($CHCl_3$) ν_{max} 3040, 2960, 1595, 1465, 1260, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 294 (M^+, 78), 280 (25), 279 (base), 264 (55), 263 (31), 248 (32). Dimethyl ether of juncusol (**23**) was prepared in yields ranging from 60–77% from **22**.

Juncusol (1). A solution of ethanethiol (8.4 mg, 0.14 mmol, 2.9 equiv) in 0.5 mL of dry HMPA at 0 °C under argon was treated slowly with 0.10 mL of 1.4 M methyllithium in ether (0.14 mmol, 2.9 equiv). Juncusol dimethyl ether (**23**, 7.2 mg, 0.024 mmol) in 1.0 mL of dry HMPA was added at 25 °C, and the resulting mixture was warmed at 160 °C for 6h.[28b] The reaction mixture was cooled to 25 °C, poured over 5 mL of cold water, acidified (ca. pH 4) with cold 5% aqueous HCl, and extracted with ether (4 × 1 mL). The combined extracts were washed with water (2 × 0.5 mL) and 0.5 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 7.0 cm, 30% ether–hexane eluant) afforded 5.4 mg (6.4 mg theoretical, 84%) of **1** as a solid: mp 174–175 °C (lit.[2] mp 175–176 °C; benzene); ^1H NMR ($CDCl_3$) δ 7.52 (d, J = 9 Hz, 1 H, C-5 H), 6.95–6.45 (overlapping dd, d and s, 3 H, vinyl and two aromatic), 5.50 (dd, J_{BX} = 12, J_{AB} = 2 Hz, CH=CH_AH_B), 5.21 (dd, J_{AX} = 18, J_{AB} = 2 Hz, CH=CH_AH_B), 4.64 (br s, 2 H, two OH), 2.66 (s, 4 H, $ArCH_2CH_2Ar$), 2.27 and 2.23 (two s, 3 H each, two $ArCH_3$); IR ($CHCl_3$) ν_{max} 3600, 3600–3100, 3005, 2960, 1590, 1450, 1395, 1275, 1100 cm^{-1}; EIMS, *m/e* (relative intensity) 266 (M^+, 98), 265 (20, 252 (23), 251 (base), 250 (35), 249 (23), 237 (22), 236 (64), 235 (28), 234 (30); HRMS, *m/e* 266.1300 ($C_{18}H_{18}O_2$ requires 266.1306.

Acknowledgment. This work was assisted financially by the Searle Scholars Program, The University of Kansas (GRF allocation 3605-X0-0038), the National Institutes of Health (CA 33668), and a Biomedical Research Grant (RR 5606). We thank Professor A. S. Kende for comparison spectra of authentic aldehyde **22** and for a comparison sample of 2,7-dimethoxy-3,8-dimethyl-4-(hydroxymethyl)-9,10-dihydrophenanthrene.

Registry No. **1**, 62023-90-9; **7**, 2987-06-6; (*cis*)-**8**, 91551-13-2; (*trans*)-**8**, 91551-14-3; (*cis*)-**9**, 91551-15-4; (*trans*)-**9**, 91551-16-5; **10**, 85559-32-6; **11**, 85559-33-7; **12**, 85559-34-8; **13**, 17215-86-0; **15**, 85531-85-7; **16**, 922-69-0; **17**, 85531-86-8; **18**, 85559-36-0; **19**, 85559-37-1; **20**, 91551-17-6; **22**, 69496-44-2; **23**, 66447-86-7; **24**, 91551-18-7; **25**, 73255-29-5; **26**, 91551-19-8; **28**, 91551-20-1; VII, 91551-21-2; ethyl vinyl ketone, 1629-58-9; dimethyl (methoxymethylene)malonate, 22398-14-7; (dimethylamino)(thiophenyl)methane, 43180-39-8; methyltriphenylphosphonium bromide, 1779-49-3.

Total Syntheses of Azafluoranthene Alkaloids: Rufescine and Imeluteine

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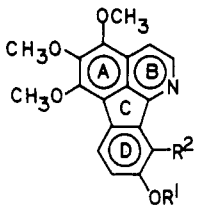
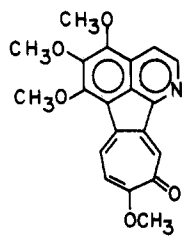
Total syntheses of rufescine and imeluteine, azafluoranthene alkaloids isolated from *Abuta imene* and *Abuta rufescens*, are detailed and are based on the utilization of the inverse electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrones for the selective and controlled introduction of oxygenated aromatics.

Recent studies of the alkaloids of *Abuta imene* and *Abuta rufescens*, bush ropes found in South America, resulted in the isolation, identification, and synthesis of the azafluoranthene alkaloids rufescine (**1**), norrufescine

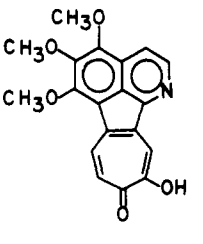


1	$R^1 = CH_3$	$R^2 = H$
2	$R^1 = H$	$R^2 = H$
3	$R^1 = CH_3$	$R^2 = OCH_3$

(**2**), and imeluteine (**3**),[2,3] condensed isoquinolines biosynthetically related to the tropoloisoquinolines imerubrine[4a] and grandirubrine.[4b]



imerubrine



grandirubrine

Herein, we describe a divergent[5] approach to the preparation of rufescine (**1**) and imeluteine (**3**) based on the utilization of the inverse electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrones[6] for the selective

(1) (a) Searle Scholar recipient, 1981–1985. Recipient of a National Institutes of Health Career Development Award (CA 00898). (b) National Institutes of Health predoctoral trainee (GM 07775).

(2) (a) Cava, M. P.; Buck, K. T.; daRocha, A. I. *J. Am. Chem. Soc.* **1972**, *94*, 5931. (b) Cava, M. P.; Buck, K. T.; Noguchi, I.; Srinivasan, M.; Rao, M. G.; daRocha, A. I. *Tetrahedron* **1975**, *31*, 1667. (c) Klein, M. D.; Buck, K. T.; Cava, M. P.; Voet, D. *J. Am. Chem. Soc.* **1978**, *100*, 662. Norrufescine has been isolated from *Telitoxicum perurianum*; see: Menachery, M. D.; Cava, M. P. *J. Nat. Prod.* **1981**, *44*, 320.

(3) For complete syntheses of azafluoranthene alkaloids, based on the Pschorr cyclization, see: (a) rufescine and imeluteine, ref 2a; (b) norrufescine, Menachery, M. D.; Cava, M. P. *Heterocycles* **1982**, *19*, 2255.

(4) (a) Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, *99*, 6708. (b) Menachery, M. D.; Cava, M. P. *Heterocycles* **1980**, *14*, 943.

(5) Two distinct classifications have been recognized as useful descriptions of the conceptual, as well as actual, strategies used in the synthesis of *individual* naturally occurring or synthetic materials: linear vs. convergent synthesis. The practical value of a convergent synthesis has been described in some detail. For example, see: Fuhrhop, J.; Penzlin, G. "Organic Synthesis–Concepts, Methods, Starting Materials"; Verlag Chemie: Basel, Switzerland, 1983; p 216. Similarly, for a *group* of related, naturally occurring or synthetic materials (e.g., azafluoranthene alkaloids) two, distinct classifications may be used to describe the strategy employed in their synthesis: independent vs. divergent. As the terminology implies: "independent" total synthesis requires nonidentity of intermediates used for the total synthesis of each member of the class while "divergent" requires that an identical intermediate (preferably an advanced intermediate) be converted, separately, to at least two members of the class of compounds. Divergent total syntheses are distinct from partial total synthesis in which one member is interconverted to a second member of the class of compounds.

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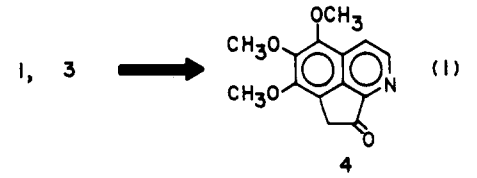
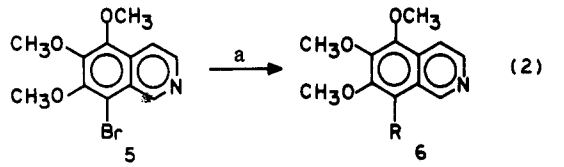
and controlled introduction of the azafluoranthene aryl D ring, eq 1. The results underscore the ease with which



a single intermediate, e.g. **4**, a potential precursor to the tropoloisoquinolines, may be used for the preparation of a series of related, natural or synthetic materials.

Metalation of 8-bromo-5,6,7-trimethoxyisoquinoline (**5**), a readily available isoquinoline prepared by a simplified isoquinoline synthesis,[7] with *n*-butyllithium followed by treatment of the resulting 8-lithio-5,6,7-trimethoxyisoquinoline with dimethyl carbonate afforded 8-methoxycarbonyl-5,6,7-trimethoxyisoquinoline (**6a**, 83%), eq 2.

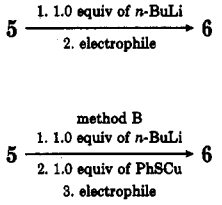


b [6a, R = CO_2CH_3; 6b, R = CHO
c [6c, R = $CH(OH)CH_3$; 6d, R = $COCH_3$
d [6g, R = $CH_2CO_2CH_3$

(a) Table I for **6a**, **6b**, **6c**. (b) 2.2 equiv of Dibal-H, −15 to 0 °C, toluene, 1 h; 10 equiv of MnO_2, CH_2Cl_2, 25 °C, 15 h, 52% overall; or 2.0 equiv of $LiAlH_4$, THF, 25 °C, 56%; 10 equiv of MnO_2, CH_2Cl_2, 25 °C, 5 days, 57%. (c) 10 equiv of MnO_2, CH_2Cl_2, 25 °C, 36 h, 70%. (d) 2.5 equiv of $Tl(NO_3)_3 \cdot 3H_2O$, CH_3OH, 25 °C, 36 h, 20%

Low-temperature diisobutylaluminum hydride reduction of **6a** followed by manganese dioxide oxidation of the benzylic alcohol afforded 5,6,7-trimethoxyisoquinoline-8-carboxaldehyde (**6b**, 52%). A direct introduction of the 8-carboxaldehyde was also accomplished by treatment of 8-lithio-5,6,7-trimethoxyisoquinoline with methyl formate, affording **6b** (43%). Efforts to effect the direct introduction of the 8-carboxaldehyde using equivalent electrophiles as well as early efforts to directly convert **5** to **6g**, a key intermediate in the syntheses detailed below, were unsuccessful.[8] A detailed study of the generation and reactions of 8-lithio-5,6,7-trimethoxyisoquinoline and the corresponding lithium phenylthio mixed cuprate derivative[9] is summarized in Table I. The results are comparable to those reported by Suggs[10] in his studies on 8-bromoquinoline.

Table I. Generation and Reactions of 8-Lithio-5,6,7-trimethoxyisoquinoline



electrophile	method (condns)[a]	product 6,[b] R	% yield[c]
D_2O	A (15 min)	D/H (96/4)	78
	A (30 min)	D/H (90/10)	73
	A (60 min)	D/H (87/13)	63
	A (120 min)	D/H (67/33)	60
$CO(OCH_3)_2$	A	**6a**, CO_2CH_3	83
HCO_2CH_3	A	**6b**, CHO	43
$HCO_2CH_2CH_3$	A	**6b**	29
$HCONMe_2$	A	**6b**	20
CH_3CHO	A	**6c**, $CH(OH)CH_3$	56[d]
$CH_3CO_2CH_2CH_3$	A	**6d**, $COCH_3$	0
CH_3I	A	**6e**, CH_3	70
CH_2=$CHCH_2Br$	A	**6f**, CH_2CH=CH_2	0
	B	**6f**	72
CH_2=$CHCH_2I$	A	**6f**	0
$BrCH_2CO_2CH_3$	A	**6g**, $CH_2CO_2CH_3$	0
	B	**6g**	0
ICH_2CN	A	**6h**, CH_2CN	0
CH_3COCH_3	A	**6i**, $C(OH)Me_2$	0
$ClSiMe_3$	A	**6j**, $SiMe_3$	23

[a] Reactions were carried out according to the general procedures detailed in the Experimental Section for method A and method B. [b] All products exhibited the expected ^1H NMR, IR, and MS spectral characteristics consistent with the assigned structure. All new compounds gave satisfactory C, H, N analysis or HRMS information. [c] All yields are based on purified product isolated by chromatography (SiO_2), unless otherwise indicated. [d] Yield determined by ^1H NMR. Compound **6c** was oxidized to **6d** and fully characterized.

Condensation of 2-lithio-2-(trimethylsilyl)-1,3-dithiane[11] with aldehyde **6b** followed by mercury(II)-promoted methanolysis[11b] of the ketene thioacetal **6k** afforded methyl 2-(5,6,7-trimethoxy-8-isoquinolyl)acetate (**6g**), Scheme I. An alternative preparation of **6g** requiring oxidation of **6c** to 8-acetyl-5,6,7-trimethoxyisoquinoline (**6d**) followed by thallium(III)-promoted aryl migration[12] did provide **6g** albiet in low yield (20%), eq 2. Treatment of **6g** with *p*-toluenesulfonyl chloride in the presence of sodium cyanide in a methylene chloride–water two-phase reaction system[13] followed by exposure of the *N*-tosyl 1-cyano-1,2-dihydroisoquinoline **7** to strong base (KO-*t*-Bu, THF–*t*-BuOH) afforded **9** *directly* via **8**. Exposure of **7** to hindered tertiary amines did allow the isolation of intermediate **8** in excellent yield.[13b] Acid-promoted hydrolysis and decarboxylation of **9** under mild conditions afforded **4** directly in high yield. Conversion of **4** to the 3-carbomethoxy-2-pyrone **10**,[6,14] which was effected by a

(6) Boger, D. L.; Mullican, M. D. *J. Org. Chem.*, first paper in a series in this issue. Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1983**, *24*, 4939; **1982**, *23*, 4551.

(7) Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron* **1981**, *37*, 3977.

(8) (a) The use of the aldehyde equivalents, 2-(methylformylamino)-pyridine (Comins, D.; Meyers, A. I. *Synthesis* **1978**, 403) and *N*,4,4-trimethyl-2-oxazalinium iodide (Brinkmeyer, R. S.; Collington, E. W.; Meyers, A. I. *Org. Synth.* **1974**, *54*, 42) did not afford the desired aldehyde product. Ethyl formate, phenylformate, and dimethylformamide gave lower yields of aldehyde than methyl formate. (b) Direct conversion of **5** to **6g** by palladium catalyzed coupling of the Reformatsky reagent (Fauvarque, J. F.; Jutland, A. *J. Organomet. Chem.* **1977**, *132*, C17); by reaction of (5,6,7-trimethoxyisoquinol-8-yl)copper or its lithium phenylthio mixed cuprate derivative with methyl bromoacetate or ethyl diazoacetate (Sata, T.; Watanabe, S. *J. Chem. Soc. D* **1969**, 515); by reaction of (5,6,7-trimethoxyisoquinolin-8-yl)cadmium with methyl bromoacetate (Jones, P. R.; Young, J. R. *J. Org. Chem.* **1968**, 33, 1675); or by reaction of the 8-lithio-5,6,7-trimethoxyisoquinoline-9-BBN ate complex with methyl bromoacetate (Brown, H. C.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 4034. Brown, H. C.; Rogic, M. M.; Nambu, H.; Rathke, M. W. *Ibid.* **1969**, *91*, 2146) yielded little or no desired product.

(9) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

(10) Suggs, J. W.; Pearson, G. D. N. *J. Org. Chem.* **1980**, *45*, 1514.

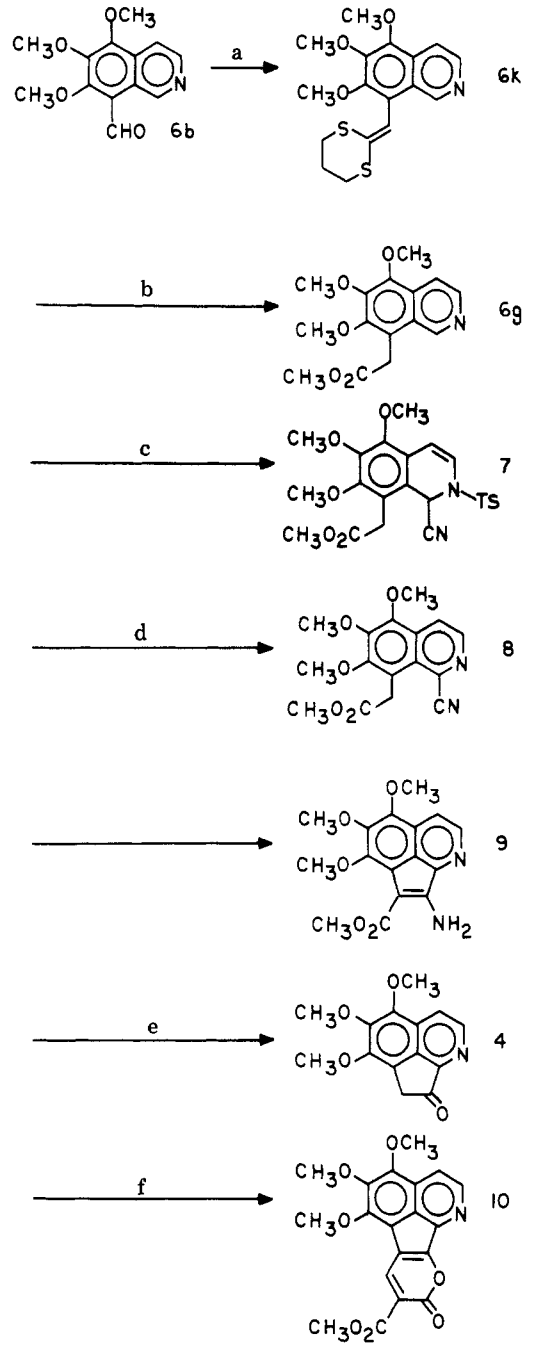
(11) (a) Seebach, D.; Kolb, M.; Grobel, B-T. *Chem. Ber.* **1973**, *106*, 2277. (b) Schubert, U. *Synthesis* **1978**, 364.

(12) McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, 3340.

(13) (a) Wefer, J. M.; Catala, A.; Popp, F. D. *J. Org. Chem.* **1965**, *30*, 3075. (b) Boger, D. L.; Brotherton, C. E.; Panek, J. S.; Yohannes, D. *J. Org. Chem.*, accompaning note in this issue.

(14) Other methods of 3-carbomethoxy-2-pyrone formation failed to provide **10**.

Scheme I[a]



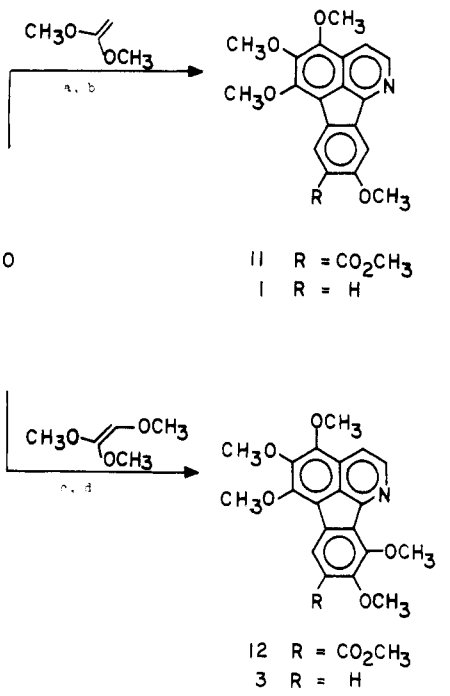
[a] (a) 1.0 equiv of 2-lithio-2-(trimethylsilyl)-1,3-dithane, THF, 25 °C, 17 h, 77%. (b) 2 equiv of $HgCl_2$, CH_3OH-H_2O, reflux, 24 h, 82%. (c) 1.5 equiv of *p*-TsCl, 3.0 equiv of KCN, CH_2Cl_2-H_2O, 25 °C, 16 h, 84%. (d) 2.6 equiv of KO-*t*-Bu, THF-*t*-BuOH, 25 °C, 6 h, 98%. (e) Dioxane:10% aqueous HCl (9:1), 100 °C, 25 min, 65%. (f) 1.1 equiv of LDA, THF, −78 °C, 45 min; 1.05 equiv of $CH_3OCH{=}C(CO_2CH_3)_2$, 0 °C, 45 min, *p*-TsOH, toluene, 110 °C, -CH_3OH, 62%.

two-step procedure requiring *p*-toluenesulfonic acid catalyzed α-pyrone closure,[14] preceded the final conversions to the azafluoranthene alkaloids.

Inverse electron demand Diels–Alder reaction of 3-carbomethoxy-2-pyrone **10** with 1,1-dimethoxyethylene[15] afforded the methyl salicylate **11** (83%), Scheme II. Ester hydrolysis and (pentafluorophenyl)copper-promoted decarboxylation[16] in quinoline gave rufescine (**1**, 47%).

(15) 1,1-Dimethoxyethylene is available commercially from Wiley Organics.

Scheme II[a]



[a] (a) 8 equiv of 1,1-dimethoxyethylene, mesitylene, 120 °C, 5 h, 83%. (b) LiOH, THF-H_2O, 80 °C, 16 h; $(C_6F_5Cu)_2$-dioxane, quinoline, 225 °C, 25 min, 47%. (c) 10 equiv of 1,1,2-trimethoxyethylene, mesitylene, 150 °C, 5 h; 1.0 equiv of DBU, toluene, 100 °C, 15 min, 89–98%. (d) LiOH, THF-H_2O, 80 °C, 2 h; $(C_6F_5Cu)_2$-dioxane, quinoline-1,3,5-triisopropylbenzene, 220 °C, 35 min, 50%.

Treatment of 3-carbomethoxy-2-pyrone **10** with 1,1,2-trimethoxyethylene[17] followed by base treatment (1.0 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, 100 °C, 15 min) of the initial Diels–Alder product[6] afforded **12** (89–98%), Scheme II. Ester hydrolysis and (pentafluorophenyl)copper-promoted decarboxylation[16] in 1,3,5-triisopropylbenzene–quinoline provided imeluteine (**3**, 50%).

Synthetic rufescine (**1**) and imeluteine (**3**) were identical in all comparable respects with the reported properties of the natural materials.

The Diels–Alder reactions of 3-carbomethoxy-2-pyrone **10** with 1,1-dimethoxyethylene (83%) and 1,1,2-trimethoxyethylene (89–98%) proceed more readily than examples previously studied.[6] In fact, treatment of **10** with 1,1,1,2-tetramethoxyethane (10–20 equiv, 150 °C, mesitylene, 17–37 h; 1.2 equiv of KO-*t*-Bu or 1 equiv of DBU) did afford **12** (36–41%, unoptimized) presumably by way of in situ generation of 1,1,2-trimethoxyethylene. While this presents no apparent advantage over the use of the preformed dienophile, it does illustrate the potential of a thermal generation and subsequent Diels–Alder reaction of a reactive, electron-rich dienophile.

(16) Cooper-catalyzed decarboxylated of **11** gave low yields of the demethylated and decarboxylated product, norrufescine. The bis[(pentafluorophenyl)copper]dioxane complex promoted decarboxylation with no competing demethylation. For the preparation of bis[(pentafluorophenyl)copper-dioxane, see: Cairncross, A.; Sheppard, W. A.; Wonchoba, E. *Org. Synth.* **1978**, *59*, 122. For its use, see: Trost, B. M.; Kinson, P. L. *J. Org. Chem.* **1972**, *37*, 1273. Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 3187.

(17) 1,1,2-Trimethoxyethylene was prepared as described: Bakker, C. G.; Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 13. Spinning band distillation used to separate 1,1,2-trimethoxyethylene from methyl methoxyacetate and 1,1,1,2-tetramethoxyethane was found to be unnecessary and material which was 25–35% pure worked satisfactorily, see ref 6.

Extentions of this approach to the preparation of the related tropoloisoquinolines, imerubrine and grandirubrine, are in progress and will be reported in due course.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra (IR) were obtained on a Beckmann IR-33, Perkin-Elmer 710B, or IBM FTIR 32 spectrophotometer. ^1H NMR spectra were recorded on a Varian FT-80A spectrometer in $CDCl_3$ unless otherwise indicated. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Varian CH-5 or Ribermag R10-10 mass spectrometer by Charles Judson and Robert Drake. Microanalysis were performed by Tho I. Nguyen on a Hewlett-Packard Model 185 CHN analyzer at the University of Kansas. Medium-pressure liquid chromatography (MPLC) was performed on silica gel 60 (230–400 mesh).[18] Preparative centrifugal thin-layer chromatography (PCTLC)[19] was performed on a Harrison Model 7924 Chromatotron using Merck silica gel 60 PF_{254} containing $CaSO_4 \cdot {}^1/_2H_2O$ binder. Dry tetrahydrofuran was distilled immediately before use from sodium benzophenone ketyl. Toluene, mesitylene, and diisopropylamine were distilled from powered calcium hydride. Methylene chloride was distilled immediately before use from phosphorus pentoxide. Quinoline was dried over Na_2SO_4 and vacuum distilled from calcium oxide. Dimethyl (methoxymethylene)malonate was obtained from Fluka Chemicals and distilled under vacuum. Extraction and chromatographic solvents (CH_2Cl_2, EtOAc, ether, hexane) were distilled before use. All reactions requiring anhydrous conditions were run under positive pressure of argon or nitrogen and reagents were introduced by syringe through a septum. Syringes and reaction flasks were oven dried.

8-Bromo-5,6,7-trimethoxyisoquinoline (5). 8-Bromo-5,6,7-trimethoxyisoquinoline (**5**) was prepared as previously described[7] or by the following procedure. 5,6,7-Trimethoxyisoquinoline[7] (1.67 g, 7.6 mmol), *N*-bromosuccinimide (1.43 g, 8.0 mmol), and 3 drops concentrated H_2SO_4 were combined in 75 mL of dry THF and stirred under nitrogen at 25 °C for 2 h. The reaction mixture was neutralized with 5% $NaHCO_3$, poured onto water (50 mL), extracted with methylene chloride (3 × 60 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 25% EtOAc–hexane eluant) afforded 1.99 g (2.27 g theoretical, 87%) of **5**[7] as a white solid: ^1H NMR δ 9.22 (s, 1 H, C1-H), 8.27 (d, 1 H, J = 6 Hz, C3-H), 7.58 (d, 1 H, J = 6 Hz, C4-H), 3.90 (s, 6 H, two $ArOCH_3$), 3.85 (s, 3 H, $ArOCH_3$).

General Procedure for Generation and Reactions of 8-Lithio-5,6,7-trimethoxyisoquinoline. Method A: 8-(Methoxycarbonyl)-5,6,7-trimethoxyisoquinoline (6a). A stirred solution of 8-bromo-5,6,7-trimethoxyisoquinoline (**5**, 596 mg, 2.0 mmol) in 12 mL dry tetrahydrofuran (THF) under argon at −78 °C was treated with *n*-butyllithium (1.2 mL of 1.66 M, 2.0 mmol), and the reaction mixture was stirred at −78 °C for 15 min before the addition of dimethyl carbonate (0.3 mL). After stirring at −78 °C for 20 min, 2 mL of saturated aqueous ammonium chloride was added, and the reaction mixture was allowed to warm to 25 °C. The mixture was poured onto water and extracted with ethyl acetate (1 × 30 mL) and methylene chloride (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. MPLC (SiO_2, 1.5 × 25 cm, 50% EtOAc–hexane eluant) afforded 460 mg (554 mg theoretical, 83%) of **6a** as a colorless oil: ^1H NMR δ 9.18 (s, 1 H, C1-H), 8.48 (d, 1 H, J = 6 Hz, C3-H), 7.87 (d, 1 H, J = 6 Hz, C4-H), 4.08, 4.05, 4.02, 4.01 (four s, 3 H each, CO_2CH_3, three $ArOCH_3$); IR (film) ν_{max} 3030, 2970, 1735 (C=O), 1610, 1585, 1490, 1465, 1425, 1400, 1378, 1350, 1308, 1250, 1230, 1185, 1142, 1108, 1062, 1040, 1020, 985, 950, 940, 835, 780, 680 cm^{-1}; mass spectrum, m/e (relative intensity) 277 (M^+, 100), 262 ($-CH_3$, 23), 246 ($-OCH_3$, 39), 234 (19); high-resolution mass spectrum, m/e 277.0946 ($C_{14}H_{15}NO_5$ requires 277.0949).

5,6,7-Trimethoxyisoquinoline-8-carboxaldehyde (6b) (Table I): mp 92–92.5 °C (ethanol/water, white needles); ^1H NMR δ 10.66 (s, 1 H, CHO), 10.44 (s, 1 H, C1-H), 8.54 (d, 1 H, J = 6 Hz, C3-H), 7.88 (d, 1 H, J = 6 Hz, C4-H), 4.20, 4.11, 4.00 (three s, 3 H each, three $ArOCH_3$), IR ($CHCl_3$) ν_{max} 3020, 2950, 2870, 1680 (C=O), 1610, 1580, 1485, 1465, 1420, 1392, 1380, 1330, 1230, 1110, 970 cm^{-1}; mass spectrum, m/e (relative intensity) 247 (M^+, 100), 246 (M − 1, 11), 232 (22), 230 (9), 214 (15), 188 (10), 186 (14), 174 (19), 161 (30), 146 (15), 133 (14), 102 (15), 90 (32).

Anal. Calcd for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.80; H, 5.42, N, 5.50.

Preparation of 6b from 6a. A stirred solution of **6a** (38.7 mg, 0.14 mmol) in 3 mL of dry toluene at −15 °C was treated with diisobutylaluminum hydride (0.31 mL of 1 M, 2.2 equiv) and allowed to warm to 0 °C over 1 h before addition of 2 drops of cold methanol. The reaction mixture was poured onto 2 mL of saturated sodium potassium tartrate and extracted with ethyl acetate (4 × 2 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, affording 38.2 mg of crude alcohol. A solution of the crude alcohol in dry methylene chloride (1.5 mL) was added dropwise to a slurry of MnO_2 (400 mg) in 3 mL of dry methylene chloride at 0 °C under nitrogen. The reaction mixture was stirred at 25 °C for 15 h, filtered through Celite, and washed with dry THF (6 × 5 mL). The combined filtrate and washes were concentrated in vacuo. MPLC (0.7 × 25 cm, 50% EtOAc–hexane eluant) afforded 18.2 mg (34.6 mg theoretical, 52%) of **6b**.

8-(1-Hydroxyethyl)-5,6,7-trimethoxyisoquinoline (6c) (Table I): ^1H NMR δ 9.9 (s, 1 H, C1-H), 8.28 (d, 1 H, J = 6 Hz, C3-H), 7.8 (d, 1 H, J = 6 Hz, C4-H), 5.82 (1 H, q, J = 7 Hz, C*H*OH), 4.7 (1 H, br, OH), 4.05 (s, 6 H, two $ArOCH_3$), 3.95 (s, 3 H, $ArOCH_3$), 1.7 (d, 3 H, J = 7 Hz, CH_3).

8-Acetyl-5,6,7-trimethoxyisoquinoline (6d). The crude alcohol **6c** (314 mg, 1.2 mmol) was oxidized with 10 weight equiv of MnO_2 (3.2 g) in CH_2Cl_2 at 25 °C (36 h) to afford 215 mg (313 mg theoretical, 70%; 45% overall yield from **5**) of **6d** as a white solid: ^1H NMR δ 9.12 (s, 1 H, C1-H), 8.48 (d, 1 H, J = 6 Hz, C3-H), 7.86 (d, 1 H, J = 6 Hz, C4-H), 4.08, 4.04, 3.99 (three s, 3 H each, three $ArOCH_3$), 2.69 (s, 3 H, $COCH_3$); IR ($CHCl_3$) ν_{max} 3000, 2960, 2870, 1690 (C=O), 1605, 1580, 1485, 1460, 1420, 1395, 1370, 1355, 1340, 1300, 1240, 1200, 1182, 1140, 1100, 1060, 1030, 1002, 980, 950, 930, 895, 835 cm^{-1}; mass spectrum, m/e (relative intensity) 261 (M^+, 70), 246 ($-CH_3$, 100), 216 (12), 202 (10), 188 (10), 145 (11), 117 (11), 89 (10); high-resolution mass spectrum, m/e 261.0983 ($C_{14}H_{15}NO_4$ requires 261.1000).

8-Methyl-5,6,7-trimethoxyisoquinoline (6e) (Table I): ^1H NMR δ 9.05 (s, 1 H, C1-H), 8.45 (d, 1 H, J = 6 Hz, C3-H), 7.80 (d, 1 H, J = 6 Hz, C4-H), 4.08, 4.04, 3.98 (three s, 3 H each, three $ArOCH_3$), 2.70 (s, 3 H, $ArCH_3$); IR (film) ν_{max} 3020, 2960, 2875, 1615, 1585, 1485, 1460, 1420, 1395, 1375, 1350, 1290, 1240, 1200, 1140, 1115, 1080, 1060, 1025, 1005, 980, 940, 895, 830 cm^{-1}; mass spectrum, m/e (relative intensity) 233 (M^+, 100), 218 ($-CH_3$, 49), 190 (23), 175 (36), 146 (17), 133 (13), 104 (21); high-resolution mass spectrum, m/e 233.1044 ($C_{13}H_{15}NO_3$ requires 233.1051).

Method B: 8-Allyl-5,6,7-trimethoxyisoquinoline (6f). A stirred solution of benzenethiol (0.25 mmol, 26 μL) in 2 mL dry THF under argon at 0 °C was treated with *n*-butyllithium (0.16 mL of 1.66 M, 0.25 mmol). After 10 min at 0 °C the clear solution was transferred to a slurry of cuprous iodide (47 mg, 0.25 mmol) in 3 mL of dry THF under argon at −78 °C. The resulting suspension was stirred at 0 °C for 10 min to yield a clear solution of cuprous thiophenoxide.

A stirred solution of **5** (75 mg, 0.25 mmol) in 2 mL of dry THF under argon at −78 °C was treated with *n*-butyllithium (0.16 mL of 1.66 M, 0.25 mmol) and maintained at −78 °C for 25 min before addition of the cuprous thiophenoxide solution. The reaction mixture was stirred at −78 °C for 30 min, treated with allyl bromide (26 μL, 1.2 equiv, 0.30 mmol), and stirred at −78 °C for an additional 2 h. After the reaction had warmed to 25 °C, 2 mL of saturated aqueous ammonium chloride was added. The reaction mixture was poured onto saturated ammonium chloride (ammonium hydroxide, pH 8.5) and extracted with ethyl acetate (2 × 10 mL) and methylene chloride (1 × 5 mL). The combined extracts were washed (saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 25% ethyl acetate–hexane eluant) afforded 45 mg (65 mg theoretical, 72%) of **6f** as a colorless oil: ^1H NMR δ 9.30 (s, 1 H, C1-H), 8.45 (d, 1 H, J = 6 Hz, C3-H), 7.86 (d, 1 H, J = 6 Hz, C4-H), 6.0 (br m, 1 H, $CH_2CH{=}CH_2$), 5.05 (d, rough q, 1 H, J = 9 Hz, J = 2 Hz,

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$CH_2CH{=}CHH$), 4.96 (d, rough q, 1 H, J = 18 Hz, J = 2 Hz, $CH_2CH{=}CHH$), 4.04, 4.03, 3.92 (three s, 3 H each, three $ArOCH_3$), 4.0 (m, 2 H, $CH_2CH{=}CH_2$); IR (film) ν_{max} 3075, 2998, 2977, 2938, 2857, 1611, 1584, 1487, 1458, 1420, 1392, 1369, 1348, 1248, 1198, 1113, 1049, 1019, 984, 681 cm^{-1}; mass spectrum, m/e (relative intensity) 259 (M^+, 100), 244 ($-CH_3$, 16), 228 (11), 213 (16), 212 (26), 197 (18), 184 (10), 169 (11), 130 (10), 103 (10); high-resolution mass spectrum, m/e 259.1192 ($C_{15}H_{17}O_3N$ requires 259.1207).

Methyl 2-(5,6,7-Trimethoxy-8-isoquinolyl)acetate (6g). A stirred solution of 2-(trimethylsilyl)-1,3-dithiane[20] (0.27 mL, 1.41 mmol) in 10 mL dry THF at 0 °C under argon was treated with n-butyllithium (0.85 mL of 1.66 M, 1.41 mmol). The reaction was stirred at 0 °C for 15 min and allowed to warm to 25 °C over 5 min before dropwise addition of a solution of **6b** (349 mg, 1.41 mmol) in 10 mL dry THF. After 17 h at 25 °C the reaction mixture was treated with 2 mL of saturated ammonium chloride, poured onto water (30 mL), and extracted with ethyl acetate (2×) and methylene chloride (1×). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. MPLC (SiO_2, 1.5 × 25 cm, 4:1:1 CH_2Cl_2:EtOAc:hexane eluant) afforded 377 mg (492 mg theoretical, 77%) of **6k** as a yellow oil and 31 mg (9%) of recovered **6b**. For **6k**: ^1H NMR δ 9.16 (s, 1 H, C1-H), 8.41 (d, 1 H, J = 6 Hz, C3-H), 7.80 (d, 1 H, J = 6 Hz, C4-H), 6.95 (s, 1 H, $C{=}CH$), 4.05, 4.04, 3.87 (three s, 3 H each, three $ArOCH_3$), 3.05, 2.84 (two t, 4 H, J = 7 Hz, $SCH_2CH_2CH_2S$), 2.16 (p, 2 H, J = 7 Hz, $SCH_2CH_2CH_2S$).

A solution of **6k** (374 mg, 1.07 mmol) and mecuric chloride (580 mg, 2.14 mmol, 2 equiv) in 40 mL of 9:1 methanol:water was warmed at reflux under nitrogen (85 °C bath temperature) for 24 h. The white precipitate was filtered, washed with ethyl acetate (2×), methylene chloride (2×), and saturated ammonium chloride (2×). The combined filtrate and washes were poured onto saturated ammonium chloride and extracted with methylene chloride (5 × 30 mL), and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in 50 mL of methylene chloride, washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. MPLC (1.5 × 25 cm, 50% EtOAc–hexane eluant) afforded 255 mg (311 mg theoretical, 82%) of **6g** as a colorless oil: ^1H NMR δ 9.18 (s, 1 H, C1-H), 8.41 (d, 1 H, J = 6 Hz, C3-H), 7.80 (d, 1 H, J = 6 Hz, C4-H), 4.15 (s, 2 H, CH_2CO_2), 4.04 (s, 6 H, two $ArOCH_3$), 3.95 (s, 3 H, $ArOCH_3$), 3.70 (s, 3 H, CO_2CH_3); IR (film) ν_{max} 3025, 2975, 2870, 1740 (C=O), 1615, 1585, 1490, 1462, 1400, 1375, 1352, 1340, 1250, 1202, 1175, 1120, 1060, 1022, 985, 960, 940, 900, 835 cm^{-1}; mass spectrum, m/e (relative intensity) 291 (M^+, 100), 276 ($-CH_3$, 8), 233 ($-CO_2CH_3$, 97), 217 (23), 202 (17), 187 (17), 174 (10), 131 (16), 103 (19); high-resolution mass spectrum, m/e 291.1105 ($C_{15}H_{17}O_5N$ requires 291.1106).

Methyl 2-(*N*-Tosyl-1-cyano-1,2-dihydro-5,6,7-trimethoxy-8-isoquinolyl)acetate (7). p-Toluenesulfonyl chloride (287 mg, 1.5 mmol, 1.5 equiv) was added to a vigorously stirred solution of **6g** (295 mg, 1.0 mmol) and potassium cyanide (195 mg, 3 mmol, 3 equiv.) in 20 mL of 1:1 methylene chloride:water, and the reaction mixture was stirred at 25 °C for ca. 16 h. The reaction mixture was poured onto water (20 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. MPLC (1.5 × 25 cm, 25% EtOAc–hexane eluant) afforded 399 mg (477 mg theoretical, 84%) of **7** as a colorless oil: ^1H NMR δ 7.72 (d, 2 H, J = 8 Hz, Ar H), 7.25 (d, 2 H, J = 8 Hz, Ar H), 6.65 (d, 1 H, J = 7 Hz, $CH{=}CHN$), 6.40 (d, 1 H, J = 7 Hz, $CH{=}CHN$), 6.36 (d, 1 H, J = 1 Hz, CHCN), 3.88, 3.82, 3.75 (three s, 6 H, 3 H and 3 H, respectively; three $ArOCH_3$, CO_2CH_3), 2.40 (s, 3 H, $ArCH_3$); IR (film) ν_{max} 3000, 2970, 1735 (C=O), 1625, 1595, 1468, 1420, 1395, 1370, 1338, 1245, 1190, 1170, 1105, 1030, 1010, 980, 710, 660 cm^{-1}.

Methyl 8-Amino-4,5,6-trimethoxycyclopentadieno[2,1,5-*ij*]isoquinoline-7-carboxylate (9). A stirred solution of **7** (399 mg, 0.85 mmol) in 15 mL dry THF under nitrogen was treated with potassium *tert*-butoxide (1.96 mL of a 0.95 M solution in *tert*-butyl alcohol, 2.6 mmol). The resulting purple solution was stirred at 25 °C for 6 h before the addition of 2 mL of aqueous saturated ammonium chloride. The red mixture was poured onto 30 mL of saturated ammonium chloride and extracted with ethyl acetate (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. MPLC (1.5 × 25 cm, 1:1:1 CH_2Cl_2:EtOAc:hexane eluant) afforded 261 mg (267 mg theoretical, 98%) of **9** as a crimson solid. A sample of **9** crystallized from benzene as crimson needles: mp 155–156 °C; ^1H NMR δ 8.58 (d, 1 H, J = 6 Hz, C2-H), 7.75 (d, 1 H, J = 6 Hz, C3-H), 6.9 (br m, 2 H, NH_2), 4.05, 4.01, 3.96, 3.94 (four s, 3 H each, three $ArOCH_3$, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3510, 3375, 1665, 1625, 1600, 1585, 1505, 1487, 1460, 1418, 1380, 1300, 1140, 1120, 1000 cm^{-1}; mass spectrum, m/e (relative intensity) 316 (M^+, 71), 301 ($-CH_3$, 6), 285 (16), 284 ($-CH_3OH$, 61), 270 (18), 269 (base, 100), 254 (10), 226 (11), 183 (13), 142 (11).

Anal. Calcd for $C_{16}H_{16}O_5N_2$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.68; H, 5.20; N, 8.88.

8-Keto-4,5,6-trimethoxycyclopenteno[1,2,3-*ij*]isoquinoline (4). A purple solution of **9** (190 mg, 0.60 mmol) in 20 mL of 9:1 dioxane:10% aqueous HCl was warmed at 100–105 °C under nitrogen with vigorous stirring for 30 min. The yellow reaction mixture was cooled to 25 °C, poured onto 5% sodium bicarbonate, and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc–hexane eluant) afforded 101 mg (155 mg theoretical, 65%) of pure **4** as a yellow solid. Recyrstallization of a small sample of **4** from ethanol gave fine yellow needles: mp 124–125 °C; ^1H NMR δ 8.75 (d, 1 H, J = 6 Hz, C2-H), 7.84 (d, 1 H, J = 6 Hz, C3-H), 4.18 (s, 2 H, $CH_2C{=}O$), 4.11, 4.05, 4.01 (three s, 3 H each, three $ArOCH_3$); IR ($CHCl_3$) ν_{max} 3025, 2970, 2870, 1730 (C=O), 1600, 1587, 1490, 1470, 1418, 1385, 1360, 1335, 1285, 1220, 1200, 1135, 1110, 1070, 1035, 1000, 950, 845 cm^{-1}; mass spectrum, m/e (relative intensity) 259 (M^+, 100), 244 ($-CH_3$, 33), 216 (41), 201 (15), 158 (20), 130 (16), 101 (27); high-resolution mass spectrum, m/e 259.0827 ($C_{14}H_{13}NO_4$ requires 259.0844).

3-Carbomethoxy-2-pyrone 10. A solution of ketone **4** (54 mg, 0.208 mmol) in 7 mL of dry THF was added dropwise to a stirred solution of freshly generated lithium diisopropylamide (0.23 mmol, 1.1 equiv) in 8 mL of THF at −78 °C under argon, and the resulting dark purple solution was stirred at −78 °C for 45 min. The reaction mixture was then allowed to warm to 0 °C, and dimethyl (methoxymethylene)malonate (38.3 mg, 0.22 mmol, 1.05 equiv) in 5 mL dry THF was added. The red reaction mixture was stirred at 0 °C for 45 min, treated with 2 mL saturated ammonium chloride, poured onto water, and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude intermediate, a yellow-orange solid, was dissolved in 10 mL of toluene and treated with ca. 5 mg of p-toluenesulfonic acid. The reaction was warmed at reflux with azeotropic removal of methanol (bath temperature at 130 °C) for 2 h. Additional p-toluenesulfonic acid (ca. 5 mg) was added twice, and the reaction was refluxed for an additional 2 h, 1 h, respectively until formation of **10** was complete. The cooled reaction mixture was poured onto 5% $NaHCO_3$ (20 mL) and extracted with methylene chloride (3 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. The orange solid was triturated with benzene and filtered, and the orange-brown filter cake was washed with cold benzene, Et_2O, and hexane to afford 47 mg (77 mg theoretical, 62%) of **10** as burnt orange needles. Chromatography of 22.5 mg of the crude **10** (SiO_2, 80% EtOAc–CH_2Cl_2 eluant) afforded 18.6 mg pure pyrone[21] **10** (83% recovery): mp 202–204 °C dec (benzene, orange prisms); ^1H NMR δ 8.78 (d, 1 H, J = 6 Hz, C3-H), 8.76 (s, 1 H, pyrone CH), 7.80 (d, 1 H, J = 6 Hz, C4-H), 4.24, 4.16, 4.03, 3.97 (four s, 3 H each, three $ArOCH_3$, CO_2CH_3); IR (KBr) ν_{max} 2952, 2924, 1771 (C=O), 1748 (C=O), 1526, 1476, 1466, 1447, 1412, 1364, 1339, 1294, 1269, 1194, 1155, 1100, 1016 cm^{-1}; mass spectrum, m/e (relative intensity) 369 (M^+, 100), 355 (11), 354 ($-CH_3$, 52), 294 (15), 240 (11), 212 (10), 140 (20), 124 (25); high-resolution mass spectrum, m/e 369.0856 ($C_{19}H_{15}NO_7$ requires m/e 369.0847).

Methyl 4,5,6,9-Tetramethoxyindeno[1,2,3-*ij*]isoquinoline-8-carboxylate (11). A solution of pyrone **10** (24.5 mg, 0.066 mmol) and 1,1-dimethoxyethylene[15] (61 μL, 8 equiv) in 0.8 mL of dry mesitylene under argon was warmed at 120 °C in a sealed vessel for 5 h. PCTLC (SiO_2, 90% EtOAc–CH_2Cl_2 eluant)

(20) 2-(Trimethylsilyl)-1,3-dithiane is commercially available from Aldrich Chemical Company.

(21) The 3-carbomethoxy-2-pyrone **10** is not completely stable to chromatography on silica gel.

afforded 21 mg (25.3 mg theoretical, 83%) of **11** as a yellow solid: mp 133–134 °C (methanol–water, gold needles): ^{1}H NMR δ 8.63 (d, 1 H, J = 6 Hz, C2-H), 8.30 (s, 1 H, C7-H), 7.78 (s, 1 H, C10-H), 7.70 (d, 1 H, J = 6 Hz, C3-H), 4.16, 4.12, 4.05, 3.96 (four s; 3 H, 3 H, 6 H, and 3 H, respectively; four $ArOCH_3$, CO_2CH_3); IR (KBr) 2948, 2926, 1734, 1624, 1466, 1435, 1410, 1389, 1368, 1240, 1190, 1150, 1100, 1071, 1011 cm^{-1}; mass spectrum, m/e (relative intensity) 381 (M^+, 100), 367 (12), 366 (–CH_3, 53), 280 (16), 264 (12), 252 (17); high-resolution mass spectrum, m/e 381.1218 ($C_{21}H_{19}O_6N$ requires 381.1211).

Rufescine (1). A solution of **11** (4 mg, 10.5 μmol) in 0.5 mL THF was treated with lithium hydroxide hydrate (1 mg) and 2 drops of water, and the resulting mixture was warmed at 80 °C for 16 h. The reaction solution was neutralized to pH 5 and extracted with ethyl acetate (3 × 2 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the crude carboxylic acid: ^{1}H NMR δ 8.69 (s, 1 H, C7-H), 8.64 (d, 1 H, J = 6 Hz, C2-H), 7.86 (s, 1 H, C10-H), 7.80 (d, 1 H, J = 6 Hz, C3-H), 4.21, 4.19, 4.13, 4.05 (four s, 3 H each, four $ArOCH_3$); IR ($CHCl_3$) ν_{max} 3320, 2970, 1735, 1625, 1590, 1470, 1440, 1400, 1370, 1300, 1235, 1220, 1150, 1115, 1095, 1075, 1060, 1015, 960 cm^{-1}.

A solution of the crude carboxylic acid in 0.2 mL of dry quinoline was treated with bis[(pentafluorophenyl)copper]·dioxane[16] (ca. 1 mg) under argon and was warmed at 225 °C for 25 min. The mixture was cooled to 25 °C, treated with an equal volume of 5% HCl (pH 2), and extracted into chloroform (6 × 1 mL). The combined extracts were washed with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 1:1:1 CH_2Cl_2:EtOAc:hexane eluant) afforded 1.6 mg (3.4 mg theoretical, 47%) of **1** as a yellow solid: mp 91–92 °C (lit.[2b] mp 88–90 °C); ^{1}H NMR δ 8.58 (d, 1 H, J = 6 Hz, C2-H), 7.82 (d, 1 H, J = 8 Hz, C8-H), 7.64 (d, 1 H, J = 6 Hz, C3-H), 7.68 (d, 1 H, J = 2 Hz, C10-H), 6.95 (dd, 1 H, J = 8 Hz, 2 Hz, C7-H), 4.12, 4.10, 4.04, 3.92 (four s, 3 H each, four $ArOCH_3$); IR ($CHCl_3$) ν_{max} 2960, 1615, 1590, 1480, 1465, 1400, 1380, 1290, 1240, 1160, 1125, 1095, 1075, 1020, 1005, 970, 835 cm^{-1}; mass spectrum, m/e (relative intensity) 323 (M^+, 100), 309 (13), 308 (–CH_3, 58), 293 (20), 278 (12), 265 (25), 250 (36), 235 (10), 222 (36), 207 (11), 194 (31), 179 (15), 151 (21), 111 (19); high-resolution mass spectrum, m/e 323.1159 ($C_{19}H_{17}O_4N$ requires 323.1157).

Methyl 4,5,6,9,10-Pentamethoxyindeno[1,2,3-*ij*]isoquinoline-8-carboxylate (12). Pyrone **10** (21.85 mg, 0.059 mmol) and 1,1,2-trimethoxyethylene[17] (0.25 mL, 10 equiv) in 0.3 mL of dry mesitylene under argon was warmed at 150 °C in a sealed vial for 5 h. The crude reaction was concentrated under vacuum (16 h), redissolved in toluene (1 mL), and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 8.8 μL, 1 equiv). The dark red solution was warmed at 100 °C under nitrogen for 15 min until the color had changed to yellow. The reaction mixture was cooled to 25 °C and chromatography (SiO_2, 50% EtOAc:hexane eluant) afforded 21.7 mg (24 mg theoretical, 89%) of **12** as a yellow solid: mp 112–114 °C (methanol–water, yellow needles); ^{1}H NMR δ 8.73 (d, 1 H, J = 6 Hz, C2-H), 8.05 (s, 1 H, C7-H), 7.67 (d, 1 H, J = 6 Hz, C3-H), 4.20, 4.16, 4.13, 4.04, 3.98 (five s, 3 H, 3 H, 3 H, 6 H, 3 H, respectively; five $ArOCH_3$, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3005, 2950, 1725, 1585, 1480, 1460, 1445, 1420, 1400, 1372, 1360, 1295, 1240, 1218, 1145, 1120, 1025, 1010 cm^{-1}; mass spectrum, m/e (relative intensity) 411 (M^+, 53), 410 (31), 397 (12), 396 (–CH_3, 39), 382 (80), 364 (30), 352 (25), 348 (18), 336 (14), 334 (19), 322 (21); high-resolution mass spectrum, m/e 411.1320 ($C_{22}H_{21}NO_7$ requies 411.1317).

Under identical conditions 12.45 mg of **10** afforded 13.6 mg (13.9 mg theoretical, 98%) of **12**.

Imeluteine (3). Following the procedure for the preparation of **1**, **12** (19.7 mg, 0.048 mmol) in 1 mL of dry THF and 10 drops water was treated with $LiOH·H_2O$ (10 mg), and the solution was warmed at 70 °C for 20 h to afford 18.1 mg (19.0 mg theoretical, 95%) of the carboxylic acid: ^{1}H NMR δ 8.76 (d, 1 H, J = 6 Hz, C2-H), 8.46 (s, 1 H, C7-H), 7.74 (d, 1 H, J = 6 Hz, C3-H), 4.25, 4.24, 4.19, 4.15, 4.04 (five s, 3 H each, five $ArOCH_3$).

A solution of the crude carboxylic acid (4.2 mg, 10.6 μmol) in 1 mL of 1,3,5-triisopropylbenzene in the presence of $(CuC_6F_5)_2$·dioxane[16] (1 equiv, 5.3 μmol, 66 μL of 0.08 M in quinoline) was warmed at 220 °C under argon for 35 min. The mixture was cooled to 25 °C, treated with 1 mL of saturated ammonium chloride, and extracted with ethyl acetate (3 × 1 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and passed through a plug of silica (50% EtOAc–hexane eluant). PCTLC (SiO_2, 50% EtOAc–hexane) afforded 1.9 mg (3.74 mg theoretical, 50%) of **3** was a yellow solid: mp 146–147 °C (lit.[2b] mp 146–147 °C); ^{1}H NMR δ 8.68 (d, 1 H, J = 6 Hz, C2-H), 7.62 (d, 1 H, J = 8 Hz, C8-H), 7.59 (d, 1 H, J = 6 Hz, C3-H), 6.94 (d, 1 H, J = 8 Hz, C7-H), 4.18, 4.11, 4.09, 4.03, 3.95 (five s, 3 H each, five $ArOCH_3$); IR ($CHCl_3$) 3025, 2960, 2850, 1580, 1485, 1460, 1420, 1400, 1375, 1285, 1255, 1110, 1070, 1020, 1005, 980, 820 cm^{-1}; mass spectrum, m/e (relative intensity) 353 (M^+, 61), 352 (48), 338 (23), 325 (24), 324 (base, 100), 308 (40), 307 (25), 294 (36), 263 (20), 237 (20), 169 (17), high-resolution mass spectrum, m/e 353.1265 ($C_{20}H_{19}NO_5$ requires 353.1262).

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Registry No. **1**, 38366-04-0; **3**, 38366-03-9; **4**, 91585-98-7; **5**, 81925-37-3; **6a**, 91585-93-2; **6b**, 91585-94-3; **6c**, 91585-95-4; **6d**, 91523-09-0; **6e**, 91523-07-8; **6f**, 91585-96-5; **6g**, 91523-11-4; **6j**, 91585-99-8; **7**, 91523-17-0; **9**, 91585-97-6; **10**, 91586-00-4; **11**, 91586-01-5; **11** (acid), 91586-02-6; **12**, 91586-03-7; **12** (acid), 91586-04-8; **6k**, 91817-54-8; 1,1,2-trimethoxyethylene, 77998-68-6; 2-(trimethylsilyl)-1,3-dithiane, 13411-42-2; dimethyl (methoxymethylene)malonate, 22398-14-7; 1,1-dimethoxyethylene, 922-69-0; CH_3CHO, 75-07-0; CH_2=$CHCH_2Br$, 106-95-6; CH_2=$CHCH_2I$, 556-56-9; ICH_2CN, 624-75-9; $CO(OCH_3)_2$, 616-38-6; HCO_2CH_3, 107-31-3; $HCO_2CH_2CH_3$, 109-94-4; $HCONMe_2$, 68-12-2; CH_3I, 74-88-4; $BrCH_2CO_2CH_3$, 96-32-2; $ClSiMe_3$, 75-77-4; $CH_3CO_2CH_2CH_3$, 141-78-6; CH_3COCH_3, 67-64-1.