Tetrahedron Letters No. 33, pp 3003 - 3006.
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0040-4039/78/0808-3003$02.00/0

TOTAL SYNTHESIS OF JUNCUSOL

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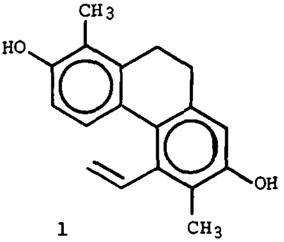
A recent communication by Miles et al. has described the structure of juncusol (1), a constituent of the extracts of the needlerush (*Juncus roemerianus*).[1] In view of the confirmed cytotoxic activity (ED_{50} = 0.3 μg/ml) of juncusol against the NCI 90 KB human epidermoid carcinoma of the nasopharynx, we have explored synthetic routes to this novel substance, and now describe its first total synthesis.



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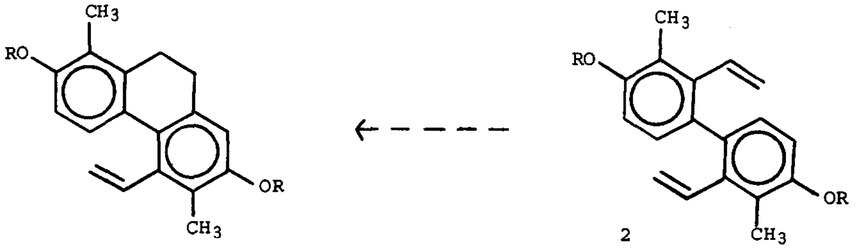
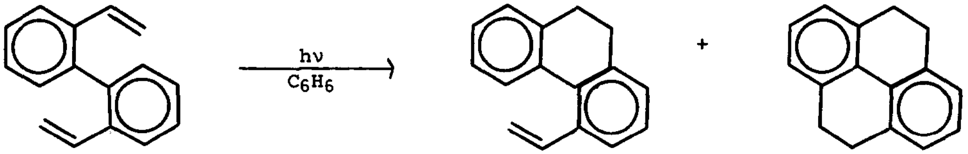
Although several simple 9,10-dihydrophenanthrene plant phytoalexins have been synthesized, all such routes have involved reduction of the 9,10 double bond of a suitable phenanthrene precursor.[2a,b] This is incompatible with the vinyl group;in addition, such selective reductions are more difficult and less specific than one might expect. Exotic catalysts and vigorous conditions are sometimes required, and indiscriminate reduction of the aromatic rings has been reported.[2a,3] For these reasons it was desirable to develop a new synthetic strategy for juncusol. The key to this strategy was the realization that antithetic transform of the juncusol system by means of a retrophotochemical step would produce the symmetrical biaryl precursor 2.

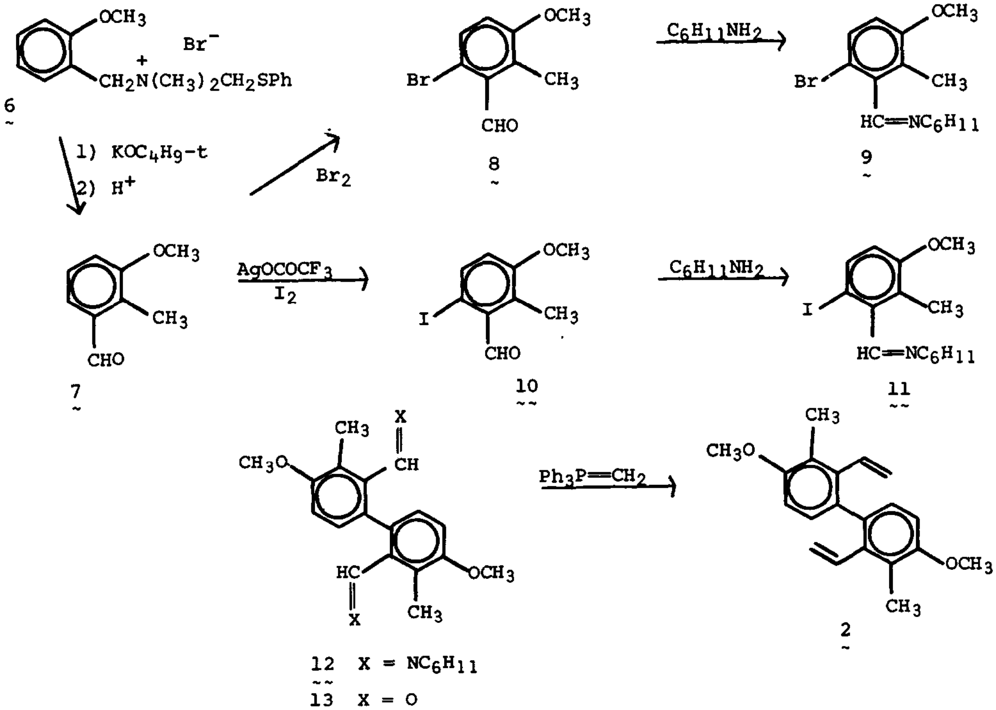


The photochemistry implicit in the above analysis rests upon several recent examples of the photocyclization of 2-vinylbiphenyl and related systems. In 1973, Morgan et al. discovered that photolysis of 2-vinylbiphenyl produced 9,10-dihydrophenanthrene as the sole product, even in the presence of oxygen.[4] More recently, Padwa et al. found that photolysis of 2,2'-divinylbiphenyl (3) produced a mixture of 4-vinyl-9,10-dihydrophenanthrene (4) and 4,5,9,10-tetrahydropyrene (5).[5] Long periods of irradiation produced only 5, presumably by a second photoreaction of 4.



3 5

In order to construct the divinylbiaryl required for the proposed strategy, 3-methoxy-2-methylbenzaldehyde 7[6] was first prepared in 78% overall yield using a modified Sommelet-Hauser rearrangement[7] as follows. Reaction of 2-methoxybenzyl bromide with dimethylaminothiophenylmethane gave the ammonium salt 6 (mp 159-162°), which on treatment with potassium t-butoxide in 1,2-dimethoxyethane (-20° to r.t., 3.5 hrs) followed by acid hydrolysis (2N H_2SO_4, r.t., 30 min) gave aldehyde 7. Bromination of 7 (Br_2, HOAc, r.t., 36 hrs) produced the single bromoaldehyde 8, mp 65-67°, in 93% yield.[8] Similarly, iodination of aldehyde 7 (I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 24 hrs)[9] gave iodoaldehyde 10, mp 68-69°, in 77% yield. These two compounds were converted to their respective cyclohexylimines ($H_2NC_6H_{11}$, C_6H_6, reflux) 9 and 11, and these were coupled by the method of Ziegler.[10] Thus bromoimine 9 was lithiated (BuLi, THF, -78°) and converted to the cuprate ($CuI\cdot(EtO)_3P$). Addition of iodoimine 11 produced the coupled diimine 12 in 93% yield (mp 103-103.5°). Hydrolysis (1:1 THF/satd. oxalic acid, r.t., 12 hrs) gave the dialdehyde 13, mp 215-218°, in 95% yield. Treatment of this dialdehyde with 2.1 equivalents of methylenetriphenylphosphorane (BuLi, THF, r.t., 12 hrs) produced the desired divinylbiaryl 2 (R = CH_3), mp 147.5-149°, in 89% yield.

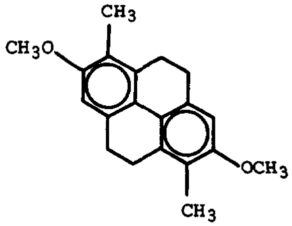


6 8 9 7 10 11 2

12 X = NC_6H_{11}

13 X = O

With the desired photochemical substrate in hand, the photolysis of 2 (R = CH_3) was carefully investigated. Even at short irradiation times the major reaction components observed were starting material and tetrahydropyrene 14. No juncusol dimethyl ether could be detected by nmr or chromatography.



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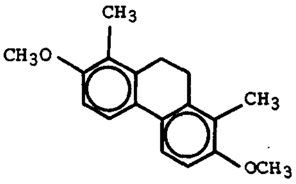

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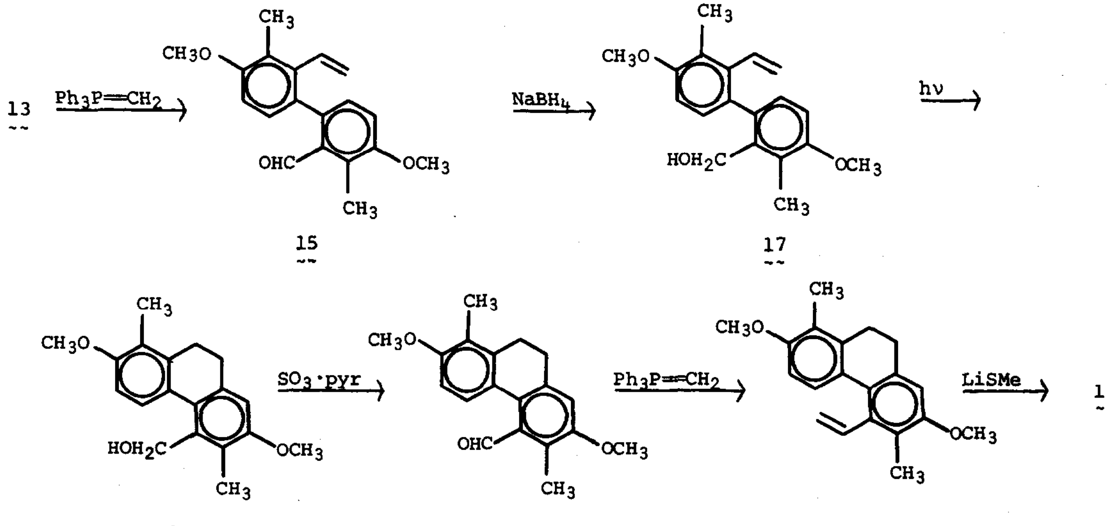
To circumvent this problem, dialdehyde 13 was converted by 0.9 eqts of $Ph_3P{=}CH_2$ to the vinyl aldehyde 15, mp 124-126° (77% yd at 71% conversion). Photolysis of this substance gave little of the desired dihydrophenanthrene but led principally to the deformylated by-product 16, as anticipated from the results of Padwa.[5] However, reduction of vinyl aldehyde 15 ($NaBH_4$, THF/EtOH, r.t., 1 hr) gave vinyl alcohol 17, mp 112-114°, in quantitative yield. Irradiation of alcohol 17 in benzene produced the desired dihydrophenanthrene alcohol 18, mp 191-193°, in 65% yield. Oxidation of alcohol 18 using SO_3-pyridine[11] (Et_3N, DMSO, r.t.) produced the dihydrophenanthrene aldehyde 19 (mp 192-194°) and this was converted by Wittig reaction to give juncusol dimethyl ether (20), mp 149-150°, in 70% yield from 18. The ^{13}C-nmr spectrum of synthetic 20 was indistinguishable from that published[12] for 20 derived from natural juncusol. Completion of our synthesis was achieved by demethylation of 20 using the Kelly procedure ($LiSCH_3$, HMPA, 160°, 2 hrs)[13] to give juncusol (1) in 81% yield. Synthetic juncusol, mp 174.5-175.5° (lit 176°) exhibited ir, 100 MHz nmr and mass spectra identical to those recorded by Miles;[1] tlc and mixed mp comparison with authentic juncusol confirmed its identity.[15]



15 17 18 19, 20

Our vinylbiphenyl photolysis route, while somewhat modified from the original strategy, provides an efficient total synthesis of juncusol in ca. 14% yield from o-anisyl alcohol. In principle, the route offers some generality for the synthesis of related 9,10-dihydrophenanthrene natural products.[14]

References:

1. D. H. Miles, J. Bhattacharyya, N. V. Mody, J. L. Atwood, S. Black and P. A. Hedin, *J. Am. Chem. Soc.*, **99**, 618 (1977).
2. (a) R. M. Letcher and L. R. M. Nhamo, *J. Chem. Soc., Perkin I*, 1263 (1973).
   (b) A. Stoessl, G. L. Rock and M. H. Fisch, *Chem. Ind.*, 703 (1974).
3. For the reduction of phenanthrene to dihydrophenanthrene *cf.* *Org. Syn.* IV, 313, and references therein.
4. S. W. Horgan, D. D. Morgan and M. Orchin, *J. Org. Chem.*, **38**, 3801 (1973).
5. A. Padwa, C. Doubleday and A. Mazzu, *J. Org. Chem.*, 42, 3271 (1977); *cf.* P. H. G. op het Veld, J. C. Langendam and W. H. Laarhoven, *Tetrahedron Lett.*, 231 (1975).
6. All new compounds were characterized by ir, ^{1}H-nmr and ms or combustion analysis. Melting points are uncorrected.
7. D. Michelot, R. Lorne, C. Huynh and S. Julia, *Bull. Chem. Soc., France*, **43**, 1482 (1976).
8. Generally, 3-hydroxybenzaldehydes halogenate first in the 6 position, *cf.* H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, **127**, 876 (1925); H. H. Hodgson and E. W. Smith, *J. Chem. Soc.*, **76** (1937).
9. *Org. Syn.* IV, 547.
10. F. E. Ziegler, K. W. Fowler and S. Kanfer, *J. Am. Chem. Soc.*, **98**, 8282 (1976).
11. K. Amura, A. K. Sharma and D. Swern, *J. Org. Chem.*, **41**, 957 (1976).
12. S. W. Pelletier, N. V. Mody, D. H. Miles and J. Bhattacharyya, *Tetrahedron Lett.*, 425 (1978)
13. T. R. Kelly, H. M. Dali and W. G. Tsang, *Tetrahedron Lett.*, 3859 (1977).
14. Partial support of this work by Grant CA-18846 from the National Cancer Institute, U. S. Public Health Service, and by Hoffmann La Roche Inc. is gratefully acknowledged. D. P. C. acknowledges with thanks a Sherman Clarke Fellowship. The authors are grateful to Dr. Jean-Pierre Gesson (Univ. Poitiers, France) for calling to their attention the modified Sommelet-Hauser procedure, and wish to thank Drs. P. M. Hendricks and J. M. Hewitt (Eastman Kodak Research Laboratories) for a ^{13}C-nmr of juncusol dimethyl ether.
15. We are grateful to Professor D. H. Miles for providing us a reference sample and to Dr. N. V. Mody for nmr spectra of authentic juncusol.

(Received in USA 2 May 1978; received in UK for publication 20 June 1978)