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JUNCUNOL : REVISION OF STRUCTURE AND SYNTHESIS

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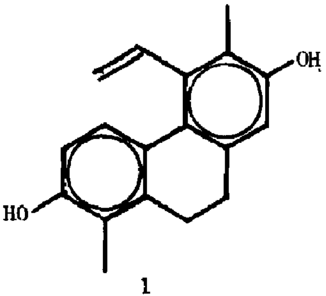
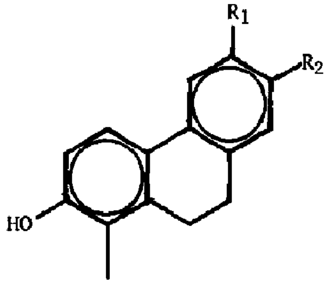
Abstract: *Synthetic studies have shown that juncunol is 2-hydroxy-1,7-dimethyl-5-vinyl-9,10-dihydrophenanthrene* **18**, *and not the 1,6-dimethyl-7-vinyl isomer* **2** *as originally assumed.*

Juncunol, isolated from the marsh grass, *Juncus roemarianus*, has been identified as a dihydrophenanthrene derivative,[1] in common with a variety of plant phytoalexins[2] and the interesting anti-neoplastic co-metabolite juncusol **1**.[3] Spectroscopic data[1,4] and biogenetic considerations appeared to be consistent with either structure **2** or **4**, but did not allow a complete identification.

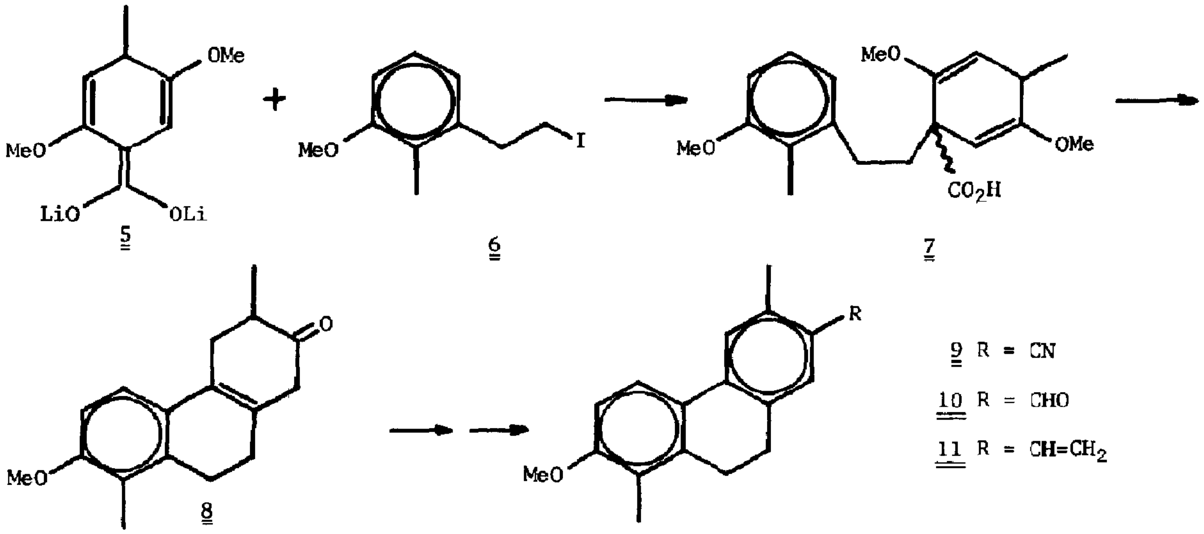


1



2 R^1 = Me, R^2 = $CH=CH_2$
3 R^1 = Me, R^2 = CH_2CH_3
4 R^1 = $CH=CH_2$, R^2 = Me

Although the interesting biological properties of these compounds have prompted considerable synthetic activity,[5,6] there is a surprizing lack of flexible and general methods for the preparation of dihydrophenanthrenes. The "reductive alkylation" of 2-methoxybenzoic acids with phenethyl halides, followed by cyclodehydration,[7] however, provides a synthetic strategy with considerable flexibility and high efficiency. To demonstrate the utility of such an approach and in an attempt to finalize the structure of juncunol, we therefore undertook the synthesis of **2**.



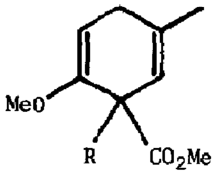
5 6 7

8

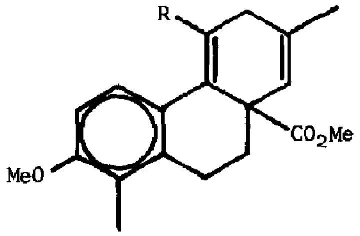
9 R = CN
10 R = CHO
11 R = $CH{=}CH_2$

Thus, enediolate 5 was prepared by lithium-ammonia reduction of 4-methyl-2,5-dimethoxybenzoic acid[8] and alkylated *in situ*[7] with iodide 6,[9] furnishing acid 7, m.p. 131-132°,[13] in 94% yield after careful acidification to pH 5.5. Cyclization of 7 in 75% w/v sulfuric acid (50°, 10 min) proceeded smoothly to give the oily enone 8 (85% yield), but attempts to add the 7-vinyl group were severely proscribed by the ease with which 8 was enolized by organometallic reagents. Hydrocyanation (KCN, HCl, THF, H_2O, 24°, 18 h) followed by dehydration ($POCl_3$, pyridine, 24°, 4 h), however, afforded the 5,6,9,10-tetrahydrophenanthrene carbonitrile (75% overall yield, m.p. 135-138°, sintering at 103-105°), which was efficiently oxidized by $CuBr_2$ in methanol[14] at reflux to the 9,10-dihydrophenanthrene 9, m.p. 120-121°, in 87% yield. The 7-vinyl group was then simply constructed by reduction (diisobutylaluminium hydride, PhH, 24°, 18 h) to aldehyde 10, m.p. 142-143° (92% yield), followed by Wittig methylenation ($Ph_3P^+MeBr^-$, *n*-BuLi, ether, 24°, 18 h). In this way the vinyl derivative 11, m.p. 156-159°, was obtained in 74% yield and then demethylated to phenol 2 (73% yield, m.p. 173-174°) with lithium thiomethoxide (hexamethylphosphoric triamide (HMPA), 150 → 180° over 2 h).[15]

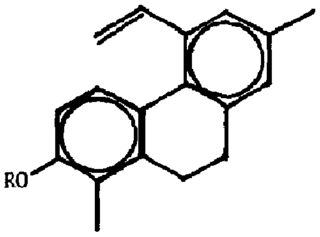
The melting point and ^1H-NMR spectrum of 2 [δ($CDCl_3$) 2.22, 2.38, s, ArMe; 2.80, s, $H_2(9)$ $H_2(10)$; 4.76, br s, OH; 5.24, 5.64, 6.92, ABX, J_{AX} 17 Hz, J_{BX} 10 Hz, J_{AB} 2 Hz, $CH{=}CH_2$; 6.68, d, *J* 8 Hz, H(3); 7.30, s, H(8); 7.38, s, H(5); 7.47, d, *J* 8 Hz; H(4)] were quite distinct from those reported[1] for juncunol (m.p. 144°). Moreover, hydrogenation of 2 gave the dihydro-derivative 3, m.p. 131-134°, [δ($CDCl_3$) 1.23, t, *J* 7 Hz, $CH_2\underline{CH_3}$; 2.22, 2.32, s, ArMe; 2.61, q, *J* 7 Hz, $\underline{CH_2}CH_3$; 2.78, s, $H_2(9)$ $H_2(10)$; 6.66, d, *J* 8 Hz; 6.93, s, H(8); 7.35, s, H(5); 7.53, d, *J* 8 Hz] which was clearly different from an authentic sample of dihydrojuncunol,[16] m.p. 116°, [δ($CDCl_3$) 1.28, t, *J* 7 Hz, $CH_2\underline{CH_3}$; 2.28, 2.35, s, ArMe; 2.70, s, $H_2(9)$ $H_2(10)$; 2.85, q, *J* 7 Hz; 6.73, d, *J* 8 Hz, H(3); 6.95, br s; 7.05, br s; 7.37, d, *J* 8 Hz, H(4)]. While the resonance at δ 7.35 clearly arises from H(5) in 3, there is no comparable signal from dihydrojuncunol. In addition, the relatively low chemical shift for the methylene protons of the ethyl group indicated that this substituent should be located at C(5), and this was confirmed by a ∿ 15% nuclear Overhauser enhancement of the signal from H(4) on irradiation at the methylene frequency (δ 2.85). The broadness of the signals arising from the C-ring aryl protons must then be assumed to be due to *meta*-coupling, indicating that juncunol should therefore possess structure 18. This new assignment was confirmed by a synthesis based on a further reductive alkylation, but with several modifications.



12 R = H
13 R = 2-(3'-methoxy-2'-methylphenyl)-ethyl



14 R = H
15 R = CHO
16 R = CH=CH$_2$



17 R = Me
18 R = H

Reductive alkylation of 2-methoxy-5-methylbenzoic acid (lithium/liquid ammonia; addition of phenethyl iodide 6) furnished a mixture of the desired product with its desmethoxy analogue. In order to avoid this undesirable side-reaction,[17] methyl 2-methoxy-5-methylbenzoate was reduced in liquid ammonia-tetrahydrofuran at -70° by sodium (2.5 equiv.) in the presence of t-butyl alcohol (2.0 equiv.)[18] and the resulting 1,4-dihydro derivative 12 alkylated subsequently by treatment with lithium diisopropylamide at -78° (0.5 h, THF) followed by iodide 6 (HMPA, 1 equiv., -78° → 25°, 16 h). The resulting adduct 13, m.p. 92-95° (85% yield), was rapidly cyclized by exposure to BF$_3$·Et$_2$O in dichloromethane (1.3 equiv., 24°, 15 min) to afford tricyclic ester 14, m.p. 150-153°, in 95% yield. The 5-vinyl substituent was then readily introduced through Vilsmeier formylation (POCl$_3$, 6 equiv., DMF, 70°, 20 h, 94% yield) to give 15, m.p. 164-166°, Wittig methylenation of which (Ph$_3$P$^+$CH$_3$Br$^-$, n-BuLi, THF, 22°, 5 min, 89% yield) furnished 16, m.p. 175-177°. Oxidative decarboxylation (Pb(OAc)$_4$, Cu(OAc)$_2$, PhH, 80°, 5 min) of the derived acid (ester 16, EtOH/3MNaOH, 4:1, reflux 8 h, 85%) m.p. 252-253°, proceeded cleanly (91% yield) to the dihydrophenanthrene 17, m.p. 103-105°, which was demethylated in 94% yield by lithium thiomethoxide (HMPA, 180°, 2 h)[15] to phenol 18, m.p. 144-145°, whose ^{1}H-NMR spectrum was essentially the same as that reported for juncunol (m.p. 144°).[1] Hydrogenation provided material which was identical (m.p., mixture m.p., t.l.c.; IR, ^{1}H and ^{13}C-NMR as well as mass spectra) with dihydrojuncunol.

References and Notes

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9. B.p. 115°/0.01 mm (Kugelrohr), prepared from the corresponding alcohol[10] (p-toluenesulfonyl chloride, pyridine; NaI, acetone) in 80% yield.
10. This alcohol has been derived from a ∿ 12 step sequence beginning with 6-nitro-2-chlorotoluene.[11] In the present study 2-methoxybenzyl alcohol was heated with N,N-dimethyl acetamide dimethyl acetal and dichlorobenzene (reflux, 40 h),[12] furnishing N,N-dimethyl 2-(3'-methoxy-2'-methylphenyl)-acetamide, m.p. 125-127°,[13] in 40% yield. Hydrolysis (10% NaOH, $MeOH/H_2O$ (1:19), reflux, 18 h, ∿ 100% yield) to the acid, m.p. 112-114° (lit.[11] 114°), esterification, and reduction ($LiAlH_4$) yielded (98%) the alcohol m.p. 56-57° (lit.[11] 57°). The modest yield in the modified Claisen rearrangement prompted an examination of other procedures. The orthoester modification [W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brocksom, T.-T. Li, D.J. Faulkner, and M.R. Peterson, *J. Amer. Chem. Soc.*, 92, 741 (1970)] gave ∿ 10% yield, but *cf.* S. Raucher and A. S.-T. Lui, *J. Amer. Chem. Soc.*, 100, 4902. The ester enolate modification [R.E. Ireland and R.H. Mueller, *J. Amer. Chem. Soc.*, 94, 5897 (1972)] gave no product of a [3,3] rearrangement.
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