references therein.
- 5 R.E. Ireland and L.N. Mander, *Tetrahedron Letters*, 2627 (1965).
- 6 A. Chatterjee and D. Banerjee, *J. Chem. Soc. (C)*, 1859 (1971).
- 7 R.H. Martin and R. Robinson, *J. Chem. Soc.*, 491 (1943).
- 8 W.S. Johnson, J.W. Peterson and C.D. Gutsche, *J. Am. Chem. Soc.*, **69**, 2942 (1947).
- 9 S. Bhattacharyya, B. Basu and D. Mukherjee, *Tetrahedron*, **39**, 4221 (1983).

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