(w), 1414 (m), 1325 (s), 1300 (m), 1251 (s), 1220–1150 (vs), 1111 (s), 1032 (s), 997 (w), 930 (w), 912 (w), 845 (m), 837 (m), 760 (m), 728 (w), 700 (w), and 514 (w) $cm^{-1}$; MS, *m/e* 123 (100), 95 (40), 121 (27), 77 (26), and 234 ($M^+$, 22). Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87. Found: C, 51.41; H, 3.88.

**2-(Trichloromethyl)-2-phenoxyoxirane (4l)**: $^1H$ NMR 3.04 (d, 1 H, $J_{AB}$ = 3.21 Hz), 3.50 (d, 1 H, $J_{AB}$ = 3.21 Hz), and 6.85–7.48 ppm (m, 5 H); IR (neat) 3065 (w), 3040 (w), 1593 (m), 1491 (s), 1455 (w), 1355 (m), 1290 (w), 1225 (vs), 1160 (w), 1140 (w), 1084 (w), 1070 (w), 1020 (w), 995 (w), 920 (s), 838 (w), 800–780 (vs), 760 (w), 730 (m), 668 (s), 628 (w), 552 (w), and 488 (w) $cm^{-1}$; MS, *m/e* 77 (100), 65 (98), 79 (89), 107 (88), 51 (67), and 252 ($M^+$, 29). Anal. Calcd for $C_9H_7Cl_3O_2$: C, 42.64; H, 2.78. Found: C, 42.69; H, 2.78.

**Methanolysis of 4a.** The oxirane **4a** (ca. 20 mg) was treated with 1 mM methanolic hydrogen chloride in a sealed tube at 70 °C during 1 h in a nitrogen atmosphere. The reaction mixture was directly analyzed by GC–MS; the oxirane **4a** had reacted completely to yield quantitatively **9** and a more volatile compound **10**: MS, *m/e* 45 (100), 46 (53), 129 (42), 59 (31), 109 (29), 63 (23), 69 (20), 95 (17), 143 (9), 105 (8), 157 (2), and 174 ($M^+$, 0.4).

**Acknowledgment.** We are indebted to the Italian Ministry of Education for grants (to A.G.G., 1985–1986, 1986–1987) and to the Italian National Research Council (to A.G.G., CNR 86.01649.03) for financial support. We thank P. Polese for technical assistance.

**Registry No.** **3a**, 500-73-2; **3b**, 122-79-2; **3c**, 114397-39-6; **3d**, 620-73-5; **3e**, 10565-20-5; **3f**, 658-78-6; **3g**, 830-03-5; **3h**, 19220-93-0; **3i**, 41190-40-3; **3j**, 398-49-2; **3k**, 42872-38-8; **3l**, 10112-13-7; **3m**, 407-38-5; **3n**, 400-61-3; **3o**, 1549-45-7; **3p**, 64487-54-3; **3q**, 36629-42-2; **3r**, 351-70-2; **3s**, 10315-85-2; **3t**, 1579-72-2; **3u**, 5672-87-7; **4a**, 113200-26-3; **4e**, 114397-40-9; **4f**, 114397-41-0; **4i**, 114397-42-1; **4j**, 114397-43-2; **4k**, 114397-44-3; **4l**, 114397-45-4; **4m**, 114397-46-5; **4r**, 114397-47-6; **4u**, 114397-48-7; **6**, 345-81-3; **7**, 39651-54-2; **8**, 360-95-2; **9**, 108-95-2; **10**, 114397-49-8; 4-$O_2NC_6H_4OH$, 100-02-7; $C_6H_5CH_2OH$, 100-51-6; $CH_2N_2$, 334-88-3; $F_3CCH_2OH$, 75-89-8; 1-$C_{10}H_7OH$, 90-15-3; 2-$C_{10}H_7OH$, 135-19-3; $C_6H_{13}OH$, 111-27-3; 4-$H_3COC_6H_4OH$, 150-76-5; $ClCH_2COCl$, 79-04-9; $Cl_2CHCOCl$, 79-36-7; $CCl_3COCl$, 76-02-8; $C_6F_5OH$, 771-61-9; $H_3CCOCl$, 75-36-5; cyclohexanone, 108-94-1; cyclohexanol, 108-93-0; 2-cyclohexen-1-ol, 822-67-3; 1,1,1,3,3,3-hexafluoro-2-propanol, 920-66-1; benzoyl chloride, 98-88-4; pentafluorobenzoyl chloride, 2251-50-5; phenyl 2-bromo-2-methylpropanoate, 114397-50-1; *N*-methylaniline, 100-61-8; *N*-methyl-4-nitroaniline, 100-15-2; morpholine, 110-91-8.

# Quinolizidine Synthesis via Intramolecular Immonium Ion Based Diels–Alder Reactions: Total Syntheses of (±)-Lupinine, (±)-Epilupinine, (±)-Cryptopleurine, and (±)-Julandine†

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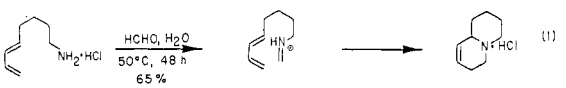
*Received March 23, 1988*

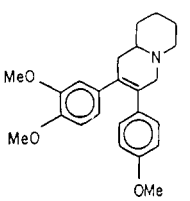
Total syntheses of (±)-julandine (**1**), (±)-cryptopleurine (**2**), (±)-lupinine (**3**), and (±)-epilupinine (**4**) have been developed that feature intramolecular immonium ion based Diels–Alder reactions. Amines **6** and **14**, prepared from stilbene ester **5** in a straightforward manner, gave rise to, upon treatment with aqueous formaldehyde solution, the corresponding immonium salts, which undergo intramolecular cyclocondensation, leading to isojulandine (**11**) and cryptopleurine (**2**), respectively, in good yield. Exposure of **11** to acid afforded (±)-julandine. Intramolecular [4 + 2] cycloaddition of immonium ion **18** derived from amine **17** provided Diels–Alder adducts **19** and **20**, which are rationalized on the basis of transition states **22** and **23**, respectively. Reduction of **19** and **20** gave (±)-epilupinine (**4**) and (±)-lupinine (**3**), respectively.

The feasibility of employing an intramolecular immonium ion based Diels–Alder reaction for the construction of quinolizidine alkaloids was established during our preliminary study on the cyclocondensation of immonium salts with dienes under Mannich-like conditions (cf. eq 1).[2]

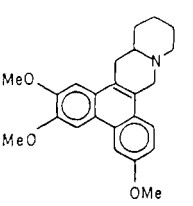



(1)

As an extension of this work, we set out to apply this methodology to the synthesis of naturally occurring alkaloids. Accordingly, we detail below the total synthesis of (±)-julandine (**1**)[3] and (±)-cryptopleurine (**2**).[3,4] In addition, studies to establish whether side-chain stereochemistry might be controlled in the construction of octahydroquinolizidines have also been examined. In this regard the total syntheses of (±)-lupinine (**3**) and (±)-epilupinine (**4**)[4,5] are described.




1

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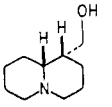


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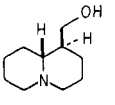


4

In order to probe the application of the immonium ion based Diels–Alder strategy to the construction of julandine,

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) Procter and Gamble Predoctoral Fellow, 1987–1988.
(2) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

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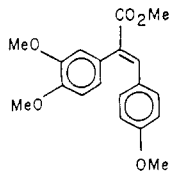
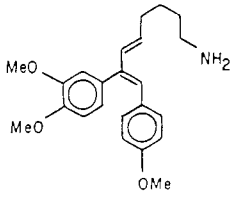
we embarked on a synthesis of requisite dienyl amine **6**.

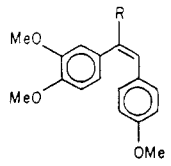


5

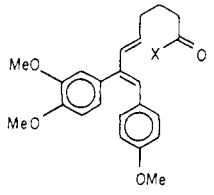


6

The synthesis of **6** commences with the known stilbene ester **5**,[5] obtained by condensation of veratric acid with *p*-anisaldehyde and subsequent esterification. Reduction of ester **5** with diisobutylaluminum hydride in toluene at 0 °C afforded upon workup an 83% yield of alcohol **7**, which was oxidized in 95% yield with activated manganese dioxide in benzene–chloroform, giving rise to aldehyde **8**. Oxidation with pyridinium chlorochromate in methylene chloride provided aldehyde **8** in only 55% yield.



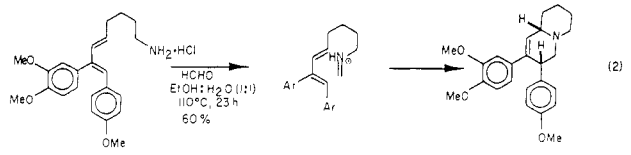
7 R = $CH_2OH$
8 R = CHO



9 X = OH
10 X = $NH_2$

Condensation of aldehyde **8** with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide gave rise to an inseparable 2.4:1 mixture of *E* and *Z* isomers of **9** in 81% yield. Transformation of **9** into amide **10** was realized in essentially quantitative yield by treatment of the mixed anhydride obtained from exposure of acid **9** to ethyl chloroformate in tetrahydrofuran containing pyridine at −5 °C with concentrated ammonium hydroxide. Reduction ($LiAlH_4$, THF) of amide **10** generated the desired dienyl amine **6** in 76% yield.

Treatment of the 2.4:1 mixture of *E* and *Z* isomers of **6** as its hydrochloride salt with 4.0 equiv of 37% aqueous formaldehyde in ethanol–water (1:1) at 110 °C in a sealed tube for 23 h generated in situ the corresponding transient immonium ion (cf. eq 2), which underwent cyclo-

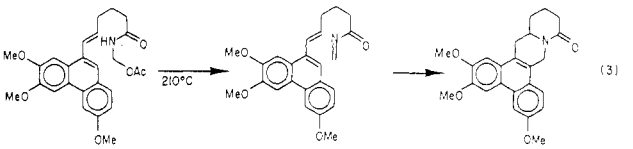


(2)

6 11

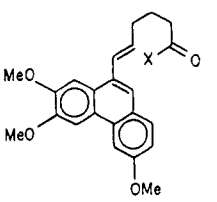
condensation, giving rise to isojulandine (**11**) in 60% yield. Double-bond isomerization employing *p*-toluenesulfonic acid in refluxing benzene afforded in 86% yield crystallized (±)-julandine, mp 137–138 °C (lit.[3a] mp 135–137 °C).

Our synthesis of cryptopleurine (**2**) originates with the known acid **12**[5] prepared previously by Weinreb in conjunction with his synthesis of **2**, which featured an intramolecular imino Diels–Alder reaction[6] employing *N*-acyl imine **16** generated in situ at 210 °C (cf. eq 3) from methylol acetate **15**. The conversion of acid **12** as a 3:1 mixture of double-bond isomers into amide **13** was carried out in a straightforward manner as detailed above for the transformation of **9** into **10**. The *E* isomer **13**, mp 173.5–174.5 °C, could be readily separated from the *Z* isomer by chromatography on silica gel. Reduction of amide **13** gave way to dienyl amine **14**.

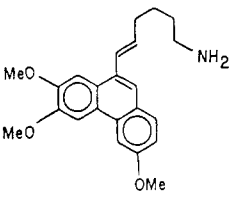


(3)

15 16



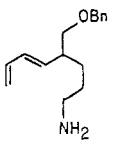
12 X = OH
13 X = $NH_2$



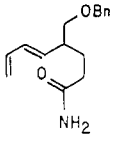
14

Exposure of the hydrochloride salt of amine **14** to 4.0 equiv of 37% aqueous formaldehyde solution in water–ethanol (1:1) at 180 °C in a sealed tube for 10 h provided, upon workup, an 84% yield of crystalline cryptopleurine, mp 199–201 °C (lit.[3a] mp 198–200 °C). The higher reaction temperature employed in the formation of cryptopleurine relative to julandine was required due to the fact that at lower temperatures the reaction, while sluggish, gave rise to numerous unidentified byproducts. The above results are not surprising in view of the fact that the intramolecular cyclocondensation of the immonium ion derived from amine **14** involves disruption of the aromatic phenanthrene unit.

In order to probe the stereochemical consequences of incorporating an appendage into the tether linking the diene and dienophile, we set out to examine the intramolecular immonium ion mediated cycloaddition of dienyl amine **17**, a logical precursor to lupinine (**3**) and epilupinine (**4**) via immonium ion **18**. The required amine was prepared in 72% yield via reduction ($LiAlH_4$, THF, 0 °C) of the known amide **21**.[5]



17



21

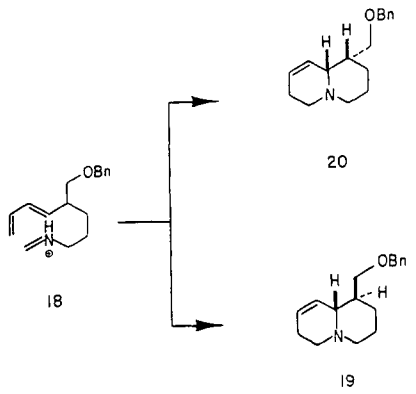
When a 0.1 M aqueous solution of the hydrochloride salt of **17** was treated with 3.0 equiv of 37% aqueous formaldehyde solution at 65 °C for 28 h, a readily separable mixture of Diels–Alder adducts **19** and **20** were isolated in 82% yield. The ratio of **19** to **20** was 1.6:1. Simultaneous hydrogenolysis of the benzyl ether and reduction of the double bond in octahydroquinolizidine **20** employing 10% Pd/C in ethanol containing 2.0 equiv of 1 N hydrochloric acid afforded (±)-lupinine (**3**) as a crystalline compound, mp 56–57 °C (lit.[5d] mp 58 °C), in quantitative

(3) For recent syntheses of (±)-julandine and (±)-cryptopleurine, see: (a) Cragg, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2487. (b) Iida, H.; Watanabe, M.; Tanaka, M.; Kibayoshi, C. *J. Org. Chem.* **1984**, *49*, 2412.

(4) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.

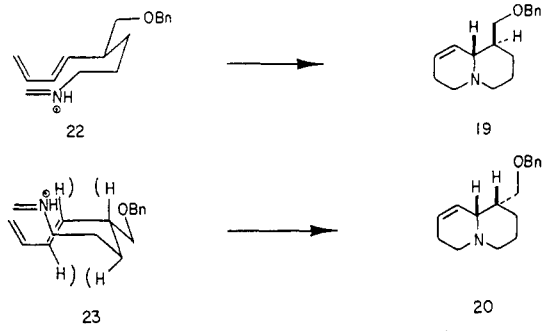
(5) For recent syntheses of lupinine and epilupinine, see: (a) Iwashita, T.; Kusumi, T.; Kahisawa, H. *J. Org. Chem.* **1982**, *47*, 230. (b) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037. (c) Okita, M.; Wakamatsu, T.; Ban, Y. *Heterocycles* **1983**, *20*, 401. (d) Haddad, M.; Célérier, J.-P.; Lhommet, G. *Ibid.* **1987**, *26*, 2335. (e) Goldberg, S. F.; Lipkin, A. H. *J. Org. Chem.* **1970**, *35*, 242.

(6) For a review of intramolecular imino Diels–Alder cycloadditions, see: Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.

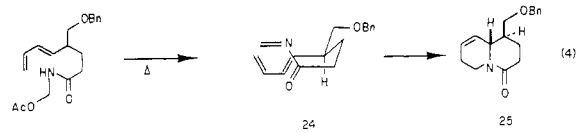



yield. Similarly, **19** was converted into epilupinine, mp 77.5–80.5 °C (lit.[5e] mp 78–79 °C). Of particular concern to us were the factors responsible for the observed product ratio of **19** to **20**. It was conceivable that the product ratio was the result of a facile equilibration between the initially formed Diels–Alder adducts **19** and **20** via an acid-catalyzed heterocycloreversion process as was observed in the case of N-substituted 2-azanorbornenes.[7] In order to probe whether heterocycloreversion was operative, an aqueous solution of pure Diels–Alder adduct **20** as its hydrochloride was heated at 65 °C for 36 h. Under the above conditions, adduct **20** was stable. No trace of **19** could be detected. It thus appears that the ratio of **19** to **20** follows directly from an analysis of the transition states **22** and **23**.

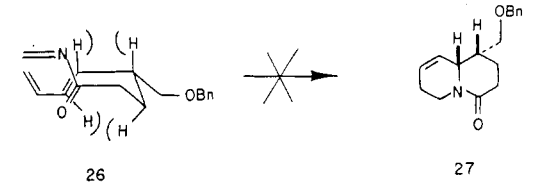
The formation of **19** and **20** arises through the chairlike transition states **22** and **23**, respectively. However, ex-




amination of transition states **22** and **23** reveals that **23** is destabilized by a serious eclipsing interaction and by a nonbonded flagpole type interaction, which undoubtedly accounts for the observed selectivity. It is of interest to note that in Weinreb's *N*-acyl imine Diels–Alder route to epilupinine (eq 4)[5] wherein a boatlike transition state (**24**)




is involved to account for the formation of **25**, none of the isomeric lactam **27** was observed. Unlike the case above




(7) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

with immonium ion induced intramolecular Diels–Alder reactions wherein no constraints are imposed on the transition states leading to [4 + 2] cycloaddition, the *N*-acyl imine approach requires that in the transition states the acyl imine adopt the s-cis endo orientation. Hence, only two transition states, **24** and **26**, emerge. Surprisingly, the chairlike transition state **26** is considerably more destabilized than **24**.

In summary, the total syntheses of (±)-julandine and (±)-cryptopleurine have been realized, which demonstrates the ability of immonium ions to participate in [4 + 2] cycloadditions with stabilized diene systems. In addition, the completed syntheses of (±)-lupinine and (±)-epilupinine clearly demonstrate that the intramolecular immonium ion mediated Diels–Alder reaction complements Weinreb's acyl imine methodology.

## Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 298 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at 360 MHz (Nicolet NT-360). Chemical shifts are reported in parts per million ($\delta$) relative to $Me_4Si$ ($\delta$ 0.00) as an internal standard. High-resolution mass spectra were recorded on a Kratos MS-80 spectrometer.

All solvents are reagent grade unless otherwise stated. "Dry" solvents were dried immediately before use. Pyridine was distilled from barium oxide. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Triethylamine, ethyl chloroformate, TMEDA, and diisopropylamine were distilled from calcium hydride. Methylene chloride was dried by passing through a column of alumina (Woelm, basic activity I) and was stored over molecular sieves (type 3A). Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 $\mu$m). Column chromatographic separations were performed on Merck silica gel 60, 70–230 mesh ASTM, whereas, Merck silica gel 60, 230–400 mesh, was used for flash chromatography.

**2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-(*E*)-propenol (7).** To a solution of 7.22 g (22.0 mmol) of ester **5** in 80 mL of toluene at 0 °C was added 110.0 mL of a 1.0 M solution of diisobutylaluminum hydride in toluene over 1 h. The reaction mixture was stirred for an additional 30 min at 0 °C. The reaction was quenched by the careful addition of 25 mL of methanol at 0 °C. The resulting gel was diluted with methanol and filtered over Celite. The filtrate was concentrated under reduced pressure, leaving a light yellow oil. The crude residue was purified by flash chromatography on 700 g of silica gel. Elution with 35% ethyl acetate–hexane afforded 5.45 g (83%) of alcohol **7** as a light yellow oil: $R_f$ 0.37 (50% ethyl acetate–hexane); IR ($CHCl_3$) 3700–3200, 3030, 3010, 2960, 2940, 2910, 2840, 1605, 1570, 1510, 1465, 1440, 1410, 1315, 1300, 1245, 1205, 1180, 1165, 1140, 1080, 1025, 905, 880, 860, 800, 700, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.84 [AB portion of an ABX system; $\Delta\nu_{AB}$ = 16.0 Hz: $H_A$ (d, 1 H, $J$ = 8.3 Hz), $H_B$ (dd, 1 H, $J$ = 8.3, 1.8 Hz), $H_X$ ($\delta$ 6.75, d, 1 H, $J$ = 1.8 Hz)], 6.81 (AB q, 4 H, $J$ = 8.7 Hz, $\Delta\nu_{AB}$ = 106.6 Hz), 6.58 (s, 1 H), 4.43 (d, 2 H, $J$ = 1.1 Hz), 3.89 (s, 3 H), 3.74 (s, 6 H), 1.69 (br s, 1 H); high-resolution MS calcd for $C_{18}H_{20}O_4$ ($M^+$) $m/e$ 300.1362, found $m/e$ 300.1361.

**2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-(*E*)-propenal (8).** To a solution of 4.50 g (15.0 mmol) of alcohol **7** in 50 mL of benzene and 2 mL of chloroform was added 12 g of activated manganese dioxide. After 23 h of stirring at room temperature, an additional 5 g of the manganese dioxide was added and the reaction mixture was stirred for an additional 12 h. The black suspension was filtered through Celite and was washed with 400 mL of chloroform. The filtrate was concentrated in vacuo, leaving 4.26 g (75%) of crude crystalline aldehyde **8**, mp 109–111 °C. Recrystallization from ether provided **8** as fine white needles, mp 110–112 °C: $R_f$ 0.45 (ethyl acetate–hexane, 1:1); IR ($CHCl_3$) 3035, 3010, 2960, 2940, 2910, 2840, 2720, 1680, 1600, 1570, 1510, 1460, 1445, 1430, 1410, 1315, 1305, 1255, 1220, 1170, 1140, 1090, 1025, 905, 830, 660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.70 (s, 1 H), 7.29 (s, 1 H),

6.98 (AB q, 4 H, $J$ = 9.0 Hz, $\Delta\nu_{AB}$ = 159.8 Hz), 6.86 [AB portion of an ABX system, $\Delta\nu_{AB}$ = 59.9 Hz: $H_A$ (d, 1 H, $J$ = 8.3 Hz), $H_B$ (dd, 1 H, $J$ = 7.9, 2.2 Hz)], 6.69 (d, 1 H, $J$ = 2.2 Hz), 3.92 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H); high-resolution MS calcd for $C_{18}H_{18}O_4$ ($M^+$) $m/e$ 298.1205, found $m/e$ 298.1197.

**7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-(*E*,*Z*)-5,7-octadienoic Acid (9).** To a solution of 15.6 mL (0.112 mol) of diisopropylamine in 39 mL of tetrahydrofuran cooled to 0 °C was added 69.8 mL (0.112 mol) of a 1.6 M solution of *n*-butyllithium in hexanes. After stirring for 15 min, the resulting lithium diisopropylamide solution (0.9 M) was added at 0 °C to a suspension of 24.7 g (0.56 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 210 mL of tetrahydrofuran containing 65 mL of tetramethylethylenediamine. After 1.2 h at 0 °C, 4.16 g (14.0 mmol) of aldehyde **8** in 250 mL of tetrahydrofuran was added dropwise over 15 min. The reaction mixture was quenched after 15 h with 1.0 L of a 5% aqueous solution of hydrochloric acid. The product was isolated by extraction with ethyl acetate (3 × 500 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown oil was purified by flash chromatography on 1.2 kg of silica gel. Elution with ethyl acetate afforded 4.28 g (81%) of **9** as an amber-colored oil. The product was an inseparable mixture of geometric isomers with an $E/Z$ ratio of 2.4:1 as determined by $^1$H NMR: $R_f$ 0.71 (0.1% acetic acid–ethyl acetate); IR (film) 3420–2500, 3000, 2960, 2930, 2910, 2830, 1705, 1600, 1580, 1505, 1455, 1440, 1405, 1300, 1250, 1175, 1135, 1025, 965, 835, 760 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.2–6.9 (m, 8.7 H), 6.15 (d, 0.3 H, $J$ = 11.5 Hz), 5.44 (dt, 0.3 H, $J$ = 11.5, 7.6 Hz), 5.27 (dt, 0.7 H, $J$ = 15.8, 7.2 Hz), 3.93 (s, 2.1 H), 3.90 (s, 0.9 H), 3.79 (s, 2.1 H), 3.74 (s, 0.9 H), 3.73 (s, 0.9 H), 3.72 (s, 2.1 H), 2.34 (t, 1.4 H, $J$ = 7.6 Hz), 2.23 (t, 0.6 H, $J$ = 7.6 Hz), 2.16 (q, 1.4 H, $J$ = 7.2 Hz), 1.93 (qd, 0.6 H, $J$ = 7.2, 1.4 Hz), 1.70 (quintet, 1.4 H, $J$ = 7.2 Hz), 1.63 (quintet, 0.6 H, $J$ = 7.4 Hz); high-resolution MS calcd for $C_{23}H_{26}O_5$ ($M^+$) $m/e$ 382.1780, found $m/e$ 382.1782.

**7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-(*E*,*Z*)-5,7-octadienamide (10).** To a solution of 1.02 g (2.68 mmol) of acid **9** in 100 mL of tetrahydrofuran cooled to −5 °C were added 650 μL (8.03 mmol) of pyridine and 768 μL (8.03 mmol) of ethyl chloroformate, respectively. After 1.5 h at −5 °C, 10 mL of concentrated ammonium hydroxide was added and the reaction mixture was warmed to ambient temperature. The solvent was removed in vacuo, leaving a residue that was diluted with 85 mL of water. The product was isolated by extraction with chloroform. The combined organic extracts were washed with a 5% aqueous hydrochloric acid solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant residue was purified by column chromatography on 100 g of silica gel. Elution with ethyl acetate afforded 1.03 g (100%) of pure amide **10** as a light yellow waxy solid. (The product was an inseparable mixture of geometric isomers with an $E/Z$ ratio of approximately 2.4:1): $R_f$ 0.21 (0.1% acetic acid–ethyl acetate); IR ($CHCl_3$) 3540, 3420, 3000, 2960, 2940, 2840, 1730, 1680, 1605, 1510, 1465, 1445, 1405, 1395, 1300, 1250, 1210, 1175, 1140, 1130, 970, 890, 865, 830 cm$^{-1}$; $^1$H NMR ($CDCl_3$–$D_2O$) $\delta$ 6.1–7.0 (m, 8.7 H), 6.14 (d, 0.3 H, $J$ = 11.5 Hz), 5.45 (dt, 0.3 H, $J$ = 11.5, 7.6 Hz), 5.27 (dt, 0.7 H, $J$ = 15.1, 7.2 Hz), 4.80 (br s, 2 H), 3.92 (s, 2.1 H), 3.90 (s, 0.9 H), 3.79 (s, 2.1 H), 3.74 (s, 0.9 H), 3.73 (s, 0.9 H), 3.72 (s, 2.1 H), 2.03–2.22 (m, 3.4 H), 1.90 (dq, 0.6 H, $J$ = 7.2, 1.1 Hz), 1.54–1.76 (m, 2 H); high-resolution MS calcd for $C_{23}H_{27}NO_4$ ($M^+$) $m/e$ 381.1940, found $m/e$ 381.1935.

**7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-(*E*,*Z*)-5,7-octadienylamine (6).** To a solution of 1.03 g (2.71 mmol) of amide **10** in 100 mL of tetrahydrofuran cooled to 0 °C was added 1.03 g (27.1 mmol) of lithium aluminum hydride in small portions. The reaction was stirred at room temperature for 7 h. The reaction mixture was quenched at 0 °C by the sequential addition of 1.0 mL of water, 1.0 mL of an aqueous 15% sodium hydroxide solution, and 3.0 mL of water. The contents of the flask were filtered and the salts were thoroughly washed with ether. The filtrate was concentrated in vacuo and the resulting residue was purified on 125 g of silica gel employing methanol–chloroform (1:9). After the purified material was washed with a 10% aqueous sodium hydroxide solution to eliminate hydrochloride contamination, 751 mg (76%) of amine **6** was obtained as a light yellow foam ($E/Z$ ratio, 2.4:1): $R_f$ 0.07 (chloroform–methanol, 85:15); IR (film, hydrochloride) 3680–3100, 3380, 3300, 3000, 2840, 1605, 1580, 1510, 1460, 1440, 1410, 1300, 1250, 1175, 1135, 1030, 955, 860, 825, 760 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.1–7.0 (m, 8.7 H), 6.15 (d, 0.3 H, $J$ = 11.5 Hz), 5.43 (dt, 0.3 H, $J$ = 11.5, 7.6 Hz), 5.27 (dt, 0.7 H, $J$ = 15.1, 7.3 Hz), 4.63 (br s, 2 H), 3.7–3.9 (6 s, 9 H), 2.82 (t, 1.4 H, $J$ = 7.3 Hz), 2.74 (t, 0.6 H, $J$ = 7.1 Hz), 2.13 (q, 1.4 H, $J$ = 7.2 Hz), 1.91 (q, 0.6 H, $J$ = 7.2 Hz), 1.3–1.7 (m, 4 H); high-resolution MS calcd for $C_{23}H_{29}NO_3$ ($M^+$) $m/e$ 367.2147, found $m/e$ 367.2173.

**Isojulandine (11).** To a solution of 50 mg (0.136 mmol) of dienyl amine **6** in 1.8 mL of ethanol was added 136 μL (0.136 mmol) of a 1.0 N aqueous hydrochloric acid solution followed by the addition of 44.2 μL (0.545 mmol) of 37% aqueous formaldehyde solution and 1.8 mL of water. The homogeneous solution was heated at 110 °C in a sealed tube. After 23 h, the reaction mixture was diluted with 60 mL of water and neutralized with 15% aqueous sodium hydroxide solution. The product was isolated by extraction with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on 20 g of silica gel. Elution with chloroform–methanol (98:2) afforded 21.5 mg (60%) of isojulandine (**11**) as a light yellow foam (the yield was corrected for the presence of 30% of the $Z$ isomer present in **6**): $R_f$ 0.73 (chloroform–methanol, 85:15); IR ($CHCl_3$) 3010, 2940, 2840, 2800, 2750, 1670, 1600, 1585, 1505, 1560, 1545, 1355, 1300, 1245, 1210, 1170, 1140, 1100, 1025, 910, 855, 830, cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.04 (AB q, 4 H, $J$ = 8.6 Hz, $\Delta\nu_{AB}$ = 178.3 Hz), 6.83 (dd, 1 H, $J$ = 8.3, 2.2 Hz), 6.80 (d, 1 H, $J$ = 2.2 Hz), 6.68 (d, 1 H, $J$ = 8.3 Hz), 5.94 (d, 1 H, $J$ = 1.8 Hz), 3.80 (s, 3 H), 3.76 (s, 6 H), 3.72 (m, 1 H), 2.81 (dd, 1 H, $J$ = 11.2, 4.3 Hz), 2.69 (dd, 1 H, $J$ = 11.2, 1.1 Hz), 2.6–2.7 (m, 2 H), 2.1–2.2 (m, 1 H), 1.82 (br t, 2 H, $J$ = 11.9 Hz), 1.4–1.6 (m, 4 H); high-resolution MS calcd for $C_{24}H_{29}NO_3$ ($M^+$) $m/e$ 379.2148, found $m/e$ 379.2152.

**Julandine (1).** To a solution of 18.6 mg (0.049 mmol) of isojulandine (**11**) in 2.0 mL of benzene was added 46.6 mg (0.245 mmol) of *p*-toluenesulfonic acid monohydrate. The reaction was heated at reflux for 2.5 h. The resulting black solution was diluted with 10 mL of water, and the acid was neutralized by the addition of a 15% aqueous sodium hydroxide solution. The product was isolated by extraction with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on 5 g of silica gel. Elution with chloroform provided 16.0 mg (86%) of pure (±)-julandine (**1**) as a light yellow oil which crystallized upon standing in a refrigerator. An analytical sample was obtained by recrystallization from acetone, mp 137–138 °C (lit.[3a] mp 135–137 °C): $R_f$ 0.58 (chloroform–methanol, 85:15); IR ($CHCl_3$, hydrochloride), 3010, 2940, 2870, 2840, 2800, 2760, 2740, 2640–2000, 1610, 1590, 1510, 1465, 1445, 1415, 1400, 1320, 1290, 1240, 1225, 1210, 1170, 1140, 1105, 1025, 970, 905, 860, 830, 810, 660 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.97 (d, 2 H, $J$ = 8.6 Hz), 6.68 (d, 2 H, $J$ = 8.6 Hz), 6.65–6.72 (m, 2 H), 6.46 (d, 1 H, $J$ = 1.1 Hz), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.53 (s, 3 H), 3.0–3.2 (m, 2 H), 1.7–2.7 (m, 9 H), 1.42 (br s, 2 H); high-resolution MS calcd for $C_{24}H_{29}NO_3$ ($M^+$) $m/e$ 379.2148, found $m/e$ 379.2140.

**6-(3,6,7-Trimethoxy-9-phenanthryl)-(*E*)-5-hexenamide (13).** To a solution 410 mg (1.08 mmol) of carboxylic acid **12** as a 3:1 $E$:$Z$ mixture of olefins in 40 mL of tetrahydrofuran cooled to −5 °C were added 262 μL (3.24 mmol) of pyridine and 310 μL (3.24 mmol) of ethyl chloroformate, respectively. After 1.5 h at −5 °C, 4.0 mL of concentrated ammonium hydroxide was added. After the mixture warmed to room temperature, the solvent was removed in vacuo. The residue was treated with 50 mL of 5% hydrochloric acid solution. The product was isolated by extraction with chloroform (3 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product (390 mg, 95%) was a mixture of double-bond isomers ($E/Z$ ratio 3:1) as determined by $^1$H NMR. The $E$ isomer could be readily separated from the $Z$ isomer by flash chromatography on 200 g of silica gel. Elution with ethyl acetate afforded 292 mg of amide **13**, which crystallized upon standing. Recrystallization from acetone provided analytically pure **13**, mp 173.5–174.5 °C: $R_f$ 0.13 (ethyl acetate); IR ($CHCl_3$) 3540, 3420, 3000, 2960, 2940, 2840, 1680, 1620, 1610, 1520, 1510, 1470, 1440, 1420, 1390, 1360, 1300, 1265, 1230,

1205, 1180, 1160, 1065, 1040, 970, 890, 855, 840, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.90 (s, 1 H), 7.82 (d, 1 H, $J$ = 2.5 Hz), 7.76 (d, 1 H, $J$ = 8.6 Hz), 7.63 (s, 1 H), 7.43 (s, 1 H), 7.18 (dd, 1 H, $J$ = 8.6, 2.5 Hz), 7.02 (d, 1 H, $J$ = 15.4 Hz), 6.23 (dt, 1 H, $J$ = 15.4, 7.2 Hz), 5.69 (m, 2 H), 4.11 (s, 3 H), 4.06 (s, 3 H), 4.02 (s, 3 H), 2.3–2.5 (m, 4 H), 1.94 (quintet, 2 H, $J$ = 7.2 Hz); high-resolution MS calcd for $C_{23}H_{25}NO_4$ ($M^+$) $m/e$ 379.1784, found $m/e$ 379.1787.

**6-(3,6,7-Trimethoxy-9-phenanthryl)-(*E*)-5-hexenylamine (14).** To a solution of 66.2 mg (0.17 mmol) of amide **13** in 6.0 mL of dry tetrahydrofuran cooled to 0 °C was added portionwise 66.4 mg (1.75 mmol) of lithium aluminum hydride. After 21 h at ambient temperature, the reaction was quenched at 0 °C by the sequential addition of 66 μL of water, 66 μL of a 15% aqueous sodium hydroxide solution, and 200 μL of water. The contents of the flask were filtered and the salts were thoroughly washed with ethyl acetate. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on 10 g of basic alumina. Elution with ethyl acetate–methanol–ammonium hydroxide (7:3:0.1) gave 30.8 mg (48%) of amine **14** as a clear oil: $R_f$ 0.18 (methanol–chloroform–ammonium hydroxide, 15:85:0.1); IR (film, hydrochloride) 3700–2000, 3380, 3000, 2930, 2850, 2840, 1670, 1510, 1455, 1435, 1420, 1380, 1360, 1295, 1265, 1230, 1205, 1160, 1130, 1115, 1065, 1035, 970, 880, 850, 830, 790 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.89 (s, 1 H), 7.81 (d, 1 H, $J$ = 2.2 Hz), 7.76 (dd, 1 H, $J$ = 8.6, 2.2 Hz), 7.62 (s, 1 H), 7.43 (s, 1 H), 7.17 (dd, 1 H, $J$ = 9.0, 2.5 Hz), 6.98 (d, 1 H, $J$ = 15.5 Hz) 6.25 (dt, 1 H, $J$ = 15.5, 6.9 Hz), 4.10 (s, 3 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 2.77 (t, 2 H, $J$ = 6.1 Hz), 2.38 (q, 2 H, $J$ = 6.9 Hz), 1.4–1.6 (m, 6 H); high-resolution MS calcd for $C_{23}H_{27}NO_3$ ($M^+$) $m/e$ 365.1991, found $m/e$ 365.1989.

**Cryptopleurine (2).** To a solution of 50.0 mg (0.137 mmol) of amine **14** in 1.15 mL of ethanol were added 137 μL (0.137 mmol) of a 1.0 N aqueous hydrochloric acid solution, 4.44 μL (0.548 mmol) of 37% aqueous formaldehyde solution, and 500 μL of water. The reaction was heated at 180 °C in a sealed tube for 10 h. The reaction was diluted by the addition of 10 mL of water, and the acid was neutralized with a 15% sodium hydroxide solution. The product was isolated by extraction with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (chloroform–methanol, 97:3) on 15 g of silica gel. The fractions containing cryptopleurine were combined and washed with dilute sodium hydroxide solution. Evaporation of the solvent in vacuo afforded 43.6 mg (84%) of cryptopleurine (**2**) as a light yellow solid. Recrystallization from acetone provided straw-colored needles, mp 199–201 °C (lit.[3a] mp 199–200 °C): $R_f$ 0.67 (chloroform–methanol, 85:15); IR (film) 3000, 2930, 2860, 2830, 2740, 2670, 1610, 1510, 1465, 1440, 1415, 1390, 1340, 1305, 1255, 1230, 1200, 1165, 1145, 1120, 1090, 1040, 1010, 905, 870, 840, 805, 780, 760, 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.88 (s, 1 H), 7.85 (d, 1 H, $J$ = 2.5 Hz), 7.77 (d, 1 H, $J$ = 9.0 Hz), 7.22 (s, 1 H), 7.18 (dd, 1 H, $J$ = 9.0, 2.5 Hz), 4.43 (d, 1 H, $J$ = 15.5 Hz), 4.09 (s, 3 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.61 (d, 1 H, $J$ = 15.5 Hz), 3.27 (d, 1 H, $J$ = 11.2 Hz), 3.05 (dd, 1 H, $J$ = 16.2, 3.8 Hz), 2.87 (dd, 1 H, $J$ = 16.2, 10.1 Hz), 2.25–2.50 (m, 2 H), 2.02 (dd, 1 H, $J$ = 11.2, 1.8 Hz), 1.7–2.0 (m, 3 H), 1.4–1.6 (m, 2 H); high-resolution MS calcd for $C_{24}H_{27}NO_3$ ($M^+$) $m/e$ 377.1991, found $m/e$ 377.1989.

**4-((Benzyloxy)methyl)-(*E*)-5,7-octadienylamine (17).** To a suspension of 998 mg (26.6 mmol) of lithium aluminum hydride in 80 mL of dry tetrahydrofuran cooled to 0 °C was added 643 mg (2.48 mmol) of amide **21** in 20 mL of tetrahydrofuran. The reaction mixture was warmed to room temperature after addition was complete. After 3 h, the reaction was quenched at 0 °C by the sequential addition of 1.0 mL of water, 1.0 mL of 15% sodium hydroxide solution, and 3.0 mL of water. The mixture was diluted with 90 mL of ether and dried over anhydrous sodium sulfate. The inorganic salts were filtered and washed with ether. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on 65 g of silica gel. Elution with chloroform–methanol–ammonium hydroxide (85:15:0.1) provided 441 mg (73%) of amine **17** as a light yellow oil: $R_f$ 0.40 (chloroform–methanol–ammonium hydroxide, 85:15:0.1, two developments); IR (film) 3370, 3300, 3080, 3060, 3030, 3005, 2925, 2850, 1810, 1740, 1650, 1600, 1495, 1455, 1360, 1310, 1245, 1205, 1100, 1030, 1005, 950, 900, 850, 815, 735, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.2–7.4 (m, 5 H), 6.30 (dt, 1 H, $J$ = 16.9, 10.1 Hz), 6.10 (dd, 1 H, $J$ = 15.1, 10.6 Hz), 5.55 (dd, 1 H, $J$ = 15.1, 8.6 Hz), 5.12 (dd, 1 H, $J$ = 16.9, 1.4 Hz), 4.99 (dd, 1 H, $J$ = 10.1, 1.4 Hz), 4.50 (s, 2 H), 3.38 (m, 2 H), 2.6–3.1 (m, 4 H), 2.37 (m, 1 H), 1.3–1.7 (m, 4 H); high-resolution MS calcd for $C_{16}H_{23}NO$ ($M^+$) $m/e$ 245.1779, found $m/e$ 245.1776.

**Octahydroquinolizidines 19 and 20.** To a vigorously stirred heterogeneous mixture of 434 mg (1.77 mmol) of dienyl amine **17** in 16.6 mL of water was added 1.9 mL of 1.0 N hydrochloric acid solution. To the resultant cloudy solution was added 461 μL (5.69 mmol) of 37% aqueous formaldehyde solution. After 28 h at 65 °C, the reaction was cooled to room temperature, diluted with 30 mL of water, and neutralized with 15% aqueous sodium hydroxide solution. The product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on 75 g of neutral alumina. Elution with hexane–ethyl acetate (4:1) afforded 375 mg (82%) of a mixture of **19** and **20** in a ratio of 1.6:1 as determined by $^1H$ NMR. The isomeric octahydroquinolizidines were separated by flash chromatography on 150 g of silica gel. Elution with chloroform–methanol–concentrated ammonium hydroxide (24:1:0.1) provided in order of elution 144 mg of octahydroquinolizidine **20** [$R_f$ 0.75 (chloroform–methanol–concentrated ammonium hydroxide, 85:15:1); IR ($CCl_4$) 3090, 3060, 3030, 2940, 2920, 2860, 2800, 2790, 2770, 2740, 2700, 1495, 1480, 1460, 1450, 1440, 1430, 1380, 1365, 1350, 1335, 1305, 1290, 1275, 1240, 1205, 1135, 1100, 1055, 1025, 1000, 950, 900, 880, 875, 850, 720, 695, 645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 7.2–7.4 (m, 5 H), 5.71 (m, 1 H), 5.46 (d, 1 H, $J$ = 9.7 Hz), 4.49 (AB q, 2 H, $J$ = 12.1 Hz, $\Delta\nu_{AB}$ = 29.2 Hz), 3.61 [AB portion of ABX system: $H_A$ (t, 1 H, $J$ = 9.4 Hz), $H_B$ (dd, 1 H, $J$ = 9.4, 3.4 Hz)], 2.7–2.8 (m, 3 H), 1.7–2.4 (m, 7 H), 1.4–1.6 (m, 2 H); high-resolution MS calcd for $C_{17}H_{23}NO$ ($M^+$) $m/e$ 257.1780, found $m/e$ 257.1760] and 230 mg of octahydroquinolizidine **19** [$R_f$ 0.68; IR ($CCl_4$) 3090, 3060, 3040, 2940, 2920, 2860, 2800, 2740, 1495, 1480, 1465, 1450, 1430, 1400, 1380, 1360, 1340, 1315, 1300, 1290, 1230, 1210, 1175, 1145, 1100, 1050, 1040, 1030, 995, 840, 725, 695, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.2–7.4 (m, 5 H), 5.81 (d, 1 H, $J$ = 10.4 Hz), 5.75 (m, 1 H), 4.50 (AB q, 2 H, $J$ = 12.1 Hz, $\Delta\nu_{AB}$ = 16.0 Hz), 3.48 (m, 2 H), 2.82 (m, 2 H), 2.3–2.5 (m, 3 H), 2.20 (td, 1 H, $J$ = 12.2, 4.3 Hz), 1.5–2.1 (m, 5 H), 1.35 (m, 1 H); high-resolution MS calcd for $C_{17}H_{23}NO$ ($M^+$) $m/e$ 257.1780, found $m/e$ 257.1811].

**Epilupinine (4).** To a suspension of 200 mg of 10% palladium on carbon in 6.0 mL of ethanol and 1.2 mL of a 1.0 N hydrochloric acid solution was added 149.5 mg (0.582 mmol) of octahydroquinolizidine **19** in 4.0 mL of ethanol. The mixture was repeatedly evacuated and flushed with hydrogen in a Parr hydrogenator. The reaction was conducted under 50 psi of hydrogen for 1.5 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in 5.0 mL of water and neutralized with 15% sodium hydroxide solution. The product was isolated by extraction with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, leaving 99 mg (100%) of (±)-epilupinine (**4**) as white crystals, mp 79.5–80.5 °C (lit.[5e] mp 78–79 °C): $R_f$ 0.22 (chloroform–methanol–$NH_4OH$, 85:15:1); IR ($CHCl_3$) 3630, 3180, 2930, 2860, 2810, 2760, 2680, 2500, 1460, 1440, 1345, 1295, 1245, 1200, 1180, 1125, 1105, 1080, 1070, 1050, 1030, 1000, 975, 960, 920, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.65 (dd, 1 H, $J$ = 10.8, 3.6 Hz), 3.55 (dd, 1 H, $J$ = 10.8, 5.8 Hz), 2.81 (br t, 2 H, $J$ = 11.1 Hz), 1.1–2.1 (m, 14 H); high-resolution MS calcd for $C_{10}H_{19}NO$ ($M^+$) $m/e$ 169.1467, found $m/e$ 169.1466.

**Lupinine (3).** To a suspension of 65 mg of 10% palladium on carbon in 3.0 mL of ethanol and 375 μL of 1.0 N hydrochloric acid was added 48.2 mg (0.188 mmol) of octahydroquinolizidine **20** in 2.0 mL of ethanol. The mixture was repeatedly evacuated and flushed with hydrogen in a Parr hydrogenator. The reaction mixture was shaken under 50 psi of hydrogen for 1.5 h at room temperature. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in 5.0 mL of water and neutralized with 15% sodium hydroxide solution. The product was isolated by extraction with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, leaving 40 mg (100%) of (±)-lupinine (**3**) as a

crystalline material, mp 56–57 °C (lit.[5d] mp 58 °C): $R_f$ 0.27 (chloroform–methanol–$NH_4OH$, 85:15:1); IR ($CHCl_3$) 3200, 2990, 2940, 2860, 2810, 2760, 2680, 1470, 1445, 1400, 1350, 1330, 1290, 1270, 1255, 1215, 1185, 1150, 1130, 1105, 1085, 1065, 1050, 1005, 935, 885, 865, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.40 (br s, 1 H), 4.16 (dd, 1 H, $J$ = 10.1, 4.3 Hz), 3.69 (d, 1 H, $J$ = 10.1 Hz), 2.82 (m, 2 H), 1.2–2.3 (m, 14 H); high-resolution MS calcd for $C_{10}H_{19}NO$ ($M^+$) $m/e$ 169.1467, found $m/e$ 169.1463.

**Acknowledgment.** This investigation was supported by a grant from the National Science Foundation.

**Registry No.** (±)-**1**, 23365-39-1; (±)-**2**, 23365-52-8; (±)-**3**, 10248-30-3; (±)-**4**, 486-72-6; **5**, 87101-68-6; (5*E*)-**6**, 114652-03-8; (5*Z*)-**6**, 114652-04-9; **7**, 114651-97-7; **8**, 114651-98-8; (5*E*)-**9**, 114651-99-9; (5*Z*)-**9**, 114652-00-5; (5*E*)-**10**, 114652-01-6; (5*Z*)-**10**, 114652-02-7; (±)-**11**, 114652-05-0; (*E*)-**12**, 87101-71-1; (*Z*)-**12**, 87101-72-2; (*E*)-**13**, 87101-73-3; (*Z*)-**13**, 87101-74-4; **14**, 114652-06-1; (±)-**17**, 114652-07-2; (±)-**19**, 114652-08-3; (±)-**20**, 114652-09-4; (±)-**21**, 85864-16-0; $(C_6H_5)_3P^+(CH_2)_4CO_2H$ $Br^-$, 17814-85-6.

# Pseudoesters and Derivatives. 29.[1a] Regioselective Reactions of the 5-(Ethylthio)furan-2(5*H*)-one Anion with Electrophiles

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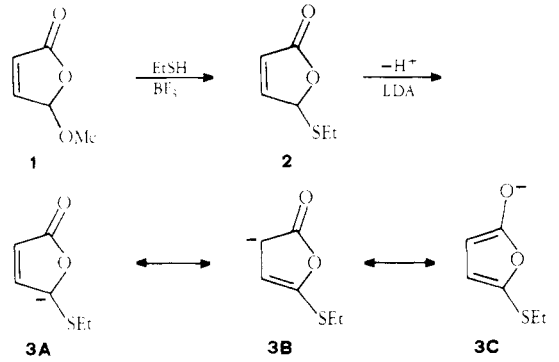
*Received December 17, 1987*

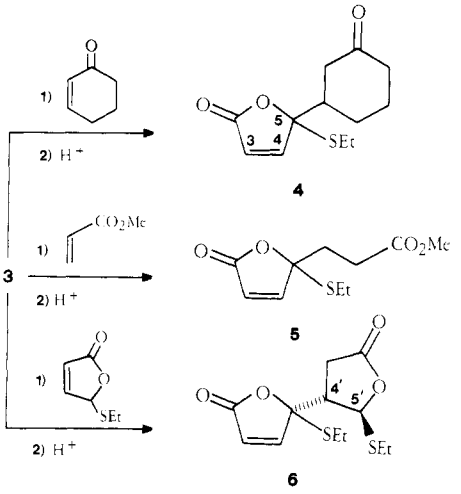
5-(Ethylthio)furan-2(5*H*)-one (**2**) was readily converted to the anion **3** by deprotonation with lithium diisopropylamide, and the reactions of **3** with a variety of electrophilic reagents were examined. The anion **3** reacted with Michael acceptors to afford exclusively the C-5-substituted adducts **4**, **5**, and **6**, while the reaction with equimolar amounts of propionaldehyde gave only the C-3-substituted adduct **9**. Anion **3** by treatment with 2.2 molar equiv of propionaldehyde afforded the 3,5-disubstituted furanone **10**. When the anion **3** was reacted with acetyl chloride or ethyl chloroformate, the electrophilic attack occurred at the carbonyl oxygen atom and the sole product was the 2,5-disubstituted furan **12** or **13**, respectively.

In a previous paper,[2] we reported the formation of 5-(ethylthio)furan-2(5*H*)-one (**2**) by treatment of 5-methoxyfuran-2(5*H*)-one (**1**) with ethanethiol in the presence of a Lewis acid such as boron trifluoride etherate as a catalyst.




We have now found that the furanone **2** is readily converted to its anion **3** by removal of the acidic proton at the 5-position by means of a suitable base such as lithium diisopropylamide (LDA). The anion is a resonance hybrid that can act as a tridentate anion through the canonical forms **3A**, **3B**, and **3C**. According to the predictions of the HSAB principle,[3] the reactive sites of the anion will probably exhibit a different hard–soft character. Thus regioselective reactions occur at either the 3- or 5-position (**3A** or **3B**) as well as at the negatively charged oxygen (**3C**), depending upon the nature of the electrophile used.

**Scheme I**




Earlier studies on the reactions of unsaturated $\delta$-lactones with alkyl halides showed that these preferentially take place at the $\alpha$-position,[4] while Michael acceptors react exclusively at the $\gamma$-position.[5] More recent studies[6] have also indicated that reactions between lithium enolates of furanones and aldehydes afforded a mixture of the $\alpha$- and $\gamma$-adducts, in which the former predominate.

The present paper describes a study of the reactivity of the 5-(ethylthio)furan-2(5*H*)-one anion (**3**) toward several electrophilic species such as Michael acceptors, carbonyl compounds, alkyl halides, and acyl halides. The reactions usually proceed in good yields and with high regioselec-

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