mass calcd for $C_{17}H_{24}O_{10}Na$ $(M + Na)^+$ 411.1267, found 411.1247.

5,6-Dideoxy-D-*xylo*-hex-5-enitol (71) (61%): ^1H NMR (CD_3OD, 500 MHz) δ 5.93 (ddd, J = 6.5, 10.5, 17.1 Hz, 1 H), 5.34 (ddd, J = 1.2, 1.8, 17.1 Hz, 1 H), 5.19 (ddd, J = 1.3, 1.8, 10.5 Hz, 1 H), 4.20 (dddd, J = 1.2, 1.3, 5.9, 6.5 Hz, 1 H), 3.69 (ddd, J = 2.8, 5.4, 6.3 Hz, 1 H), 3.62 (dABq, J_{ax} = 5.4 Hz, J_{bx} = 6.5 Hz, J_{ab} = 11.0 Hz, $\Delta\nu$ = 17.7 Hz, 2 H), 3.47 (dd, J = 2.9, 5.9 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.8 MHz) δ 140.5, 118.1, 76.2, 76.1, 74.1, 65.7. For further confirmation of the structure, the O-methylated compound was synthesized by using NaH/MeI in DMF: ^1H NMR (acetone-d_6, 500 MHz) δ 5.77 (ddd, J = 7.7, 10.5, 18.2 Hz, 1 H), 5.3–5.25 (m, 2 H), 3.76 (m, 1 H), 3.49 (dABq, J_{bx} = 5.1 Hz, J_{bx} = 5.5 Hz, J_{ab} = 9.9 Hz, $\Delta\nu$ = 27.1 Hz, 2 H), 3.42 (s, 3 H), 3.39 (m, 1 H), 3.33 (s, 3 H), 3.30 (s, 3 H), 3.23 (s, 3 H), 3.19 (dd, J = 4.1, 6.1 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.8 MHz) δ 135.5, 118.5, 83.4, 83.2, 80.0, 71.8, 61.0, 59.1, 58.7, 56.6; HRMS (FAB) for $C_{10}H_{21}O_4$ $(M^+ + H)$ calcd 205.1440, found 205.1443.

General Experimental Procedure for the Ozonolysis of Alkenepolyols. Into a solution of alkene (0.2–0.5 mM) in MeOH at −78 °C was bubbled a stream of O_3 until a light blue color persisted, indicating the presence of excess O_3. After flushing out excess O_3 with N_2, Na_2SO_3 (ca. 2–4 g) was added. The mixture was vigorously stirred for 1 h at −78 °C and 15 h at room temperarture. After filtration and concentration, column chromatography over silica gel (20–50% MeOH in CH_2Cl_2) gave the desired aldose.

2-Deoxy-L-xylohexose (67) (84%). The product showed the same ^1H and ^{13}C NMR spectra as a sample of 2-deoxy-L-xylohexose prepared according to ref 33: $[\alpha]^{21}_D$ = −6.1 (c = 1.5, H_2O) (authentic sample: $[\alpha]^{21}_D$ = −5.6 (c = 0.8, H_2O)).[37]

L-Gulose (69) (76%). The product showed the same ^1H and ^{13}C NMR spectra as authentic L-gulose: $[\alpha]^{21}_D$ = 17 (c = 2.5, H_2O (authentic sample: $[\alpha]^{20}_D$ = 20 (c = 13.6, H_2O)).[37]

L-Idose (70) (68%). The product showed the same ^1H and ^{13}C NMR spectra as authentic L-idose: $[\alpha]^{21}_D$ = −14 (c = 1.2, H_2O (authentic sample: $[\alpha]^{21}_D$ = −17.4 (c = 3.6, H_2O)).[37]

L-Xylose (72) (67%). The product showed the same ^1H and ^{13}C NMR spectra as authentic L-xylose: $[\alpha]^{21}_D$ = −17.4 (c = 0.32, H_2O) (authentic sample: $[\alpha]^{21}_D$ = −18.8 (c = 0.30, H_2O)).

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Registry No. **5**, 136-08-3; **15**, 67928-92-1; **16**, 67928-93-2; **17**, 60041-31-8; (±)-**18**, 96243-33-3; (*S*)-**18**, 96243-33-3; (±)-**19**, 143106-64-3; (*S*)-**19**, 143168-75-6; **20**, 132531-96-5; **21**, 1191-99-7; **22**, 56072-67-4; **23**, 143106-66-5; **24**, 143168-68-7; (±)-**25**, 143106-65-4; (*S*)-**25**, 143168-76-7; (±)-**26**, 105181-79-1; (*S*)-**26**, 139629-50-8; **27**, 143106-63-2; **28**, 3054-95-3; **29**, 143168-73-4; **29** diethyl acetal, 143106-73-4; **29** dimethyl acetal, 143106-76-7; **31**, 4137-56-8; **32**, 38838-06-1; **34**, 89886-12-4; **34** dimethyl acetal, 143106-74-5; **34** dimethyl acetal dimethyl ether, 143106-78-9; α-**35**, 1824-96-0; α-**35** 5-*o*-tosyl derivative, 143168-80-3; β-**35**, 1824-97-1; β-**35** 5-*o*-tosyl derivative, 143168-81-4; α-**36**, 143168-69-8; β-**36**, 143168-70-1; α-**37**, 143168-71-2; β-**37**, 143168-72-3; **39**, 143168-74-5; **39** dimethyl acetal, 143106-75-6; **39** dimethyl acetal dimethyl ether, 143106-79-0; (±)-**40**, 3913-65-3; (*S*)-**40**, 3913-64-2; **41**, 141-46-8; **42**, 533-50-6; **43**, 80648-97-1; **44**, 117625-98-6; **45**, 143106-67-6; **46**, 143106-68-7; **47**, 143106-69-8; **48**, 143106-70-1; **49**, 143106-71-2; **50**, 143106-72-3; **51**, 92574-10-2; **65**, 131484-31-6; **66**, 143168-77-8; **66** pentaacetate derivative, 143168-83-6; **67**, 143168-78-9; **67** pentaacetate derivative, 143168-82-5; **68**, 143168-79-0; **69**, 6027-89-0; **70**, 5934-56-5; **71**, 139404-79-8; **71** tetra-*o*-methyl ether, 143106-77-8; **72**, 609-06-3; TK, 9014-48-6; MeSH, 74-93-1; vinylmagnesium bromide, 1826-67-1; trimethylacetaldehyde, 680-19-3; β-hydroxypyruvic acid, 1113-60-6; lithium β-hydroxypyruvate, 3369-79-7; sorbitol dehydrogenase, 9028-21-1.

Supplementary Material Available: Spectrometric information (^1H and ^{13}C NMR) for new compounds (68 pages). This material is contained in many 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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Intermolecular Benzyne Cycloaddition (IBC), a Versatile Approach to Benzophenanthridine Antitumor Alkaloids. Formal Synthesis of Nitidine and Chelerythrine

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A new approach to the synthesis of benzophenanthridine alkaloids is described which is based on cycloaddition of arynes to pyrrolinediones, the pyrrolinediones behaving as aza diene equivalents. The synthesis of 2,3,8,9-substituted benzophenanthridines and the regioselective synthesis of a 2,3,7,8-substituted benzophenanthridine were performed. The formal synthesis of chelerythrine and the antitumor alkaloid nitidine is described.

Planar benzophenanthridinium salts 1 (Figure 1) have been recognized as being potentially useful as antitumor agents, having been shown to intercalate into the minor groove of DNA and bind to it covalently.[1] However, some 2,3,8,9-substituted derivatives, though among the most active in L1210 and P388 tests, have been reported to be toxic.[2] Efforts have accordingly been made to develop

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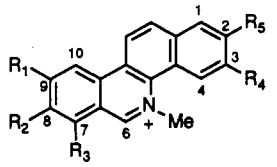
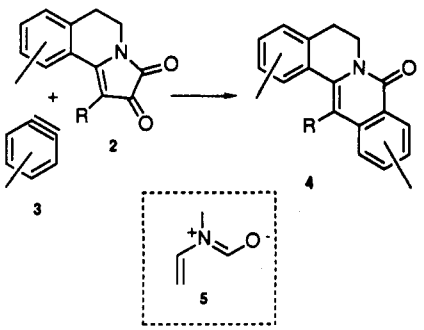


	1a R_1=R_2=R_3=R_4=R_5=H
Avicine	1b R_1+R_2=R_4+R_5=OCH_2O, R_3=H
Nitidine	1c R_1=R_2=OMe, R_3=H, R_4+R_5=OCH_2O
Fagaronine	1d R_1=R_2=R_4=OMe, R_3=H, R_5=O^{i}Pr
Chelerythrine	1e R_1=H, R_2=R_3=OMe, R_4+R_5=OCH_2O

Figure 1.

Scheme I



more efficient synthetic approaches[3] to this family so as to facilitate the search for members with no undesirable side effects; a flexible approach capable of supplying a variety of benzophenanthridines would hopefully allow acquisition of enough information on structure–activity relationships to allow the best candidate for further tests to be selected.

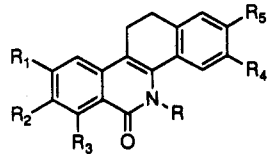
In this paper we show the usefulness of intermolecular benzyne cycloaddition (IBC) for the synthesis of benzophenanthridines. The three chief features of the IBC approach are its convergence, its high regioselectivity, and its reliability and flexibility.

Results and Discussion

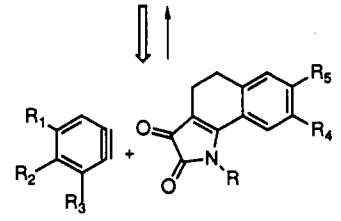
On the basis of a [4 + 2] cycloaddition[4] the intermolecular benzyne cycloaddition approach was initially developed as a highly convergent strategy for the synthesis of aporphinoids, several classes of which were successfully obtained by this method.[5] [3 + 2] cycloaddition[4] also occurs under certain circumstances, which affords a novel route to the dibenzindolizidine skeleton of the dibenzopyrrocoline alkaloids.[6]

Recently, it has been found that when isoquinolinopyrrolinediones **2** are reacted with arynes **3**, they do not behave as above but instead lead to another prototypical isoquinoline alkaloid skeleton, that of the protoberberines **4**.[5c,7] In this reaction, isoquinolinopyrrolinediones apparently undergo formal [4 + 2] cycloaddition followed by extrusion of carbon monoxide, behaving as the highly interesting 2-aza diene synthon **5** (Scheme I).[8]

Scheme II

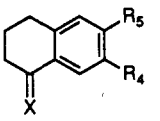


6a R_1=R_2=R_3=R_4=R_5=H, R=Me
6b R_1=R_2=R_3=R_4=H, R_5=OMe, R=Me
6c R_1=R_2=R_3=H, R_4=R_5=OMe, R=Me
6d R_1+R_2=R_4+R_5=OCH_2O, R_3=H, R=Me
6e R_1=R_2=OMe, R_3=H, R_4+R_5=OCH_2O, R=Me
6f R_1=R_2=R_4=OMe, R_3=H, R_5=O^{i}Pr, R=Me
6g R_1=H, R_2=R_3=OMe, R_4+R_5=OCH_2, R=Me
6h R_1=R_2=R_3=R_4=R_5=H, R=Bn



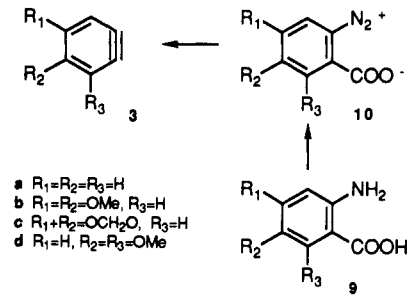
3a R_1=R_2=R_3=H
3b R_1=R_2=OMe, R_3=H
3c R_1+R_2=OCH_2O, R_3=H
3d R_1=H, R_2=R_3=OMe

7a R_4=R_5=H, R=Me
7b R_4=H, R_5=OMe, R=Me
7c R_4=R_5=OMe, R=Me
7d R_4+R_5=OCH_2O, R=Me
7e R_4=OMe, R_5=O^{i}Pr, R=Me
7f R_4=R_5=H, R=Bn



8a R_4=R_5=H
8b R_4= H, R_5=OMe
8c R_4=R_5=OMe
8d R_4+R_5=OCH_2O
8e R_4=OMe, R_5=O^{i}Pr

Scheme III



a R_1=R_2=R_3=H
b R_1=R_2=OMe, R_3=H
c R_1+R_2=OCH_2O, R_3=H
d R_1=H, R_2=R_3=OMe

It occurred to us that it might be possible for benzophenanthridines to be constructed in the same way. Scheme II shows the retrosynthetic path from the benzophenanthridinones **6** to the tetralones **8** (X = O); synthetically, the cycloaddition of dihydronaphthalenopyrrolinediones **7** and arynes **3** led to 11,12-dihydrobenzophenanthridin-6-ones **6**, which can easily be transformed into benzophenanthridines **1**.[9]

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In a preliminary communication[10] we reported that the above strategy worked well for the synthesis of the unsubstituted and monosubstituted benzophenanthridinones **6a** and **6b**. The commercially available tetralones **8a** (X = O) and **8b** (X = O) were first converted uneventfully into the corresponding methylimines **8a** (X = NMe) and **8b** (X = NMe), and these, without further purification, were reacted (under carefully controlled conditions) with oxalyl chloride (see Experimental Section), providing the desired dihydronaphthalenepyrrolinediones **7a** and **7b** as red crystalline solids whose spectral properties were in full agreement with the structures postulated. **7a** and **7b** were then reacted with benzyne (**3a**), which was generated by Logullo's[11] preformed salt method (aprotic diazotization of anthranilic acid (**9a**), isolation of the diazonium salt **10a**, and thermal decomposition in refluxing DME; Scheme III). The expected 11,12-dihydrobenzophenanthridin-6-ones **6a** and **6b** were isolated in 37% and 34% yields, respectively. In the same way, pyrrolinedione **7c**, prepared from tetralone **8c** (X = O) as above, reacted with benzyne to afford the 11,12-dihydrobenzophenanthridin-6-one **6c** in 49% yield.

We next investigated whether the IBC strategy is generally valid for the synthesis of benzophenanthridine alkaloids with 2,3,8,9 or the more common 2,3,7,8 substitution patterns. In particular, simple syntheses of nitidine (**1c**),[12] avicine (**1b**),[12] and chelerythrine (**1e**)[12] derivatives were devised in which the appropriate arynes (**3b–d**) were to be combined with the dihydronaphthalenopyrrolinediones **7d** and **7e**. **7d** was derived from the 6,7-dioxygenated tetralone **8d** (X = O): **8d** (X = O)[3f] was reacted with methylamine hydrochloride, and the crude methylimine **8d** (X = NMe), without further purification, was treated with oxalyl chloride under carefully controlled conditions to yield the required dione **7d** in 66% yield as a red crystalline solid with IR absorption at 1680 and 1740 cm^{-1}. **7e** was prepared similarly from **8e**. The arynes **3b**, **3c**, and **3d** were prepared via **10** from anthranilic acids **9b**, **9c**, and **9d**. After considerable experimentation we found that the procedure for the key cycloaddition step with these oxygenated benzynes was to add a slurry of the diazonium salt hydrochloride[13] in DME to a refluxing solution of pyrrolinediones **7** in DME.

The reaction of pyrrolinedione **7d** with aryne **3c** afforded the adduct **6d**[14] in 16% yield. The reaction of pyrrolinediones **7d** and **7e** with aryne **3b**, followed by standard workup and chromatographic purification, gave the expected dihydrobenzophenanthridinones **6e**[14] and **6f** in 29 and 30% yield, respectively. Since **6e** has been transformed into nitidine (**1c**),[3b] this constitutes formal synthesis of this antitumour alkaloid. Presumably, adduct **6f** can be transformed into the antitumour alkaloid fagaronine (**1d**) and adduct **6d** into avicine (**1b**) by the same procedure.

The synthesis of chelerythrine derivatives required the use of 3,4-dimethoxybenzyne (**3d**). Our experience[5c] of the reactions of pyrrolinediones with unsymmetrically substituted arynes led us to predict the desired regioisomer as the major cycloadduct. When a solution of pyrrolinedione **7d** and the diazonium salt **10d** was refluxed, **6g** was indeed the only isomer detected (^1H NMR)[15a] in the crude mixture, confirming the regioselective nature of the reaction. It was isolated in 29% yield. Since **6g** has been transformed into chelerythrine (**1e**),[15b] this constitutes formal synthesis of this alkaloid.

To approach norbenzophenanthridines by the IBC procedure required protection of the nitrogen atom against phenylation. We decided to synthesize *N*-benzylbenzophenanthridines, which should be easily transformable into norbenzophenanthridines by classical procedures. Tetralone **8a** (X = O) was treated with benzylamine to afford imine **8a** (X = NBn), which was reacted with oxalyl chloride to yield pyrrolinedione **7f**. As expected, pyrrolinedione **7f** reacted with benzyne (**3a**) to afford the adduct **6h** in 50% yield.[16,17]

In summary, intermolecular cycloaddition between a benzyne and a dihydronaphthalenopyrrolinedione, followed by CO extrusion, is a highly reliable method for the synthesis of benzophenanthridine alkaloids, allowing simple and convergent synthesis of benzophenanthridine and norbenzophenanthridine alkaloids with 2,3,7,8- and 2,3,8,9-substitution patterns.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 250 and 62.83 MHz in $CDCl_3$. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded at an ionization voltage of 70 eV. Combustion analyses were performed at the Servei de Microanalisi de la Universitat de Barcelona. Solvents were dried by standard procedures.[18]

General Procedure for the Synthesis of Pyrrolinediones. A saturated solution of $MeNH_2$ in $CHCl_3$ was prepared by bubbling a stream of $MeNH_2$ generated by heating 40% aqueous $MeNH_2$. The mixture was cooled to 0 °C under argon or nitrogen, and a solution of freshly distilled $TiCl_4$ in dry $CHCl_3$ was slowly added. The reaction mixture was stirred for 15 min at 0 °C and then 24 h at room temperature, the reaction being monitored by TLC on alumina plates or NMR. The titanium complexes were removed by filtration, and the solution was concentrated to yield the methylimines, which were examined by NMR and used for the next reaction without further purification.

Oxalyl chloride was added dropwise to a stirred solution of the imine and freshly distilled Et_3N in dry 1,2-dimethoxyethane (DME) cooled to −60 °C under argon or nitrogen. After 1 h at −60 °C the cooling bath was removed, and when room temperature was reached the mixture was stirred for 2 h. The pyrrolinedione precipitated was removed by filtration, and the liquid phase was washed with 5% HCl, dried with Na_2SO_4, and concentrated. Variable amounts of pyrrolinediones were recovered from the residue by chromatography on silica gel (CH_2Cl_2).

4,5-Dihydro-1-methyl-1*H*-benz[*g*]indole-2,3-dione (7a). The imine **8a** (X = NMe) was obtained as an oil in 97% yield from tetralone **8a** (X = O, 500 mg, 3.40 mmol), $MeNH_2$ (50 mL $CHCl_3$ solution), and $TiCl_4$ (0.2 mL, 350 mg, 1.84 mmol). ^1H NMR

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($CDCl_3$) δ: 1.90–1.99 (m, 2 H), 2.57 (t, J = 6.9 Hz, 2 H), 2.80 (t, J = 6.0 Hz, 2 H), 3.31 (s, 3 H), 7.29–7.15 (m, 3 H), 8.10 (d, J = 7.6 Hz, 1 H).

1-(*N*-Methylimino)naphthalene (156 mg, 0.98 mmol) and triethylamine (0.4 mL, 290 mg, 2.88 mmol) in DME (40 mL) and oxalyl chloride (1.0 mL, 148 mg, 1.17 mmol) yielded the pyrrolinedione **7a** (150 mg, 72%) as a red solid. Mp: 160–162 °C (MeOH). UV (EtOH) λ_{max}: 255, 296 nm. IR (KBr): 1720, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.42–2.49 (m, 2 H), 2.87–2.94 (m, 2 H), 3.47 (s, 3 H), 7.35–7.41 (m, 2 H), 7.47–7.49 (m, 1 H), 7.72 (d, J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ: 16.23, 28.86, 29.88, 109.51, 125.38, 125.54, 127.11, 129.56, 132.69, 142.27, 161.51, 164.61, 181.40. LRMS m/e: 213 (M^+, 72), 184 (24), 156 (100), 128 (40). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.16; N, 6.57. Found: C, 73.18; H, 5.02; N, 6.53.

4,5-Dihydro-1-benzyl-1*H*-benz[*g*]indole-2,3-dione (7f). To a solution of tetralone (**8a**) (X = O) (1.50 g, 0.01 mol) in toluene (60 mL) were added freshly distilled benzylamine (2.20 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid, and the mixture was refluxed for 12 h in a flask connected to a Dean-Stark apparatus. The mixture was then filtered, the solvent evaporated in vacuo, and excess benzylamine distilled off in a Kugelrohr apparatus to afford the imine **8a** (X = NBn) (2.46 g, 100%) as an oil. ^1H NMR ($CDCl_3$) δ: 1.95–2.00 (m, 2 H), 2.64–2.69 (m, 2 H), 2.81–2.86 (m, 2 H), 4.71 (s, 2 H), 7.16–7.46 (m, 8 H), 8.28–8.32 (m, 1 H).

From 1-(*N*-benzylimino)naphthalene (2.46 g, 10 mmol) and Et_3N (4.0 mL, 2.90 g, 28 mmol) in DME (80 mL) and oxalyl chloride (1.0 mL, 1.48 g, 12.0 mmol) was obtained the pyrrolinedione **7f** (1.60 g, 74% yield) as a red solid. Mp: 170–171 °C (MeOH). UV (EtOH) λ_{max}: 256, 294 nm. IR (KBr): 1740, 1690, 1420 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.44–2.50 (m, 2 H), 2.84–2.90 (m, 2 H), 5.06 (s, 2 H), 7.45–7.15 (m, 9 H). ^{13}C NMR ($CDCl_3$) δ: 16.42, 28.77, 46.06, 110.89, 125.08, 125.70, 126.33, 127.08, 127.72, 128.97, 129.43, 132.69, 136.41, 142.16, 162.24, 164.23, 181.21. LRMS m/e: 289 (M^+, 33), 232 (33), 198 (100). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.88; H, 5.23; N, 4.84. Found: C, 78.82; H, 5.27; N, 4.81.

4,5-Dihydro-7-methoxy-1-methyl-1*H*-benz[*g*]indole-2,3-dione (7b). From 6-methoxytetralone (**8b**) (X = O) (500 mg, 2.00 mmol) in 50 mL of $MeNH_2$ solution and $TiCl_4$ (0.28 mL, 484 mg, 2.55 mmol) in 20 mL of $CHCl_3$ was obtained (24 h) the imine **8b** (X = NMe) (494 mg, 92% yield) as an oil. ^1H NMR ($CDCl_3$) δ: 1.90–1.98 (m, 2 H), 2.54–2.59 (m, 2 H), 2.75–2.80 (m, 2 H), 3.28 (s, 3 H), 3.81 (s, 3 H), 6.64 (d, J = 2.6 Hz, 1 H), 6.79 (dd, J = 8.8 and 2.6 Hz, 1 H), 8.09 (d, J = 8.8 Hz, 1 H).

From this imine (287 mg, 1.50 mmol) and Et_3N (0.5 mL, 363 mg, 3.6 mmol) in 40 mL of DME and oxalyl chloride (0.17 mL, 252 mg, 1.9 mmol) was obtained the pyrrolinedione **7b** (213 mg, 57% yield) as red crystals. Mp: 168–169 °C. UV (EtOH) λ_{max}: 266, 340 nm. IR (KBr): 1735, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.40–2.47 (m, 2 H), 2.84–2.90 (m, 2 H), 3.44 (s, 3 H), 3.89 (s, 3 H), 6.87–6.89 (m, 2 H), 7.69 (d, J = 9.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ: 16.38, 29.61, 29.89, 65.57, 107.63, 112.45, 115.63, 118.10, 127.80, 145.46, 162.31, 163.37, 165.00, 180.38. LRMS m/e: 243 (M^+, 91), 214 (32), 186 (100), 115 (35). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 69.29; H, 5.39; N, 5.76.

4,5-Dihydro-7,8-dimethoxy-1-methyl-1*H*-benz[*g*]indole-2,3-dione (7c). From 6,7-dimethoxytetralone (**8c**) (X = O)[3f] (1.00 g, 4.90 mmol) in 70 mL of $MeNH_2$ solution and $TiCl_4$ (0.5 mL, 863 mg, 4.5 mmol) was obtained the imine **8c** (X = NMe) (885 mg, 82% yield) as an amorphous solid. ^1H NMR ($CDCl_3$) δ: 1.90–1.98 (m, 2 H), 2.51–2.55 (m, 2 H), 2.72–2.77 (m, 2 H), 3.29 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 6.60 (s, 1 H), 7.66 (s, 1 H).

From 6,7-dimethoxy-*N*-methylimine (760 mg, 3.47 mmol) and Et_3N (1.55 mL, 1.125 g, 11.0 mmol) in DME (10 mL) and oxalyl chloride (0.39 mL, 572 mg, 4.51 mmol) was obtained the pyrrolinedione **7c** (630 mg, 66% yield). Mp: 205–206 °C. UV (EtOH) λ_{max}: 273, 324 nm. IR (KBr): 1740, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.42–2.48 (m, 2 H), 2.82–2.89 (m, 2 H), 3.48 (s, 3 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 6.87 (s, 1 H), 7.21 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ: 16.50, 28.99, 29.91, 56.14, 56.35, 107.87, 109.13, 112.59, 117.48, 138.01, 147.94, 153.16, 162.43, 165.06, 180.19; LRMS m/e: 273 (M^+, 100), 244 (38), 216 (72), 192 (52). HRMS calcd for $C_{15}H_{15}NO_4$: 273.1001. Found: 273.1010. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.43; N, 5.14.

4,5-Dihydro-1-methyl-1*H*-1,3-benzodioxolo[5,6-*g*]indole-2,3-dione (7d). The imine **8d** (X = NMe) was obtained in 100% yield from 6,7-(methylenedioxy)tetralone (**8d**) (X = O)[3f] (900 mg, 4.73 mmol) in 70 mL of a solution of $MeNH_2$ in $CHCl_3$ and $TiCl_4$ (0.5 mL, 863 mg, 4.5 mmol) in 30 mL of $CHCl_3$. ^1H NMR ($CDCl_3$) δ: 1.87–1.96 (m, 2 H), 2.50–2.54 (m, 2 H), 2.71–2.74 (m, 2 H), 3.27 (s, 3 H), 5.93 (s, 2 H), 6.58 (s, 1 H), 7.61 (s, 1 H).

From this imine (925 mg, 4.60 mmol) and triethylamine (1.53 mL, 1.11 g, 11.0 mmol) dissolved in 40 mL DME and oxalyl chloride (0.42 mL, 622 mg, 4.9 mmol) was obtained the pyrrolinedione **7d** (948 mg, 81% yield) as red crystals. Mp: 224–226 °C (EtOH). UV (EtOH) λ_{max}: 273, 315, 369 nm. IR (KBr): 1740, 1670 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.39–2.45 (m, 2 H), 2.80–2.86 (m, 2 H), 3.42 (s, 3 H), 6.08 (s, 2 H), 6.86 (s, 1 H), 7.18 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ: 16.42, 29.64, 29.94, 102.23, 105.58, 108.14, 110.38, 118.61, 139.76, 147.10, 151.48, 162.26, 165.02, 180.40. LRMS m/e: 257 (M^+, 100), 228 (26), 200 (77). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 64.99; H, 4.24; N, 5.42.

4,5-Dihydro-7-isopropoxy-8-methoxy-1-methyl-1*H*-benz[*g*]indole-2,3-dione (7e). From 6-isopropoxy-7-methoxytetralone (**8e**) (X = O)[3f] (1.73 g, 7.3 mmol) in 90 mL of $MeNH_2$ solution and $TiCl_4$ (1.35 mL, 2.33 g, 12.3 mmol) in 100 mL of $CHCl_3$ (in this case the solution of $TiCl_4$ was added to the tetralone–$MeNH_2$ mixture at 0 °C) was obtained the imine **8e** (X = NMe) (2.36 g, 100% yield) as an oil. ^1H NMR ($CDCl_3$) δ: 1.40 (d, J = 6.1 Hz, 6 H), 1.94–1.99 (m, 2 H), 2.56–2.61 (m, 2 H), 2.72–2.77 (m, 2 H), 3.31 (s, 3 H), 3.94 (s, 3 H), 4.56–4.65 (m, 1 H), 6.62 (s, 1 H), 7.88 (s, 1 H).

From imine **8e** (X = NMe) (1.90 g, 7.26 mmol) and NEt_3 (2.8 mL, 2.02 g, 20.1 mmol) in dry DME (50 mL) and oxalyl chloride (0.6 mL, 890 mg, 6.99 mmol) was obtained **7e** (1.4 g, 64% yield), which crystallized from hexane/ether as black needles. Mp: 167–168 °C. UV (EtOH) λ_{max}: 224, 276, 326, 372 nm. IR (KBr): 1740, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (d, J = 6.1 Hz, 6 H), 2.41–2.48 (m, 2 H), 2.80–2.86 (m, 2 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 4.67–4.76 (s, 1 H), 6.86 (s, 1 H), 7.21 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ: 16.44, 21.81, 28.88, 29.80, 56.45, 71.47, 107.60, 109.99, 114.94, 117.03, 137.87, 148.62, 151.91, 162.45, 165.13, 179.97. LRMS m/e: 301 (M^+, 22), 259 (18), 230 (16), 202 (27), 188 (18), 149 (18), 91 (52). HRMS calcd for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1325. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.53; H, 5.94; N, 4.35.

General Procedure for the Reaction of Pyrrolinediones with Benzyne.[11] Excess isoamyl nitrite was added over 1–2 min to a stirred ice-cooled solution of the appropriate anthranilic acid in dry DME containing a catalytic amount of trichloroacetic acid. The ice-bath was removed after 15 min, and the mixture turned red brown as it reached room temperature. The mixture was stirred for an additional 90 min. The following is the recommended procedure for appropriate handling: *after dilution with DME, most of the solvent was aspirated by means of a plastic syringe with Teflon tubing (instead of the standard metallic needle) and discarded.* **Caution! when dry, benzenediazonium-2-carboxylate detonates violently on being scraped or heated.** *The remaining material was washed several times with DME as above until the washing liquors were neutral and the resulting brownish precipitate was suspended in solvent (DME). This suspension was aspirated portionwise into a plastic syringe through a Teflon tube (instead of the standard metallic needle) and added dropwise to a refluxing solution of pyrrolinediones in DME (40 mL).* When the addition was complete (TLC monitoring), the reaction mixture was refluxed until the starting material had disappeared, and the solvent was evaporated in vacuo. The residue thus obtained was purified by chromatography (silica gel, CH_2Cl_2) to afford the benzophenanthridinone.

5-Methyl-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6a). From pyrrolinedione **7a** (500 mg, 2.34 mmol), anthranilic acid (**9a**) (2.62 g, 16.40 mmol), and isoamyl nitrite (3.66 g, 31.30 mmol) was obtained the benzophenanthridinone **6a** (230 mg, 37% yield) and crystallized from MeOH. Mp: 142–143 °C (lit.[17] mp 143–154 °C).

2-Methoxy-5-methyl-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6b). From methoxypyrrolinedione **7b** (100 mg, 0.40 mmol), anthranilic acid (**9a**) (318 mg, 2.00 mmol), and isoamyl nitrite (358 mg, 3.06 mmol) was obtained the benzophenanthridinone **6b** (40 mg, 34% yield) and crystallized from

MeOH. Mp: 171-172 °C (lit.[3f] mp 188-190 °C).

2,3-Dimethoxy-5-methyl-11,12-dihydrobenz[*c*]phenanthridin-6(5*H*)-one (6c). From dimethoxypyrrolinedione **7c** (450 mg, 1.65 mmol), anthranilic acid (**9a**) (1.45 g, 10.64 mmol), and isoamyl nitrite (2.04 g, 17.45 mmol) was obtained the benzophenanthridinone **6c** (250 mg, 49% yield) and crystallized from MeOH. Mp: 184-185 °C (lit.[19] mp 184-186 °C).

5-Methyl-12,13-dihydro-1,3-benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*j*]phenanthridine-6(5*H*)-one (6d). Dihydrooxyavicine. From pyrrolinedione **7d** (60 mg, 0.23 mmol), 4,5-methylenedioxyanthranilic acid (**9c**) (426 mg, 2.35 mmol), and isoamyl nitrite (450 mg, 3.86 mmol) was obtained the benzophenanthridinone **6d** (13 mg, 16% yield). Mp: 242-243 °C (benzene-hexane) (lit.[14] mp 237-241 °C).

2-Isopropoxy-5-methyl-3,8,9-trimethoxy-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6f). Dihydrooxyfagaronine. From pyrrolinedione **7e** (200 mg, 0.66 mmol), 4,5-dimethoxyanthranilic acid (**9b**) (1.14 g, 5.81 mmol), and isoamyl nitrite (1.11 g, 9.52 mmol) was obtained the benzophenanthridinone **6f** (81 mg, 30% yield) and crystallized from MeOH. Mp: 218 °C. UV (EtOH) λ_{max}: 234, 266, 344, 358 nm. IR (KBr): 1630, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (d, J = 6 Hz, 6 H), 2.79 (s, 4 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.57-4.66 (m, 1 H), 6.85 (s, 1 H), 7.02 (s, 1 H), 7.04 (s, 1 H), 7.88 (s, 1 H). LRMS m/e: 409 (M^+, 88), 367 (100), 352 (51). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.43; N, 5.14.

5-Benzyl-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6h). From pyrrolinedione **7f** (230 mg, 0.79 mmol) in DME (40 mL), anthranilic acid (**9a**) (634 mg, 4.63 mmol), and isoamyl nitrite (888 mg, 7.59 mmol) was obtained the benzophenanthridinone **6h** (136 mg, 50% yield) and crystallized from MeOH. Mp: 128-129 °C (lit.[17] mp 128-131 °C).

Modification of the General Procedure for the Reaction of 7d with Arynes 3b and 3d. To a stirred ice-cooled solution of the appropriate anthranilic acid in EtOH were added concd HCl and isoamyl nitrite, and the mixture was stirred for 45 min at 0 °C, diluted with ether, and stirred for a further 45 min. The diazonium salt, now as hydrochloride, was washed as above and aspirated into a plastic syringe. **Caution! The same precautions as above should be observed!** The suspended diazonium salt was added to a refluxing solution of **7d** containing propylene oxide.

2,3-Dimethoxy-12-methyl-5,6-dihydro[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one (6e). Dihydrooxynitidine. From pyrrolinedione **7d** (60 mg, 0.233 mmol), propylene oxide (5.3 mL), dichloroethane (40 mL), 4,5-dimethoxyanthranilic acid (**9b**) (766 mg, 3.89 mmol), isoamyl nitrite (842 mg, 7.20 mmol) and concentrated HCl (0.4 mL) was obtained the benzophenanthridinone **6e** (25 mg, 29% yield). Mp: 236-237 °C (EtOH) (lit.[14] mp 242-245 °C (benzene-hexane)).

1,2-Dimethoxy-12-methyl-5,6-dihydro[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one (6g). Dihydrooxychelerythrine. From pyrrolinedione **7d** (123 mg, 0.48 mmol), propylene oxide (6.3 mL), dichloroethane (30 mL), 3,4-dimethoxyanthranilic acid (**9d**) (914 mg, 4.64 mmol), isoamyl nitrite (1.15 mL, 8.59 mmol), and concd HCl (0.5 mL) was obtained the benzophenanthridinone **6g** (51 mg, 29% yield). Mp: 202-204 °C (lit.[15a] mp 208-209 °C).

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Registry No. **1c**, 6872-57-7; **1e**, 34316-15-9; **6a**, 51066-35-4; **6b**, 98799-71-4; **6c**, 65332-25-4; **6d**, 56221-63-7; **6e**, 56221-66-0; **6f**, 143237-38-1; **6g**, 65341-23-3; **6h**, 51066-28-5; **7a**, 111865-20-4; **7b**, 111865-21-5; **7c**, 143237-35-8; **7d**, 143237-36-9; **7e**, 143237-37-0; **7f**, 143237-34-7; **8a** (X = O), 529-34-0; **8a** (X = NMe), 111865-18-0; **8a** (X = NBn), 32851-51-7; **8b** (X = O), 1078-19-9; **8b** (X = NMe), 111865-19-1; **8c** (X = O), 13575-75-2; **8c** (X = NMe), 143237-32-5; **8d** (X = O), 41303-45-1; **8d** (X = NMe), 55950-08-8; **8e** (X = O), 98799-45-2; **8e** (X = NMe), 143237-33-6; **9a**, 118-92-3; **9b**, 5653-40-7; **9c**, 20332-16-5; **9d**, 5701-87-1; oxalyl chloride, 79-37-8.

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A New Approach to the Synthesis of Antitumor Benzophenanthridine Alkaloids. Formal Synthesis of Nitidine

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The synthesis of benzophenanthridine alkaloids by an efficient new convergent strategy based on the Diels-Alder reaction between an α-pyrone and an aryne is described. With minor modifications, norbenzophenanthridines and phenanthridines and their 12-amino derivatives were obtained in good overall yields.

The benzophenanthridine alkaloids, a group of isoquinoline alkaloids with more than 60 members,[1] is characterized by the basic skeleton **1**. The most important members of this group from a pharmacological point of view are quaternary salts. In particular, the alkaloids fagaronine (**2a**) and nitidine (**2b**) have marked antitumor properties.[2] Both have shown activity against leukemia in the P-388 test, but the trials of nitidine were interrupted because of toxicity problems.

There are many classical methods[3] for the synthesis of benzophenanthridines using one-bond reactions (formation of one bond/step) but very few involving a two-bond key step; the first to be reported was the formation of ring B by cycloaddition between an *o*-quinodimethane and an alkyne.[4] Our experience with the synthesis of aporphi-

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