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TOTAL SYNTHESIS OF JUNCUSOL

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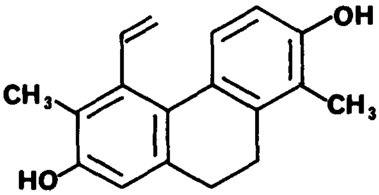
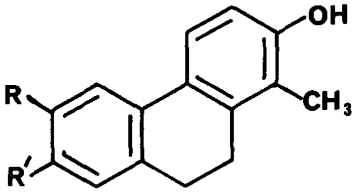
Juncusol (1) was recently isolated[1] from the marsh grass Juncus roemerianus, extracts of which were active against mouse lymphocytic leukemia Juncusol itself was found to be highly active against a human nasopharynx carcinoma test system, and its structure was established following an X-ray diffraction analysis of its diacetate. We now report an efficient total synthesis of juncusol (1).[2]

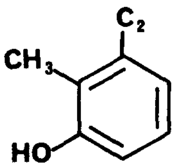


(1)

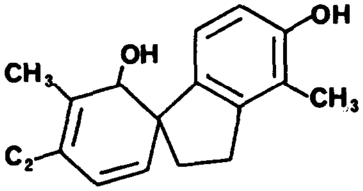


(2a) $R = CH_3; R' = CH{=}CH_2$
(2b) $R = CH{=}CH_2; R = CH_3$

The synthetic approach is loosely based on our speculations about the biosynthetic origin of this novel natural product and the closely related monophenol juncunol[3] (2a or 2b) which is also present in J.roemerianus. Both compounds may be derived from a common precursor (3) via electrophilic aromatic subsitution and oxidative phenol coupling.[†] A dienol-benzene rearrangement of intermediate (4) would account for the absence of a second -OH group in juncunol (2) and either of the proposed structures[3] could be formed in this way.



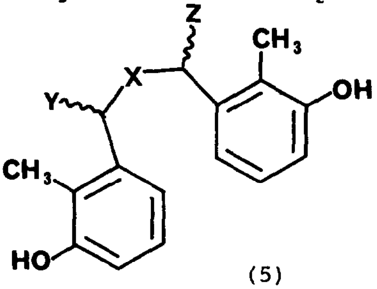
(3)



(4)

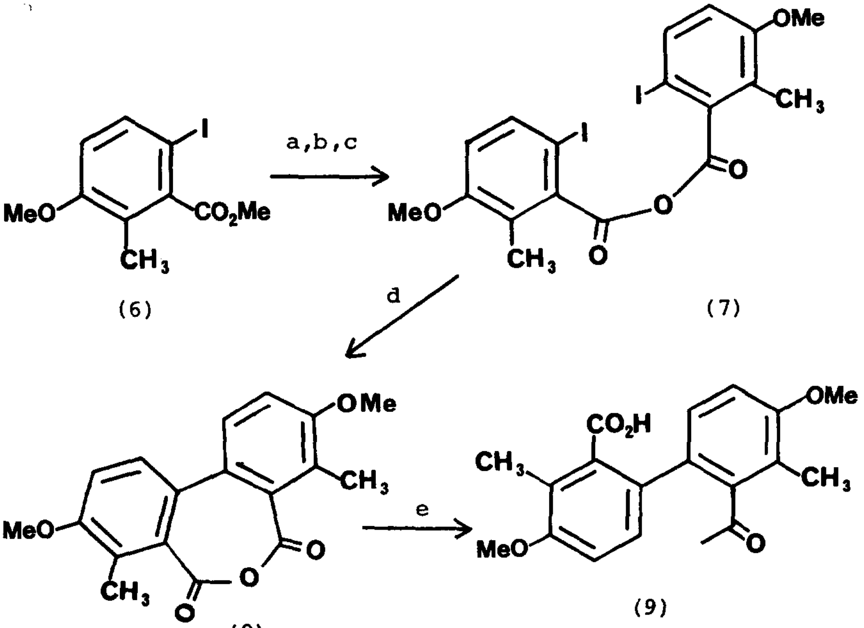
[†] Not necessarily in that order. The exact nature of the C_2 unit is not specified.

Oxidation of monomer (3) in vitro should give a mixture of dimeric (and other) products, but the required regiospecificity for the synthesis of juncusol (1) would be ensured by linking a pair of monomers temporarily via their embryonic C_2 units as in (5). Following preliminary experiments along these lines a synthesis of juncusol was accomplished as follows.



(5)

Iodination[4] of methyl 3-methoxy-2-methyl benzoate[5] ($I_2/AgOCOCF_3/CH_2Cl_2$; 98%) gave exclusively the 6-iodo derivative (6) which was converted (94%) via the corresponding acid and acid chloride to the anhydride (7), m.p. 160-161° Ullman coupling[6] (Cu/1,10-phenanthroline/toluene; 91%) gave the biphenyl (8), m.p. 240-241° and unsymmetrical opening[7] of the cyclic anhydride (Me Mg I/Et_2O/PhH; 97%) afforded the keto acid (9), m.p. 162-163°. The 2-vinyl biphenyl (10) m.p. 102-103° was then prepared by the sequence $COCH_3 \rightarrow CHOHCH_3 \rightarrow CH = CH_2$, with esterification of the 2'-CO_2H after the reduction step (82% overall yield for the 3 reactions).



(6) (7) (8) (9)

Photolysis[8] of the 2-vinylbiphenyl (10) in degassed benzene gave the dihydrophenanthrene (11) m.p. 170-172° (85%) together with traces of the corresponding phenanthrene.† The dimethyl ether of juncusol (12) m.p. 144-146° (lit.[2] 149-150°) was then prepared (59% overall) from (11) by the sequence $CO_2Me \rightarrow CH_2OH \rightarrow CHO \rightarrow CH = CH_2$, and O-demethylation of (12) (NaSEt/DMF; 59%) afforded juncusol (1), m.p. 173-174° (lit.[1] 176°), δ ($CDCl_3$) 2.27 and 2.31 (each 2H, s, Ar-CH_3) 2.70 (4H, s, $(CH_2)_2$); 5.25 (1H, dd, J = 18, 2Hz), 5.53 (1H dd, J = 11.5, 2 Hz), 6.82 (1H, d, J = 18, 11.5 Hz) CH_2 = CH-Ar); 6.64 and 7.55 (each 1H, d, J = 8.7 Hz, H-3 and H-4); 6.68 (1H, s, H-8). Juncusol was thus obtained in 20% overall yield.

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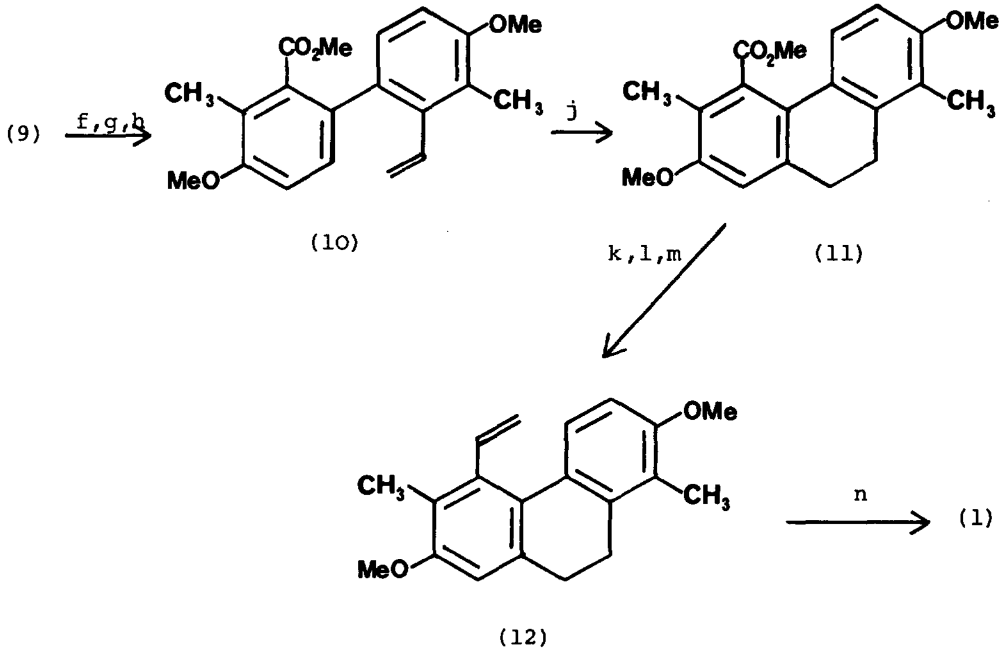

a: KOH, aq MeOH, reflux. b: $SOCl_2$ reflux. c: condensation in benzene, pyridine 0 - 20°. f: $NaBH_4$, aq NaOH, reflux.
g: CH_2N_2,Et_2O,25°. h: I_2, xylene, reflux. k: $NaAlH_4$,THF, reflux. l: pyridinium chlorochromate, CH_2Cl_2,25°.
m: $Ph_3P=CH_2$,THF, 0 - 20°. d,e,j,n: see text.

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† Substantial amounts of the oxidised product were obtained without strict exclusion of O_2.

1. D.H. Miles, J. Bhattacharyya, N.V. Mody, J.L. Atwood, S. Black, and P.A. Hedin, J. Amer. Chem. Soc., 1977, 99, 618

2. An alternative synthesis of juncusol appeared during the preparation of this manuscript; A.S. Kende and D.P. Curran, Tetrahedron Lett., 1978, 3003

3. J. Bhattacharyya and D.H. Miles, Tetrahedron Lett., 1977, 2749; S.W. Pelletier, N.V. Mody, J. Bhattacharyya and D.H. Miles, Tetrahedron Lett., 1978, 425

4. D.E. Janssen and C.V. Wilson, "Organic Syntheses", Coll. Vol. 4. Wiley, New York, 1963, p.547

5. F. Fringnelli, V. Mancini and A. Taticchi, Tetrahedron, 1969, 25, 4249

6. cf M.S. Newman and J.A. Cella, J.Org. Chem., 1974, 39, 2084

7. cf. M.S. Newman and A.S. Smith, J. Org. Chem., 1948, 13, 592

8. This type of photo chemical cyclisation has been studied in some detail in simpler systems: A. Padwa, C. Doubleday and A. Mazzu, J. Org. Chem., 1977, 42, 3271

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