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AROMATIC RING SYNTHESIS BY N-AMINOPYRROLE DIELS-ALDER REACTION. TOTAL SYNTHESIS OF JUNCUSOL

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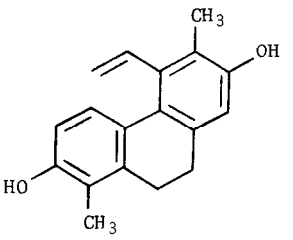
A total synthesis of the cytotoxic phytoalexin juncusol (1) is described.

The 9,10-dihydrophenanthrene juncusol (1), isolated from Juncus roemerianus,[1] has been found to be highly active against human nasopharynx carcinoma. Two total syntheses of juncusol have been reported[2,3] and Kende has noted the synthetic difficulties inherent in approaches toward unsymmetrical and highly substituted dihydrophenanthrenes of this type.[2] Both published syntheses of juncusol rely on a 2-vinyl biphenyl photocyclization to establish the 9,10-dihydrophenanthrene ring system; an unsuccessful approach founded on a stilbene oxidative-photocyclization has been reported.[2,4] We, on the other hand, have elected to use an aromatic ring construction via the Diels-Alder based N-aminopyrrole → benzene ring methodology recently developed in our laboratory.[5] The clear advantage of this strategy is that a preformed, readily available tetralone ring system may serve as starting material (e.g., 2); thus, problems associated with aromatic ring coupling are avoided.



1

Our initial goal[6] became synthesis of the highly developed dihydrophenanthrene 6, in as much as Kende had already detailed the conversion of 6 to juncusol (1).[2] Tetralone 2 is prepared in five steps from commercially available[7] 2,6-dihydroxynaphthalene in 72% overall yield.[8] Condensation of 2 (Scheme 1) with pyrrolidine (benzene, reflux) followed by reaction of the resulting enamine with ethyl 3-carbomethoxyazo-2-butenoate[5] in THF solution gives pyrrole 3 (82%, mp 197-198°C from methanol; Anal. Calcd. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.71; H, 6.34; N, 7.57).

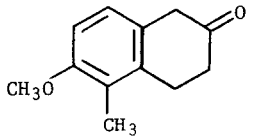
The conversion of 3 to 4h requires a regioselective Diels-Alder addition of 3 to a methoxyacetylene equivalent. While electron-rich acetylenes do not readily add to N-amino-pyrroles (not even when electron-withdrawing substituents are on the pyrrole nucleus), we expected that carbonyl-substituted acetylenes would undergo smooth addition to 3.[5] Furthermore, the (electronic) substitution pattern of 3 appeared particularly suited to the induction of a high degree of regioselectivity in Diels-Alder addition to mono-carbonyl substituted acetylenes to give substitution of type 4 rather than 5; Baeyer-Villiger methodology would then provide the means to 4h.

Diels-Alder reaction of 3 with propiolaldehyde is unsuccessful; however, with methyl propiolate (dry xylene solvent, N_2 atm., reflux 24 h), 4a (mp 98-99°C from methanol)[10] and 5a (mp 73-74°C from hexane) are produced in 70% HPLC-isolated yield;[11] 4a:5a (3:1). Using similar reaction conditions, ethyl propiolate gives 4b and 5b (2:1, respectively), and 3-butyne-2-one gives 4c (mp 139-140°C) and 5c (mp 112-114°C; 3.2:1, respectively).

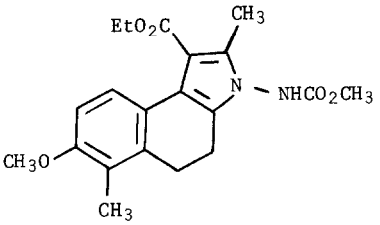
Pure 4a can be obtained in multigram quantities and conversion to 6 begins by diisobutylaluminum hydride reduction to 4d (94%, mp 118-119°C), followed by pryidinium dichromate[12] oxidation of 4d to 4e (79%, mp 121-123°C). Reaction of 4e with m-chloroperbenzoic acid in methylene chloride at room temperature for 48 h gives formate 4f (64%, oil) and this undergoes saponification (KOH, H_2O/THF) to phenol 4g (70%, oil). Methylation of 4g (CH_3I, K_2CO_3, DMF, N_2 atm.) gives 4h (74%),[13] and this is converted to 6 by lithium aluminum hydride reduction in refluxing THF solution (87%, mp 190-192°C, lit. mp 191-193°C).[2] Alcohol 6 is identical (tlc, vpc and ^1H NMR) to a sample of 6 kindly provided by Andrew Kende.

With a formal total synthesis of juncusol complete, we intend to pursue a more direct route to 1, perhaps via methyl ketone 4c; 4c also should provide access to a compound recently

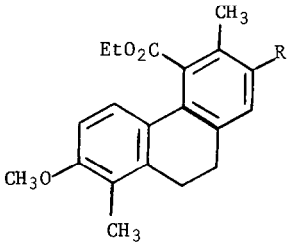
Scheme 1



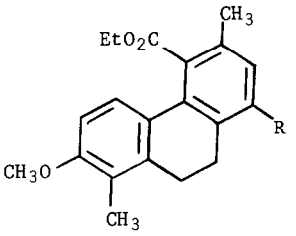
2



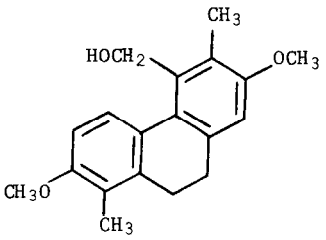
3



4a, R = CO_2CH_3
b, R = $CO_2C_2H_5$
c, R = $COCH_3$
d, R = CH_2OH
e, R = CHO
f, R = OCHO
g, R = OH
h, R = OCH_3



5a, R = CO_2CH_3
b, R = $CO_2C_2H_5$
c, R = $COCH_3$



6

formulated as the natural product juncunol.[14,15] The simplicity of this annelation approach to 9,10-dihydrophenanthrenes suggests that the method may be generally useful for preparation of other highly substituted aromatic ring systems.

Acknowledgment

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6. A. preliminary report of the synthesis of 1 was presented at the Second Chemical Congress of the North American Continent, Las Vegas, Nevada, A. G. Schultz and M. Shen, ORGN 153.
7. Aldrich Chemical Co.
8. We have improved a procedure for preparation of 2 that was described by B. R. Davis and L. J. Forrest, J. Chem. Soc.(c), 2678 (1967); details of our procedure will be found in A. G. Schultz and M. Shen, Org. Prep. Proc. Intl., submitted for publication.
9. Microanalysis was carried out by Spang Microanalytical Laboratories, Eagle Harbor, MI.
10. Satisfactory elemental analyses also were obtained for 4a, 5a, 4c, 4d, and 4e. All reported compounds gave IR, ^{1}H NMR and mass spectra completely in accord with the assigned structures.
11. A Waters Prep LC/system 500 (using Prep PAK-500 silica cartridges) was used.
12. E. J. Corey and G. Schmidt, Tetrahedron Lett., 399 (1979).
13. The methyl ester analog of 4h is an intermediate in the McDonald and Martin synthesis of Juncusol; see reference 3.
14. J. Bhattacharyya and D. H. Miles, Tetrahedron Lett., 2749 (1977).
15. On the basis of total synthesis, the structure of juncunol very recently has been reformulated; see A. L. Cossey, M. J. Gunter, and L. N. Mander, Tetrahedron Lett., 21, 3309 (1980).

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