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REGIOSPECIFIC TOTAL SYNTHESIS OF JUNCUSOL

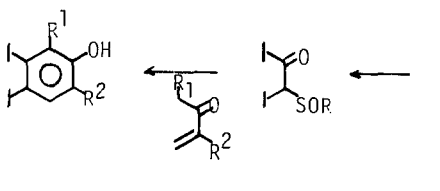
Dale L. Boger*[1a] and Michael D. Mullican[1b]
Department of Medicinal Chemistry, The University of Kansas
Lawrence, Kansas 66045

Abstract: A regiospecific total synthesis of juncusol (1) based on the use of two consecutive phenol annulations is detailed.

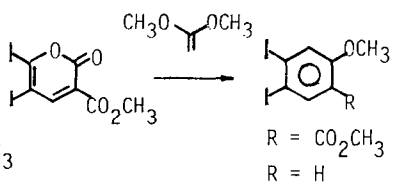
A recent search for the antileukemic constituents in the extracts of needle rush, Juncus roemerianus, resulted in the isolation and identification of juncusol (1), a highly substituted 9,10-dihydrophenanthrene[2] possessing modest antitumor and antimicrobial properties. The unusual structure of juncusol (1), its confirmed cytotoxic properties, and the notable lack of synthetic methodology capable of easily accommodating the aromatic substitution patterns found in this and related dihydrophenanthrenes have provided the incentive for much synthetic work in the interval since its initial identification.[3,4,5]

In recent communications we described the development of two different phenol annulations: the first based on the Robinson annulation of β-keto sulfoxides, equation 1, and the second based on the inverse electron demand Diels-Alder reaction of 3-carbomethoxy α-pyrones with 1,1-dimethoxyethylene, equation 2.[6] Herein we would like to disclose our efforts on the development of a conceptually simple and regiospecific total synthesis of juncusol (1) based on the use

eqn. 1

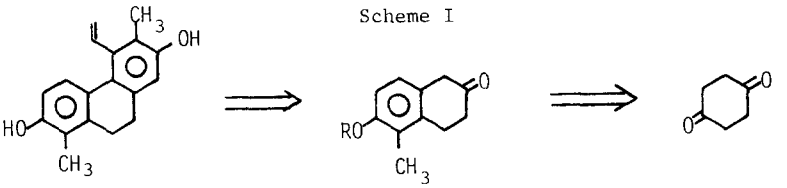


eqn. 2



of two such phenol annulations, Scheme I. Implicit in the design of this approach is the ease with which the substitution pattern of either phenol may be introduced or altered.

Scheme I



1

Conversion of 4-benzyloxy-cyclohexanone (2)[7] to the β-keto-sulfoxide 4 (80%)[8] followed by application of the first phenol annulation[6] (1.4 equiv. ethyl vinyl ketone; 0.1 equiv. t-BuOK/t-BuOH in THF, 0°C, 22.5 h; 1.2 equiv. t-BuOK/t-BuOH in THF, 25°C, 23 h) and immediate methylation of the crude, free phenol 6 (3.0 equiv. Me_2SO_4, 3.0 equiv. K_2CO_3, refluxing acetone 72 h) afforded 7 (60%). The simplicity of this sequence allows multigram quantitites of 7, and related compounds, to be prepared with ease. The removal of the benzyl protecting group (H_2, 10% Pd/C cat., 98%) followed by Oppenhauer oxidation gave tetralone 9[10] and preceded application of the second phenol annulation. Treatment of tetralone 9 with dimethyl methoxymethylenemalonate (10)[11] in the presence of sodium hydride afforded the 3-carbomethoxy α-pyrone 11 (81%)[6] and subsequent inverse electron demand Diels-Alder reaction of 11 with 1,1-dimethoxyethylene (12, 140°C, 21h, toluene) afforded cleanly the dihydrophenanthrene 13 (75%).[6] Conversion of 13 to juncusol (1) required introduction of the C-4 vinyl substituent and was completed as follows: lithium aluminum hydride reduction, 13 → 14; anhydrous HBr, benzene, 14 → 15; $PhSCH_2NMe_2$,[12,3a] acetonitrile, 15 → 16; t-BuOK, dimethoxyethane, 16 → 17;[12,3a] and aqueous hydrolysis of 17 gave aldehyde 18[13] which was converted to juncusol (1) as previously described.[3,13]

Thus, the successful implementation of two consecutive and regiospecific phenol annulations provided the basis for a simple preparation of juncusol (1) and minor modification of this approach, in principle, allows the preparation of related dihydrophenanthrenes. Additional applications of these phenol annulations to problems of synthetic and medicinal interest are currently in progress.

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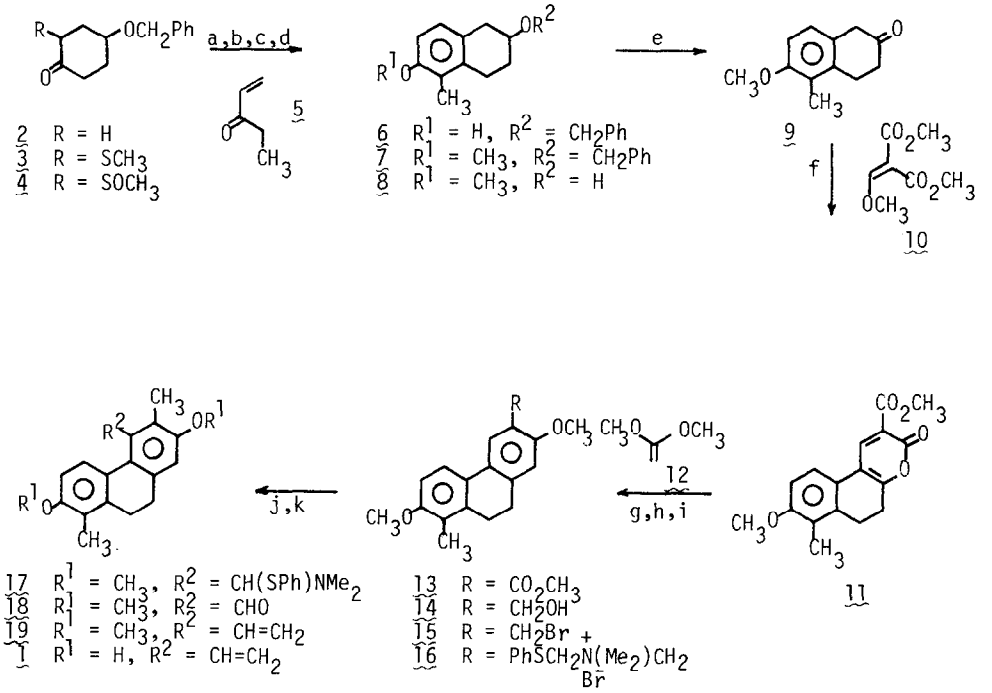
Scheme II



(a) 2.2 equiv. LDA, -78° to 30°C, 1.5 h, THF; 2.2 equiv. CH_3SSCH_3, THF-HMPA, -30° to 25°C, 4.5 h. 75%. (b) 1.0 equiv. $NaIO_4$, MeOH-H_2O, 27 h, 0 - 25°C, 88% (c) 1.4 equiv. ethyl vinyl ketone, 0.1 equiv. t-BuOK/t-BuOH - THF, 22.5 h, 0°C; 1.2 equiv. t-BuOK/t-BuOH-THF, 23 h, 25°C; 3.0 equiv. Me_2SO_4, 3.0 equiv. K_2CO_3, acetone, 56°C, 72 h, 60% (d) 1 atm H_2, 10% Pd/C cat., THF, 24 h, 25°C, 98%. (e) 1.0 equiv. Al(i-OPr)$_3$, 23 equiv. cyclohexanone, toluene, 110°C, 1.5 h, 72%. (f) 2.2 equiv. NaH, THF; 1.2 equiv. dimethyl methoxymethylenemalonate, 0 - 25°C, 2.5 h, 81%. (g) 10.0 equiv. 1,1-dimethoxyethylene, toluene, 140°C, 22 h, 75%. (h) $LiAlH_4$, THF, 0°C, 1 h, 99%. (i) HBr(g), benzene, 25°C, 5 min.; Me_2NCH_2SPh, CH_3CN, 25°C, 14 h. (j) 3.0 equiv. t-BuOK, DME, -20° to 25°C, 4.5 h; H_2O-HOAc-THF (1:3:3), 15 h, 25°C, 25% from 14. (k) Ph_3PCH_2, THF, 16 h, 25°C, PhSLi; HMPA, 2 h, 160°C,[3a] 65%.

References and Notes.

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13. All intermediates exhibited the expected or reported IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data and satisfactory elemental analysis (± 0.40%) or high resolution mass spectra were obtained for all isolated intermediates: 3, 4, 7-9, 11, 12, 14-16, 18, 1. Spectra of synthetic aldehyde 18 was identical in all respects to spectra of authentic aldehyde 18 kindly provided by Professor A. S. Kende.

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