Regiospecific Total Synthesis of Juncusol

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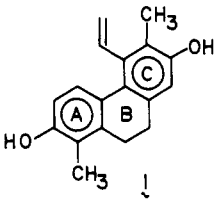
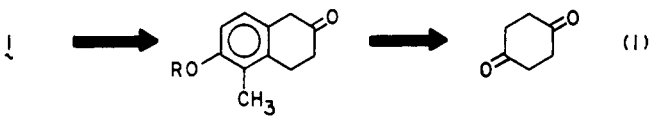
A regiospecific, total synthesis of juncusol, a substituted 9,10-dihydrophenanthrene possessing antimicrobial and cytotoxic properties, based on two sequential aryl annulations is described.

A search for the antileukemic constituents in the extracts of needle rush, *Juncus roemerianus*, resulted in the isolation and identification[2] of juncusol (**1**), a substituted



9,10-dihydrophenanthrene shown to possess antitumor[2,3a] and antimicrobial properties.[3b] The unusual structure of juncusol, its confirmed cytotoxic properties, and the notable lack of methodology capable of easily accommodating its aryl substitution patterns have provided the incentive for synthetic efforts in the interval since its identification.[4,5]

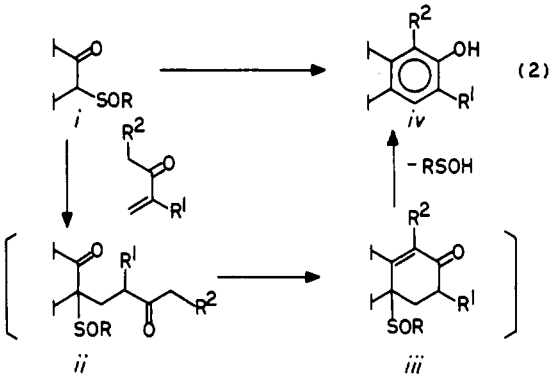
Herein we report full details[6] of a simple and regiospecific, total synthesis of juncusol based on the sequential implementation of two aryl annulations, eq 1. A Robinson



(1)

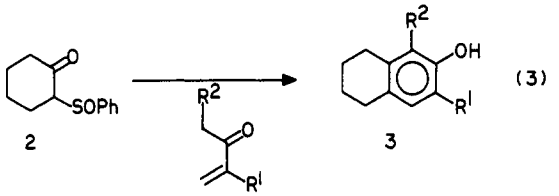
annulation of a β-keto sulfoxide[7] is used for introduction of ring A and an inverse electron demand Diels–Alder reaction of a 3-carbomethoxy-2-pyrone[8] is employed for introduction of ring C. Implicit in the design of this approach is the ease with which the substitution pattern of either phenol may be introduced or altered.

The initial phenol annulation, used for introduction of ring A of juncusol, is based on the Robinson annulation of β-keto sulfoxides, eq 2.[7] Results of a previous study[7]



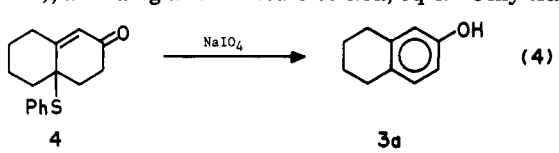
(2)

with 2-(phenylsulfinyl)cyclohexanone (**2**)[9a] outlined the scope of this reaction and demonstrated the facility with which this process can be accomplished in a single operation under mild conditions (0–25 °C), eq 3. The room



(3)

temperature elimination of phenylsulfenic acid (iii → iv, R = Ph) was unexpected[9] but not unprecedented.[9b] In order to confirm that this aromatization step is a low temperature, syn elimination of phenylsulfenic acid and not a base-catalyzed elimination,[7b] 10-(phenylthio)-$\Delta^{1,9}$-octalone (**4**) was prepared by the Robinson annulation of 2-(phenylthio)cyclohexanone with methyl vinyl ketone (1.2 equiv, 0.1 equiv of MeONa, MeOH, 0 °C, 25 h; 1.2 equiv of MeONa, 25 °C, 7 h, 41%) and subjected to neutral periodate oxidation[9a] (1.5 equiv of $NaIO_4$, MeOH–H_2O, 25 °C, 48 h), affording a 1:1 mixture of **4**:**3a**, eq 4. Only traces



(4)

of the intermediate sulfoxide could be detected at any given time. Thus, the aromatization step appears to be a low temperature, syn elimination of phenylsulfenic acid,

(1) (a) Searle Scholar Recipient, 1981–1984. Recipient of a Career Development Award, 1983–1988, from the National Cancer Institute of the National Institutes of Health (CA 00898). (b) National Institutes of Health Predoctoral Trainee, 1980–1983 (GM 07775).

(2) (a) Miles, D. H.; Bhattacharyya, J.; Mody, N. V.; Atwood, J. L.; Black, S.; Hedin, P. A. *J. Am. Chem. Soc.* **1977**, *99*, 618. (b) Miles, D. H., Pelletier, S. W.; Bhattacharyya, J.; Mody, N. V.; Hedin, P. A. *J. Org. Chem.* **1978**, *43*, 4371. (c) Pelletier, S. W.; Mody, N. V.; Bhattacharyya, J.; Miles, D. H. *Tetrahedron Lett.* **1978**, 425.

(3) (a) De'la Cruz, A. A.; Miles, D. H.; Chapatwala, K. D. *Life Sci.* **1982**, *30*, 1805; (b) De'la Cruz, A. A.; Miles, D. H.; Chapativala, K. D. *Ibid.* **1981**, *29*, 1997. (c) For a discussion of the phytoalexin properties of hydroxy-substituted 9,10-dihydrophenanthrenes, see: Fritzemeier, K.-H.; Kindl, H. *Eur. J. Biochem.* **1983**, *133*, 545.

(4) For total syntheses of juncusol, see: (a) Kende, A. S.; Curran, D. P. *Tetrahedron Lett.* **1978**, 3003; *J. Am. Chem. Soc.* **1979**, *101*, 1857. (b) McDonald, E.; Martin, R. T. *Tetrahedron Lett.* **1978**, 4723. (c) Schultz, A. G.; Shen, M. *Ibid.* **1981**, *22*, 1775.

(5) For additional studies on juncusol and related synthetic materials, see: (a) Leed, A. R.; Boettiger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098. (b) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.

(6) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4555.

(7) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002. For related work, see: (b) Jaxa-Chamiec, A. A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 170. Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc., Chem. Commun.* **1978**, 118. (c) Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *Ibid.* **1980**, 1183; (d) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (e) Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. S.; Shew, D. C. *J. Org. Chem.* **1976**, *41*, 1005.

(8) Boger, D. L.; Mullican, M. D. *J. Org. Chem.*, first paper in a series in this issued; *Tetrahedron Lett.* **1982**, *23*, 4551.

(9) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887; (b) Dean, F. M.; Park, B. K. *Tetrahedron Lett.* **1974**, 4275. (c) The thermal elimination of unactivated sulfoxides require temperatures in excess of 200 °C and the elimination of activated sulfoxides, e.g. β-keto sulfoxides, usually require temperatures of 70 °C (β-keto phenylsulfoxide) to 110 °C (β-keto methylsulfoxides).

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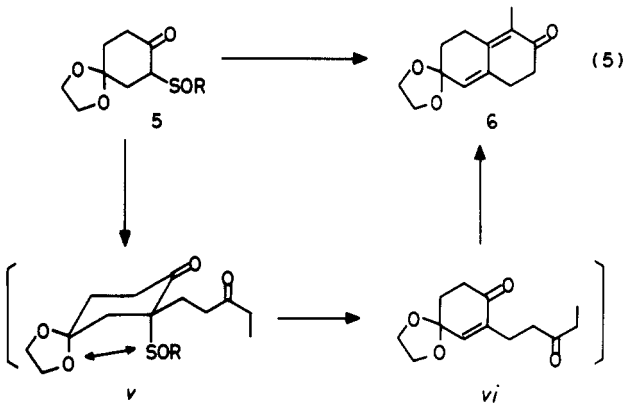
and the results of this experiment suggest a useful, two-step alternative to the reaction detailed in eq 2.

Initial attempts to apply this reaction to the introduction of ring A of juncusol were unsuccessful. Treatment of **5** (R = Ph) with ethyl vinyl ketone afforded the dienone **6** (40%) as the predominate product,[10] eq 5. This suggested

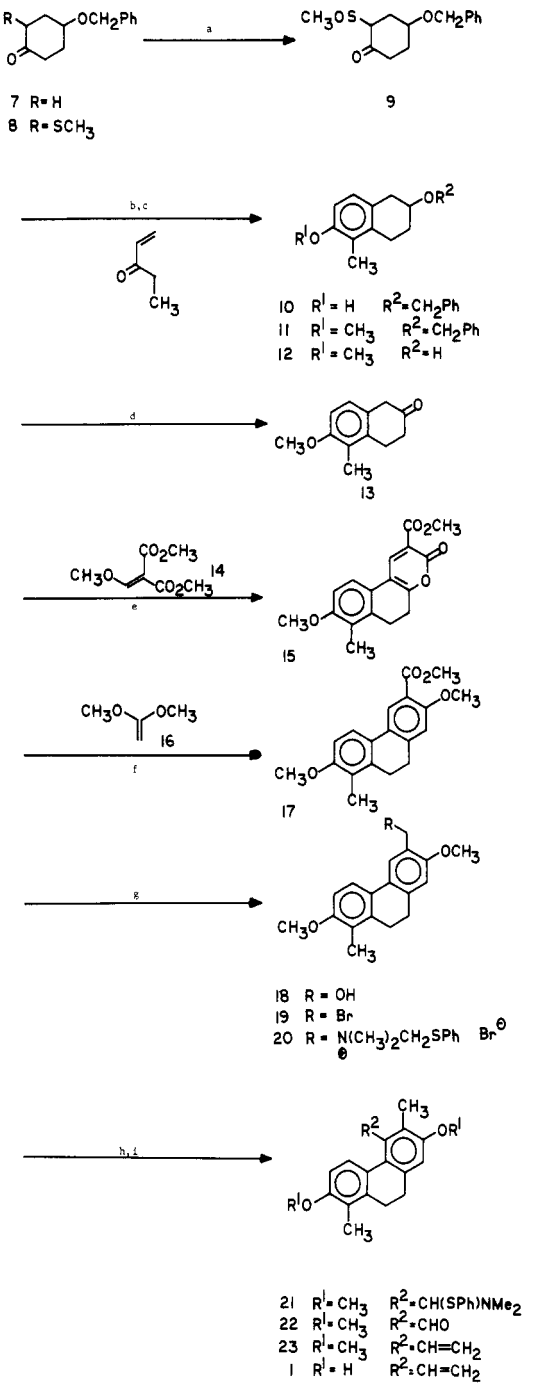


(5)

that the elimination of phenylsulfenic acid was preceding aldol condensation. Attempts to prevent this premature elimination using the methyl sulfoxide **5**[9c] (R = CH_3) were modestly successful but did not suppress it completely. Dienone **6** could be isolated in low yield (10%) from the reaction of **5** (R = CH_3) with ethyl vinyl ketone. Intermediates v must suffer an unfavorable 1,3-diaxial interaction, thus promoting the low-temperature elimination of phenyl- or methylsulfenic acid. Removal of this 1,3-diaxial interaction using methylsulfoxide **9** proved successful in suppressing dienone formation and its use in the synthesis of juncusol is summarized in Scheme I.

Conversion of 4-(benzyloxy)cyclohexanone[11] (**7**) to 4-(benzyloxy)-2-(methylsulfinyl)cyclohexanone (**9**) followed by treatment with ethyl vinyl ketone (1.4 equiv, 0.1 equiv of *t*-BuOK/*t*-BuOH, THF, 0 °C, 22.5 h; 1.2 equiv of *t*-BuOK/*t*-BuOH, THF, 25 °C, 23 h) and subsequent methylation of the crude phenol **10** afforded **11** (61%). The fact that this reaction has been reproducibly executed on scales ranging from 0.3 mmol to 0.1 mol attests to the generality of the procedural conditions employed for this phenol annulation. Removal of the benzyl protecting group and Oppenhauer oxidation[12] afforded tetralone **13**.[13] All other methods of oxidation, including chromic acid,[14a] chromium trioxide–pyridine,[14b] pyridine chlorochromate,[14c] pyridinium dichromate,[14d] and dimethyl sulfoxide/oxalyl chloride,[14e] failed to produce the β-tetralone **13** cleanly. Treatment of tetralone **13** with dimethyl (methoxymethylene)malonate (**14**)[8] in the presence of sodium hydride afforded the 3-carbomethoxy-2-pyrone **15** (81%), and subsequent methyl salicylate formation[8] utilizing the inverse electron demand Diels–Alder reaction of **15** with 1,1-dimethoxyethylene (**16**) cleanly provided 9,10-dihydrophenanthrene **17** (75%). The final conversion of **17** to juncusol (**1**) required introduction of the C-4 vinyl substituent and was accomplished utilizing a modified

Scheme I[a]



[a] (a) 2.2 equiv of LDA, −78 to −30 °C, 1.5 h, THF; 2.2 equiv of CH_3SSCH_3, THF–HMPA, −30 to 25 °C, 4.5 h; 1.0 equiv of $NaIO_4$, MeOH–H_2O, 27 h, 0 to 25 °C, 80%. (b) 1.5 equiv of ethyl vinyl ketone, 0.1 equiv of *t*-BuOK/*t*-BuOH–THF, 22.5 h, 0 °C; 1.2 equiv of *t*-BuOK/*t*-BuOH–THF, 23 h, 25 °C; 4.8 equiv of Me_2SO_4, 5.1 equiv of K_2CO_3, acetone, 56 °C, 72 h, 61%. (c) H_2, 10% Pd/C, THF, 24 h, 25 °C, 98%. (d) 3.4 equiv of Al(*i*-OPr)$_3$, 23 equiv of cyclohexanone, toluene, 110 °C, 1.5 h, 72%. (e) 2.2 equiv of NaH, THF, 1.2 equiv of dimethyl (methoxymethylene)malonate (**14**), 0 to 10 °C, 2.5 h, 81%. (f) 10.0 equiv of 1,1-dimethoxyethylene (**16**), toluene, 140 °C, 22 h, 75%. (g) $LiAlH_4$, THF, 0 °C, 1 h; HBr (g), benzene, 25 °C, 15 min; Me_2NCH_2SPh, CH_3CN, 25 °C, 14 h, 99%. (h) 3.0 equiv of *t*-BuOK, DME, −20 to 25 °C, 4.5 h; H_2O:HOAc:THF (1:3:3), 16 h, 25 °C, 27%. (i) 7.3 equiv of Ph_3PCH_2, THF, 16 h, 25 °C; 6 equiv of EtSLi, HMPA, 2 h, 160 °C, 65%.

(10) (a) This type product has been observed in the Robinson annulation of 2-acetoxycyclohexanone with an ethyl vinyl ketone equivalent, see: Szmuszkovicz, J.; Born, H. *J. Am. Chem. Soc.* **1953**, *75*, 3350.

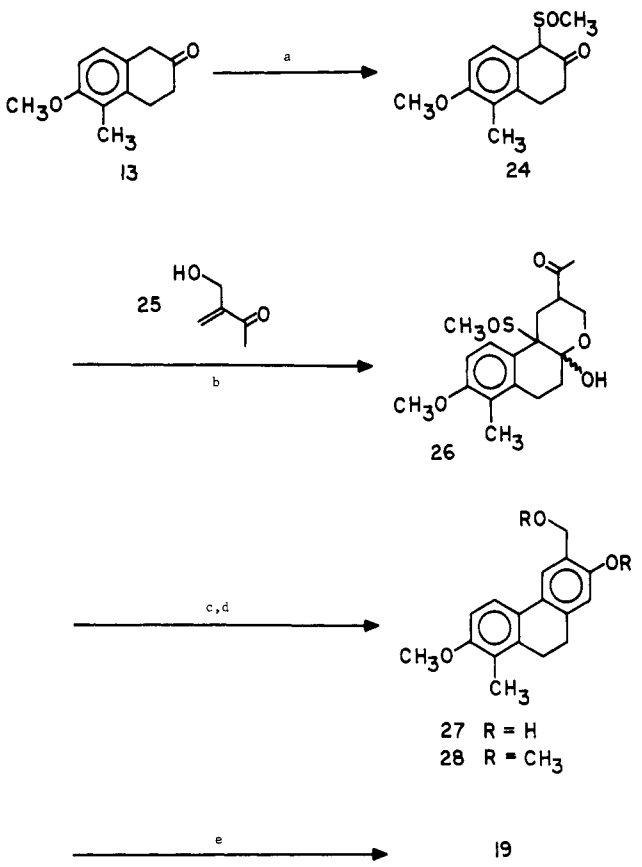
(11) Prins, D. A. *Helv. Chim. Acta* **1957**, *40*, 1621.

(12) Eastham, J. F.; Teranishi, R. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 192.

(13) (a) Davis, B. R.; Forest, L. J. *J. Chem. Soc. C* **1967**, 2677. (b) Shen, M.; Schultz, A. G. *Org. Prep. Proc. Int.* **1983**, *15*, 145.

(14) (a) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548. (b) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000. (c) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (d) Corey, E. J.; Schmidt, G. *Ibid.* **1979**, 399. (e) Mancuso, A. J.; Huang, S-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

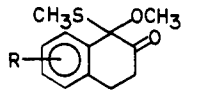
Scheme II[a]

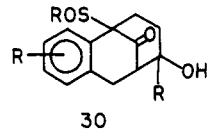


[a] (a) 2.2 equiv of LDA, −78 to −30 °C, 1.5 h, THF; 2.2 equiv of CH_3SSCH_3, THF-HMPA, 27 h (25 °C), 19 h (36 °C), 75%; 1.0 equiv of *m*-CPBA, CH_2Cl_2, −78 °C, 0.5 h, 67%. (b) 1.32 equiv of **25**, 1.1 equiv of DBU, THF, 0 °C, 5 h, 73%. (c) 1.1 equiv of *t*-BuOK, benzene, 4 h, 5 °C. (d) 3.5 equiv of NaH, excess CH_3I, THF, 18 h, 25 °C. (e) HBr (g), benzene, 25 °C, 5 min.

Sommelett–Hauser rearrangement.[15] Lithium aluminum hydride reduction of **17** to the primary alcohol **18**, conversion to the benzylic bromide **19**, and subsequent formation of the quaternary ammonium salt **20** preceded the [2,3]-sigmatropic rearrangement (6.0 equiv of *t*-BuOK, DME, −20 to 25 °C, 4.5 h) and aqueous acid hydrolysis afforded the aldehyde **22**.[4,16] The final conversion of aldehyde **22** to juncusol (**1**) was carried out as described by Kende[4a] and provided material which displayed properties identical with that reported for natural juncusol.[2,4]

An alternative, and less satisfactory, introduction of the C ring of juncusol based on the Robinson annulation of β-keto sulfoxides is summarized in Scheme II. Conversion of β-tetralone **13** to the α-methylsulfinyl ketone **24** and treatment with 2-(hydroxymethyl)-2-buten-3-one[18] (**25**) under aprotic conditions [1.1 equiv of diazabicycloundecane (DBU), THF, 0 °C, 5 h addition of **25**, 73%] afforded **26**.[19] Base treatment of **26** followed by extensive methylation afforded 9,10-dihydrophenanthrene **28**.[20] Treatment of **28** with anhydrous hydrogen bromide gave **19** identical with material utilized in Scheme I. A number of unsuccessful alternatives to the route detailed in Scheme II were investigated. Exposure of α-methylsulfinyl ketones, such as **24**, to protic conditions (MeONa, MeOH) in the presence of α,β-unsaturated ketones produced the Pummerer product **29**.[21] Under aprotic conditions α,β-unsaturated ketones, e.g., methyl or ether vinyl ketone, produced principally the bridge aldol products **30** or failed to undergo Michael addition with **24**, e.g., 3-acetyl-5,6-dihydro-2*H*-pyran and 3-acetyl-5,6-dihydro-2*H*-pyran-2-one. The modest success with **25** can be attributed, in part, to the hemiacetal formation in **26**.

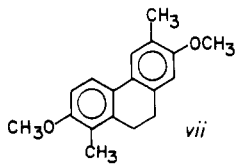




Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33, a Beckman Acculab-3, or a Perkin-Elmer 727 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM 360 or a Varian FT-80A spectrometer. ^{13}C NMR were recorded on a Varian FT-80A spectrometer. Electron-impact mass spectra (EIMS) and high-resolution mass spectra (HRMS) were obtained on a Varian CH-5 or a Ribermag R10-10 mass spectrometer by Charles Judson and Robert Drake. Microanalysis were performed by Tho I. Nguyen on a Hewlett-Packard Model 1858B CHN analyzer at the University of Kansas. Medium-pressure liquid chromatography (MPLC) was performed

(15) Michelot, D.; Lorne, R.; Huynh, C.; Julia, S. *Bull. Soc. Chim. Fr.* **1976**, *43*, 1482. In addition to aldehyde **22**, 9,10-dihydrophenanthrene **vii** was isolated in 20–28% yield: mp 177–178 °C (methanol); ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 9 Hz, 1 H, C-5 H), 7.44 (s, 1 H, C-4 H), 6.79 (d, J = 9 Hz, 1 H, C-6 H), 6.68 (s, 1 H, C-1 H), 3.84 (s, 6 H, two $ArOCH_3$), 2.80 (s, 4 H, $ArCH_2CH_2Ar$), 2.25 and 2.21 (two s, 3 H each, two $ArCH_3$); EIMS, m/e (relative intensity) 268 (M^+, base), 254 (24), 253 (97), 238 (20); HRMS, m/e 268.1466 ($C_{18}H_{20}O_2$ requires 268.1462). See also: Pine, S. H. *Org. React. (N.Y.)* **1970**, *18*, 403.



vii

(16) The spectra of aldehyde **22** were identical with spectra of authentic aldehyde **22** supplied by Professor A. S. Kende.

(17) Sulfoxide **24**, an unstable solid, was characterized: ^1H NMR ($CDCl_3$) δ 7.09 (d, J = 9 Hz, 1 H, C-8 H), 6.83 (d, J = 9 Hz, 1 H, C-7 H), 4.26 and 4.21 (two s, 1 H, $ArCHS(O)CH_3$), 3.84 (s, 3 H, $ArOCH_3$), 3.35–2.65 (m, 4 H, $ArCH_2CH_2$), 2.69 and 2.60 (two s, 3 H, $S(O)CH_3$), 2.19 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3020, 2980, 1710, 1600, 1590, 1480, 1260, 1090, 1040, 800 cm^{-1}; EIMS, m/e (relative intensity) 252 (M^+, 4), 190 (20), 189 (base), 161 (65), 146 (17), 115 (15), 91 (12), 63 (21); HRMS, m/e 252.0795 ($C_{13}H_{16}O_3S$ requires 252.0819).

(18) Gault, H.; Germann, L. A. *C. R. Hebd. Seances Acad. Sci.* **1933**, *197*, 620. Germann, L. A.; Delepine, M. *Ibid.* **1936**, *203*, 568.

(19) **26**: ^1H NMR ($CDCl_3$) δ 7.08 (d, J = 9 Hz, 1 H, Ar), 6.81 (m, 2 H, Ar), 4.15 (m, 2 H, $-CH_2O-$), 3.92 (s, 3 H, $ArOCH_3$), 3.10–1.80 (m, 7 H), 2.60 and 2.45 (two s, diastereoisomers, 3 H, $SOCH_3$), 2.14 and 2.09 (two s, isomers, 3 H, $COCH_3$), 2.12 (s, 3 H, $ArCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 208.2 (ketone), 93.5 (hemiacetal); IR ($CHCl_3$) ν_{max} 3600–2500, 2950, 2870, 1715, 1600, 1460, 1265, 1095 cm^{-1}; EIMS, m/e (relative intensity) 352 (M^+, 2), 335 (28), 281 (51), 273 (82), 272 (63), 261 (53), 253 (35), 93 (82), 64 (base).

(20) **28**: ^1H NMR ($CDCl_3$) δ 7.64 (s, 1 H, C-4 H), 7.58 (d, J = 9 Hz, 1 H, C-5 H), 6.79 (d, J = 9 Hz, 1 H, C-6 H), 6.73 (s, 1 H, C-1 H), 4.52 (s, 2 H, $ArCH_2OCH_3$), 3.85 and 3.84 (two s, 3 H each, two $ArOCH_3$), 3.43 (s, 3 H, CH_2OCH_3), 2.81 (s, 4 H, $ArCH_2CH_2Ar$), 2.19 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3020, 2960, 1620, 1595, 1480, 1460, 1260, 1240, 1095, 1060, 800 cm^{-1}; EIMS, m/e (relative intensity) 298 (M^+, base), 283 (20), 267 (12); HRMS, m/e 298.1555 ($C_{19}H_{20}O_3$ requires 298.1568).

(21) Moore, T. L. *J. Org. Chem.* **1967**, *32*, 2786. Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1975**, *97*, 596.

on silica gel 60 (230–400 mesh).[22] High-pressure liquid chromatography (HPLC) was performed on a Perkin-Elmer Series 2 liquid chromatograph. All dry solvents were distilled under argon or nitrogen. Tetrahydrofuran (THF) was distilled immediately before use from benzophenone ketyl. Benzene and 1,2-dimethoxyethane (DME) were distilled from benzophenone ketyl. Toluene, hexamethylphosphoric triamide (HMPA), and diisopropylamine were distilled from calcium hydride. Acetonitrile was distilled from phosphorus pentoxide (P_2O_5), and *tert*-butyl alcohol was distilled from calcium oxide. Extraction and chromatographic solvents (dichloromethane, ethyl acetate, ether, and hexane) were distilled before use. All reactions requiring anhydrous conditions were run under positive pressure of argon and reagents were introduced by syringe through a septum unless otherwise indicated. Syringes and reaction flasks for these reactions were oven-dried. All other reactions were sealed from the atmosphere or run under positive pressure of nitrogen.

4-(Benzyloxy)-2-(methylthio)cyclohexanone (8). A solution of 4-(benzyloxy)cyclohexanone[11] (7, 409 mg, 2.0 mmol) in 1.5 mL of dry THF was added over 15 min to a −78 °C solution of freshly generated lithium diisopropylamide[23] (4.3 mmol, 2.2 equiv) in 4.0 mL of dry THF under argon, and the mixture was stirred at −78 to −25 °C for 1.5 h. Dimethyl disulfide (413 mg, 4.4 mmol, 2.2 equiv) in 2.0 mL of THF and 1.5 mL of dry HMPA was added over 15 min to the −25 °C reaction mixture, and the resulting solution was stirred at −25 to 25 °C for 3.75 h. The reaction mixture was poured onto 20 mL of 10% aqueous HCl and 40 mL of ether. The layers were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with 10 mL of 10% aqueous HCl, 10% aqueous $NaHCO_3$ (3 × 10 mL), and 20 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 2 × 20 cm, 30% ether–hexane eluant) afforded 370 mg (501 mg theoretical, 74%) of a diastereomeric mixture (10:1) of 8[24] as yellow oil. The major isomer was characterized: ^1H NMR ($CDCl_3$) δ 7.23 (s, 5 H, C_6H_5), 4.50 (s, 2 H, OCH_2Ph), 3.83 (m, 1 H, C*H*SCH_3), 3.35 (m, 1 H, C*H*OCH_2Ph), 2.80–1.65 (m, 6 H, three CH_2), 2.00 (s, 3 H, SCH_3); IR (film) ν_{max} 2940, 1710, 1085, 725, 680 cm^{-1}; EIMS, *m/e* (relative intensity) 250 (M^+, 19), 158 (32), 97 (38), 91 (95), 85 (base).

Anal. Calcd for $C_{14}H_{18}SO_2$: C, 67.17; H, 7.25. Found: C, 67.58; H, 7.23.

4-(Benzyloxy)-2-(methylsulfinyl)cyclohexanone (9). Sodium periodate (300 mg, 1.4 mmol, 1.0 equiv) in 20 mL of water was added slowly (15 min) to a 0 °C solution of sulfide 8 (350 mg, 1.4 mmol) in 15 mL of methanol, and the resulting mixture was stirred at 25 °C for 12 h. The reaction was filtered, concentrated in vacuo, dissolved in ether, dried ($MgSO_4$), and concentrated again. Chromatography (SiO_2, 2 × 15 cm, ethyl acetate eluant) afforded 337 mg (373 mg theoretical, 90%) of a diastereomeric mixture (10:1) of 9 as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H, C_6H_5), 4.70 and 4.60 (two s, 2 H, OCH_2Ph), 4.25–3.21 (several m, 2 H, C*H*OCH_2Ph/C*H*$S(O)CH_3$), 2.61 and 2.50 (two s, 3 H, $S(O)CH_3$), 3.00–1.83 (m, 6 H, three CH_2); IR (film) ν_{max} 2940, 2870, 1715, 1045, 730, 690 cm^{-1}; EIMS, *m/e* (relative intensity) 266 (M^+, 0.1), 250 (1.4), 203 (3), 159 (10), 97 (11), 91 (10), 91 (base), 85 (20).

Anal. Calcd for $C_{14}H_{18}SO_3$: C, 63.10; H, 6.81. Found: C, 62.89; H, 6.78.

Sulfoxide 9 was prepared from 7 (132 mmol) in 80% yield (28 g) without purification of sulfide 8.

2-(Benzyloxy)-6-methoxy-5-methyl-1,2,3,4-tetrahydronaphthalene (11). Ethyl vinyl ketone (12.7 g, 150 mmol, 1.5 equiv) was added over 1 h to a 0–5 °C solution of sulfoxide 9 (26.6 g, 100 mmol), 20.0 mL of 0.5 M potassium *tert*-butoxide/*tert*-butyl alcohol (10.0 mmol, 0.10 equiv) in 500 mL of dry *tert*-butyl alcohol–THF (3:1) under argon, and the resulting mixture was stirred at 0–5 °C for 22.5 h. Additional potassium *tert*-butoxide (13.5 g, 120 mmol, 1.2 equiv) in 130 mL of dry *tert*-butyl alcohol was added through a dropping funnel (30 min), and the mixture was allowed to warm to 25 °C where it stirred for 23 h. The reaction solution was poured onto 300 mL of saturated aqueous NH_4Cl and extracted with ether–dichloromethane (5 × 150 mL of 3:1). The combined extracts were washed with 250 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to give crude phenol **10**.[25]

A mixture of crude phenol **10**, dimethyl sulfate (60.5 g, 480 mmol), and anhydrous potassium carbonate (70.1 g, 510 mmol) in 400 mL of acetone was warmed at reflux for 72 h under nitrogen. The reaction mixture was vacuum filtered through Celite (dichloromethane wash) and concentrated in vacuo. Medium-pressure liquid chromatography (SiO_2, 2.5 × 50 cm scrubber—2.5 × 100 cm, 15% ether–hexane eluant) afforded 17.0 g (28.0 g theoretical, 61%) of 11 as a pale yellow, crystalline solid: mp 85–86 °C (ether–hexane); ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H, C_6H_5), 6.91 (d, J = 9 Hz, 1 H, C-8 H), 6.68 (d, J = 9 Hz, 1 H, C-7 H), 4.63 (s, 2 H, OCH_2Ph), 3.78 (s, 3 H, $ArOCH_3$), 3.76 (m, 1 H, C*H*OCH_2Ph), 3.05–2.55 (m, 4 H, two CH_2Ar), 2.10 (s, 3 H, $ArCH_3$), 2.10–1.70 (m, 2 H, C*H*$_2CH_2Ar$); IR ($CHCl_3$) ν_{max} 3020, 2950, 1600, 1480, 1260, 1080, 785, 680 cm^{-1}; EIMS, *m/e* (relative intensity) 282 (M^+, 60), 191 (60), 174 (38), 149 (base), 91 (38).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.50; H, 8.00.

6-Methoxy-5-methyl-1,2,3,4-tetrahydro-2-naphthalenol (12). A solution of 11 (7.8 g, 27.6 mmol) in 75 mL of dry THF was added slowly (15 min) through a dropping funnel to 25 °C suspension of 10% palladium on carbon (1.52 g) in 75 mL of THF under hydrogen (1 atm). The resulting mixture was stirred at 25 °C for 24 h, vacuum filtered through Celite, and concentrated in vacuo to give 5.2 g (5.3 g theoretical, 98%) of 12 as a white, crystalline solid: mp 109–110 °C (ether–hexane); ^1H NMR ($CDCl_3$) δ 6.92 (d, J = 9 Hz, 1 H, C-8 H), 6.69 (d, J = 9 Hz, 1 H, C-7 H), 4.06 (m, 1 H, C*H*OH), 3.79 (s, 3 H, $ArOCH_3$), 2.82 (m, 4 H, two CH_2Ar), 2.11 (s, 3 H, $ArCH_3$), 1.96 (m, 2 H, C*H*$_2CH_2Ar$), 1.58 (s, 1 H, OH); IR ($CHCl_3$) ν_{max} 3590, 3440, 2940, 1590, 1485, 1260, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 192 (M^+, base), 175 (18), 174 (73), 159 (65), 148 (47), 91 (38).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.59; H, 8.74.

6-Methoxy-5-methyl-3,4-dihydro-2(1*H*)-naphthalenone (13). Toluene (60 mL) was introduced into a flame-dried, two-necked, 100-mL round-bottomed flask equipped with a septum and a Dean–Stark trap under nitrogen and 12 mL was distilled. The alcohol 12 (2.03 g, 10.5 mmol) in cyclohexanone (23.7 g, 241.1 mmol, 22.9 equiv) was added to the hot toluene and 24 mL of solvent was distilled. A solution of aluminum isopropoxide (2.40 g, 11.8 mmol, 3.4 equiv) in 18 mL of dry toluene was added over 30 min, and the reaction mixture was warmed at reflux for 1.5 h while 12 mL of solvent distilled.[12] The reaction mixture was cooled to 25 °C, treated with 20 mL of saturated aqueous NH_4Cl, and vacuum filtered, washing with 250 mL of an ether–dichloromethane solution (3:1). The layers were separated and the aqueous phase was extracted with an ether–dichloromethane solution (4 × 20 mL, 3:1). The combined organic layers were washed with 75 mL of water and 100 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo (0.5 torr at 60 °C). Medium-pressure liquid chromatography (SiO_2, 2.5 × 75 cm, 10 to 60% ether–hexane eluant; gradient elution) afforded 1.44 g (2.00 g theoretical, 72%) of 13 as a white solid: mp 53–55 °C (lit.[13a] mp 48–57 °C); ^1H NMR ($CDCl_3$) δ 6.94 (d, J = 9 Hz, 1 H, C-8 H), 6.72 (d, J = 9 Hz, 1 H, C-7 H), 3.81 (s, 3 H, $ArOCH_3$), 3.52 (s, 2 H, $ArCH_2C{=}O$), 3.05 (m, 2 H, CH_2CH_2Ar), 2.58 (m, 2 H, C*H*$_2CH_2Ar$), 2.21 (s, 3 H, $ArCH_3$); ^{13}C NMR ($CDCl_3$) δ 210.7 (C=O), 156.5 (C-6), 136.3 (C-4a), 125.9 (C-8), 125.4 (C-8a), 123.7 (C-5), 108.8 (C-7), 55.5 (OCH_3), 44.8 (C-1), 37.9 (C-3), 24.8 (C-4),

(22) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

(23) Prepared immediately before use by the addition of 1.0 equiv of *n*-butyllithium to 1.0 equiv of diisopropylamine at −78 °C (5 min) and 0 °C (15 min).

(24) The diastereomeric ratio of 8 was determined by HPLC (SiO_2, 2.5 mL/min, 15% ethyl acetate–heptane eluant).

(25) Phenol 10, a colorless oil, prepared under similar conditions was characterized: ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H, Ar), 6.80 (d, J = 8 Hz, 1 H, C-8 H), 6.56 (d, J = 8 Hz, 1 H, C-7 H), 4.70 (s, 1 H, OH), 4.63 (s, 2 H, OCH_2Ph), 3.76 (m, 1 H, C*H*OCH_2Ph), 2.95–2.55 (m, 4 H, two CH_2Ar), 2.20–1.70 (m, 2 H, C*H*$_2CH_2Ar$), 2.10 (s, 3 H, $ArCH_3$); IR (film) ν_{max} 3400, 2950, 1600, 1495, 1455, 1280, 1060, 900, 795, 725, 685 cm^{-1}; EIMS, *m/e* (relative intensity) 268 (M^+, 14), 177 (33), 160 (22), 135 (base), 91 (65); HRMS, *m/e* 268.1454 ($C_{18}H_{20}O_2$ requires 268.1462).

11.4 (-CH_3); IR (film) ν_{max} 2940, 1710, 1590, 1250, 1090, 790 cm^{-1}; EIMS, *m/e* (relative intensity) 190 (M^+, base), 162 (29), 161 (37), 148 (56), 147 (80), 131 (36), 117 (33), 91 (40), 77 (33).

Methyl 8-Methoxy-7-methyl-3-oxo-5,6-dihydro-3*H*-naphtho[2,1-*b*]pyran-2-carboxylate (15). A solution of ketone **13** (302 mg, 1.59 mmol) in 2.0 mL of dry THF, was added over 30 min to a 0 °C slurry of sodium hydride (139 mg of 60% in oil, 3.48 mmol, 2.19 equiv) in 4.0 mL of dry THF under argon, and the resulting mixture was stirred for 30 min at 0 °C and 10 min at 25 °C. The reaction mixture was recooled to 0 °C, a solution of dimethyl (methoxymethylene)malonate[26] (**14**, 335 mg, 1.92 mmol, 1.21 equiv) in 1.8 mL of dry THF was added over 15 min, and the reaction mixture was stirred at 0 to 10 °C for 2.5 h. The purple reaction mixture turned yellow when poured onto 15 mL of cold 5% aqueous HCl, and the aqueous phase was extracted with chloroform (7 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 2 × 30 cm, 50 to 100% chloroform–hexane eluant; gradient elution) afforded 385 mg (477 mg theoretical, 81%) of **15** as a yellow, crystalline solid: mp 186–187 °C (ethyl acetate); ^1H NMR ($CDCl_3$) δ 8.62 (s, 1 H, vinyl), 7.29 (d, J = 9 Hz, 1 H, C-10 H), 6.78 (d, J = 9 Hz, 1 H, C-9 H), 3.92 and 3.83 (two s, 3 H each, OCH_3/CO_2CH_3), 2.94 and 2.88 (two d, J = 6, 6 Hz, 2 H each, benzylic/allylic CH_2), 2.17 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3025, 2970, 1760, 1745, 1550, 1250, 1095 cm^{-1}; EIMS, *m/e* (relative intensity) 300 (M^+, 92), 269 (27), 268 (base), 225 (32), 141 (20), 115 (19), 83 (21); HRMS, *m/e* 300.0981 ($C_{17}H_{16}O_5$ requires 300.0997).

Methyl 2,7-Dimethoxy-8-methyl-9,10-dihydrophenanthrene-3-carboxylate (17). A solution containing α-pyrone **15** (835 mg, 2.78 mmol) and 1,1-dimethoxyethylene[27] (**16**, 2.48 g, 28.2 mmol, 10.1 equiv) in 1.9 mL of dry toluene was warmed at 140 °C for 21 h in a sealed vessel.[28a] The cooled reaction mixture was concentrated in vacuo. Medium-pressure liquid chromatography (SiO_2, 1.5 × 50 cm, 25% ether–hexane eluant) afforded 652 mg (868 mg theoretical, 75%) of **17** as a white, crystalline solid: mp 128–129 °C (methanol); ^1H NMR ($CDCl_3$) δ 8.05 (s, 1 H, C-4 H), 7.54 (d, J = 9 Hz, 1 H, C-5 H), 6.78 (s, 1 H, C-1 H), 6.77 (d, J = 9 Hz, 1 H, C-6 H), 3.90, 3.89 and 3.84 (three s, 3 H each, two OCH_3 and CO_2CH_3), 2.88 (s, 4 H, $ArCH_2CH_2Ar$), 2.21 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3040, 2980, 2860, 1725, 1485, 1470, 1440, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 312 (M^+, base), 298 (8), 297 (36), 165 (8); HRMS, *m/e* 312.1340 ($C_{19}H_{20}O_4$ requires 312.1360).

2,7-Dimethoxy-3-(hydroxymethyl)-8-methyl-9,10-dihydrophenanthrene (18). The salicylate **17** (571 mg, 1.90 mmol) in 5.0 mL of dry THF was added to a 0 °C slurry of lithium aluminum hydride (76 mg, 2.0 mmol, 4.21 equiv) in 4.0 mL of dry THF under argon, and the resulting mixture was stirred for 1.5 h at 0 to 25 °C. The reaction was recooled to 0 °C, treated with 80 μL of water, 160 μL of 10% aqueous NaOH, and 240 μL of water, vacuum filtered through a Celite plug (ether wash), and concentrated in vacuo to give 540 mg (542 mg theoretical, quantitative) of **18** as a white, crystalline solid: mp 175–177 °C (benzene); ^1H NMR ($CDCl_3$) δ 7.49 (s, 1 H, C-4 H), 7.45 (d, J = 9 Hz, 1 H, C-5 H), 6.72 (d, J = 9 Hz, 1 H, C-6 H), 6.66 (s, 1 H, C-1 H), 4.63 (s, 2 H, $ArCH_2OH$), 3.80 and 3.76 (two s, 3 H each, two $ArOCH_3$), 2.74 (s, 4 H, $ArCH_2CH_2Ar$), 2.13 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3610, 3700–3260, 3030, 2980, 1620, 1595, 1490, 1470, 1260, 1250, 1100, 1060, 1010 cm^{-1}; EIMS, *m/e* (relative intensity) 284 (M^+ base), 269 (33), 226 (10), 224 (12), 178 (13), 165 (17); HRMS, *m/e* 284.1413 ($C_{18}H_{20}O_3$ requires 284.1411).

3-(Bromomethyl)-2,7-dimethoxy-8-methyl-9,10-dihydrophenanthrene (19). Hydrogen bromide (g) was bubbled through a solution of alcohol **18** (540 mg, 1.90 mmol) in 20 mL of dry benzene until the reaction was complete (ca. 15 min, as determined by TLC). The reaction mixture was carefully treated with 5% aqueous $NaHCO_3$ (ca. 10 mL), and the aqueous phase was extracted with dichloromethane (7 × 5 mL). The combined extracts were dried (Na_2SO_4), concentrated in vacuo, and passed through a plug of silica gel to give 658 mg (659 mg theoretical, quantitative) of **19** as a white solid: mp 152–154 °C dec; ^1H NMR ($CDCl_3$) δ 7.50 (s, 1 H, C-4 H), 7.41 (d, J = 10 Hz, 1 H, C-5 H), 6.69 (d, J = 10 Hz, 1 H, C-6 H), 6.63 (s, 1 H, C-1 H), 4.55 (s, 2 H, $ArCH_2Br$), 3.85 and 3.78 (two s, 3 H each, two $ArOCH_3$), 2.75 (s, 4 H, $ArCH_2CH_2Ar$), 2.14 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3020, 2970, 2850, 1615, 1590, 1460, 1435, 1260, 1245, 1095, 1055 cm^{-1}; EIMS, *m/e* (relative intensity) 348/346 (M^+, 1/1, 4), 268 (23), 267 (base), 237 (26), 222 (21), 165 (18); HRMS, *m/e* 346.0550 ($C_{18}H_{19}O_2Br$ requires 346.0567).

2,7-Dimethoxy-3,8-dimethyl-9,10-dihydrophenanthrene-4-carboxaldehyde (22). A solution of (dimethylamino)(thiophenyl)methane[29] (251 mg, 1.50 mmol, 1.25 equiv) in 1.0 mL of dry acetonitrile was added to a solution of bromide **19** (402 mg, 1.16 mmol) in 3.0 mL of dry acetonitrile under argon at 25 °C, and the resulting mixture was stirred for 18 h at 25 °C. The reaction mixture was concentrated in vacuo, suspended in benzene, and filtered to give 590 mg (595 mg theoretical, 99%) of **20** as a white solid: mp 173–175 °C (ethanol); ^1H NMR ($CDCl_3$) δ 8.02 (s, 1 H, C-4 H), 7.78–7.63 (m, 3 H, Ar), 7.41–7.27 (m, 3 H, Ar), 6.82 (s, 1 H, C-1 H and d, J = 9 Hz, 1 H, C-6 H), 5.44 (s, 2 H, $R_3N^+CH_2SPh$), 4.96 (s, 2 H, $ArCH_2N^+R_3$), 3.89 and 3.82 (two s, 3 H each, two $ArOCH_3$), 3.22 (s, 6 H, $R_2N^+(CH_3)_2$), 2.83 (s, 4 H, $ArCH_2CH_2Ar$), 2.19 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3020, 2975, 1620, 1590, 1480, 1260, 1245, 1095, 1010, 795 cm^{-1}.

Anal. Calcd for $C_{27}H_{32}BrNO_2S$: C, 63.03; H, 6.27; N, 2.72. Found: C, 63.00; H, 6.40; N, 2.73.

A solution of 1.3 M potassium *tert*-butoxide in dry DME (2.0 mL, 2.6 mmol, 6.0 equiv) was added slowly (5 min) in four equal portions at 0.5-h intervals to a suspension of ammonium salt **20** (224 mg, 0.435 mmol) in 1.5 mL of dry DME at −15 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 1.5 h. A solution of water–acetic acid–THF (1.35 mL of 1:3:3) was added at 25 °C where the resulting mixture was stirred for 16 h. The reaction mixture was diluted with 10 mL of water, and the aqueous phase was extracted with chloroform (7 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1 × 15 cm, 10% ether–hexane eluant) afforded 29.0 mg (129.0 mg theoretical, 23%) of **22** as a white solid:[16] mp 191–192 °C (lit.[4a] mp 192–194 °C; ethanol–dichloromethane); ^1H NMR ($CDCl_3$) δ 9.95 (s, 1 H, CHO), 6.96 (s, 1 H, C-1 H and d, J = 9 Hz, 1 H, C-5 H), 6.77 (d, J = 9 Hz, 1 H, C-6 H), 3.89 and 3.86 (two s, 3 H each, two $ArOCH_3$), 2.79 (s, 4 H, $ArCH_2CH_2Ar$), 2.43 and 2.26 (two s, 3 H each, two $ArCH_3$); IR ($CHCl_3$) ν_{max} 3025, 2920, 2840, 1690, 1590, 1475, 1255, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 296 (M^+, base), 295 (24), 282 (20), 281 (73), 253 (24), 165 (26).

Aldehyde **22** was prepared from **20** in yields ranging from 20–27%.[15]

Juncusol Dimethyl Ether (23). A solution of 1.61 M *n*-butyllithium in hexane (0.39 mL, 0.63 mmol, 7.3 equiv) was added dropwise (15 min) to a 0 °C suspension of dry methyltriphenylphosphonium bromide (224 mg, 0.63 mmol, 7.3 equiv) in 2.0 mL of dry THF under argon and stirred at 25 °C for 15 min. The aldehyde **22** (25.5 mg, 0.086 mmol) in 1.8 mL of dry THF was added to the mixture at 25 °C and stirred for 17 h. The reaction mixture was poured onto 5 mL of water and extracted with dichloromethane (7 × 3 mL). The combined extracts were washed with 5 mL of water, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 6 cm, 15 to 100% dichloromethane–hexane eluant; gradient elution) afforded 15.2 mg (25.3 mg theoretical, 60%) of **23** as a white solid: mp 148–149 °C (lit.[4a] mp 149–150 °C; methanol); ^1H NMR ($CDCl_3$) δ 7.63 (d, J = 9 Hz, 1 H, C-5 H), 7.00–6.55 (overlapping dd, d, and s, 3 H, vinyl and two aromatic), 5.50 (dd, J_{BX} = 12, J_{AB} = 2 Hz, 1 H, CH=CH_AH_B), 5.22 (dd, J_{AX} = 17, J_{AB} = 2 Hz, CH=CH_AH_B), 3.85 and 3.83 (two s, 3 H each, two $ArOCH_3$), 2.71 (s, 4 H, $ArCH_2CH_2Ar$), 2.25 and 2.22 (two s, 3 H each, two $ArCH_3$); IR

(26) Technical grade dimethyl (methoxymethylene)malonate (**14**) is available from Fluka Chemical Corporation and was used after recrystallization (ether, 2×). It may be prepared by the procedure described for diethyl (ethoxymethlene)malonate: Fuson, R. C.; Parham, W. E.; Reed, L. J. *J. Org. Chem.* **1946**, *11*, 194.

(27) 1,1-Dimethoxyethylene is available from Wiley Organics.

(28) (a) The reaction was run in a 7-mL thick-walled tube internally threaded on one end and sealed under argon with a solid threaded Teflon plug. The reaction vessel was fabricated from a chromatography column purchased from Ace Glass Company. (b) The reaction was run in a 3-mL Kontes microflex vial sealed under argon with a screw cap equipped with a Teflon-lined rubber liner.

(29) Grillot, G. F.; Thompson, H. G. *J. Org. Chem.* **1957**, *22*, 706.

($CHCl_3$) ν_{max} 3040, 2960, 1595, 1465, 1260, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 294 (M^+, 78), 280 (25), 279 (base), 264 (55), 263 (31), 248 (32). Dimethyl ether of juncusol (**23**) was prepared in yields ranging from 60–77% from **22**.

Juncusol (1). A solution of ethanethiol (8.4 mg, 0.14 mmol, 2.9 equiv) in 0.5 mL of dry HMPA at 0 °C under argon was treated slowly with 0.10 mL of 1.4 M methyllithium in ether (0.14 mmol, 2.9 equiv). Juncusol dimethyl ether (**23**, 7.2 mg, 0.024 mmol) in 1.0 mL of dry HMPA was added at 25 °C, and the resulting mixture was warmed at 160 °C for 6h.[28b] The reaction mixture was cooled to 25 °C, poured over 5 mL of cold water, acidified (ca. pH 4) with cold 5% aqueous HCl, and extracted with ether (4 × 1 mL). The combined extracts were washed with water (2 × 0.5 mL) and 0.5 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 7.0 cm, 30% ether–hexane eluant) afforded 5.4 mg (6.4 mg theoretical, 84%) of **1** as a solid: mp 174–175 °C (lit.[2] mp 175–176 °C; benzene); ^1H NMR ($CDCl_3$) δ 7.52 (d, J = 9 Hz, 1 H, C-5 H), 6.95–6.45 (overlapping dd, d and s, 3 H, vinyl and two aromatic), 5.50 (dd, J_{BX} = 12, J_{AB} = 2 Hz, CH=CH_AH_B), 5.21 (dd, J_{AX} = 18, J_{AB} = 2 Hz, CH=CH_AH_B), 4.64 (br s, 2 H, two OH), 2.66 (s, 4 H, $ArCH_2CH_2Ar$), 2.27 and 2.23 (two s, 3 H each, two $ArCH_3$); IR ($CHCl_3$) ν_{max} 3600, 3600–3100, 3005, 2960, 1590, 1450, 1395, 1275, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 266 (M^+, 98), 265 (20, 252 (23), 251 (base), 250 (35), 249 (23), 237 (22), 236 (64), 235 (28), 234 (30); HRMS, *m/e* 266.1300 ($C_{18}H_{18}O_2$ requires 266.1306.

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Registry No. **1**, 62023-90-9; **7**, 2987-06-6; (*cis*)-**8**, 91551-13-2; (*trans*)-**8**, 91551-14-3; (*cis*)-**9**, 91551-15-4; (*trans*)-**9**, 91551-16-5; **10**, 85559-32-6; **11**, 85559-33-7; **12**, 85559-34-8; **13**, 17215-86-0; **15**, 85531-85-7; **16**, 922-69-0; **17**, 85531-86-8; **18**, 85559-36-0; **19**, 85559-37-1; **20**, 91551-17-6; **22**, 69496-44-2; **23**, 66447-86-7; **24**, 91551-18-7; **25**, 73255-29-5; **26**, 91551-19-8; **28**, 91551-20-1; VII, 91551-21-2; ethyl vinyl ketone, 1629-58-9; dimethyl (methoxymethylene)malonate, 22398-14-7; (dimethylamino)(thiophenyl)methane, 43180-39-8; methyltriphenylphosphonium bromide, 1779-49-3.

Total Syntheses of Azafluoranthene Alkaloids: Rufescine and Imeluteine

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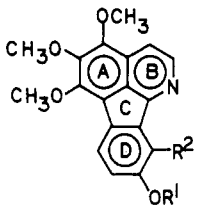
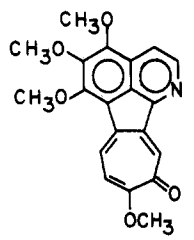
Total syntheses of rufescine and imeluteine, azafluoranthene alkaloids isolated from *Abuta imene* and *Abuta rufescens*, are detailed and are based on the utilization of the inverse electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrones for the selective and controlled introduction of oxygenated aromatics.

Recent studies of the alkaloids of *Abuta imene* and *Abuta rufescens*, bush ropes found in South America, resulted in the isolation, identification, and synthesis of the azafluoranthene alkaloids rufescine (**1**), norrufescine

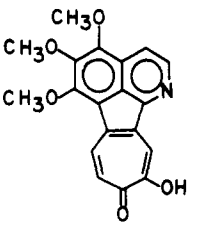


1	$R^1 = CH_3$	$R^2 = H$
2	$R^1 = H$	$R^2 = H$
3	$R^1 = CH_3$	$R^2 = OCH_3$

(**2**), and imeluteine (**3**),[2,3] condensed isoquinolines biosynthetically related to the tropoloisoquinolines imerubrine[4a] and grandirubrine.[4b]



imerubrine



grandirubrine

Herein, we describe a divergent[5] approach to the preparation of rufescine (**1**) and imeluteine (**3**) based on the utilization of the inverse electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrones[6] for the selective

(1) (a) Searle Scholar recipient, 1981–1985. Recipient of a National Institutes of Health Career Development Award (CA 00898). (b) National Institutes of Health predoctoral trainee (GM 07775).

(2) (a) Cava, M. P.; Buck, K. T.; daRocha, A. I. *J. Am. Chem. Soc.* **1972**, *94*, 5931. (b) Cava, M. P.; Buck, K. T.; Noguchi, I.; Srinivasan, M.; Rao, M. G.; daRocha, A. I. *Tetrahedron* **1975**, *31*, 1667. (c) Klein, M. D.; Buck, K. T.; Cava, M. P.; Voet, D. *J. Am. Chem. Soc.* **1978**, *100*, 662. Norrufescine has been isolated from *Telitoxicum perurianum*; see: Menachery, M. D.; Cava, M. P. *J. Nat. Prod.* **1981**, *44*, 320.

(3) For complete syntheses of azafluoranthene alkaloids, based on the Pschorr cyclization, see: (a) rufescine and imeluteine, ref 2a; (b) norrufescine, Menachery, M. D.; Cava, M. P. *Heterocycles* **1982**, *19*, 2255.

(4) (a) Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, *99*, 6708. (b) Menachery, M. D.; Cava, M. P. *Heterocycles* **1980**, *14*, 943.

(5) Two distinct classifications have been recognized as useful descriptions of the conceptual, as well as actual, strategies used in the synthesis of *individual* naturally occurring or synthetic materials: linear vs. convergent synthesis. The practical value of a convergent synthesis has been described in some detail. For example, see: Fuhrhop, J.; Penzlin, G. "Organic Synthesis–Concepts, Methods, Starting Materials"; Verlag Chemie: Basel, Switzerland, 1983; p 216. Similarly, for a *group* of related, naturally occurring or synthetic materials (e.g., azafluoranthene alkaloids) two, distinct classifications may be used to describe the strategy employed in their synthesis: independent vs. divergent. As the terminology implies: "independent" total synthesis requires nonidentity of intermediates used for the total synthesis of each member of the class while "divergent" requires that an identical intermediate (preferably an advanced intermediate) be converted, separately, to at least two members of the class of compounds. Divergent total syntheses are distinct from partial total synthesis in which one member is interconverted to a second member of the class of compounds.

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