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TOWARDS PASPALICINE : SYNTHESIS OF RINGS D-G

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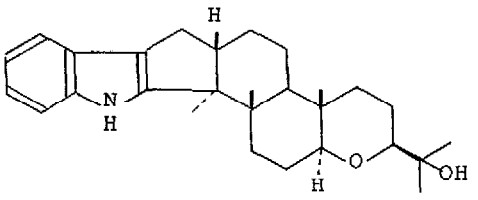
The synthesis of the β-pyrone ketal (13), which constitutes rings D-G of the mould metabolite paspalicine, is described.

The metabolites of Claviceps paspali Stevens et Hall include[1] three indole-diterpene derivatives paspaline (1), paspalinine (2) and paspalicine (3). Whereas a notable synthesis of (-)-paspaline has recently been reported,[2] no synthetic work has hitherto been described on the tremorgenic paspalinine or its deoxy derivative paspalicine.

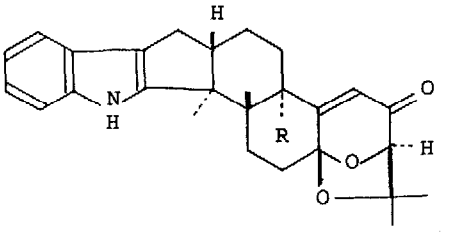
In exploring synthetic routes to paspalinine and paspalicine we focussed our attention on the unusual β-pyrone ketal function which constitutes rings F and G, and we therefore investigated initially the synthesis of the simple bicyclic model compound (5). This was readily accomplished by Wittig reaction of 5-methylfurfural with isopropylidenetriphenylphosphorane, which gave 2-(2'-methylpropenyl)-5-methylfuran. Hydroxylation of this alkene by means of osmium tetroxide-N-methylmorpholine N-oxide[3] gave a mixture of diols (4), which was subjected to further oxidation by m-chloroperbenzoic acid.[4] The β-pyrone diol thus obtained cyclised spontaneously, and the product isolated was the desired β-pyrone ketal, 3,7-epoxy-2,2-dimethyl-4-oxo-2,3,4,7-tetrahydro-oxepin (5).[5,6]

For the synthesis of rings D-G of the paspalicine molecule by this same approach the crucial intermediate was the aldehyde (9). After much experimentation this was eventually prepared in 50% overall yield from the monoketal (6) of the Wieland-Miescher ketone[7] by reductive alkylation with lithium-liquid ammonia followed by allyl bromide. The alkylated ketone (7) so obtained was ozonised, and the resulting keto-aldehyde was cyclised to the furanodecalin derivative (8) by means of acetic acid-acetic anhydride. Formylation of (8) by the Vilsmeier-Haack procedure then gave the required aldehyde (9).

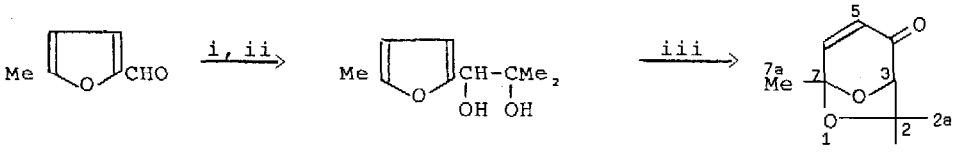
Completion of the synthesis of the tetracyclic β-pyrone ketal (13) followed the route of the earlier, model investigation. Condensation of the aldehyde (9) with isopropylidenetriphenylphosphorane gave the alkene (10), which on osmium tetroxide-N-methylmorpholine N-oxide hydroxylation[3]



Paspaline (1)



Paspalinine (2) R = OH
Paspalicine (3) R = H



(4)

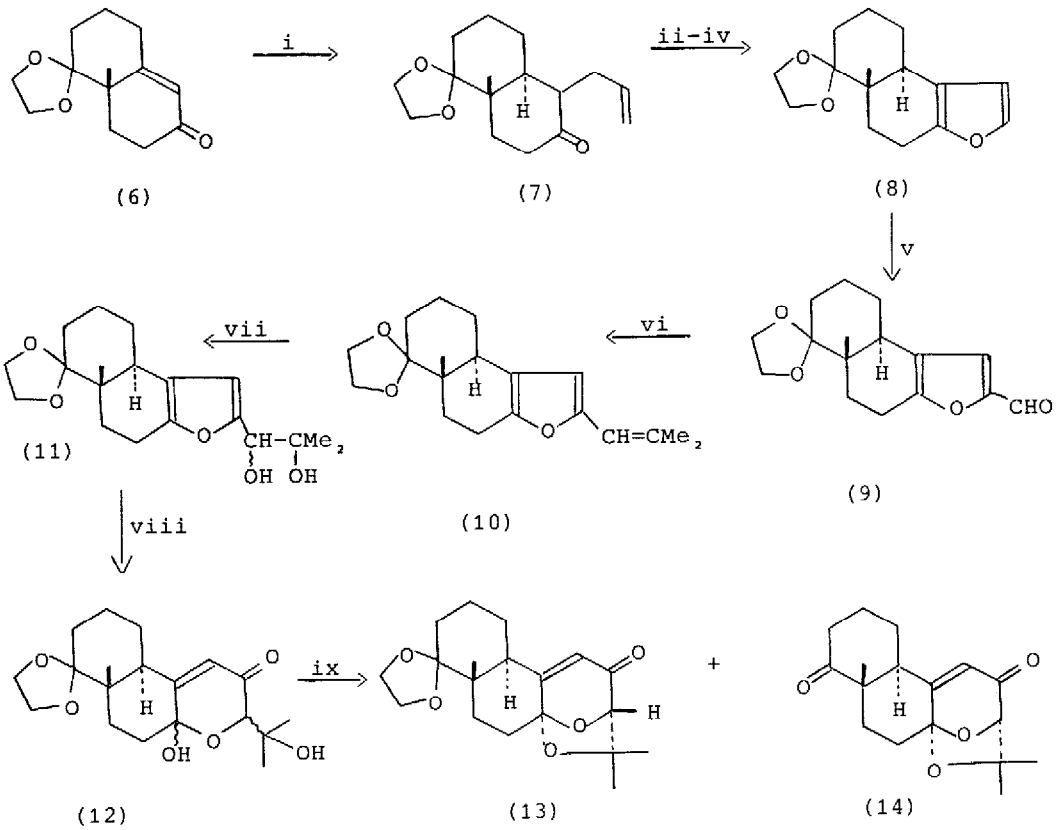
(5)

Reagents : i, $Me_2C{=}P.Ph_3$; ii, OsO_4, N-methylmorpholine N-oxide; iii, m-$ClC_6H_4CO_3H$, CH_2Cl_2.

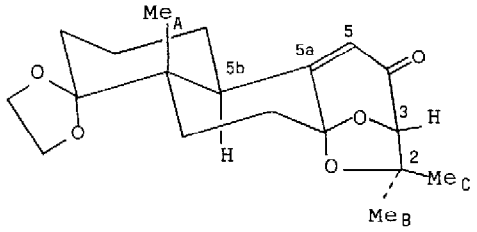
gave a mixture of diols (11). Further oxidation by means of m-chloroperbenzoic acid[4] gave two β-pyrone diols (12), which were readily separated by chromatography. At this stage the complete stereochemistry of the two diols was not elucidated, since it was observed that both cyclised in the presence of copper(II) sulphate and a catalytic amount of p-toluenesulphonic acid in benzene at room temperature to give the same β-pyrone ketal (13);[8] some diketone (14), obtained by loss of the ethylene ketal function from (13), was also isolated.

Experiments are currently under way to find alternative ways of cyclising the diols (12) with the aim of preparing both stereoisomers of the β-pyrone ketal (13), so that the stereochemistry can be securely established. Preliminary experiments indicate that the isomer of (13) already prepared has the undesired stereochemistry, with a trans disposition of the angular methyl group with respect to the isopropoxy bridge, as depicted in (15), since irradiation of the protons of methyl group B resulted in a 0.7% n.O.e. on the C-5b proton signal.[9] This effect, while authentic, is small owing to the relatively large internuclear distance (≲ 3.5 Å) between the relevant protons; nevertheless it would seem desirable to obtain independent confirmation by preparation of its stereoisomer with the alternative disposition of the ketal function.

Acknowledgement : A.A. thanks the S.E.R.C. for a maintenance award.



Reagents : i, Li, NH_3, then $CH_2{=}CH.CH_2Br$; ii, O_3, -60°C; iii, Ph_3P; iv, Ac_2O—AcOH, heat; v, $H.CONMe_2$, $POCl_3$; vi, $Me_2C{=}P.Ph_3$; vii, OsO_4, N-methylmorpholine N-oxide; viii, m-$ClC_6H_4CO_3H$; ix, $CuSO_4$, TsOH, C_6H_6, r.t.



(15)

References and Notes

1. T. Fehr and W. Acklin, Helv.Chim.Acta, 1966, 49, 1907; J.P. Springer and J. Clardy, Tetrahedron Lett., 1980, 21, 231; R.T. Gallagher, J. Finer, J. Clardy, A. Leutwiler, F. Weibel, W. Acklin, and D. Arigoni, ibid., p. 235.

2. A.B. Smith and R. Mewshaw, J.Am.Chem.Soc., 1985, 107, 1769; A.B. Smith and T. Leenay, Tetrahedron Lett., 1988, 29, 2791.

3. V. VanRheenen, R.C. Kelly, and D. Ya Cha, Tetrahedron Lett., 1976, 23, 1973.

4. Y. Lefebvre, Tetrahedron Lett., 1972, 133; P.G. Sammes and L.J. Street, J.Chem.Soc., Chem.Commun., 1982, 1056; 1983, 666.

5. Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported in this Communication.

6. Compound 4. M.p. 56-57°C, $\nu_{max.}$ 1690 cm^{-1}; δ_H ($CDCl_3$) 1.20 (3H, s, H-2a), 1.45 (3H, s, H-2b), 1.7 (3H, s, H-7a), 4.3 (1H, d, J 1.8 Hz, H-3), 6.0 (1H, dd, J 1.8 and 9 Hz, H-5), and 7.1 ppm (1H, d, J 9 Hz, H-6); δ_C ($CDCl_3$) 23 and 23.5 (C-2a and C-2b), 28 (C-7a), 78 (C-2), 103 (C-7), 126 (C-5), 153 (C-6), and 194 ppm (C-4).

7. G. Baudin and Y. Pietrasanta, Tetrahedron, 1973, 29, 4225.

8. Compound 10. M.p. 110-112°C; $\nu_{max.}$ 1675 and 1600 cm^{-1}; δ_H ($CDCl_3$) 1.05 (3H, s, Me_A), 1.20 (3H, s, Me_B), 1.40 (3H, s, Me_C), 2.90 (1H, dt, J 12 and 2Hz, H-5b), 4.30 (1H, d, J 1Hz, H-3), and 5.75 ppm (1H, m, H-5); δ_C ($CDCl_3$) 15.41, 21.79, 21.85, 23.0, 26.40, 29.06, 29.71, 29.81, 43.03, 44.50, 65.24, 65.27, 80.09, 86.86, 103.55, 111.94, 120.72, 167.04, and 194.67 ppm.

9. We thank Dr. Cs. Szántay Jr., for the n.O.e. experiments.

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