The crude material was chromatographed on a silica gel column by using chloroform with increasing proportions of EtOAc as eluant. The desired compound 8 was obtained, after recrystallization from $CHCl_3/Et_2O$, as a colorless solid: 2.5 g (59%); mp 206–207 °C; IR (Nujol) 3300–2800, 2920, 2280, 1720, 1605 cm^{-1}; NMR (Me_2SO-d_6, $CDCl_3$) δ 7.20–6.88 (q, 2 H, J = 8 Hz), 7.00 (s, 1 H), 6.27 (s, 1 H), 6.00 (m, 2 H), 5.38 (s, 1 H), 4.07 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 4 H), 3.04 (s, 3 H); mass spectrum, m/e (relative intensity) 424 (M^+, 10), 380 (60), 178 (100). Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60, Found: C, 62.17; H, 4.83; N, 6.40.

***trans*-*N*-Methyl-3-[(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (9).** Excess CH_2N_2 in Et_2O was added to a solution of the trans acid 8 (500 mg, 1.18 mmol) in MeOH (15 mL). The solution was kept at 0 °C for 4 h, and the excess CH_2N_2 was then quenched with AcOH. Water (100 mL) was added and the mixture extracted with EtOAc (2 × 200 mL). The organic layer was washed with H_2O and dilute $NaHCO_3$. It was then dried ($MgSO_4$) and the solvent evaporated, leaving the crystalline ester: 480 mg (93%); mp 162–163 °C; IR (Nujol) 2900, 2240, 1720, 1635 cm^{-1}; NMR δ 7.07 (d, 1 H, J = 8 Hz), 6.93 (s, 1 H), 6.87 (d, 1 H, J = 8 Hz), 6.47 (s, 1 H), 5.97 (m, 2 H), 5.33 (d, 1 H, J = 2 Hz), 4.11 (s, 3 H), 3.97 (s, 3 H), 3.90–3.60 (m, 3 H), 3.83 (s, 3 H), 3.13 (s, 3 H); mass spectrum, m/e (relative intensity) 438 (M^+, 75), 380 (14), 236 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.72; H, 5.16; N, 6.19.

3,4-Dimethyl-5-oxo-9,10-(methylenedioxy)-6-benzo[*b*]naphtho[2,3-*d*]pyran (10). Sodium hydride (50% dispersion, 100 mg, 2.08 mmol) was added to a solution of the ester 9 (200 mg, 0.46 mmol) in THF (20 mL). After the mixture was stirred at room temperature for 6 h, the THF was evaporated, and water and EtOAc were added to the residue. The organic layer was separated and extracted with 1 N NaOH. The aqueous layer and NaOH wash were combined and acidified with concentrated HCl. The precipitate was filtered, washed with water, and dried over P_2O_5, yielding a white solid (75 mg, 44%). The analytical sample was prepared by sublimation: mp 358–360 °C; IR (Nujol) 2900, 2205, 1730 cm^{-1}; NMR (Me_2SO-d_6) δ 7.63 (s, 1 H), 7.19 (s, 1 H), 7.11 (s, 1 H), 7.10 (d, 1 H, J = 8.5 Hz), 6.92 (d, 1 H, J = 8.5 Hz), 6.11 (s, 2 H), 3.87 (s, 3 H), 3.78 (s, 3 H); mass spectrum, m/e (relative intensity) 375 (M^+, 100), 360 (35), 346 (35), 332 (15), 175 (20); calcd for $C_{21}H_{13}NO_6$ m/e 375.0743, found m/e 375.072.

Anal. Calcd for $C_{21}H_{13}NO_6$: C, 67.20; H, 3.49; N, 3.73. Found: C, 67.17; H, 3.17; N, 3.71.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (11).** Dry HCl gas was bubbled slowly through a solution of the cyano acid 8 (430 mg, 1.01 mmol) in MeOH at −40 to −20 °C for 1 h. The mixture was then kept at 0 °C for 24 h, concentrated to half the original volume, poured into water (200 mL), and extracted with EtOAc. The organic layer was washed with water, dilute $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was crystallized from Et_2O/hexane to give the diester 11 as a colorless solid: 350 mg (73%); mp 192–193 °C; IR (Nujol) 1725, 1645 cm^{-1}; NMR δ 7.07 (d, 1 H, J = 8 Hz), 6.87 (d, 1 H, J = 8 Hz), 6.77 (s, 1 H), 6.42 (s, 1 H), 5.90 (m, 2 H), 5.40 (d, 1 H, J = 1 Hz), 4.10 (s, 3 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.67–4.10 (obscured m, 3 H), 3.10 (s, 3 H); mass spectrum, m/e (relative intensity) 471 (M^+, 28), 439 (5), 412 (14), 408 (5), 236 (100).

Anal. Calcd for $C_{24}H_{25}NO_9$: C, 61.14; H, 5.34; N, 2.97. Found: C, 61.11; H, 5.42; N, 2.90.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12).** A 1 M solution of $Et_3O^+BF_4^-$ in CH_2Cl_2 (1.25 mL, 1.25 mmol) was added to a solution of compound 10 (500 mg, 1.06 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 20 h. The CH_2Cl_2 was evaporated, and the residue was dissolved in EtOH (3 mL). The solution was cooled to −10 °C before addition of $NaBH_4$ (0.10 g, 2.64 mmol). The mixture was stirred at room temperature for 18 h, decomposed with water, and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on a column of silica gel by using $CHCl_3$ with increasing proportions of EtOAc as eluant. The desired compound 12 (300 mg, 52%) crystallized from benzene/Et_2O/hexane: mp 155–157 °C; IR (Nujol) 1720 cm^{-1}; NMR δ 7.00 (s, 1 H), 6.90 (s, 2 H), 6.77 (s, 1 H), 6.03 (s, 2 H), 4.40–3.60 (m, 6 H), 3.93 (s, 6 H), 3.75 (s, 3 H), 3.63 (s, 3 H), 2.13 (s, 3 H).

Anal. Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 62.75; H, 6.10; N, 3.00.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(hydroxymethyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (13).** Continued elution of the above column used for isolation of compound 12 gave an additional product which crystallized from benzene/$CHCl_3$/hexane as a colorless solid: 85 mg (18%); mp 163–164 °C; IR (Nujol) 3880, 1730, 1630 cm^{-1}; NMR δ 7.00 (d, 1 H, J = 8 Hz), 6.77 (s, 1 H), 6.77 (d, 1 H, J = 8 Hz), 6.43 (s, 1 H), 5.90 (m, 2 H), 5.30 (s, 1 H), 4.10 (s, 3 H), 4.10–3.50 (m, 6 H), 3.93 (s, 3 H), 3.83 (s, 3 H), 3.17 (s, 3 H).

Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found: C, 61.94; H, 5.53; N, 3.06.

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Registry No. 3, 38489-93-9; 4, 75283-80-6; 5, 75299-09-1; 6, 75283-81-7; 8, 75283-82-8; 9, 75283-83-9; 10, 75283-84-0; 11, 75299-10-4; 12, 75283-85-1; 13, 75283-86-2; 5,6-(methylenedioxy)-1-indanone, 6412-87-9; 3,4-dimethoxyhomophthalic anhydride, 68408-56-0.

Total Synthesis of (±)-Chelidonine

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Condensation of the Schiff base 8 with 3,4-(methylenedioxy)homophthalic anhydride (13) was exploited as the key step in a total synthesis of the benzophenanthridine alkaloid (±)-chelidonine (1). A variety of reaction conditions were investigated in order to maximize the production of the desired thermodynamically less stable cis diastereomer. A method was devised for the conversion of 24 to its acid chloride without production of the indeno[1,2-*c*]isoquinoline 30. The migration of an aromatic ring was observed on treatment of the diazo ketone 26 with acid. This reaction is reminiscent of the Hayashi rearrangement.

(+)-Chelidonine is a member of the group of isoquinoline alkaloids known as the benzophenanthridines. It was first isolated from *Chelidonium majus* in 1839,[1] and extensive chemical[2] and spectroscopic[3] studies led to structure 1. An

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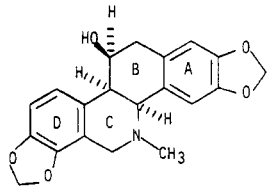

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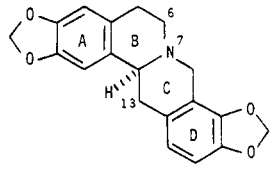
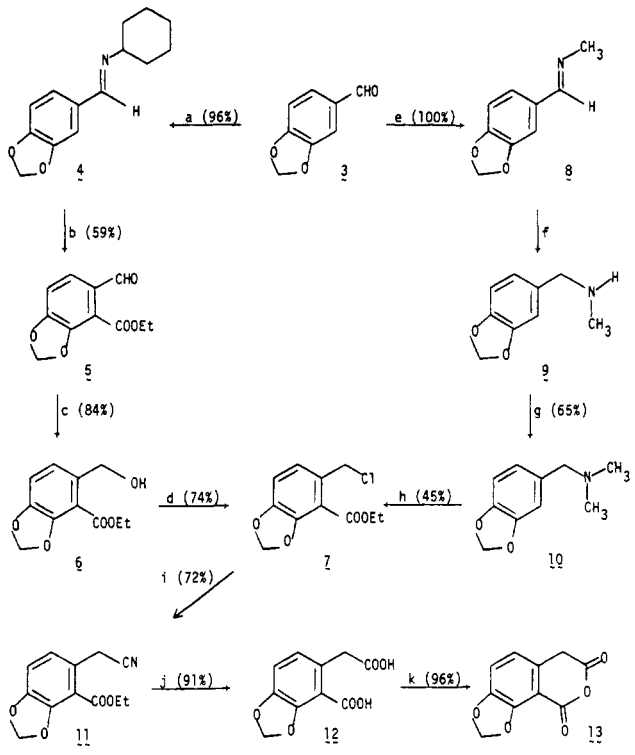


2

X-ray diffraction analysis of the *p*-bromobenzoate has confirmed this assignment and provided evidence for the absolute configuration depicted here.[4] Different plants of the family Papaveraceae are capable of providing either enantiomer[5] as well as the racemate (diphylline).[6] The suggestion that benzophenanthridines arise in nature from protoberberines by oxidative cleavage of the 6,7 bond followed by the joining of C-6 to C-13 has been substantiated in biosynthesis studies involving the feeding of (−)-stylopine (**2**) and subsequent isolation of appropriately labeled (+)-chelidonine (**1**).[8] This observation has stimulated recent work on the synthetic transformation of protoberberine to benzophenanthridine alkaloids.[9] The total synthesis of (±)-chelidonine reported in 1971 by Oppolzer and Keller is based on the intramolecular cycloaddition of *o*-quinodimethanes.[10,11] We now report an alternative synthesis which exploits the condensation reaction of Schiff bases with homophthalic anhydrides.[12,13]

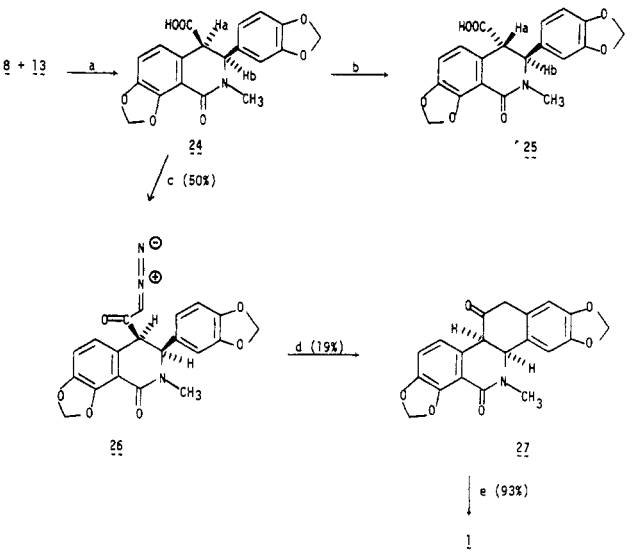
For (±)-chelidonine synthesis, this strategy requires the anhydride **13** (Scheme I).[12] The diacid **12** and compound **13** are themselves significant objectives because they are also useful intermediates for the preparation of a variety of protoberberine[14] and benzophenanthridine alkaloids.[15]

Scheme I[a]



[a] (a) Cyclohexylamine, PhH, reflux, 12 h. (b) (1) *n*-BuLi, THF, −78 °C, 3 h; (2) EtOOCCl, −78 to 23 °C, 4 h; (3) 5% HCl(aq), 23 °C, 12 h. (c) H_2, 10% Pd/C, EtOH. (d) $SOCl_2$, CH_2Cl_2, 23 °C, 2 h 15 min, N_2 bubbling. (e) CH_3NH_2(aq), 23 °C, 3 h. (f) $LiAlH_4$, Et_2O, 70 min. (g) $(CH_3)_2SO_4$, Et_2O, NaOH(aq), −6 °C, 1 h 50 min. (h) (1) *n*-BuLi, THF, −78 °C, 2 h; (2) EtOOCCl, −78 to 23 °C, 3 h 45 min. (i) KCN, Me_2SO, 23 °C, 12 h. (j) KOH(aq), reflux, 3 h. (k) AcCl, reflux, 6 h.

Scheme II[a]



[a] (a) CH_3CN, reflux, 1 h. (b) CH_3COOH, reflux, 13 h. (c) (1) Et_3N; (2) $SOCl_2$, CH_2Cl_2, 0 to 23 °C, 2 h; (3) CH_2N_2. (d) CF_3COOH, 0 °C, 1 min. (e) $LiAlH_4$, THF, 23 °C, 18 h.

A recent modification of the Haworth synthesis led from piperonal (**3**) to the diacid **12** in 8.3% overall yield.[15] We have devised two new syntheses of the anhydride **13** (Scheme I) which exploit the well-known ortho-directing abilities of certain tertiary amines,[16] cyclohexylimines, and

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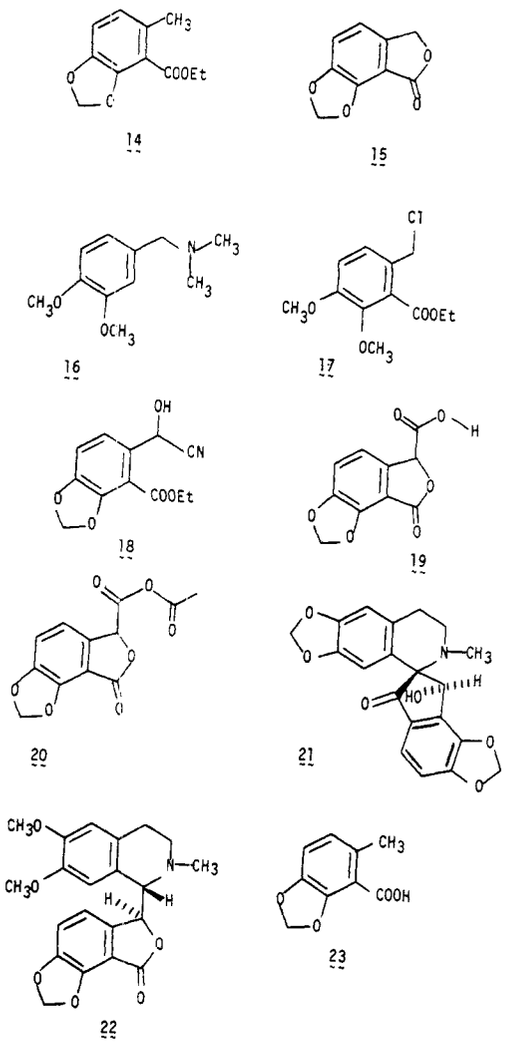
Chart I



methylenedioxy groups[17] during metalation reactions of aromatic compounds with alkyllithium reagents. By utilization of this technique the alignment of the four contiguous substituents on the aromatic ring becomes feasible without the unattractive installation and removal of bromine as a protecting group.[15] It was thus possible to increase the overall yield of the anhydride **13** from piperonal (**3**) to 22.1%.

Piperonylidenecyclohexylamine (**4**)[17,18] reacted with 1.76 equiv of *n*-BuLi at −78 °C to afford a metalated intermediate which was carbethoxylated in situ by addition of excess ethyl chloroformate. By use of an extraction with dilute acid during the workup, the aldehyde **5** could be obtained directly. The catalytic hydrogenation of the aldehyde **5** to the alcohol **6** had to be monitored closely in order to avoid overreduction to the corresponding toluene **14** (see Chart I), which was obtained in 90% yield when the hydrogenation was allowed to go to completion. The conversion of the benzyl alcohol **6** to the benzyl chloride **7** also proved to be more troublesome than anticipated. Simple treatment of alcohol **6** with thionyl chloride gave only the undesired lactone **15**. The production of the lactone **15** in this case can be rationalized as an acid-catalyzed reaction. It forms rapidly when methanolic solutions of **6** are subjected to a trace of HCl.

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Table I. Effect of Reaction Conditions on the Stereochemical Outcome of the Condensation of 3,4-(Methylenedioxy)homophthalic Anhydride (**13**) and Piperonylidenemethylamine (**8**)[a]

solvent	temp, °C (time)[b]	% cis[c]	% trans
CH_3CN	82 (1 h)	67	33
CH_3CN/Et_3N (9:1)	23 (40 min)	58	42
CH_3NO_2	23 (30 min)	38	62
t-BuOH	23 (27 min)	23	77
THF	23 (65 min)	20	80
neat[d]	23 (1 min)	20	80
CH_3CN	−22 (57 min)	20	80
CH_2Cl_2	23 (15 min)	17	83
CH_2Cl_2	−78 (72 min)	11	89
$ClCH_2CH_2Cl$	83 (103 min)	11	89
$PhCH_2CN$	183 (59 min)	8	92

[a] The combined yields of the diastereomers are essentially quantitative. [b] Reaction times include slow additions of the reagents. [c] Estimated by NMR integrations. [d] The neat reaction was performed by shaking the two solids in a wiggle-bug ball mill.

We attempted to favor the production of **7** by removal of HCl from solution by vigorous bubbling of dry nitrogen through the reaction mixture. In this fashion acceptable yields of the benzyl chloride **7** were finally obtained.

A second route to the benzyl chloride **7** was based on the recently reported conversion of [(3,4-dimethoxyphenyl)methyl]dimethylamine (**16**) to ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate (**17**).[19] Since large quantities of the Schiff base **8** were already on hand for later use in the synthesis (Scheme II), the required compound **10** was prepared from **8** by reduction and methylation. Metalation of the amine **10** with *n*-BuLi followed by addition of excess ethyl chloroformate to the ortholithiated intermediate did afford the desired benzyl chloride **7**. However, in this case the yield was only 45%.

The synthesis of 3,4-(methylenedioxy)homophthalic anhydride (**13**) was completed by displacement of the chloride of compound **7** with cyanide, basic hydrolysis of compound **11**, and cyclodehydration of the diacid **12**.

Several reactions were also tried in order to shorten the synthesis of the anhydride **13**. The cyanohydrin **18** of the aldehyde **5** was treated with stannous chloride and HCl in refluxing acetic acid in an attempt to convert it directly to the diacid **12**.[20] This resulted only in the formation of the lactone **19**. Both compound **19** and its acetate **20**, as well as the simpler lactone **15**, resisted hydrogenolysis of the benzylic carbon to oxygen bond under a variety of conditions. Although compound **19** did not lend itself to our purposes, it has nevertheless proven to be a useful intermediate for the synthesis of a variety of spirobenzylisoquinoline and phthalide–isoquinoline alkaloids including (±)-sibericine (**21**) and (±)-adlumidine (**22**).[21]

The acid **23** was also prepared by hydrolysis of **14**. The lithium dianion of **14** could hopefully be converted directly to the diacid **12** by reaction with dimethyl carbonate, followed by hydrolysis.[22] However, the dianion did not form under the usual conditions (lithium diisopropylamide, THF, −78 °C). Attempts to generate it and then react it

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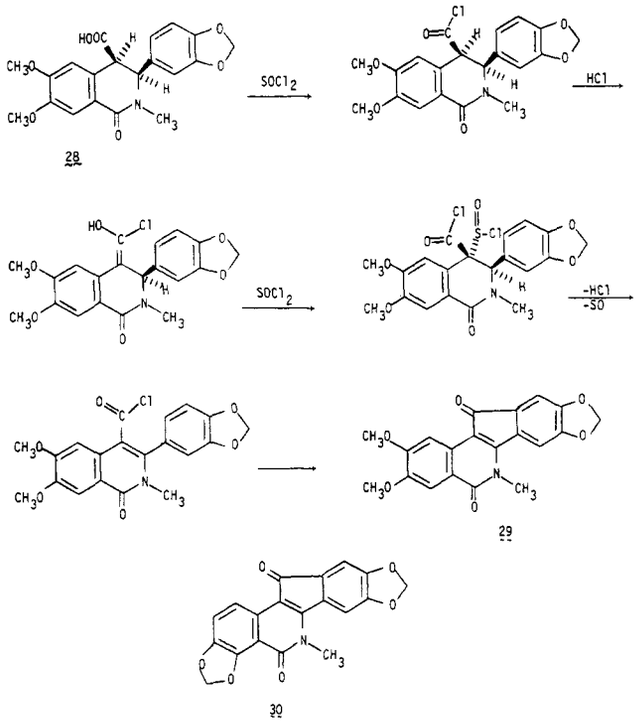
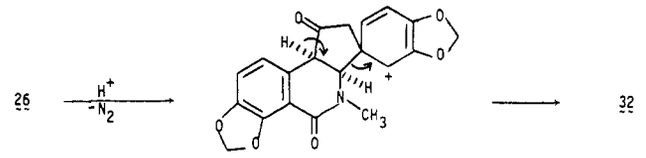
Scheme III



Scheme IV



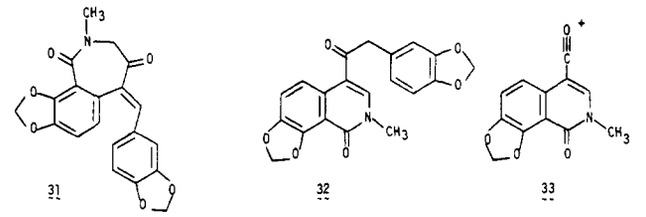
with dimethyl carbonate, oxalyl chloride, ethyl chloroformate, or D_2O gave back the starting material.

With the required anhydride **13** in hand, attention could be directed toward its condensation with Schiff base **8**. This reaction always produced a mixture of cis and trans diastereomers, and many different reaction conditions were tried in order to maximize the production of the desired cis isomer (J_{AB} = 6 Hz) **24** as the kinetic product. Performance of the condensation in refluxing acetonitrile proved to be the most advantageous (Table I). As expected, the cis diastereomer **24** is thermodynamically less stable.[12] It was transformed completely to the unwanted trans isomer **25** (J_{AB} = 0 Hz) on heating in acetic acid. The NMR spectrum of **25** (J_{AB} = 0 Hz) is consistent with the conformation in which the carboxyl and methylenedioxyphenyl substituents on the isoquinolone ring are pseudoaxial.

The acid chloride of **24** was desired as an intermediate in the conversion of **24** to the diazo ketone **26**. This apparently trivial transformation actually poses a significant obstacle since the related compound **28** proved to be unreactive toward reagents commonly employed to make acid chlorides except thionyl chloride. It reacted with thionyl chloride to afford the indeno[1,2-*c*]isoquinoline **29**.[23] The first step in the conversion of the acid chloride of **28** to compound **29** is an acid-catalyzed enolization (Scheme III). Perhaps the acid chloride of **24** could be made with thionyl chloride under nonacidic conditions. The triethylamine salt of **24** was therefore prepared and the reaction performed in benzene–CH_2Cl_2 (2:1) in the presence of 4 equiv of thionyl chloride. Triethylamine hydrochloride precipitated from the solution as the reaction proceeded, and a crude acid chloride of **24** could be obtained without contamination by compound **30**. This was treated immediately with excess diazomethane in Et_2O, affording the cis diazo ketone **26**.

Compound **26** on brief exposure to trifluoroacetic acid gave a mixture of products from which the cyclized ketone **27** (J_{AB} = 4 Hz) could be isolated by fractional crystallization in 19% yield. Lithium aluminum hydride reduction of **27** provided (±)-chelidonine (**1**). The 360-MHz NMR spectra and IR spectra (KBr) of the synthetic compound and (±)-chelidonine[24] are identical.

The 19% yield obtained of the tetracyclic compound **27** has been a matter of some concern. Thin-layer chromatography of the reaction mixture demonstrated the formation of two major products which are difficult to separate. One of these is the desired compound **27**. The mass spectrum of the other product indicated that it was an isomer of **27**. The IR spectrum showed the absence of an N–H proton, and only one broad band at 1640 cm^{-1} was present in the carbonyl region. The proton NMR spectrum revealed the disappearance of the two methine protons of **26** and the appearance of a low-field (δ 7.82) singlet. All five of the aromatic protons were still present, but one of them appeared as a doublet (J = 8.8 Hz) at low field (δ 8.42). On the basis of this evidence, structures **31** and **32**



were considered. The ^{13}C NMR spectrum revealed three-bond coupling (J = 3.66 Hz) between the *N*-methyl group and one proton. This coupling should remain intact after deuterium exchange of the two methylene protons only if structure **32** is correct. Accordingly, the compound was treated with CD_3OD and triethylamine in $CDCl_3$. The exchange reaction could be conveniently followed by proton NMR, and it had gone to completion within 1 h at room temperature. The ^{13}C NMR spectrum of the deuterated compound again displayed the three-bond coupling in question, and therefore the correct structure is **32**. This is also in agreement with the m/e 230 base peak in the mass spectrum which corresponds to ion **33**.[25] Mechanistically this undesired reaction can be viewed as proceeding through a spirocyclic cation **34** (Scheme IV). This is somewhat reminiscent of the Hayashi rearrangement.[26]

This work was conducted as part of an ongoing program to devise total syntheses of cytotoxic alkaloids. (+)-Chelidonine (**1**) was recently reported to have a cytotoxic ED_{50} value of 0.27 μg/mL in HeLa cell cultures.[27] It has also been tested in the Purdue Cell Culture Laboratory, and it showed significant cytotoxicity in KB and P388 cell cultures. The ED_{50} values were 0.0069 and 0.052 μg/mL, respectively. (+)-Chelidonine has also displayed moderate

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in vivo activity against L-1210 lymphoid leukemia, P388 lymphocytic leukemia, and Walker carcinosarcoma 256.[28]

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz spectrometer or on an FT-80 spectrometer in $CDCl_3$ solvent, except where noted. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Du Pont 21-492 B double-focusing spectrometer using an ion-source temperature of 230–270 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA. The 360-MHz proton NMR spectra were obtained on a Nicolet NTC-360 instrument.

2-(Ethoxycarbonyl)-3,4-(methylenedioxy)benzaldehyde (5). In an oven-dried, 1000-mL, round-bottomed flask was placed recrystallized piperonylidenecyclohexylamine (48.27 g, 0.209 mol). The flask was purged with nitrogen and then capped with a septum. Dry THF (650 mL) was injected, and the clear solution was cooled on a dry ice–acetone bath for 45 min. A solution of *n*-butyllithium in hexane (2.45 M, 150 mL, 0.368 mol) was added dropwise with vigorous magnetic stirring during 2 h. After an additional 1 h, a solution of freshly distilled ethyl chloroformate (76.25 g, 0.703 mol) in THF (40 mL) was added dropwise to the clear, amber reaction mixture over 1 h. After warming to room temperature over a 3 h period, the mixture was poured into 5% aqueous $NaHCO_3$ (200 mL). Ether (200 mL) was added, and the organic layer was separated and washed with ice-cold 5% aqueous $NaHCO_3$ (3 × 100 mL). The organic layer was then quickly extracted with four portions of ice-cold 5% aqueous HCl (200, 150, 150, and 100 mL). The combined aqueous layers were stored under nitrogen at room temperature overnight, saturated with NaCl, and extracted with ether (5 × 120 mL). The ether layers were combined, dried ($MgSO_4$), and evaporated, yielding a reddish brown oil (41.50 g). This was applied to a silica gel column (56 g, 60–200 mesh, packed in hexane) with $CHCl_3$ and subsequently eluted with $CHCl_3$ (200 mL). The clear, orange eluant was concentrated under reduced pressure, hexane was added, and the solution was placed in the freezer. This yielded three crops of the desired product **5**: 27.56 g (59%); mp 71–73 °C; IR (KBr) 1695, 1661, 1600, 1575, 1450, 1260, 1210 cm^{-1}; NMR δ 10.33 (s, 1 H), 7.65 (d, 1 H, J = 9 Hz), 7.09 (d, 1 H, J = 9 Hz), 6.26 (s, 2 H), 4.52 (q, 2 H, J = 7 Hz), 1.39 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 222 (M^+, 37), 194 (20), 193 (100), 177 (54), 149 (26), 148 (20), 136 (24), 120 (20), 65 (31), 63 (37).

Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.75; H, 4.61.

2-(Ethoxycarbonyl)-3,4-(methylenedioxy)benzyl Alcohol (6). A mixture of the aldehyde **5** (4.99 g, 22.5 mmol), 10% Pd on charcoal (0.28 g), and EtOH (100 mL) was hydrogenated on a Paar apparatus at 50–27 psia of H_2 until exactly 22.5 mmol of H_2 was taken up. The mixture was filtered through a Celite layer and the filtrate evaporated under reduced pressure to yield greenish yellow crystals (5.09 g). This residue was recrystallized ($CHCl_3$, hexane) to give pale yellow crystals of the product **6**: 4.24 g (84%); mp 65–68 °C; IR (KBr) 3448, 1680, 1470, 1290, 1251, 1225 cm^{-1}; NMR δ 6.89 (s, 2 H), 6.07 (s, 2 H), 4.68 (s, 2 H), 4.40 (q, 2 H, J = 7 Hz), 4.13 (br s, 1 H), 1.37 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 224 (M^+, 32), 179 (27), 178 (37), 177 (100), 149 (47).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.36. Found: C, 59.18; H, 5.37.

2-(Ethoxycarbonyl)-3,4-(methylenedioxy)benzyl Chloride (7). Method A. Thionyl chloride (15.08 g, 0.127 mol) and dry CH_2Cl_2 (100 mL) were placed in a 250-mL, three-necked, round-bottomed flask fitted with a fritted-glass gas-dispersion tube. Nitrogen was bubbled through the vigorously stirred solution at room temperature as a solution of the alcohol **6** (17.86 g, 0.08 mol) in dry CH_2Cl_2 (60 mL) was slowly injected with a syringe beneath the surface of the liquid over a 75-min period. The stirring and bubbling were then continued for 1 h. The solvent was evaporated, affording a clear, yellow oil (20.3 g). This material may be used directly in the next step. However, the benzyl chloride **7** may also be crystallized from ether and hexane in 74% yield: mp 37–39 °C; IR (melt) 2975, 1705, 1440, 1230, 1040, 915, 680 cm^{-1}; NMR δ 6.93 (s, 2 H), 6.13 (s, 2 H), 4.93 (s, 2 H), 4.45 (q, 2 H, J = 7 Hz), 1.39 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 244 (M^+ + 2, 24), 242 (M^+, 68), 207 (33), 197 (48), 196 (25), 179 (100), 177 (66), 149 (45), 121 (22), 81 (32), 77 (28), 75 (22), 65 (25), 57 (44), 51 (28), 50 (22), 45 (39).

Method B. In an oven-dried, 1000-mL, round-bottomed flask was placed the dimethylamine **10** (49.53 g, 0.276 mol). The flask was purged with nitrogen and then capped with a septum. Dry THF (550 mL) was injected through the septum, and the flask was placed in a dry ice–acetone bath. After the mixture was stirred for 45 min at −78 °C, *n*-butyllithium in hexane (150 mL of a 2.2 M solution, 0.33 mol) was added dropwise during 1 h. After an additional 1 h, a solution of freshly distilled (from $CaCO_3$) ethyl chloroformate (75.89 g, 0.699 mol) in THF (40 mL) was added dropwise over 45 min. The yellow slurry was allowed to warm to room temperature over a 4-h period. The THF was evaporated to yield a brown oil containing a fine powder. Water (150 mL) and CH_2Cl_2 (150 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and evaporated. Anhydrous ether (100 mL) was added to the dark amber oil. The precipitate which formed immediately (lactone **15**) was filtered off and discarded. The filtrate was evaporated to afford an amber oil (91.86 g). This material was carefully vacuum distilled by using a short-path distillation apparatus, first removing ethyl dimethylcarbamate [bp 32–38 °C (0.47 mm)] and then a second fraction, bp 75–131 °C (0.90–1.20 mm). The desired fraction was collected at a boiling point of 143–154 °C (1.48–0.97 mm), yielding an oily residue (31.20 g) containing a small amount of the solid lactone **15**. This was diluted with a small amount of anhydrous ether, and the lactone **15** (0.46 g, mp 228–232 °C) was removed by filtration. The filtrate was evaporated, yielding the benzyl chloride **7** (30.69 g, 45%).

***N*-Methyl-3,4-(methylenedioxy)benzylamine (9).** Anhydrous ether (100 mL) and $LiAlH_4$ (8.34 g, 0.22 mol) were placed in a 500-mL, round-bottomed flask. A solution of the imine **8** (80.74 g, 0.495 mol) in anhydrous ether (150 mL) was added dropwise to the stirred reaction mixture at a rate which maintained a gentle reflux. After an additional 30 min of stirring, water (40 mL) was added dropwise. The resulting white suspension was filtered. The precipitate was washed thoroughly with ether (100 mL), and the combined filtrates were used directly in the next reaction. The analytical sample was prepared by evaporation of ether from a portion of the solution and distillation of the residue: bp 73 °C (0.12 mm); IR (neat) 3280, 2845, 1492, 1468, 1422, 1230, 1020, 913, 790 cm^{-1}; NMR δ 7.00–6.80 (m, 3 H), 5.99 (s, 2 H), 3.69 (s, 2 H), 2.44 (s, 3 H), 2.05 (s, 1 H).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.18; H, 6.76; N, 8.63.

***N,N*-Dimethyl-3,4-(methylenedioxy)benzylamine (10).** To the ether solution from the previous reaction, which contained the amine **9** (0.495 mol), was added a solution of NaOH (24.88 g, 0.622 mol) in water (100 mL). The reaction mixture was cooled in an ice–salt bath, and a solution of dimethyl sulfate (78.09 g, 0.619 mol) in ether (100 mL) was added dropwise with vigorous stirring over 80 min. After an additional 30 min, the layers were separated, the aqueous layer was extracted with ether (2 × 20 mL), and the combined ether layers were dried ($MgSO_4$) and evaporated under reduced pressure to yield a clear yellow oil (58.85 g). The oil was distilled to afford a clear, colorless oil: 57.77 g (65%); bp 92–95 °C (2.5 mm); IR (neat) 2950, 2920, 2860, 2800, 2740, 1489, 1475, 1429, 1225, 1025 cm^{-1}; NMR δ 6.95–6.70 (m, 3 H), 5.99 (s, 2 H), 3.35 (s, 2 H), 2.21 (s, 6 H); mass spectrum, m/e (relative intensity) 179 (35), 178 (17), 136 (22), 135 (100), 105 (7).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.81; H, 7.35; N, 7.75.

2-(Ethoxycarbonyl)-3,4-(methylenedioxy)benzyl Cyanide (11). Potassium cyanide (11.39 g, 0.175 mol) was added to a solution of the benzyl chloride **7** (26.14 g, 0.108 mol) in dry Me_2SO (50 mL). After being stirred at room temperature for 12 h, the dark brown reaction mixture was poured into water (200 mL) and

(28) NCI screening data summaries for NSC 406034.

extracted with EtOAc (150, 150, 100, and 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated, yielding a brown solid (25.73 g). This was dissolved in $CHCl_3$ (50 mL) and applied to a silica gel column (25 g, 60–200 mesh, packed in hexane). The column was eluted with $CHCl_3$ (125 mL). The eluant was concentrated, hexane was added, and the solution was cooled in the freezer to obtain the product as a yellow, crystalline powder: 18.20 g (72%); mp 93–95 °C; IR (KBr) 2230, 1699, 1458, 1430, 1296, 1262, 1231, 1208, 1130, 1040, 1021 cm^{-1}; NMR δ 7.01 (s, 2 H), 6.19 (s, 2 H), 4.50 (q, 2 H, J = 7 Hz), 4.07 (s, 2 H), 1.39 (t, 3 H); mass spectrum, m/e (relative intensity) 233 (57), 205 (46), 204 (26), 188 (75), 187 (100), 177 (21), 174 (19), 160 (19), 159 (50), 149 (19), 102 (20), 77 (26), 76 (26), 75 (27), 63 (19), 51 (27), 50 (20).

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.01; H, 4.60; N, 5.91.

2-Carboxy-3,4-(methylenedioxy)phenylacetic Acid (12). A mixture of the benzyl cyanide 11 (16.05 g, 68.8 mmol), KOH (11.57 g, 206 mmol), and water (50 mL) was heated at reflux for 3 h. The resulting light brown solution was then cooled in an ice bath and acidified with concentrated HCl. The precipitate was filtered, washed with water, and recrystallized from acetone–hexane to yield the solid diacid 12: 14.13 g (92%); mp 203–204 °C (lit.[14a] mp 203–204 °C); IR (KBr) 3300–2500, 1705, 1670, 1470, 1435, 1285, 1225, 1035 cm^{-1}; NMR (Me_2SO-d_6–$CDCl_3$, 1:5) δ 7.00 (d, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 6.13 (s, 2 H), 3.92 (s, 2 H).

3,4-(Methylenedioxy)homophthalic Anhydride (13). A mixture of the diacid 12 (14.43 g, 64.4 mmol) and acetyl chloride (60 mL) was heated at reflux for 6 h. The mixture was cooled to −10 °C before filtration of the anhydride 13: 12.73 g (96%); mp 199–201 °C (lit.[14a] mp 195 °C); IR (KBr) 1775, 1748, 1620, 1420, 1257, 1037, 961 cm^{-1}; NMR δ 7.33 (d, 1 H, J = 8 Hz), 6.90 (d, 1 H, J = 8 Hz), 6.28 (s, 2 H), 4.20 (s, 2 H); mass spectrum, m/e (relative intensity) 206 (M^+, 76), 162 (58), 134 (100), 81 (16), 78 (37), 76 (26), 69 (18), 51 (16), 50 (33), 45 (16), 43 (15), 41 (15), 39 (68).

2-(Ethoxycarbonyl)-3,4-(methylenedioxy)toluene (14). The aldehyde 5 (12.03 g, 54.14 mmol) was added to EtOH (100 mL) in a hydrogenation bottle. A suspension of palladium on carbon (10%, 0.89 g) in EtOH (50 mL) was then added. The mixture was purged with nitrogen and then hydrogenated at 50 psia of H_2 on a Paar apparatus. After 3 h the mixture was filtered through Celite. The filtrate was evaporated to yield a clear, colorless oil. Distillation of the residue yielded compound 14: 10.19 g (90%); bp 121 °C (2.3 mm); IR (neat) 2940, 1695, 1415, 1220, 1100, 1005, 760 cm^{-1}; NMR δ 6.90 (d, 1 H, J = 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 6.10 (s, 2 H), 4.47 (q, 2 H, J = 7 Hz), 2.45 (s, 3 H), 1.37 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 208 (M^+, 100), 179 (46), 163 (98), 134 (47), 105 (15).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.75; H, 5.78.

3,4-(Methylenedioxy)phthalide (15). Method A. A solution of the benzyl alcohol 6 (3.83 g, 17.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of $SOCl_2$ (2.39 g, 20.1 mmol) in CH_2Cl_2 (15 mL) during 69 min. After the mixture was stirred for an additional 55 min, the solvent was evaporated. The residue was triturated with hexane and the solid lactone 15 (1.73 g, 57%) filtered: mp 230–232 °C; IR (KBr) 1735, 1460, 1230, 1020, 840 cm^{-1}; NMR (Me_2SO-d_6–$CDCl_3$, 4:1) δ 7.32 (d, 1 H, J = 7 Hz), 7.07 (d, 1 H, J = 7 Hz), 6.28 (s, 2 H), 5.37 (s, 2 H); mass spectrum, m/e (relative intensity) 178 (M^+, 84), 149 (100), 120 (33).

Anal. Calcd for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.90; H, 3.63.

Method B. The benzyl alcohol 6 (0.20 g, 0.892 mmol) was added to a solution of concentrated HCl (2 drops) in MeOH (5 mL). After 2 min, a flocculent white precipitate began to appear. After 30 min, the slurry was poured into water (20 mL) and extracted with EtOAc (10 mL) followed by CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield pure lactone 15 (0.13 g, 82%).

α-Hydroxy[2-(ethoxycarbonyl)-3,4-(methylenedioxy)phenyl]acetonitrile (18). The aldehyde 5 (32.26 g, 0.145 mol) was added to water (65 mL) and the suspension heated on a steam bath until the solid changed to an orange oil. A saturated solution of aq $NaHSO_3$ (47 mL) at 100 °C was then added to the mixture. After vigorous stirring a clear yellow solution resulted. The solution was then cooled to −5 °C. A solution of KCN (19.6 g, 0.301 mol) in water (33 mL) was then added over a period of 45 min. After an additional 1 h at −5 °C, 5 N H_2SO_4 (59 mL) was added during 33 min as the temperature rose to 0 °C. The resulting slurry was extracted repeatedly with a total of 900 mL of Et_2O. The ether extracts were dried ($MgSO_4$) and the solvent evaporated to yield a yellow solid. Recrystallization from a mixture of ethylene chloride and hexane gave yellow needles of the cyanohydrin 18: 23.97 g (66%); mp 105–107 °C; IR (KBr) 2935, 1695, 1660, 1600, 1575, 1450, 1350, 1250, 1210, 1130, 1040, 1020, 905, 830, 770 cm^{-1}; NMR δ 7.20 (d, 1 H, J = 8 Hz), 7.00 (d, 1 H, J = 8 Hz), 6.23 (s, 2 H), 5.73 (s, 1 H), 4.91 (br s, 1 H, exchangeable with D_2O), 4.57 (q, 2 H, J = 7 Hz), 1.43 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 249 (M^+, 100), 220 (31), 120 (12), 119 (9).

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.95; H, 4.37; N, 5.53.

α-Carboxy-3,4-(methylenedioxy)phthalide (19). The cyanohydrin 18 (19.03 g, 76.4 mmol) was added to acetic acid (19 mL). The mixture was warmed to 100 °C until all of the solid had dissolved. A solution of $SnCl_2 \cdot 2H_2O$ in concentrated HCl (23 mL) was added in one portion. The mixture was heated at reflux for 6.75 h. The mixture was filtered hot before addition of water (100 mL). The mixture was transferred to a continuous extractor and extracted with $CHCl_3$ for 12 h. The organic layer was separated and the solvent evaporated. The yellow powder was triturated with a small amount of Et_2O and then filtered. The solid was then dissolved in hot water (175 mL) and the solution filtered through Celite in order to remove the turbidity. The phthalide 19 (8.63 g, 51%) crystallized from the filtrate: mp 208–210 °C (lit.[21] mp 210 °C); IR 2950, 1770, 1730, 1470, 1250, 1030, 950, 895 cm^{-1}; NMR (Me_2SO-d_6–$CHCl_3$, 4:1) δ 7.23 (s, 2 H), 6.30 (s, 2 H), 5.90 (s, 1 H).

3,4-(Methylenedioxy)phthalide-α-carboxylic Acetic Anhydride (20). The acid 19 (7.94 g, 35.7 mmol) was added to freshly distilled acetyl chloride (50 mL). The mixture was heated at reflux for 9 h. Anhydrous ether (50 mL) was added to the solution at room temperature. After the mixture was allowed to stand at −10 °C overnight, the solid anhydride 20 (4.76 g, 50%) was filtered: mp 125–127 °C; IR (KBr) 2950, 1815, 1750, 1630, 1465, 1240, 1090, 1030, 950, 800 cm^{-1}; NMR (Me_2SO-d_6–$CDCl_3$, 1:1) δ 7.28 (s, 2 H), 6.33 (s, 2 H), 5.98 (s, 1 H), 1.98 (s, 3 H).

2-Carboxy-3,4-(methylenedioxy)toluene (23). The ester 14 (9.06 g, 43.5 mmol) was added to a solution of NaOH (10 g) in water (40 mL). The mixture was heated at reflux for 1 h and then allowed to stand at room temperature overnight. It was then washed with CH_2Cl_2 (4 × 30 mL), acidified with concentrated HCl, saturated with NaCl, and extracted with ethyl acetate (4 × 100 mL). The organic layer was separated and extracted with 5% $NaHCO_3$ (4 × 20 mL). The combined aqueous extracts were acidified with concentrated HCl, saturated with NaCl, and extracted with ethyl acetate (4 × 25 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was evaporated. The solid residue was extracted with boiling water (100 mL) and filtered. Light tan crystals were obtained from the filtrate. The solid was recrystallized from a mixture of EtOH (10 mL) and water (70 mL) to give the pure acid 23: 2.07 g (26%); mp 156–158 °C; IR (KBr) 3300–2500, 2950, 1680, 1625, 1470, 1445, 1275, 1225, 1050, 970, 905 cm^{-1}; NMR (Me_2SO-d_6–$CDCl_3$, 1:8) δ 6.90 (d, 1 H, J = 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 6.10 (s, 2 H), 2.47 (s, 3 H); mass spectrum, m/e (relative intensity) 180 (M^+, 29), 151 (21), 150 (100), 134 (96), 121 (17), 105 (17).

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.07; H, 4.57.

***cis*-*N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-4-carboxy-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (24).** To a solution of anhydride 13 (10.88 g, 52.8 mmol) in acetonitrile (125 mL) at reflux was added dropwise a solution of piperonylidenemethylamine (8.63 g, 52.9 mmol) in acetonitrile (125 mL) over 1 h. After an additional 1 h at reflux, the solvent was evaporated and the residue washed with acetone (3 × 300 mL). This yielded the product 24 as a white solid: 12.09 g (62%); mp 219–224 °C dec; IR (KBr) 3400–2800, 1740, 1730, 1610, 1480, 1449, 1245, 1030 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 7.13 (d, 1 H, J = 9 Hz), 6.92 (d, 1 H, J = 9 Hz), 6.68 (m, 3 H), 6.19

(s, 2 H), 5.97 (s, 2 H), 4.98 (d, 1 H, J = 6 Hz), 4.49 (d, 1 H, J = 6 Hz), 2.99 (s, 3 H); mass spectrum, m/e (relative intensity) 369 (M^+, 9), 325 (11), 256 (32), 178 (21), 164 (100), 163 (18), 162 (32), 134 (18), 122 (19), 97 (16), 83 (18), 71 (24), 69 (29), 57 (46), 56 (17), 55 (56), 45 (28).

Anal. Calcd for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09. Found: C, 61.50; H, 4.33.

***trans*-*N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-4-carboxy-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (25).** The cis diastereomer **24** (0.09 g, 0.24 mmol) was added to AcOH (10 mL). The mixture was heated at reflux for 13 h. The acetic acid was evaporated, leaving the trans isomer **25**: 0.09 g; mp 250–252 °C dec; IR (KBr) 3300–2500, 1720, 1690, 1625, 1580, 1480, 1440, 1235, 1035, 920, 800 cm^{-1}; NMR (Me_2SO-d_6–$CDCl_3$, 2:1) δ 6.75 (m, 5 H), 6.17 (s, 2 H), 5.97 (s, 2 H), 5.17 (s, 1 H), 3.93 (s, 1 H), 3.07 (s, 3 H).

***cis*-*N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-4-[(diazomethyl)carbonyl]-7,8-(methylenedioxy)-3,4-dihydro-1-(2*H*)-isoquinolone (26).** Triethylamine (10 mL) was added to the acid **24** (500 mg, 1.35 mmol), and the mixture was stirred at room temperature for 12 h. Excess triethylamine was then evaporated, yielding a white salt (620 mg, 98%). The triethylamine salt (1.12 g, 2.38 mmol) of **24** was dissolved in benzene–CH_2Cl_2 (20 mL, 10 mL), and the solution was cooled in an ice bath. Thionyl chloride (0.4 mL) was added, and the reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated, and benzene (20 mL) was added to the residue. The resulting light brown solution was added to a solution of CH_2N_2 (0.75 g) in alcohol-free ether (50 mL) at −10 °C. The reaction mixture was stirred at room temperature for 20 min before the precipitate (0.84 g) was filtered and dissolved in $CHCl_3$ (100 mL). The solution was washed with water (3 × 15 mL), dried ($MgSO_4$), and evaporated. Crystallization of the residue from CH_2Cl_2 gave pure diazo ketone **26**: 0.47 g (50%); mp 165 °C dec; IR (KBr) 2899, 2100, 1640, 1480, 1455, 1370, 1330, 1240, 1030 cm^{-1}; NMR δ 7.00–6.50 (m, 5 H), 6.23 (s, 2 H), 6.00 (s, 2 H), 5.09 (s, 1 H), 4.79 (d, 1 H, J = 6 Hz), 4.44 (d, 1 H, J = 6 Hz), 3.01 (s, 3 H); mass spectrum, m/e (relative intensity) 369 (M^+ − 24, 74), 325 (26), 324 (15), 323 (26), 206 (41), 164 (100), 162 (41).

***cis*-*N*-Methyl-1,2-(methylenedioxy)-5,11-dioxo-7,8-(methylenedioxy)-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (27).** The diazo ketone **26** (100 mg, 0.25 mmol) was added to CF_3COOH (0.5 mL) at 0 °C. Nitrogen gas evolved immediately. After 1 min, CH_2Cl_2 (20 mL) was added, and the solution was washed with H_2O (3 × 5 mL), dried ($MgSO_4$), and evaporated. The cyclized ketone **27** (17 mg, 19%) was obtained by preparative TLC on silica gel, eluting three times with $CHCl_3$/MeOH (200:1). The analytical sample was recrystallized from benzene: mp 248 °C dec; IR (KBr) 2980, 2860, 1700, 1630, 1480, 1470, 1450, 1230, 1040, 1020, 780 cm^{-1}; NMR δ 7.40 (s, 1 H), 6.93 (d, 1 H, J = 8 Hz), 6.73 (s, 1 H), 6.66 (d, 1 H, J = 8 Hz), 6.17 (s, 2 H), 6.05 (s, 2 H), 5.00 (d, 1 H, J = 4 Hz), 3.85 (d, 1 H, J = 4 Hz), 3.67 (s, 2 H), 3.02 (s, 3 H); mass spectrum, m/e (relative intensity) 365 (M^+, 26), 334 (100), 306 (14).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83. Found: C, 66.04; H, 4.13; N, 4.02.

(±)-Chelidonine (1). A mixture of compound **27** (20 mg, 0.055 mmol) and $LiAlH_4$ (30 mg) in THF (15 mL) was heated at reflux for 17 h. The reaction mixture was cooled to 0 °C and decomposed by addition of water (0.3 mL), 15% aqueous NaOH (0.3 mL), and finally water (0.3 mL). The mixture was stirred at 0 °C for 20 min and then filtered. The aluminates were washed with $CHCl_3$, and the combined organic layers were dried ($MgSO_4$). The solvents were evaporated, and $CHCl_3$ (20 mL) was added to the residue. The solution was extracted with 1% aqueous HCl (3 × 10 mL). The aqueous extracts were combined, basified with NH_4OH, and extracted with $CHCl_3$ (3 × 30 mL). Evaporation of $CHCl_3$ gave chromatographically pure (±)-chelidonine (18 mg, 93%). The analytical sample was recrystallized once from EtOH: mp 215–216 °C (lit.[5a] mp 216 °C); 360-MHz NMR δ 6.76 (d, 1 H, J = 7.9 Hz), 6.73 (d, 1 H, J = 7.9 Hz), 6.66 (s, 1 H), 6.64 (s, 1 H), 5.99 (d, 1 H, J = 1.5 Hz), 5.95 (d, 1 H, J = 1.3 Hz), 5.934 (d, 1 H, J = 1.5 Hz), 5.927 (d, 1 H, J = 1.5 Hz), 4.23 (br s, 1 H, W_{112} = 7.9 Hz), 4.08 (d, 1 H, J = 15.7 Hz), 3.57 (br s, 1 H, W_{112} = 6.8 Hz), 3.43 (d, 1 H, J = 15.7 Hz), 3.21 (d, 1 H, J = 17.5 Hz), 3.08 (dd, J = 17.5, 4.3 Hz), 2.98 (t, 1 H, J = 2.8 Hz), 2.27 (s, 3 H).

***N*-Methyl-4-[1-oxo-2-[3,4-(methylenedioxy)phenyl]-ethyl]-7,8-(methylenedioxy)isocarbostyril (32).** This compound (20 mg, 22%) was obtained from the above reaction mixture which yielded **27**. It was also isolated by preparative TLC on silica gel, eluting three times with $CHCl_3$/MeOH (200:1). The analytical sample was prepared by recrystallization from acetone: mp 199–200 °C; IR (KBr) 2900, 1640, 1455, 1240, 1030, 930, 745 cm^{-1}; NMR δ 8.42 (d, 1 H, J = 8.8 Hz), 7.82 (s, 1 H), 7.20 (d, 1 H, J = 8.8 Hz), 6.74 (m, 3 H), 6.20 (s, 2 H), 5.94 (s, 2 H), 4.06 (s, 2 H), 3.59 (s, 3 H); mass spectrum, m/e (relative intensity) 365 (M^+, 18), 230 (100), 202 (12), 172 (4), 161 (7), 133 (8); ^{13}C NMR (proton coupled) δ 195.918 (q, J = 4 Hz), 158.758 (br s), 147.163 (s), 146.526 (s), 146.192 (s), 145.827 (s), 141.650 (dd, J = 180, 4 Hz), 129.348 (q, J = 6.71 Hz), 128.330 (t, J = 7.94 Hz), 122.553 (dq, J = 161.14, 6.10 Hz), 118.476 (d, J = 167.24 Hz), 113.673 (dd, J = 165.41, 2.5 Hz), 112.823 (t, J = 3 Hz), 110.590 (s), 109.984 (dq, J = 162.97, 6.11 Hz), 108.066 (d, J = 164.80 Hz), 102.265 (t, J = 175.78 Hz), 100.785 (t, J = 174.56 Hz), 45.042 (t, J = 149.39 Hz), 36.499 (qd, J = 142.82, 3.66 Hz).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83. Found: C, 65.95; H, 4.29; N, 3.89.

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