Synthesis of Antitumor Lycorines by Intramolecular Diels−Alder Reaction†

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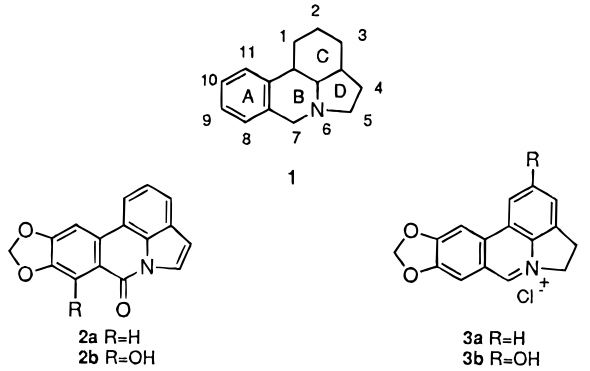
Pharmacologically interesting lycorines were obtained by a short, efficient method based on an intramolecular Diels−Alder reaction between an α-pyrone and an alkyne, followed by loss of CO_2 in a retro Diels−Alder reaction. The cyclization precursors (pyrones **9**) were obtained in good yields in two or three steps from the corresponding homophthalic acid or anhydride.

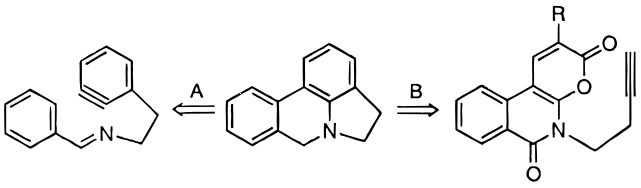
Introduction

The lycorine alkaloids, a group of compounds isolated from Amaryllidaceae plants[1] and characterized by the skeleton **1**, have attracted the attention of chemists and pharmacologists due to the interesting properties of certain known lycorines. For example, hippadine (**2a**) inhibits fertility in mice,[2] anhydrolycorinium chloride[3] (**3a**) is active against P-388 leukemia, and kalbretorine[4] (**2b**) and ungeremine[5] (**3b**) are active against several types of tumor.



Retrosynthetic analysis of the basic skeleton of lycorines **1** has led us to develop two new approaches to these compounds. One, based on intramolecular cycloaddition of an aryne and an azadiene (Scheme 1, route A), was reported recently.[6] We now report the results of the second approach, which is based on an intramolecular Diels−Alder reaction between a pyrone and an alkyne, followed by loss of CO_2 in a retro Diels−Alder reaction (Scheme 1, route B). Reactions of α-pyrones with alkynes and arynes to afford aromatic compounds are well known,[7] and our group has used intermolecular cycloaddition with benzyne for the synthesis of benzophenanthridine alkaloids.[8]

Scheme 1



Results and Discussion

Suitable substrates for the intended intramolecular Diels−Alder reaction, compounds **9**, were first prepared via pyrones **6**.[9] Condensation of 4,5-dimethoxyhomophthalimide[10] (**4a**) with trimethyl orthoformate in Ac_2O/DMF afforded **5a**, and treatment of **5a** with ethyl cyanoacetate and NaOMe gave pyrone **6a**. Reaction of **6a** with the tosylate **7**[11] afforded the O-alkylation and N-alkylation products **8a** and **9a** in 1:1 ratio and joint 93% yield. Modification of the reaction conditions did not change the ratio between the two products, which were separated by chromatography. Compound **8a** was recycled by hydrolysis to **6a**. Heating of compound **9a** in refluxing nitrobenzene afforded the cycloadduct **10a** in 95% yield. A similar route was applied to the synthesis of the methylenedioxy derivative **10b** (Scheme 2).

Although the above procedure was efficient for the synthesis of **10** (the overall yield from the imides **4** was around 50%), the preparation of the cyclization precursors was complicated by the need to separate the N- and O-alkylated products and recycle the latter. To avoid this problem we introduced the substituent on the nitrogen

† Dedicated to Prof. Antonio González in celebration of his half-century of contribution to natural product chemistry.

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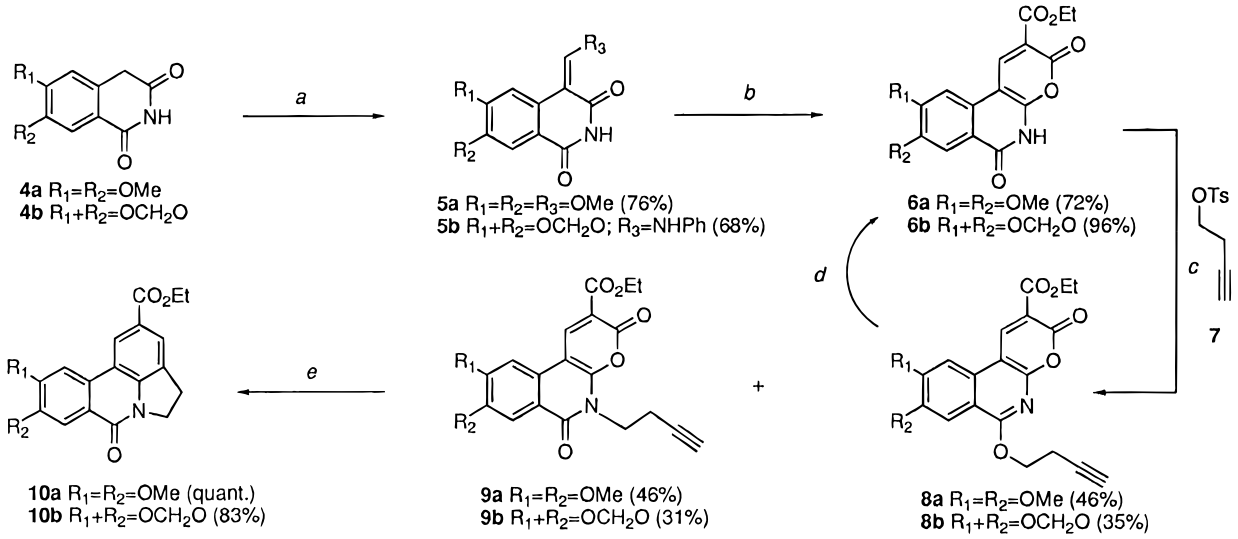
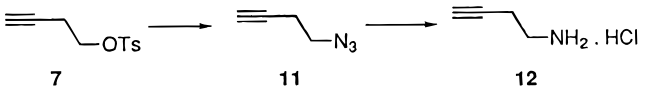
Scheme 2



a: $HC(OCH_3)_3$, Ac_2O-DMF 4:1 (for **5a**); $HC(OCH_3)_3$; $PhNH_2$, AcOH, DMF (for **5b**). *b*: $NCCH_2CO_2Et$, NaOMe, DMF (for **6a**); $NCCH_2CO_2Et$, KO*t*-Bu, DMF (for **6b**). *c*: i. KO*t*-Bu, DMF; ii. **7**, DMF. *d*: conc. HCl, EtOH. *e*: Nitrobenzene, Δ.

Scheme 3



7 **11** **12**

atom at an earlier stage. To this end, 3-butyn-1-amine hydrochloride (**12**) was prepared from tosylate **7** by the one-pot, two-step route shown in Scheme 3, which improves on previously reported methods:[12] treatment of **7** with sodium azide and reduction of the crude product with tin(II) chloride, followed by acidic workup, afforded the stable hydrochloride **12** in quantitative yield (88% overall from 3-butyn-1-ol).

Since the thermal instability and low boiling point of the amine prevented the condensation of 3-butyn-1-amine with homophthalic acids under the usual conditions (200 °C), we tried alternative procedures for imide synthesis under milder conditions. Treatment of 4,5-(methylenedioxy)homophthalic anhydride[13] (**13**) with a solution of 3-butyn-1-amine (freshly obtained by treatment of **12** with 10% NaOH solution), followed by heating of the resulting salt, afforded imide **14** in 78% yield. Transformation of imide **14** into pyrone **9b** was accomplished by two routes (Scheme 4): treatment with methyl orthoformate, aniline, and HOAc furnished enamine **15**, which reacted with ethyl cyanoacetate and *t*-BuOK to give pyrone **9b** in 68% overall yield; while simply heating **14** with the malonyl derivative **16a** achieved the same transformation in one pot and 60% yield. The key step in our procedure, heating a solution of **9b** in nitrobenzene at 210 °C, now brought about both intramolecular cycloaddition between pyrone and alkyne, and subsequent loss of CO_2 through a retro-Diels−Alder reaction, affording **10b** in 83% yield. Synthesis of the naturally occurring alkaloid anhydrolycorin-7-one (**10d**)[2a,14] was completed in 80% yield by hydrolysis of the ethyl ester (KOH) followed by decarboxylation (Cu, quinoline). As transformation of **10d** into hippadine (**2a**)[15] and anhydrolycorinium chloride (**3a**)[16] has already been reported, our approach provides a route to these biologically active compounds.

Other pharmacologically interesting lycorines, such as ungeremine (**3b**), have an oxygen atom linked to C-2 in ring C. We achieved this substitution pattern by synthesizing pyrone **9c**, in which the desired oxygen is incorporated in a methoxy group. After several unfruitful attempts to get **9c** by reaction of enamine **15** with methyl methoxyacetate and various bases under diverse reaction conditions, we finally obtained the desired pyrone in 90% yield by reaction of imide **14** with methyl 3-dimethylamino-2-methoxyacrylate (**16b**), which was prepared by a published procedure.[17] It is important to point out that as condensation of **14** and **16b** involves elimination of dimethylamine, it is necessary to pass a strong current of an inert gas through the reaction vessel to remove the amine from the medium; otherwise, nucleophilic attack on the pyrone leads to decomposition. Heating pyrone **9c** in refluxing nitrobenzene promotes intramolecular cyclization to compound **10c** (60% yield).

In conclusion, this paper describes a versatile new approach to lycorines with various substitution patterns that can be applied to the synthesis of natural alkaloids with biological activity. This approach and that previously reported[6] may be considered as complementary: the latter, based on intramolecular aryne cycloaddition, is more suitable for the synthesis of lycorines that are polysubstituted on ring C; the new approach, based on intramolecular alkyne cycloaddition, is more useful for the synthesis of lycorines that are polysubstituted on ring A.

Experimental Section

General Procedures. Solvents were dried by distillation from a drying agent: THF from Na/benzophenone; CH_2Cl_2,

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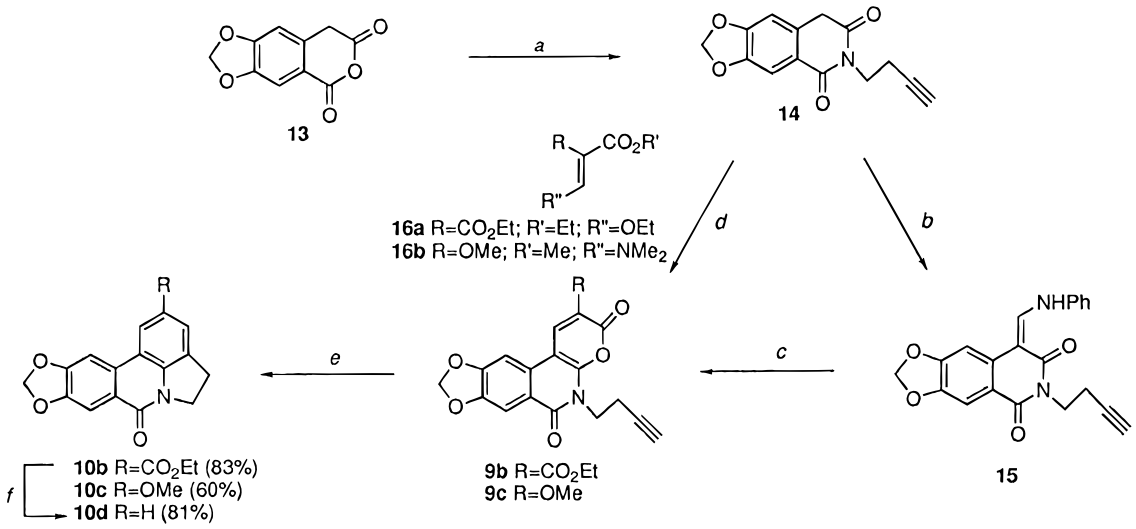
Scheme 4



a: i. 3-Butyn-1-amine, CH_2Cl_2, rt; ii. Δ (79%). *b:* $HC(OMe)_3$, $PhNH_2$, AcOH, DMF (89%). *c:* $NCCH_2CO_2Et$, KO*t*-Bu, DMF (76%). *d:* Δ (60% for **9b**, 90% for **9c**). *e:* Nitrobenzene, Δ. *f:* i. KOH, ii. Cu, quinoline, Δ.

pyridine, and diisopropylamine from CaH_2; DMF from P_2O_5; MeOH from Mg/I_2. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 250.13 and 62.83 MHz. LR and HR mass spectra were recorded at 70 eV or using FAB. TLC was performed on Merck silica gel 60 F_{254} or Merck aluminum oxide 60 F_{254} (type E); chromatograms were visualized with UV light (254 and 360 nm), iodine vapors, and *p*-anisaldehyde. Flash column chromatography was performed on Merck silica gel 60 (ASTM 230−400 mesh). 3,4-Dimethoxyhomophthalic acid and 3,4-(methylenedioxy)homophthalic acid were prepared following the procedure described by McKillop.[18]

6,7-Dimethoxy-4-(methoxymethylene)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (5a). Methyl orthoformate (200 mg, 1.887 mmol) was added to a suspension of 6,7-dimethoxyhomophthalimide (**4a**)[10] (200 mg, 0.905 mmol) in 4:1 Ac_2O−DMF (8 mL), and the mixture was gently refluxed for 20 min. After being cooled to rt, the solution was concentrated to half its volume, and methanol (5 mL) was added. The precipitate was collected by filtration affording **5a** (180 mg, 76%) as a pale yellow solid. Mp 216−217 °C (C_2H_5OH). ^1H NMR ($CDCl_3$) δ 8.15 (bs, 1 H); 7.96 (s, 1 H), 7.80 (s, 1 H); 7.63 (s, 1 H); 4.21 (s, 3 H); 3.97 (s, 6 H). IR (KBr): 1725, 1640 cm^{-1}. UV (C_2H_5OH), λ_{max}: 228, 270, 348 nm. LRMS, *m*/*z* (%): 263 (M^+, 100); 248 (21); 131 (15); 81 (13). HRMS for $C_{13}H_{13}NO_5$. Calcd: 263.0794. Found: 263.0767.

4-(Anilinomethylene)-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (5b). To a solution of 6,7-(methylenedioxy)homophthalimide (**4b**)[10] (150 mg, 0.732 mmol) in DMF (3 mL) were successively added trimethyl orthoformate (115 mg, 1.085 mmol), aniline (70 mg, 0.753 mmol), and one drop of acetic acid. The mixture was stirred at 90 °C for 1 h and then cooled to 50 °C before addition of ethanol (5 mL). The precipitate was collected by filtration, affording **5b** (105 mg) as yellow crystals. The filtrate was concentrated and chromatographed (8:1 $CHCl_3$−ethyl ether) to give further **5b** (46 mg, 68%). Mp 328−330 °C (C_2H_5OH). ^1H NMR ($CDCl_3$) δ 10.92−10.80 (m, 1 H); 8.28 (d, *J* = 12.7 Hz, 1 H); 8.17 (bs, 1 H); 7.61 (s, 1 H); 7.57−7.35 (m, 2 H); 7.24−7.17 (m, 3 H); 7.03 (s, 1 H); 6.07 (s, 2 H). IR (KBr): 3330, 1655, 1605, 1590, 1565 cm^{-1}. UV (C_2H_5OH), λ_{max}: 232, 248, 276, 402 nm. LRMS, *m*/*z* (%): 308 (M^+, 100); 291 (16); 279 (8). HRMS for $C_{17}H_{12}N_2O_4$. Calcd: 308.0797. Found: 308.0786. Anal. for $C_{17}H_{12}N_2O_4$. Calcd: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.21; H, 3.93; N, 8.92.

Ethyl 8,9-Dimethoxy-3,6-dioxo-5,6-dihydro-3*H*-pyran-[2,3-*c*]isoquinoline-2-carboxylate (6a). Freshly prepared NaOMe (50 mg, 0.93 mmol) was added to a solution of **5a** (180 mg, 0.68 mmol) and ethyl cyanoacetate (100 mg, 0.93 mmol) in dry DMF (2 mL), and the mixture was stirred at 90 °C for 45 min, poured on water (5 mL) containing concd HCl (0.5 mL), and stirred at rt for 30 min. The resulting orange suspension was filtered, the solid was redissolved in hot methanol, HCl was added to pH 4, and stirring was kept up overnight. The yellow precipitate was filtered out and vacuum-dried, affording pyrone **6a** (155 mg). The filtrate was concentrated and chromatographed (SiO_2; 99:1 CH_2Cl_2/CH_3OH) to obtain additional **6a** (20 mg, 72%). Mp 290 °C dec, C_2H_5OH. ^1H NMR (DMSO-d_6) δ 9.14 (s, 1 H); 7.63 (s, 1 H); 7.53 (s, 1 H); 4.29 (q, *J* = 7.1 Hz, 2 H); 4.00 (s, 3 H); 3.86 (s, 3 H); 1.30 (t, *J* = 7.1 Hz, 3 H). IR (KBr): 1765, 1700, 1670, 1620, 1580 cm^{-1}. UV (C_2H_5OH), λ_{max}: 222, 252, 278, 412 nm. LRMS, *m*/*z* (%): 345 (M^+, 100); 317 (14); 300 (10); 271 (11). HRMS for $C_{17}H_{15}NO_7$. Calcd: 345.0848. Found: 345.0856.

Ethyl 8,9-(Methylenedioxy)-3,6-dioxo-5,6-dihydro-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (6b). A solution of **5b** (100 mg, 0.325 mmol) in dry DMF (2 mL) was treated with ethyl cyanoacetate (45 mg, 0.390 mmol) and KO*t*-Bu (54 mg, 0.482 mmol), following the procedure described for **6a**. Pyrone **6b** (102 mg, 96%) was obtained as yellow crystals. Mp 293−294 °C dec, C_2H_5OH. ^1H NMR (DMSO-d_6) δ: 9.02 (s, 1 H); 7.87 (s, 1 H); 7.50 (s, 1 H); 6.21 (s, 2 H); 4.26 (q, *J* = 7.0 Hz, 2 H); 1.30 (t, *J* = 7.1 Hz, 3 H). UV (C_2H_5OH), λ_{max}: 252, 284, 422 nm. LRMS, *m*/*z* (%): 329 (M^+, 19); 149 (37); 97 (88); 69 (100). HRMS for $C_{16}H_{11}NO_7$. Calcd: 329.0535. Found: 329.0536.

Reaction of Pyrones 6 with Tosylate 7. Reaction of 6a with 7. KO*t*-Bu (23 mg, 0.20 mmol) was added to a solution of **6a** (58 mg, 0.17 mmol) in dry DMF (1.5 mL) under N_2, and the mixture was refluxed for 1.5 h. A solution of tosylate **7**[11] (100 mg, 0.446 mmol) in DMF (1 mL) was added, and stirring under reflux was was continued for an additional 10 min. Water (5 mL) and 10% HCl (5 mL) were added, and the mixture was stirred for 15 min and extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried with Na_2SO_4, the solvent was evaporated, and the residue was chromatographed (15:85 ethyl ether−$CHCl_3$) to afford ethyl 5-(3-butynyl)-8,9-dimethoxy-3,6-dioxo-5,6-dihydro-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (**9a**) (31 mg, 46%) as a yellow solid. Mp 205−206 °C (C_2H_5OH). ^1H NMR ($CDCl_3$) δ 9.00 (s, 1 H); 7.77 (s, 1 H); 7.22 (s, 1 H); 4.57 (t, *J* = 6.7 Hz, 2 H); 4.46 (q, *J* = 7.1 Hz, 2 H); 4.10 (s, 3 H); 4.02 (s, 3 H); 2.76 (dt, *J* = 6.7, 2.6 Hz, 2 H); 1.96 (t, *J* = 2.6 Hz, 1 H); 1.44 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.2; 160.1; 155.3; 154.8; 154.3; 149.7; 146.4; 126.5; 116.1; 109.1; 107.1; 101.5; 95.6; 79.7; 71.1; 62.1; 56.7; 56.6; 40.6; 17.9; 14.5. IR (KBr): 1775, 1670 cm^{-1}. UV (C_2H_5OH), λ_{max}: 226, 272, 320, 400 nm. LRMS (FAB), *m*/*z* (%): 398 ($M^+ + 1$,

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20.5); 397 (16); 231 (32); 154 (100). Anal. for $C_{21}H_{19}NO_7$ Calcd: C, 63.47; H, 4.82; N, 3.53. Found: C, 63.21; H, 4.90; N, 3.49. Ethyl 6-(3-butynyloxy)-8,9-dimethoxy-3-oxo-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (**8a**) was also isolated (31 mg, 46%). Mp 235−237 °C (C_2H_5OH). ^{1}H NMR ($CDCl_3$) δ 9.08 (s, 1 H); 7.56 (s, 1 H); 7.38 (s, 1 H); 4.73 (t, J = 6.6 Hz, 2 H); 4.44 (q, J = 7.1 Hz, 2 H); 4.11 (s, 3 H); 4.03 (s, 3 H); 2.83 (dt, J = 6.6, 2.7 Hz, 2 H); 2.05 (t, J = 2.7 Hz, 1 H); 1.43 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 164.5; 162.8; 158.2; 157.0; 155.3; 149.8; 145.1; 131.5; 113.2; 112.1; 104.2; 101.3; 100.7, 80.0; 70.2; 65.7; 61.9; 56.5; 56.2; 19.1; 14.3. IR (KBr): 1740, 1715 cm^{-1}. UV (C_2H_5OH), λ_{max}: 226, 252, 276, 282, 318, 392 nm. LRMS, *m*/*z* (%): 397 (M^+, 30); 167 (100). HRMS for $C_{21}H_{19}NO_7$. Calcd: 397.1162. Found: 397.1161. Treatment of a solution of **8a** (10 mg, 0.025 mmol) in C_2H_5OH (2 mL) with 36% HCl (1 mL) for 1 h at 70 °C, removal of the ethanol, partition of the mixture between H_2O and CH_2Cl_2, and chromatography (1% CH_2Cl_2−MeOH) recovered **6a** (7 mg, 80%).

Reaction of 6b with 7. Pyrone **6b** (125 mg, 0.380 mmol) in DMF (4 mL) was reacted with KO*t*-Bu (54 mg, 0.408 mmol) and tosylate **7** (225 mg, 1 mmol) for 1.5 h, as described above, to afford 5-(3-butynyl)-8,9-(methylenedioxy)-3,6-dioxo-5,6-dihydro-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (**9b**) (45 mg, 31%) and 6-(3-butynyloxy)-8,9-(methylenedioxy)-3-oxo-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (**8b**) (50 mg, 35%). **Data for 9b.** Mp 210−211 °C (acetone). ^{1}H NMR ($CDCl_3$−CD_3OD 50:1) δ 8.94 (s, 1 H); 7.51 (s, 1 H); 7.40 (s, 1 H); 6.14 (s, 2 H); 4.63 (t, J = 6.6 Hz, 2 H); 4.39 (q, J = 7.1 Hz, 2 H); 2.76 (dt, J = 6.6, 2.6 Hz, 2 H); 2.04 (t, J = 2.6 Hz, 1 H); 1.39 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$−CD_3OD 50:1) δ 163.8; 162.9; 158.0; 157.0; 153.8; 148.2; 145.2; 133.4; 113.3; 113.0; 102.5; 102.1; 101.7; 98.7; 79.9; 70.1; 65.7; 61.8; 18.9; 14.1. IR (KBr): 1775, 1735, 1675 cm^{-1}. UV (C_2H_5OH), λ_{max}: 226, 242, 284, 392 nm. LRMS, *m*/*z* (%): 381 (M^+, 100); 329 (86); 301 (59). HRMS for $C_{20}H_{15}NO_7$. Calcd: 381.0848. Found: 381.0844. Anal. for $C_{20}H_{15}NO_7$. Calcd: C, 62.99; H, 3.96; N, 3.67. Found: C, 62.72; H, 3.81; N, 3.97. **Data for 8b.** Mp 220−221 °C (acetone). ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1 H); 7.60 (s, 1 H); 7.47 (s, 1 H); 6.19 (s, 2 H); 4.70 (t, J = 6.6 Hz, 2 H); 4.44 (q, J = 7.1 Hz, 2 H); 2.80 (dt, J = 6.6, 2.6 Hz, 2 H); 2.06 (t, J = 2.6 Hz, 1 H); 1.45 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 163.8; 162.8; 158.2; 156.8; 153.7; 148.2; 144.9; 133.5; 113.4; 102.2; 101.7; 98.7; 80.0; 70.1; 65.7; 61.8; 19.0; 14.2. IR (film): 1755 cm^{-1}. UV (C_2H_5OH), λ_{max}: 222, 254, 268, 330, 382 nm. LRMS, *m*/*z* (%): 381 (M^+, 35); 329 (35); 280 (85); 229 (55); 69 (100). HRMS for $C_{20}H_{15}NO_7$. Calcd: 381.0848. Found: 381.0847.

3-Butyn-1-amine Hydrochloride (12). (i) NaN_3 (5.62 g, 117.19 mmol) was added to a solution of 3-butynyl *p*-toluenesulfonate (**7**)[11] (5.25 g, 23.44 mmol) in dry DMF (30 mL), and the resulting suspension was stirred for 24 h. The mixture was partitioned between H_2O (100 mL) and ethyl ether (100 mL), the aqueous phase was extracted with ethyl ether (50 mL), and the combined organic phase was thoroughly washed with H_2O (5 × 25 mL), dried with $MgSO_4$, and concentrated to remove most of the ether. The resulting clear liquid, containing 3-butynyl azide, was used in step ii without further purification. (ii) The reaction crude obtained as above was dissolved in CH_3OH (75 mL), $SnCl_2{\cdot}2H_2O$ (10.58 g, 46.88 mmol) was added, and stirring at rt was kept up for 24 h. The solvent was evaporated at reduced pressure, the residue was dissolved in 10% aqueous NaOH, and this solution was extracted with CH_2Cl_2 (5 × 40 mL). The combined organic phase was dried with Na_2SO_4, a saturated solution of HCl in ethyl ether (20 mL) was added, and the resulting precipitate was collected by filtration, affording **12** (2.14 g) as a white solid; the filtrates were concentrated to dryness to obtain additional **12** (310 mg, quantitative yield). Spectroscopic data were identical with those reported in the literature.[12c]

2-(3-Butynyl)-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (14). Hydrochloride **12** (650 mg, 6.16 mmol) was dissolved in 10% aqueous NaOH (5 mL), the solution was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic phase was dried over Na_2SO_4. The solution of 3-butyn-1-amine so obtained was added at rt to a solution of anhydride **13**[13] (258 mg, 1.22 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 20 h. The solvent was distilled off at atmospheric pressure, and the flask containing the white solid residue was evacuated and filled with argon twice before being heated at 220 °C (external temperature, sand bath) until 5 min after the solid melted. The residue was chromatographed (SiO_2, CH_2Cl_2) to afford imide **14** (249 mg, 79%) as a white solid. Mp 171−176 °C (sublimed). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H); 6.66 (s, 1 H); 6.07 (s, 2 H); 4.16 (t, J = 7.3 Hz, 2 H); 3.94 (s, 2 H); 2.55 (dt, J = 7.3, 2.6 Hz, 2H); 1.97 (t, J = 2.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 169.7; 163.9; 152.66; 147.8; 130.3; 119.3; 107.9; 106.4; 102.1; 80.7; 69.7; 38.2; 36.4; 17.5. UV (C_2H_5OH), λ_{max}: 208, 228, 272, 310 nm. LRMS, *m*/*z* (%): 257 (M^+, 77.8); 218 (24.9); 205 (34.7); 189 (100). HRMS for $C_{14}H_{11}NO_4$. Calcd: 257.0688. Found: 257.0691.

4-(Anilinomethylene)-2-(3-butynyl)-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (15). To a solution of imide **14** (45 mg, 0.175 mmol) in DMF (3 mL) containing one drop of acetic acid, solutions of trimethyl orthoformate (56 mg, 0.526 mmol) and aniline (50 mg, 0.526 mmol) in DMF (1 mL each) were successively added. The resulting mixture was heated at 90 °C for 3.5 h, concentrated under reduced pressure, and treated with CH_3OH (3 mL). The resulting suspension was filtered to afford enamine **15** (36 mg) as a yellow solid, and the filtrate was concentrated to dryness and chromatographed (5% ethyl ether−CH_2Cl_2), yielding additional **15** (20 mg, 89% yield). Mp 214−216 °C (C_2H_5OH), bright yellow crystals. ^{1}H NMR ($CDCl_3$) δ 12.29 (bd, J = 12 Hz, 1 H); 8.25 (d, J = 12.5 Hz, 1 H); 7.63 (s, 1 H); 7.45−7.39 (m, 2 H); 7.26−7.16 (m, 3 H); 6.99 (s, 1 H); 6.05 (s, 2 H); 4.32 (t, J = 7.3 Hz, 2 H); 2.65−2.60 (m, 2 H); 1.99 (bs, 1 H). ^{13}C NMR ($CDCl_3$) δ 166.1; 162.9; 153.0; 146.0; 142.9; 139.4; 132.1; 130.0; 125.0; 117.3; 115.9; 107.3; 101.8; 97.0; 96.6; 81.2; 69.6; 38.2; 17.6. UV (C_2H_5OH), λ_{max}: 232, 312, 402 nm. LRMS, *m*/*z* (%): 360 (M^+, 100); 308 (67); 292 (31); 291 (20). HRMS for $C_{21}H_{16}N_2O_4$. Calcd: 360.1110. Found: 360.1111. Anal. for $C_{21}H_{16}N_2O_4$. Calcd: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.48; H, 4.54; N, 7.62.

Ethyl 5-(3-Butynyl)-8,9-(methylenedioxy)-3,6-dioxo-5,6-dihydro-3*H*-pyran[2,3-*c*]isoquinoline-2-carboxylate (9b). From enamine 15. KO*t*-Bu (34 mg, 0.3 mmol) was added to a solution of **15** (72 mg, 0.2 mmol) and ethyl cyanoacetate (34 mg, 0.3 mmol) in dry DMF (2 mL), and the mixture was stirred at 90 °C for 1 h. HCl (36%, 1 mL) was added, stirring was continued at rt for 3 h, and the resulting orange suspension was filtered. The solid was redissolved in hot methanol, HCl was added to pH 4, and stirring was continued overnight. The solvent was removed under reduced pressure, water (2 mL) was added, and the resulting suspension was extracted with CH_2Cl_2 (3 × 3 mL). The organic phase was dried with Na_2SO_4 and was chromatographed (4% ethyl ether−CH_2Cl_2) to afford pyrone **9b** (30 mg, 76%). **From imide 14.** A mixture of imide **14** (26 mg, 0.10 mmol) and ethoxymethylene diethyl malonate (**16a**) (24 mg, 0.11 mmol) was sealed in a tube in an argon atmosphere and heated for 10 min at 200 °C (external temperature, sand bath). Chromatography of the mixture (2:8 ethyl ether−CH_2Cl_2) then afforded pyrone **9b** (23 mg, 60%).

5-(3-Butynyl)-2-methoxy-8,9-(methylenedioxy)-5,6-dihydro-3*H*-pyran[2,3-*c*]isoquinoline-3,6-dione (9c). A solution of methyl 3-(dimethylamino)-2-methoxyacrylate (**16b**)[17] (48 mg, 300 mmol) in CH_2Cl_2 (0.5 mL) was added to imide **14** (51 mg, 0.198 mmol). The mixture was heated for 10 min at 180 °C (external temperature, sand bath) under a strong current of argon. The crude residue was chromatographed (4% ethyl ether−CH_2Cl_2) to afford pyrone **9c** (60 mg, 90%) as a white solid. Mp 227−228 °C (CH_2Cl_2−hexanes). ^{1}H NMR (DMSO-d_6) δ 7.81 (s, 1 H); 7.70 (s, 1 H); 7.51 (s, 1 H); 6.20 (s, 2 H); 4.24 (t, J = 7.2 Hz, 2 H); 3.85 (s, 3 H); 2.87 (t, J = 2.4 Hz, 1 H); 2.60 (m, 2 H). ^{13}C NMR (DMSO-d_6) δ 158.4; 154.7; 153.0; 147.3; 143.8; 139.7; 129.3; 117.3; 113.6; 105.2; 102.6; 100.9; 94.2; 80.7; 73.1; 57.0; 17.2. UV (C_2H_5OH), λ_{max}: 226, 260, 278, 360 nm. LRMS, *m*/*z* (%): 339 (M^+, 100); 296 (63); 244 (79); 177 (28). HRMS for $C_{18}H_{13}NO_6$. Calcd: 339.0743. Found: 339.0736.

Cyclization of Pyrones 9. General Procedure. A solution of pyrone **9** in nitrobenzene is heated under argon until the starting material has been consumed (TLC). The

solvent is removed by vacuum distillation, and the residue is chromatographed to afford **10**.

Ethyl 9,10-Dimethoxy-7-oxo-4,5-dihydro-7*H*-pyrrolo-[3,2,1-*de*]phenanthridine-2-carboxylate (10a). Pyrone **9a** (4 mg, 0.01 mmol) was refluxed for 8 h in nitrobenzene (2 mL). Chromatography (0.5% CH_2Cl_2−MeOH) afforded **10a** (4 mg, quantitative yield) as a white solid. Mp 228−229 °C (C_6H_6−hexanes). ^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1 H); 7.96 (s, 1 H); 7.92 (s, 1 H); 7.60 (s, 1 H), 4.53 (t, J = 8.2 Hz, 2 H); 4.42 (q, J = 7.1 Hz, 2 H); 4.12 (s, 3 H); 4.05 (s, 3 H); 3.46 (t, J = 8.2 Hz, 2 H); 1.45 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 166.8; 160.0; 153.4; 150.2; 142.8; 131.1; 128.3; 125.7; 124.5; 122.5; 121.4; 116.1; 108.9; 103.3; 61.1; 56.4; 56.3; 46.9; 27.0; 14.4. IR (film): 1710, 1645, 1605 cm^{-1}. UV (C_2H_5OH), λ_{max}: 254, 266, 274, 302, 314, 328, 344 nm. LRMS, m/z (%): 353 (M^+, 100); 308 (23). HRMS for $C_{20}H_{19}NO_5$. Calcd: 353.1263. Found: 353.1262. Anal. for $C_{20}H_{19}NO_5$. Calcd: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.92; H, 5.15; N, 4.33.

Ethyl 9,10-(Methylenedioxy)-7-oxo-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridine-2-carboxylate (10b). Pyrone **9b** (15 mg, 0.04 mmol) was refluxed for 7 h in nitrobenzene (2 mL). Chromatography (0.5% CH_2Cl_2−MeOH) afforded **10b** (11 mg, 83%) as a white solid. Mp 237−238 °C (CH_3OH). ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1 H); 7.97 (s, 1 H); 7.91 (s, 1 H); 7.66 (s, 1 H); 6.16 (s, 2 H); 4.53 (t, J = 8.2 Hz, 2 H); 4.43 (q, J = 7.1 Hz, 2 H); 3.46 (t, J = 8.2 Hz, 2 H); 1.45 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 166.7; 155.2; 152.3; 148.4; 131.1; 130.4; 125.8; 124.7; 123.1; 122.6; 116.1; 106.8; 102.3; 101.1; 61.1; 46.9; 27.0; 14.4. IR (film): 1710, 1645, 1605 cm^{-1}. UV (C_2H_5OH), λ_{max}: 220, 232, 242, 252, 268, 276, 302, 328, 344 nm. LRMS, m/z (%): 337 (M^+, 100); 308 (29); 292 (39); 264 (21); 206 (13); 178 (14). HRMS for $C_{19}H_{15}NO_5$. Calcd: 337.0950. Found: 337.0940. Anal. for $C_{19}H_{15}NO_5$. Calcd: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.39; H, 4.70; N, 4.06.

2-Methoxy-9,10-(methylenedioxy)-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (10c). Pyrone **9c** (19 mg, 0.056 mmol) was heated for 4 h at 230 °C (external temperature, sand bath) in nitrobenzene (0.5 mL). Chromatography (4% ethyl ether−CH_2Cl_2) afforded **10c** (10 mg, 60%) as a white solid. Mp 268−269 °C (CH_3OH). ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1 H); 7.46 (s, 1 H); 7.16 (s, 1 H); 6.94 (s, 1 H); 6.13 (s, 2 H); 4.47 (t, J = 8.0 Hz, 2 H); 3.89 (s, 3 H); 3.39 (t, J = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 158.9; 156.9; 151.7; 148.5; 133.9; 132.2; 130.3; 123.4; 116.6; 112.9; 106.9; 102.4; 102.0; 100.8; 56.1; 46.1; 27.4. UV (C_2H_5OH), λ_{max}: 204, 244, 284, 360, 344 nm. LRMS, m/z (%): 295 (M^+, 96); 280 (100); 222 (13). HRMS for $C_{17}H_{13}NO_4$. Calcd: 295.0845. Found: 295.0841.

Anhydrolycorin-7-one (10d). A solution of **10b** (11 mg, 0.033 mmol) in a 10% ethanolic solution of KOH (1 mL) was heated at 80 °C for 15 min. The solvent was removed under reduced pressure, and the solid residue was suspended in cold 10% HCl (1 mL) and stirred for 15 min. The solvent was decanted, the solid was dried under vacuum and suspended in freshly distilled quinoline (2 mL), Cu bronze was added (15 mg), and the mixture was heated under argon for 2.5 h at 220 °C (external temperature, sand bath). The crude reaction mixture was filtered through Celite, using CH_2Cl_2 (20 mL) to wash the solid. The filtrate was extracted with 10% HCl (3 × 10 mL), and the organic phase was dried with Na_2SO_4, concentrated, and chromatographed (10% ethyl ether−CH_2Cl_2) to afford **10d** (9 mg, 80%) as a white solid. Mp 230−231 °C (C_2H_5OH) [lit.: 228−230 °C[2a] (C_6H_6−C_2H_5OH); 232−234 °C[14] ($CHCl_3$−CH_3OH). Spectroscopic data were identical with those reported in the literature.[14]

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Supporting Information Available: Copies of NMR spectra for compounds **5a**, **6a**,**b**, **8a**,**b**, **14**, **9c**, and **10c** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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