Total Synthesis of *Amaryllidaceae* Alkaloids Utilizing Sequential Intramolecular Heterocyclic Azadiene Diels−Alder Reactions of an Unsymmetrical 1,2,4,5-Tetrazine

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Convergent total syntheses of anhydrolycorinone, hippadine, and anhydrolycorinium chloride are detailed, enlisting sequential inverse electron demand Diels−Alder reactions of an unsymmetrical *N*-acyl-6-amino-1,2,4,5-tetrazine.

Lycorine alkaloids, isolated from *Amaryllidaceae* plants, are characterized by their pyrrolophenathridine skeleton and potent biological activity. For instance, hippadine[1] (**1**) inhibits fertility in male mice, while kalbretorine[2] (**2**), ungeremine[3] (**3**), and anhydrolycorinium chloride[4] (**4**) exhibit cytotoxic activity against a number of tumor cell lines (Figure 1). Anhydrolycorinone[5] (**5**), itself a natural product, serves as an advanced intermediate for the total synthesis of hippadine and anhydrolycorinium chloride, both of which can be generated from anhydrolycorinone in one or two steps.[5,6]

Herein, we describe a concise synthesis of **1**, **4**, and **5** complementary to efforts described to date.[6,7] Central to the approach is the implementation of two sequential intramolecular inverse electron demand Diels−Alder reactions of an unsymmetrical 1,2,4,5-tetrazine in a tetrazine → diazine → benzene strategy.[8] The intramolecular Diels−Alder reactions of *N*-tethered dienophiles with both 6-acyl(amino)-1,2,4,5-tetrazines[9] and 6-acyl(amino)-1,2-diazines[8,10] are well-precedented, and it has been shown that *N*-acylation of 6-amino-3-(methylthio)-1,2,4,5-tetrazine accelerates its rate of participation in a $LUMO_{diene}$-controlled Diels−Alder reaction to the extent that cycloaddition can be confidently expected to occur at 25 °C.[9]

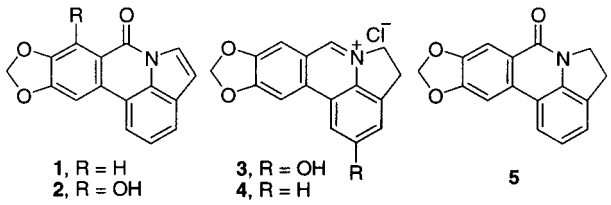

Figure 1.

The approach enabled the exploration of two possible orders for implementation of the key heteroaromatic azadiene Diels−Alder reactions (Scheme 1). Both approaches in which either the fused five-membered or six-membered ring may be introduced first through use of an intramolecular tetrazine Diels−Alder reaction were examined. The former proved straightforward, and preparation of suitably substituted unsymmetrical 1,2,4,5-tetrazines from 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**), followed by a tandem *N*-acylation/intramolecular Diels−Alder reaction, acylation with a substituted piperonylic acid, and a second intramolecular Diels−Alder reaction furnished the pyrrolophenanthridine core.

Total Synthesis of Anhydrolycorinone, Anhydrolycorinium Chloride, and Hippadine. 2-Bromopiperonal was protected as its diethyl ketal [$HC(OEt)_3$, *p*-TsOH, EtOH, 80 °C, 24 h] and converted to the known aldehyde **7**[11] via lithium−halogen exchange (*n*-BuLi,

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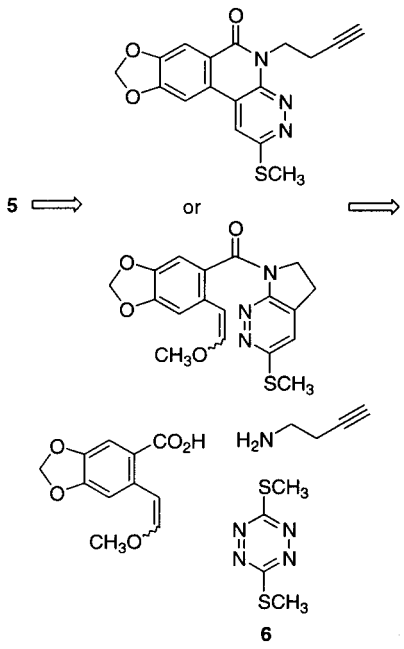
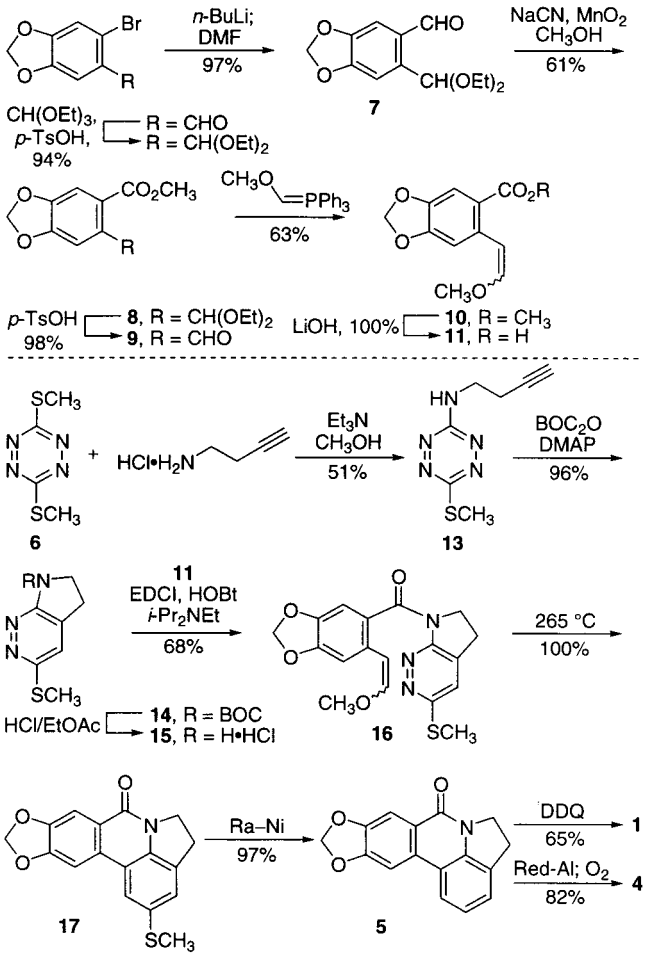
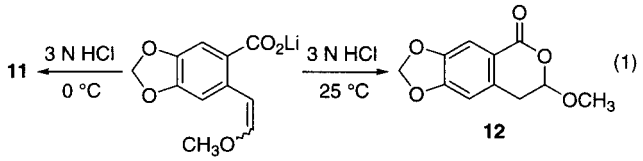
Scheme 1



Scheme 2



Et_2O, −30 °C, 15 min) and subsequent DMF trap (−78 °C to 25 °C, 18 h) (Scheme 2). Aldehyde **7** was transformed to the corresponding methyl ester **8** by oxidation according to a modification of the Corey−Ganem procedure[12] (NaCN, MnO_2, CH_3OH, 25 °C, 18 h, 61%). Following mild deprotection of the ketal **8** with *p*-TsOH (98%), conversion of **9** to the carboxylic acid **11** was accomplished via Wittig reaction (2.0 equiv of $CH_3OCH{=}PPh_3$, THF, −78 to 25 °C, 3.5 h, 63%, 1:1 cis:trans) and subsequent ester hydrolysis (LiOH, $THF/CH_3OH/H_2O$ 3:1:1, 55 °C, 18 h, 100%). Acidification of the hydrolysis reaction was carried out at 0 °C to prevent a facile cyclization[13] to form **12** (eq 1).[14]



The substrate **13** for the key inverse electron demand Diels−Alder reactions was prepared by clean, selective displacement of one of the methylthio groups from 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**)[9,10,15] with 1-amino-3-butyne[16] (CH_3OH, Et_3N, 51%). The first intramolecular [4 + 2] cycloaddition was accomplished at room temperature in superb conversion upon *N*-acylation of **13** with BOC_2O and catalytic DMAP (THF, 23 h, 96%),[9] and the intermediate *N*-BOC derivative prior to cyclization was not detected. The resulting 1,2-diazine **14** was *N*-BOC-deprotected (4 M HCl/EtOAc, 2 h, 25 °C, 100%) and used directly in the coupling reaction with **11**.

The ease with which **11** cyclized to **12**, even in the absence of an acid catalyst, presented an impediment to the preparation of **16**, which could be overcome by the addition of excess *i*-Pr_2NEt and HOBt (2 equiv of EDCI, 2 equiv of HOBt, 10 equiv of *i*-Pr_2NEt, DMF, 24 h, 25 °C, 68%). This set the stage for the second key intramolecular [4 + 2] cycloaddition and subsequent aroma-

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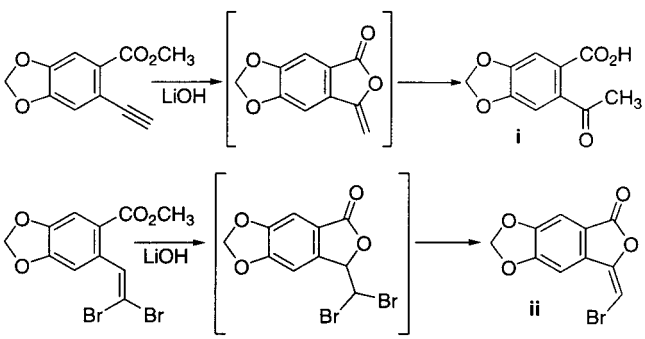
(13) This acid-catalyzed cyclization has been observed for the benzoic acid analogue of **11**. See: Kirby, A. J.; Williams, N. H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 643. For 7-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isochromen-5-one (**12**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 6.66 (s, 1H), 6.03 (d, J = 1.2 Hz, 1 H), 6.02 (d, J = 1.2 Hz, 1H), 5.39 (t, J = 3.8 Hz, 1H), 3.55 (s, 3H), 3.21 (dd, J = 3.5 Hz, J = 18.2 Hz, 1H), 2.98 (dd, J = 3.8 Hz, J = 16.4 Hz, 1H); MALDIFTMS (DHB) *m/z* 223.0598 ($C_{11}H_{10}O_5 + H^+$ requires 223.0601).

(14) Similar cyclizations prevented the preparation of the *o*-ethynyl and *o*-dibromovinyl acids by producing **i** and **ii**, respectively. For 6-acetylbenzo[1,3]dioxole-5-carboxylic acid (**i**): ^{1}H NMR (CD_3OD, 250 MHz) δ 7.10 (s, 1H), 7.03 (s, 1H), 6.14 (s, 2H), 1.78 (s, 3H); FABHRMS (NBA/NaI) *m/z* 231.0267 ($C_{10}H_8O_5 + Na^+$ requires 231.0269). For 7-bromomethylene-7*H*-furo[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxol-5-one (**ii**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (s, 1H), 6.93 (s, 1H), 6.15 (s, 2H), 6.14 (s, 1H); MALDIFTMS (DHB) *m/z* 268.9451 ($C_{10}H_5BrO_4$ requires 268.9449).



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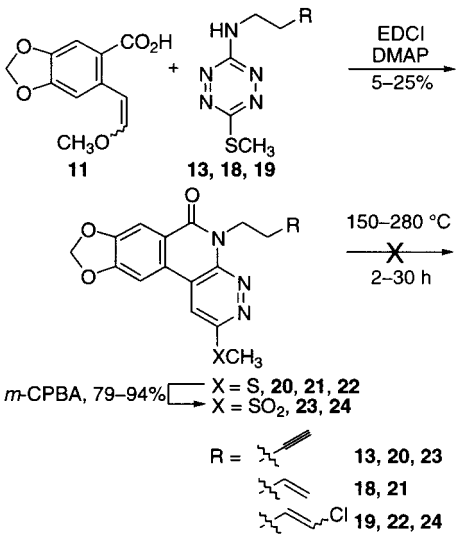
Scheme 3



tization via elimination of methanol, which was accomplished in superb yield to provide the anhydrolycorinone precursor **17** (*N*,*N*-diethylaniline, 265 °C, 20 h, 100%). Reductive desulfurization with Raney nickel provided anhydrolycorinone (**5**, EtOH, 25 °C, 18 h, 97%), which was subsequently converted to hippadine[5] (**1**, DDQ, 80 °C, 24 h, 65%) and anhydrolycorinium chloride[6] (**4**, Red-Al, 25 °C, 2 h; O_2, HCl/EtOH, 25 °C, 24 h, 82%). The synthetic samples of **1**, **4**, and **5** were identical in all respects (^{1}H and ^{13}C NMR, IR, mp) with properties reported for authentic materials.[1,4,5]

Sequence of Azadiene Diels−Alder Reactions. Complementary to these studies in which the five-membered ring of the pyrrolophenanthridine system was formed first, a series of approaches in which the six-membered ring was formed first were also examined. In these approaches, the aminotetrazines **13**, **18**, and **19** were coupled directly to **11** (Scheme 3). The aminotetrazines **13** and **18** were produced upon direct displacement of one methylthio group of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) (CH_3OH, 25 °C). The tetrazine **19** was produced in 51% overall yield by methylthio group displacement with 3-amino-1-propanol (CH_3OH, 25 °C), oxidation to the corresponding aldehyde (PCC, CH_2Cl_2, 25 °C, 5 h), and Wittig olefination ($ClCH{=}PPh_3$, NHMDS, −78 to 25 °C, 3 h). As expected, acylation with **11** was accompanied by room temperature [4 + 2] cycloadditions and with the enol ether serving as the exclusive dienophile. Thus, [4 + 2] cycloaddition reaction with closure of the fused six-membered ring was observed in preference to the fused five-membered ring presumably dictated by the electron-rich character of the competing dienophiles. The modest conversions proved to be a consequence of a poor *N*-acylation reaction of **11** with **13** and **18**−**19** (75−95% recovered tetrazine), with the subsequent in situ cycloaddition proceeding without detection of the intermediate *N*-acylaminotetrazine. The resulting 1,2-diazines **20**−**22** were subjected to thermal conditions to induce a second intramolecular Diels−Alder reaction. Despite the use of a range of solvents (1,3,5-triisopropylbenzene, 2-chloronaphthalene, *o*-dichlorobenzene, *N*,*N*-diethylaniline), high temperatures (150−280 °C), and prolonged reaction times (2−30 h), only recovered starting materials and small amounts of the corresponding sulfoxides were obtained. Oxidation of diazines **20** and **22** to the corresponding sulfones **23** and **24** (*m*-CPBA, −78 to 25 °C, 79−94%) did not improve their [4 + 2] cycloaddition reactivity. This lack of reactivity is due to the intrinsically poor reactivity of aromatic 1,2-diazines toward Diels−Alder reactions, especially in comparison to the successful, closely analogous pyrone system of Castedo et al.[7]

Conclusions

A convergent total synthesis of anhydrolycorinone, anhydrolycorinium chloride, and hippadine was described enlisting a tetrazine → diazine → benzene strategy featuring two sequential intramolecular [4 + 2] cycloaddition reactions of an unsymmetrical 6-(acylamino)-1,2,4,5-tetrazine.[17]

Experimental Section

Methyl 6-(Diethoxymethyl)benzo[1,3]dioxole-5-carboxylate (8). A solution of **7**[11] (5.2 g, 20.6 mmol) in 200 mL of anhydrous CH_3OH was treated with NaCN (5.05 g, 103 mmol) and the mixture was stirred at 25 °C until all solid had dissolved (15 min). The reaction mixture was then treated with activated MnO_2 (27 g, 309 mmol) and stirred at 25 °C for 24 h before being filtered through Celite and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 4.5 × 18 cm, 15% EtOAc/hexanes) to afford **8** (4.03 g, 61%) as a colorless oil:^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (s, 1H), 7.27 (s, 1H), 6.17 (s, 1H), 6.00 (s, 2H), 3.85 (s, 3H), 3.74−3.48 (m, 4H), 1.21 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 150.6, 147.1, 137.1, 123.1, 110.0, 107.3, 101.8, 99.0, 62.9, 52.1 (2C), 15.1 (2C); IR (film) ν_{max} 2975, 1720, 1487, 1281 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.71; H, 6.71.

Methyl 6-Formylbenzo[1,3]dioxole-5-carboxylate (9). A solution of **8** (4.03 g, 14.3 mmol) in 100 mL of CH_2Cl_2 was treated with *p*-TsOH (280 mg, 1.4 mmol) and H_2O (10 mL), and the mixture was stirred at 25 °C for 18 h. The reaction mixture was diluted with H_2O (90 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (SiO_2, 6.5 × 15 cm, CH_2Cl_2) provided **9** (2.9 g, 98%) as a white solid: mp 112−113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.53 (s, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 6.12 (s, 2H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.8, 166.3, 151.8, 151.5, 134.1, 128.8, 110.6, 107.9, 103.1, 53.1; IR (film) ν_{max} 2919, 1714, 1493, 1283 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 209.0447 ($C_{10}H_8O_5$ + H^+ requires 209.0450).

Methyl 6-(2-Methoxyvinyl)benzo[1,3]dioxole-5-carboxylate (10). A solution of methoxymethyltriphenylphosphonium chloride (362 mg, 1.06 mmol) in 2.0 mL of anhydrous THF at −78 °C was treated with *t*-BuLi (0.76 mL of a 1.26 M solution in pentane, 0.96 mmol) dropwise and stirred for 20 min. The resulting deep red solution was warmed to −40 °C for 30 min and then cooled to −78 °C before **9** (100 mg as a solution in 2.0 mL THF, 0.48 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and stirred for 15 h. The reaction mixture was quenched with the addition of H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 4 × 14 cm, 10% EtOAc/hexanes) to provide **10** as a 1:1 mixture of cis and trans isomers (71 mg, 63%) as an off-white solid: mp 61−63 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) cis, δ 7.66 (s, 1H), 7.41 (s, 1H), 6.24 (d, J = 7.3 Hz, 1H), 6.22 (d, J = 7.3 Hz, 1H), 6.05 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H); trans, δ 7.46 (s, 1H), 6.97 (d,

(17) L1210 IC_{50} values: **1**, >100 μM; **4**, 0.9 μM; **5**, 23 μM; **17**, 9 μM; **16**, 16 μM.

J = 13.2 Hz, 1H), 6.91 (s, 1H), 6.89 (d, J = 12.9 Hz, 1H), 6.05 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7 and 167.5, 151.4 and 150.6, 150.3 and 148.5, 146.1 and 145.6, 135.4 and 133.5, 121.6 and 120.7, 110.8 and 110.5, 110.4 and 106.1, 104.7 and 103.2, 102.0 and 101.9, 61.0 and 56.7, 52.2 and 52.1; IR (film) ν_{max} 2950, 1710, 1633, 1484, 1293 cm^{-1}; MALDIFTMS (DHB) m/z 237.0759 ($C_{12}H_{12}O_5$ + H^+ requires 237.0763).

6-(2-Methoxyvinyl)benzo[1,3]dioxole-5-carboxylic Acid (11). A solution of **10** (63 mg, 0.27 mmol) in 1.0 mL of 3:1:1 THF/CH_3OH/H_2O was treated with LiOH (57 mg, 1.35 mmol) and stirred at 55 °C for 8 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (1.0 mL), and washed with Et_2O (1.0 mL). The aqueous phase was cooled to 0 °C, acidified with 3 M aqueous HCl, and quickly extracted with Et_2O (3 × 1.5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide pure **11** (60 mg, 100%) as an unstable white solid which was used immediately in subsequent reactions: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (s, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 6.91 (d, J = 12.9 Hz, 1H), 6.85 (s, 1H), 6.84 (d, J = 12.9 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 6.19 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H); MALDIFTMS (DHB) m/z 223.0598 ($C_{11}H_{10}O_5$ + H^+ requires 223.0601).

But-3-ynyl-(6-methylthio-1,2,4,5-tetrazin-3-yl)amine (13). A solution of 3,6-bis(thiomethyl)-1,2,4,5-tetrazine[15] (**6**, 622 mg, 3.6 mmol) in 15 mL of anhydrous CH_3OH at 25 °C was treated with Et_3N (1.0 mL, 7.2 mmol) and 1-amino-3-butyne[16] (460 mg, 4.4 mmol). After the reaction mixture was stirred for 18 h, the solvent was removed under reduced pressure and the resulting oil was dissolved in CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (SiO_2, 4.5 × 15 cm, 10−15% EtOAc/hexanes gradient elution) provided **13** (360 mg, 51%) as a bright red solid: mp 75−76 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.83 (br s, 1H), 3.73 (dt, J = 6.4, 6.4 Hz, 2H), 2.66 (s, 3H), 2.59 (dt, J = 2.6, 6.4 Hz, 2H), 2.05 (t, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 160.8, 80.9, 70.7, 39.9, 18.9, 13.6; IR (film) ν_{max} 3298, 2928, 2855, 1699, 1574, 1435 cm^{-1}; FABHRMS (NBA/NaI) m/z 196.0656 ($C_7H_9N_5S$ + H^+ requires 196.0657).

7-*tert*-Butyloxycarbonyl-3-methylthio-5,6-dihydropyrrolo[2,3-*c*]pyridazine (14). A solution of **13** (179 mg, 0.92 mmol) in 10 mL of anhydrous THF at 25 °C under N_2 was treated with BOC_2O (800 mg, 3.67 mmol) and DMAP (17 mg, 0.14 mmol) and stirred for 24 h. After solvent was removed under reduced pressure, the residue was subjected to flash chromatography (SiO_2, 2.5 × 11 cm, 20−40% EtOAc/hexanes gradient elution) to provide **14** (256 mg, 96%) as a tan oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (s, 1H), 3.98 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 8.0 Hz, 2H), 2.64 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 155.9, 150.8, 132.3, 122.4, 82.2, 46.0, 28.2, 24.4, 13.5; IR (film) ν_{max} 2977, 2927, 1728, 1622, 1538, 1484 cm^{-1}; FABHRMS (NBA/NaI) m/z 290.0948 ($C_{12}H_{17}N_3O_2S$ + Na^+ requires 290.0939).

6-(2-Methoxyvinyl)benzo[1,3]dioxol-5-yl-(3-methylthio-5,6-dihydropyrrolo[2,3-*c*]pyridazin-7-yl)methanone (16). A sample of **14** (11 mg, 0.048 mmol) was dissolved in 4.0 M HCl/EtOAc (2.5 mL), and the solution was stirred for 2 h at 25 °C. The solvents were removed under reduced pressure, and the residual salt **15** was dried thoroughly under high vacuum. The salt was treated with a solution of EDCI (18 mg, 0.09 mmol), HOBt (12 mg, 0.09 mmol), *i*-Pr_2NEt (79 μL, 0.45 mmol), and **11** in anhydrous DMF (1.0 mL), and the reaction was stirred under N_2 at 25 °C for 24 h. The reaction mixture was diluted with CH_3OH (3.0 mL), and solvents were removed under reduced pressure. The resulting residue was diluted with H_2O (1.5 mL) and extracted with CH_2Cl_2 (3 × 1.5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 1.5 × 12 cm, 0.5−2% CH_3OH/CH_2Cl_2 gradient elution) to provide **16** as a 2:1 mixture (trans:cis) of isomers (11.3 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) trans, δ 7.09 (s, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 6.68 (d, J = 12.9 Hz, 1H), 5.96 (s, 2H), 5.81 (d, J = 12.5 Hz, 1H), 4.19 (t, J = 8.1 Hz, 2H), 3.51 (s, 3H), 3.07 (t, J = 8.5 Hz, 2H), 2.60 (s, 3H); cis, δ 7.56 (s, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 5.96 (s, 2H), 5.95 (d, J = 7.4 Hz, 1H), 5.21 (d, J = 7.4 Hz, 1H), 4.17 (t, J = 8.1 Hz, 2H), 3.67 (s, 3H), 3.07 (t, J = 8.5 Hz, 2H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.9 (2C), 157.7 and 157.6, 157.5 and 157.4, 150.2 and 149.8, 149.1 and 148.3, 146.4 and 145.8, 133.3 and 133.1, 129.5 and 128.6, 128.4 and 127.7, 123.2 (2C), 110.1 and 108.4, 107.7 and 106.4, 102.9 and 102.3, 101.8 and 101.7, 61.0 and 57.1, 47.0 (2C), 24.9 (2C), 14.0 (2C); IR (film) ν_{max} 2923, 1636, 1412, 1250, 1037 cm^{-1}; MALDIFTMS (DHB) m/z 394.0844 ($C_{18}H_{17}N_3O_4S$ + Na^+ requires 394.0832).

2-Methylthio-4,5-dihydro[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (17). A solution of **16** (11 mg, 0.03 mmol) in degassed *N*,*N*-diethylaniline was warmed at 265 °C in a sealed tube under N_2 for 20 h. The reaction mixture was cooled to 25 °C and loaded directly onto SiO_2 (2.5 × 10 cm) equilibrated in CH_2Cl_2. *N*,*N*-Diethylaniline was eluted with CH_2Cl_2, and the column was then eluted with 1% CH_3OH/CH_2Cl_2 to afford **17** (9.4 mg, 100%) as a white solid: mp 218−219 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.71 (s, 1H), 7.53 (s, 1H), 7.29 (s, 1H), 6.13 (s, 2H), 4.48 (t, J = 7.9 Hz, 2H), 3.41 (t, J = 7.9 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 152.3, 149.1, 138.4, 132.9, 132.2, 130.3, 125.0, 123.7, 120.0, 117.4, 107.3, 102.5, 101.2, 47.1, 27.7, 18.6; IR (film) ν_{max} 2913, 1641, 1610, 1492, 1390 cm^{-1}; MALDIFTMS (DHB) m/z 312.0691 ($C_{17}H_{13}NO_3S$ + H^+ requires 312.0689).

Anhydrolycorin-7-one (5). A slurry of Raney nickel (110 mg wet, 50 wt equiv) and **17** (2.3 mg, 0.007 mmol) in 0.3 mL of absolute EtOH was stirred vigorously at 25 °C for 18 h. The Raney nickel was removed by filtration (EtOAc wash) through Celite. The removal of solvents under reduced pressure and PTLC (SiO_2, 3% MeOH/CH_2Cl_2) afforded **5** (1.8 mg, 97%) as a white solid: mp 257−259 °C (lit.[5] mp 262−264 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.12 (s, 2H), 4.48 (t, J = 8.1 Hz, 2H), 3.43 (t, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 152.3, 148.9, 139.9, 131.3, 131.1, 124.3, 123.7, 123.6, 119.9, 117.2, 107.3, 102.5, 101.3, 47.0, 27.9; IR (film) ν_{max} 2923, 1608, 1557, 1254 cm^{-1}; MALDIFTMS (DHB) m/z 266.0821 ($C_{16}H_{11}NO_3$ + H^+ requires 266.0812).

Hippadine (1). According to the method of Ghosal et al.,[5] a solution of anhydrolycorin-7-one (**5**, 2.1 mg, 0.007 mmol) and DDQ (12 mg, 0.048 mmol) in 2.0 mL of anhydrous benzene was stirred at 80 °C. After 24 h, the reaction mixture was cooled to 25 °C, solvents were removed under reduced pressure, and the residue was subjected to PTLC (SiO_2, 2.5% CH_3OH/CH_2Cl_2) to afford **1** (1.3 mg, 65%) as a white solid: mp 218−219 °C (lit.[5] mp 217−218 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, J = 3.7 Hz, 1H), 7.99 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.47 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 6.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 152.8, 148.8, 131.9, 131.2, 128.7, 124.2, 123.8, 122.8, 118.6 (2C), 117.0, 111.0, 108.3, 102.5, 102.0; IR (film) ν_{max} 2921, 1707, 1591, 1447 cm^{-1}; MALDIFTMS (DHB) m/z 264.0662 ($C_{16}H_9NO_3$ + H^+ requires 264.0655).

Anhydrolycorinium Chloride (4). According to a modification of the method of Humber et al.,[6] a solution of anhydrolycorin-7-one (**5**, 0.7 mg, 0.003 mmol) in 0.3 mL of anhydrous toluene was treated with Red-Al (7 μL of a 65 wt % solution in toluene, 0.02 mmol) and stirred at 25 °C under Ar. After 1.5 h, saturated aqueous NH_4Cl (0.5 mL) was added and the mixture was extracted with EtOAc (5 × 0.5 mL). The combined organic extracts were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was immediately dissolved in 0.5 mL EtOH and treated with 0.1 mL of concentrated HCl, and air was bubbled through the solution for 18 h. The solvents were removed under reduced pressure to afford **4** (0.7 mg, 82%) as a light yellow solid: dec 279−281 °C (lit.[6] dec 280−285 °C); ^{1}H NMR (D_2O, 500 MHz) δ 9.33 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.84 (t, J = 7.3 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.58 (s, 1H), 6.33 (s, 2H), 5.13 (t, J = 6.6 Hz, 2H), 3.72 (t, J = 6.6 Hz, 2H); ^{13}C NMR (D_2O, 125 MHz) δ 156.7, 150.5, 144.4, 136.7, 136.6, 133.4, 131.5, 126.2, 123.7, 122.7, 120.2, 107.6, 104.4, 101.2, 60.0, 27.6;

IR (film) ν_{max} 3439, 1502, 1478, 1267, 1031, 925 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 250.0836 ($C_{16}H_{12}ClNO_2 - Cl^-$ requires 250.0836).

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Supporting Information Available: Copies of ^1H NMR spectra of bromopiperonal diethyl ketal, **7**−**14**, **16**−**24**, **1**, **4**, and **5** and experimental details for the preparation of **18**−**24** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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