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A STRATEGY FOR THE CONSTRUCTION OF NOVEL TETRACYCLIC LYCOPODIUM ALKALOIDS OF PANICULATINE- AND MAGELLANINE-TYPE

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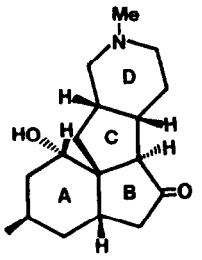
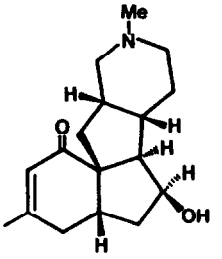
Summary: An approach is outlined for the obtention of the complete tetracyclic skeleton present in the novel lycopodium alkaloids of paniculatine-type.

Lycopodium alkaloids are notable for their rich structural diversity and close biogenetic relationships.[1] Among the various structural arrays present in them, a group of closely related tetracyclic alkaloids, bearing a diquinane-core, represented by paniculatine 1 (from L. paniculatum),[2] magellanine 2 and magellaninone 3 (from L. magellanicum)[3] hold considerable synthetic appeal. Recently, some model studies directed towards the construction of part structures present in 1-3 have been reported.[4] However, no successfull synthesis of this class of alkaloids or even the construction of their complex tetracyclic framework has been accomplished so far. In this letter, we disclose complete acquisition of the ABCD skeleton present in 1-3 with correct stereochemical disposition at five stereogenic centres and appropriate functionalisation for further elaboration to the natural products.



1



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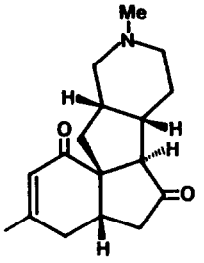
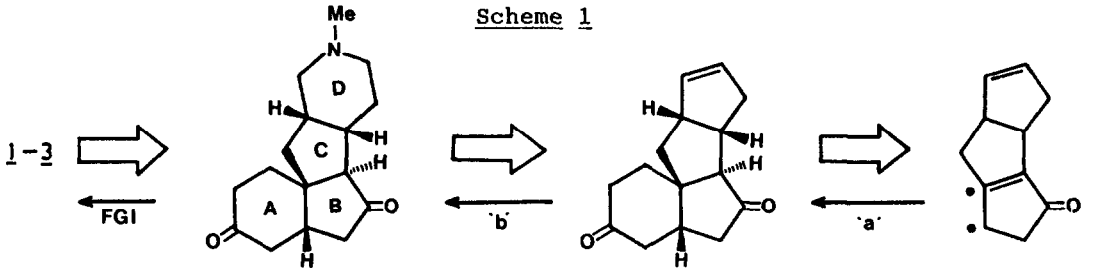


3

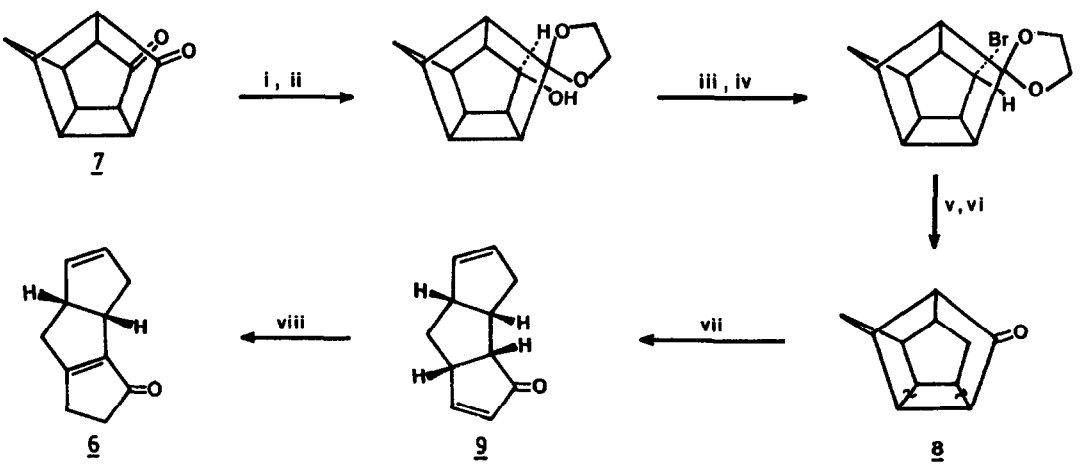
Scheme 1



4 5 6

Our synthetic strategy towards the framework of 1-3 was revealed through the retrosynthetic theme depicted in Scheme 1 and led to the identification of triquinane-dienone 6 as an advanced building-block. Evolution of 6 towards the target framework required 4C annulation with quaternarisation (6-5, 'a' leading to ring A) and establishment of equivalency of cyclopentene with N-methylpiperidine (5-4, 'b' leading ring D). To begin with, the tricyclic dienone 6 was synthesised from the readily available pentacyclic dione 7 as shown in Scheme 2, in which the thermally induced (2+2)-cycloreversion (8-9), under flash vacuum pyrolysis conditions, was the pivotal step.[5] Enone transposition in 9[6] to the desired dienone 6[6] was readily accomplished under static thermal activation.

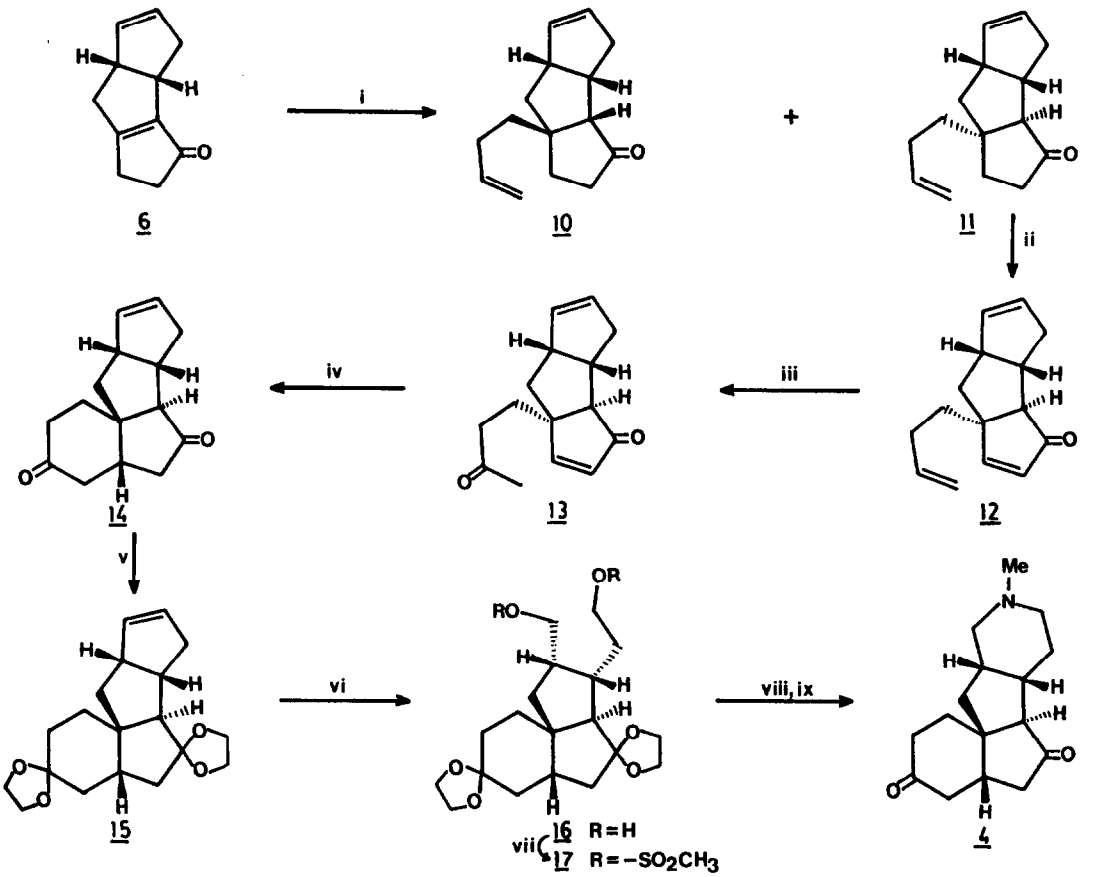
Scheme 2



7 6 9 8

Reagents and Conditions: (i) $HOCH_2CH_2OH$, PTSA, Benzene, 90°C, 5h, 83%; (ii) $NaBH_4$, aq.EtOH, R.T., 3h, 90%; (iii) 48% HBr, 80°C, 3h, 90%; (iv) $HOCH_2CH_2OH$, PTSA, Benzene, 90°C, 2h, 90%; (v) Li/NH_3, EtOH, -50°C, 45 min.; (vi) 20% HCl, THF, R.T., 1h, 60%; (vii) 600-650°C, quartz tube, 18%; (viii) Benzyl bezoate, 305°C, 5 min. 60%.

Scheme 3



Reagents and Conditions: (i) ~MgBr, Me_2S.CuBr, THF, Me_2S -78°C, 1h, 68%; (ii) LHMDS, PhSeCl, THF, -78°C —> 25°C and then H_2O_2, Py-CH_2Cl_2, 0°C —> 20°C, 48%; (iii) $PdCl_2$, CuCl, DMF, H_2O, O_2, R.T., 2h, 78%; (iv) NaH, THF, 50°C, 1h, 75%; (v) $HOCH_2CH_2OH$, PTSA, Benzene, 90°C, 2h, 88%; (vi) O_3, MeOH, -78°C then $NaBH_4$, -78°C —> R.T., 82%; (vii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, -23°C —> 0°C, 2h, 80%; (viii) CH_3NH_2, DMSO, 85°C, seal tube 18h, 40%; (ix) 15% HCl, THF, 1h, 50%.

Conjugate 1,4-addition of the Grignard reagent prepared from 4-bromo-1-butene to 6 in the presence of Cu(I) furnished a 1:2 mixture of cis,syn,cis-10[6] and cis,anti,cis-11[6] respectively, Scheme 3.[7] The major required isomer 11 was cleanly transformed to the trienone 12 via phenylselenylation-selenoxide elimination sequence. Regioselective Wacker-type oxidation of the butenyl side chain, according to the Tsuji methodology,[8] gave the ene-dione 13. Deprotonation of 13 with base resulted in the contemplated intramolecular Michael addi-

tion and the tetracyclic dione 14[6] having desired stereochemistry at all the five ring junction stereogenic centres was obtained. The stereochemistry at the newly generated stereocentre is based on the well precedented expectation that bicyclo[3.3.0]octanes predominantly react on the convex surface.

The stage was now set for the transformation of the cyclopentene ring in 14 to the N-methyl piperidine moiety. For this purpose, the carbonyl groups in 14 were duly protected to give the bis-ketal 15. Ozonolysis of 15 followed by reductive work-up led to the bis-ketal diol 16 which was converted into the dimesylate 17. Exposure of 17 to methylamine in DMSO resulted in facile double displacement and formation of the N-methyl piperidine ring. The reaction product was hydrolysed to unmask the carbonyl groups and the tetracyclic diketone 4[6] was realised as envisaged in Scheme 1. We have thus achieved the construction of the complete framework present in 1-3 with correct stereochemistry and proper functionalisation in rings A and B. Further elaboration of this approach to natural products 1-3 is being actively pursued.[9]

References and Notes: 1. D.B. McLean in 'The Alkaloids, Chemistry and Physiology', Edited by R.H.F. Manske, Academic Press, New York, 1973.
2. M. Castillo, G. Morales, L.A. Loyola, I. Singh, C. Calvo, H.L. Holland and D.B. McLean, Can. J. Chem., 1976, 54, 2900.
3. M. Castillo, L.A. Loyola, G. Morales, I. Singh, C. Calvo, H.L. Holland and D.B. McLean, ibid, 1976, 54, 2893; L.A. Loyola, G. Morales and M. Castillo, Phytochemistry, 1979, 18, 1721.
4. (a) D.R. St.Laurent and L.A. Paquette, J. Org. Chem., 1986, 51, 3861. (b) G. Mehta and K.S. Rao, J. Chem. Soc., Chem. Commun., 1987, 1578. (c) G.C. Hirst, P.N. Howard and L.E. Overman, J. Am. Chem. Soc., 1989, 111, 1514.
5. G. Mehta, A. Srikrishna, A.V. Reddy and M.S. Nair, Tetrahedron, 1981, 37, 4543.
6. All new compounds were fully characterised on the basis of spectral/analytical data. Selective values for some key compounds is given below: 9: 1H NMR: δ 7.5-7.4 (1H, dd, J1 = 7 Hz, J2 = 3 Hz), 5.92-5.84 (1H, dd, J1 = 7 Hz, J2 = 3 Hz), 5.6-5.4 (2H, m), 3.6-1.4 (8H, m); 13C NMR: δ 212.2, 167.2, 136.1, 133.4, 130.8, 54.2, 52.6, 50.1, 46.1, 33.7, 33.3. 6: 1H NMR: δ 5.9-5.5 (2H, m), 3.96-2.0 (10H, m); 13C NMR: δ 204.2, 184.7, 150.2, 133.2, 129.1, 54.1, 40.8, 40.2, 37.1, 35.3, 25.3. 10: 1H NMR: δ 6.02-5.4 (3H, m), 5.24-4.8 (2H, m), 3.5-1.2 (15H, m); 13C NMR: δ 222.2, 138.9, 135.2, 130.1, 114.5, 61.2, 53.9, 52.3, 46.2, 42.0, 40.1, 38.3, 33.3, 30.9, 29.4. 11: 1H NMR: δ 6.0-5.44 (3H, m), 5.1-4.8 (2H, m), 3.4-1.2 (15H, m); 13C NMR: δ 222.2, 138.9, 135.4, 128.7, 114.5, 67.6, 53.4, 51.6, 45.3, 41.3, 40.3, 38.3, 36.2, 30.6, 29.6. 14: 1H NMR: δ 5.74-5.5 (2H, m), 3.52-1.2 (16H, m); 13C NMR: δ 218.9, 211.2, 135.0, 128.8, 67.1, 51.5(2C), 44.9, 43.2, 42.3(2C), 40.0, 39.8, 38.1, 33.5. 4: 1H NMR: δ 2.8-1.6 (m), 2.24 (3H, s); 13C NMR: δ 218.3, 211.6, 63.5, 56.8, 54.1, 48.6, 46.6, 45.8, 42.1(2C), 41.5, 40.1, 39.0, 37.5, 35.0, 27.7.
7. Stereochemistry of 11 was unambiguously secured through correlation with a known compound prepared earlier in our laboratory. K.S. Rao, Ph.D. Thesis, University of Hyderabad (1988).
8. J. Tsuji, I. Shimizu and K. Yamamoto, Tetrahedron Lett., 1976, 2965; G. Mehta and K.S. Rao, J. Am. Chem. Soc., 1986, 108, 8015.
9. This research was supported by UGC through SAP and COSIST Programmes.

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