An Oxazoline-Mediated Synthesis of the Pyrrolophenanthridine Alkaloids and Some Novel Derivatives

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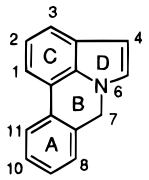
Received August 8, 1995[⊗]

An unsymmetrical biaryl coupling between the Grignard of *N*-benzyl-7-bromoindoline **25** and the appropriately substituted (*o*-methoxyaryl)oxazoline **15** leads to an intermediate biaryl which can be elaborated in one step to the 1*H*-pyrrolo[3,2,1-*de*]phenanthridine ring system. This simple two-step sequence provides general access to the pyrrolophenanthridine alkaloids **2**−**6**.

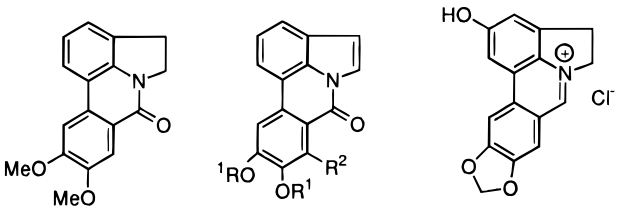
The construction of biaryl compounds, particularly unsymmetrical and axially chiral biaryls, continues to represent a challenging goal in organic synthesis.[1] Indeed, the biaryl axis constitutes an important structural feature in numerous natural products of diverse biosynthetic origin[2] including a variety of lignans,[3] tannins,[4] and alkaloids.[5] Moreover, compounds which contain a biaryl axis have proven to be an important source of therapeutic agents,[6] reagents,[7] and auxiliaries for asymmetric synthesis.[8] Chiral 2-substituted-1,1′-binapthyls, for example, have demonstrated significant utility as both catalytic and stochiometeric auxiliaries in a variety of asymmetric carbon−carbon bond-forming reactions.[8a] In addition, synthetic biaryls have been used as crown ethers,[9] chiral host molecules,[10] and molecular spacers.[11]

It is not suprising that a key step in most biaryl syntheses involves the introduction of a new carbon−carbon bond between two aromatic rings. While this is a task familiar to organic chemists,[12] many early methods which were developed to effect aryl−aryl bond formation are limited in utility. Thus, recent work in this area has focused on the development of new biaryl coupling strategies which specifically address the problems of regio- and stereoselectivity in aryl−aryl bond formation.[1] Accordingly, work in our laboratory has demonstrated that aryloxazolines are useful precursors for the construction of both constitutionally unsymmetrical and axially chiral biaryls.[13] In conjunction with these studies, we now report the application of this methodology to a general synthesis of the pyrrolophenanthridine class of alkaloids.[14,15]

The 1*H*-pyrrolo[3,2,1-*de*]phenanthridine ring system **1** constitutes the core structural framework of the pyrrolophenanthridine alkaloids. These compounds have been isolated from various species of Amaryllidaceae,[16] and representative members of this class include the alkaloids oxoassoanine (**2**) and pratosine (**3**). Moreover, since their discovery several of these alkaloids have been shown to possess significant levels of biological activity. The alkaloid hippadine (**4**), for example, was found to reversibly inhibit fertility in male rats with a remarkable decrease in both testicular weight and in DNA content.[17] Kalbretorine (**5**), was found to markedly inhibit the growth and viability of S-180 tumor cells in mice,[16c] and the betaine ungeremine (**6**) has generated a good deal of interest due to its antitumor and antileukemic activity.[18]



1, 1-H-pyrrolo[3,2,1-de]phenanthridine



2, Oxoassoanine **3**, Pratosine (R^1 = Me, R^2 =H) **6**, Ungeremine
4, Hippadine (R^1 = -CH_2-, R^2 =H)
5, Kalbretorine (R^1 = -CH_2-, R^2 =OH)

⊗ Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) For a recent review on biaryl synthesis, see: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−91.

(2) (a) Thomson, R. H. In *The Chemistry of Natural Products*; Blackie and Son: Glasgow, 1985. (b) Torssell, K. G. B. In *Natural Product Chemistry*; Wiley: Chichester, 1983.

(3) Whiting, D. A. *Nat. Prod. Rep.* **1987**, 499.

(4) *Plant polyphenols: Synthesis, Properties, Significance*; Hemingway, R. W., Lakes, P. E., Eds.; Plenum: New York, 1992.

(5) Cordell, G. A. In *Introduction to Alkaloids, A Biogenetic Approach*; Wiley: New York, 1981.

(6) For leading references and examples, see: Meyers, A. I.; Nelson, T. D. *J. Org. Chem.* **1994**, *59*, 2577.

(7) For example lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB) is an important electron transfer agent used to prepare alkyllithiums; Freeman, P. K.; Hutchinson, L. L. *Tetrahedron Lett.* **1976**, 1849.

(8) For recent review of the synthetic applications of C_2-symmetric biaryls, see: (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Narasaka, K. *Synthesis* **1991**, 1. Tomioka, K. *Synthesis* **1990**, 541.

(9) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.

(10) Webber, E. *J. Mol. Graphics* **1989**, *7*, 12.

(11) Brandmeier, V.; Feigel, M.; Bremer, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 486.

(12) Sainsbury, M. M. *Tetrahedron* **1980**, *36*, 3327. See also ref 1.

(13) (a) Meyers, A. I.; Nelson, T. D. *Tetrahedron Lett.* **1994**, *35*, 3259. (b) Meyers, A. I.; Nelson, T. D. *J. Org. Chem.* **1994**, *59*, 2655. (c) Meyers, A. I.; Nelson, T. D. *Tetrahedron Lett.* **1993**, *34*, 3061. (d) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989. (e) Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853. (f) Rawson, D. J.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494. (g) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. (h) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. For applications in natural product synthesis, see: (i) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090. (j) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.

(14) For a general introduction to the amaryllidaceae alkaloids, see: (a) Martin, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 3, pp 252−369. (b) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1952; Vol. 2, Chapter 11, pp 331. (c) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 339.

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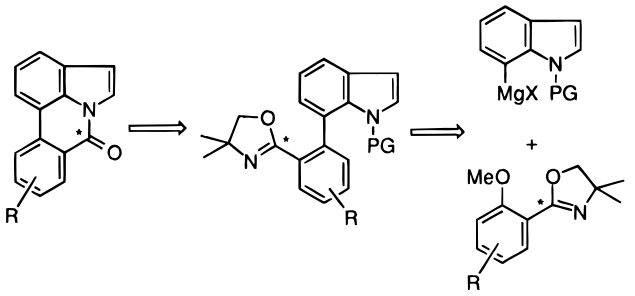
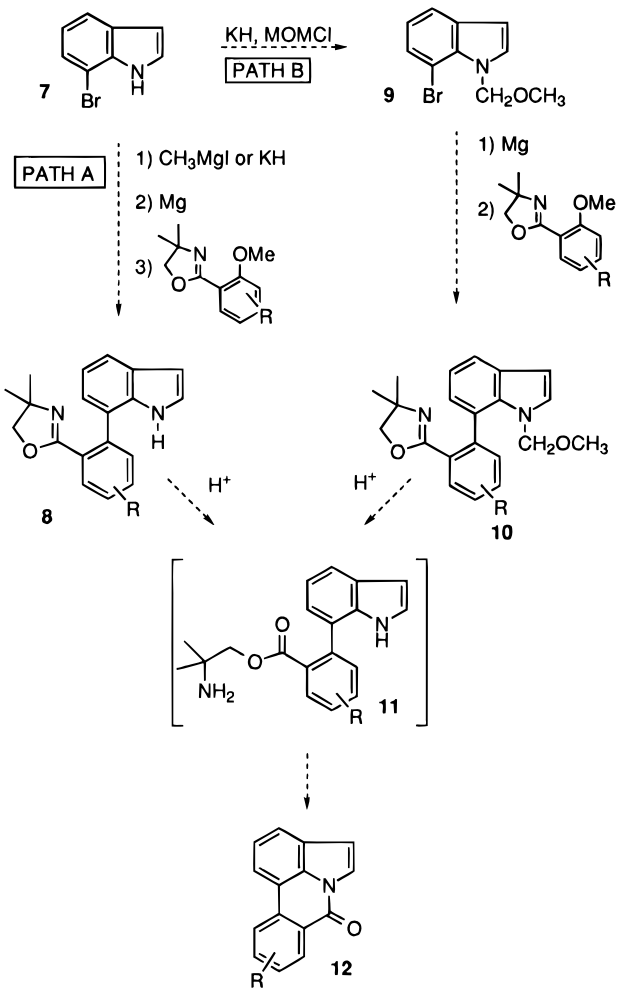
Scheme 1



Although a number of alternative synthetic routes are available for construction of the pyrrolophenanthridine ring system,[19,20] many of these are characterized by low yields and/or a lack of generality. Accordingly, we felt that a mild aryloxazoline coupling to a 7-haloindole derivative could provide an efficient and high-yielding route to this class of compounds. On the basis of a simple retrosynthetic analysis (Scheme 1), it was envisioned that an oxazoline-mediated (unsymmetrical) biaryl coupling could be employed to form the pivotal biaryl carbon−carbon bond of the pyrrolophenanthridone system. It was, therefore, envisioned that the oxazoline moiety not only would function as a directing group for the pivotal coupling step but would also contain the protected carboxyl group which would ultimately become the C-7 lactam carbonyl of the pyrrolophenanthridone ring. In view of the ready availability of a wide array of substituted aryloxazolines, this approach seemed well suited to provide access to a wide variety of pyrrolophenanthridine derivatives.

Following the above retrosynthetic sequence as a guide, two possible routes to the core pyrrolophenanthridine ring system were initially considered (Scheme 2). The synthesis outlined as path A attracted us initially because it would avoid additional protection of the bromoindole **7**. Simple transformation of **7**, to its magnesium or potassium salt, followed by Grignard formation and aryl coupling should provide a direct route to the biaryl **8**. Subsequent acid hydrolysis of the oxazoline moiety should yield the intermediate amino ester **11**, which was expected to spontaneously cyclize to the pyrrolophenanthridin-7-one(s) **12**. Previous studies by Rapoport and co-workers, however, showed that 7-lithio-*N*-metalated indoles were generally unreactive species due to their poor solubility in ethereal solvents.[21] It was, therefore, decided to pursue an oxazoline-mediated biaryl coupling via *N*-(methoxymethyl)-7-bromoindole (**9**) (path B). In this instance, the methoxymethyl ether (MOM) protecting group was selected not only for its stability to the reaction conditions but also because its small size may have a minimal steric impact on the biaryl coupling reaction. Moreover, exposure of the biaryl intermediate **10** to mild acid might result in simultaneous *N*-deprotection and hydrolysis of the oxazoline moiety, providing intermediate amino ester **11**. We were also aware that **11** may undergo a spontaneous cyclization to the desired pyrrolophenanthridin-7-one(s) **12**.

Scheme 2



A series of the potential precursors (2-aryl-4,4-dimethyl-2-oxazolines) **15** were prepared from the corre-

(15) For a preliminary communication on this work, see: Meyers, A. I.; Hutchings, R. H. *Tetrahedron Lett.* **1993**, *34*, 6185.

(16) Hippadine: (a) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochem.* **1981**, *20*, 2003. (b) El Mehgazi, A. M.; Ali, A. A.; Mesbah, M. K. *Planta Med.* **1975**, *28*, 336. Kalbretorine: (c) Ghosal, S.; Lochan, R.; Ashutosh; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825. Pratorinine, pratorimine, pratosine: (d) Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 2305. Oxoassoanine, assoanine: (e) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637. Anhydrolycorin-7-one: (f) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003. Ungeremine, criasbetaine, zefbetaine, zeflabetaine: (g) Ghosal, S.; Singh, S. K.; Srivastava, R. S. *Phytochemistry* **1986**, *25*, 1975. Vasconine: (h) Bastida, J.; Codina, C.; Viladomat, F. *J. Nat. Prod.* **1992**, *55*, 122.

(17) Chattopadhyay, S. C.; Chattopadhyay, U.; Mathur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983**, *49*, 252.

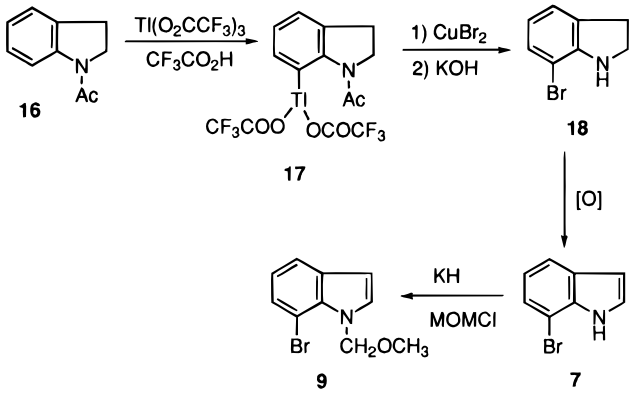
(18) Cheng, R. K. Y.; Yan, S. J.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 199.

(19) (a) Fales, H. M.; Guiffrida, L. D.; Wildman, W. C. *J. Am. Chem. Soc.* **1956**, *78*, 4145. (b) Humber, L. C.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Talyor, W. I.; Thomas, B. R.; Tsuda, Y.; Tsukamoto, K.; Uyeo, H.; Yajima, H.; Yanaihara, N. J. *J. Chem. Soc.* **1954**, 4622. (c) Cook, J. W.; Loudon, J. D.; McCloskey, P. J. *J. Chem. Soc.* **1954**, 4176. (d) Bennington, F.; Morin, R. D. *J. Org. Chem.* **1962**, *27*, 142. (e) Olson, D. R.; Wheeler, W. J.; Wells, J. N. *J. Med. Chem.* **1974**, *17*, 167. (f) Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 2305. (g) Carruthers, W.; Evans, N. *J. Chem. Soc.* **1974**, 1523. (h) Onaka, T.; Kanda, Y.; Natsume, M. *Tetrahedron Lett.* **1974**, 1179. (i) Black, D. St. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151. (j) Black, D. St. C.; Keller, P. A.; Kumar, N. *Tetrahedron Lett.* **1989**, *30*, 5807. (k) Snieckus, V.; Siddiqui, M. A. *Tetrahedron Lett.* **1990**, *31*, 1523. (l) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859. (m) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2597. (n) Castedo, L.; Guitian, E.; Perez, D. *Tetrahedron Lett.* **1992**, *33*, 2407. (o) Castedo, L.; Guitian, E.; Meiras, D. P. *Tetrahedron Lett.* **1990**, *31*, 2331. (p) Kanematsu, K.; Yasukouchi, T.; Hayakawa, K. *Tetrahedron Lett.* **1987**, *28*, 5895. (q) Prabhakar, S.; Lobo, A. M.; Marques, M. M. *J. Chem. Res.* **1987**, 167.

(20) Several syntheses appeared in the literature durring the course of this work: (a) Parnes, J. S.; Carter, D. S.; Kurz, L. J.; Flippin, L. A. *J. Org. Chem.* **1994**, *59*, 3497. (b) Iwao, M.; Takehara, H.; Obata, S.; Watanabe, M. *Heterocycles* **1994**, *38*, 1717.

(21) Rapoport, H.; Shiurba, J. F.; Moyer, M. P. *J. Org. Chem.* **1986**, *51*, 5106.

Scheme 3



sponding benzoic acids via the "one-pot" three-step procedure employed previously.[13,46]

We next proceeded toward a synthesis of the requisite MOM-protected 7-haloindole **9**. Initially, the Fischer,[22a] Batcho−Leimgruber,[22b] and Sugasawa[22c] indole syntheses were identified as potential methods for the construction of 7-substituted indoles from benzenoid precursors. A review of the literature, however, revealed that these classical methods had met with little success when applied to a synthesis of the 7-haloindoles.[23] An alternative approach to **9** involved the directed thallation−halogenation of *N*-acetyl-2,3-dihydroindole recently reported by Somei and co-workers (Scheme 3).[24] Thus, treatment of the protected indoline **16** with 1.6 equiv of thallium trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) provided the crude organothallium compound **17** as a crystalline residue. Reaction of the (crude) indoline **17** with cupric bromide in DMF followed by basic hydrolysis of the *N*-acetyl group subsequently provided the 7-bromoindoline **18** (30−40%). Air oxidation of **18** and protection as the MOM ether ultimately afforded 7-bromoindole **9** in moderate overall yield.[25,26]

It was found, however, that the bromoindole **9** was unreactive toward magnesium metal, even after sonication for several hours. It has been previously observed[27] that organohalides which contain ether, hydroxy, amino, and other functional groups can form an insoluble coating on the magnesium surface during their Grignard preparation. Thus, such compounds may appear inert toward Grignard formation under standard conditions. In these instances, the method of entrainment or continuous activation has proven to be a highly effective method for the preparation of "inert" organomagnesium halides.[28,29] It was found that addition of 1,2-dibromotetrafluoroethane, over a period of 60 min, to a mixture of **9** (THF) and magnesium shot provided the desired Grignard **19** (>90% as determined by protolytic quench and GC analysis). The Grignard reagent, thus generated, was allowed to react with either the simple aryloxazoline **15a** or the (trimethoxyaryl)oxazoline **15c** (Scheme 4). After heating, the biaryl compounds **20** and **21** were clearly indicated by thin layer chromatography. Workup and silica gel chromatography subsequently provided the corresponding biaryls in good yield (60−70%).

According to the original synthetic route (Scheme 2), it was anticipated that acid hydrolysis of the the intermediate indole biaryls (**20** or **21**) would result in ring opening and cyclization to the corresponding pyrrolophenanthridones. This procedure of oxazoline removal is well precedented[30] and has previously been applied to a wide variety of aryl and alkyl systems.[31] Unfortunately, treatment of the biaryl **21** with aqueous 3 N HCl or trifluoroacetic acid resulted in complete decomposition of the starting material. Moreover, attempts to reductively cleave the oxazoline ring (methyl triflate, $NaBH_4$, oxalic acid) also led to decomposition of the biaryl **21**.

It was also observed that treatment of **21** with sodium hypochlorite (aqueous phosphate buffer), under phase transfer conditions,[32] provided a new compound whose ^{1}H NMR indicated that both the oxazoline and *N*-methoxymethyl groups were still intact. Moreover, the only significant change that was observed by ^{1}H NMR was the disappearance of the indolyl methine protons at C-1 and C-2. Further spectroscopic analysis (^{13}C NMR, infrared, and mass spectroscopy) indicated that the oxindole **22** was the sole product from this reaction (Scheme 5). The propensity of indoles to undergo oxidations are well documented in the literature,[33] and a reasonable mechanism for this transformation is presented.

On the basis of the latter result, it was clear that some modification of the indole fragment would be required in order to achieve the final deprotection−cyclization step. It was decided to pursue a biaryl coupling between an aryloxazoline and the Grignard derived from *N*-benzyl-7-bromoindoline (**25**). The resulting biaryls from this process should exhibit greater stability under the acidic conditions required for hydrolysis of the oxazoline moiety. Furthermore, 2,3-dihydroindoles (indolines) more closely resemble *N*-alkylanilines than indoles in their reactivity.[34]

The recent report by Iwao and Kuraishi[35] on 7-substituted-2,3-dihydroindoles seemed to contain the ideal solution to our indole precursors. This work was based on a selective C-7 lithiation of 1-(*tert*-butoxycarbonyl)-indoline (**23**) and offered some significant advantages (higher yields and avoiding the use of highly toxic thallium reagent) over the method of Somei previously employed. Lithiation (*sec*-BuLi, TMEDA, THF) and bromination of **23** with 1,2-dibromotetrafluoroethane indeed provided the 7-bromoindoline (**24**) in ~68% yield. Subsequent removal of the Boc group (TFA, THF, 0 °C)

(22) (a) Fischer, E. *Chem. Ber.* **1886**, *19*, 1567. (b) Sundberg, R. J. In *The Chemistry of Indoles*; Academic: New York, 1970. (c) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578.

(23) (a) Stevens, F. J.; Higginbotham, D. H. *J. Am. Chem. Soc.* **1954**, *76*, 2206. (b) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195. (c) Glennon, R. A.; Schubert, E.; Jacyno, J. M. *J. Med. Chem.* **1980**, *23*, 1222.

(24) Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146.

(25) While this work was in progress, a report appeared (Dobson, D. R.; Gilmore, J.; Long, D. *Synlett* **1992**, 79) which described the synthesis of **1** using the Bartoli procedure.[26]

(26) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.

(27) Lai, Y.-H. *Synthesis* **1981**, 585.

(28) Kharasch, M. S.; Reinmuth, O. In *Grignard Reactions of nonmetallic Substances*; Prentice-Hall: New York, 1954; Chapter 2, p 38.

(29) Grignard, V. *Compt. Rend.* **1934**, 198, 625.

(30) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 265−266.

(31) For example, see: Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.

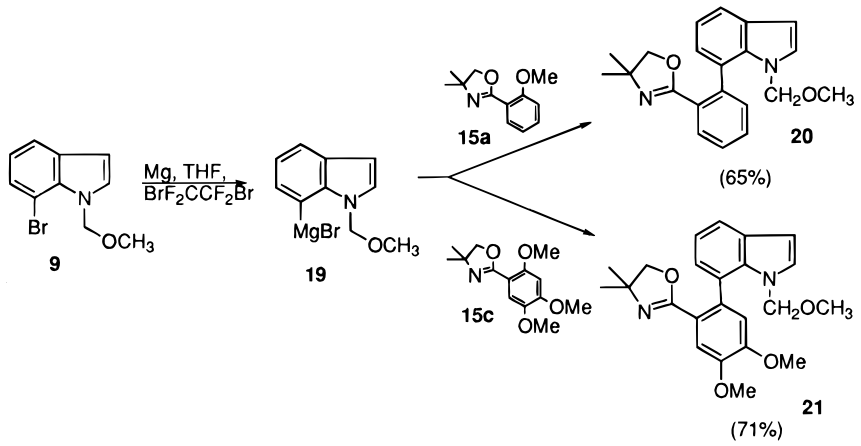
(32) Weinreb, S. M.; Levin, J. I. *Tetrahedron Lett.* **1982**, *23*, 2347.

(33) *The Acid Catalyzed Polymerization of Pyrroles and Indoles*; Smith, G. F. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. 2; p 287.

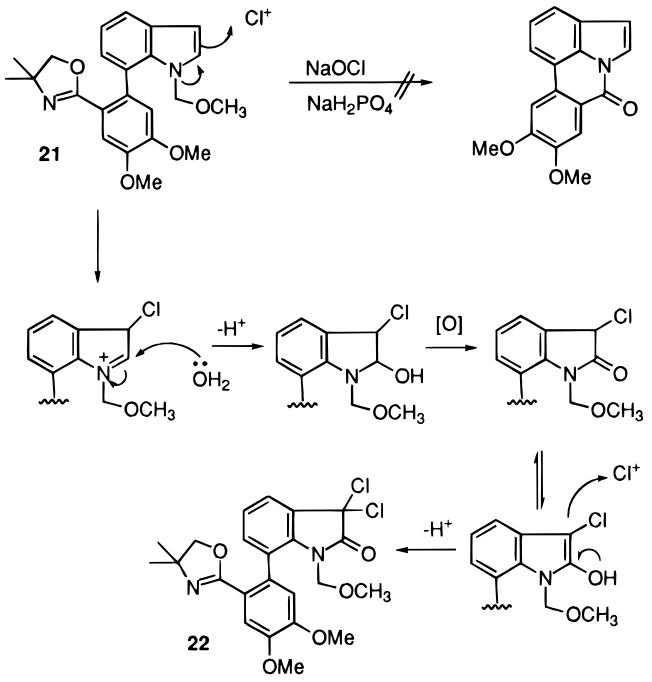
(34) Albert, A. In *Heterocyclic Chemistry; an Introduction*; 2nd ed.; Oxford University Press: New York, 1968; p 321.

(35) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1032.

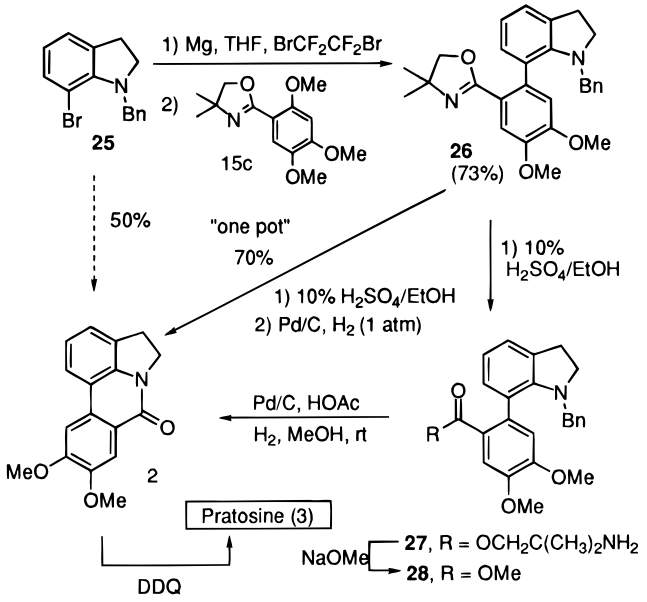
Scheme 4



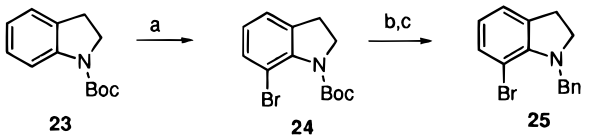
Scheme 5



Scheme 6



and treatment of the corresponding free amine with butyllithium and benzyl bromide furnished *N*-benzyl-7-bromoindoline (**25**) in good yield over three steps (60%).



a) *sec*-BuLi, TMEDA, THF, BrF_2CCF_2Br, -78 °C - 0 °C (68%);
b) CH_2Cl_2, TFA (95%); c) *n*-BuLi, THF, BnBr, -78 °C - 0 °C (99%).

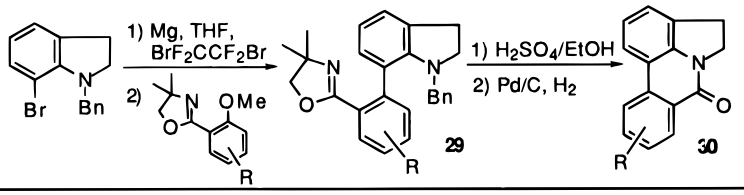
When the Grignard of **25** was coupled with the aryloxazoline **15c**, the desired biaryl **26** was obtained, but with much lower yields than expected (30−40%). Moreover, it appeared that the low yields in this reaction were due to incomplete Grignard formation as indicated by the presence of the bromoindoline **25** in the crude reaction mixture (GC). In a separate study of the Grignard formation step, we found that the entrainer (1,2-dibromotetrafluoroethane) was reacting with the intermediate organomagnesium compound and regenerating the starting material.[36] To overcome this undesirable side reaction, it was found that nearly complete Grignard formation (85−95%, determined by protolytic quench and GC) could be achieved by initiating Grignard formation with a single addition of 1,2-dibromotetrafluoroethane.

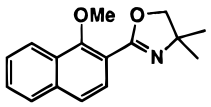
A reaction between the Grignard of **25** (generated by a single addition of dibromotetrafluoroethane) and the oxazoline **15c** subsequently provided the coupled product **26** in a 73% yield (Scheme 6). Moreover, treatment of the biaryl **26** with 10% ethanolic H_2SO_4 resulted only in hydrolysis of the oxazoline to the amino ester **27**, which could be subsequently trans esterified to the methyl ester **28** using methanolic sodium methoxide. In order to effect the final ring closure to **2**, the *N*-benzylindoline **28** was subjected to hydrogenation. The intermediate amine smoothly underwent spontaneous acylation by the adjacent carbomethoxyl group affording oxoassoanine (**2**) (56%). It was also found that a "one-pot" cyclization of the biaryl **26** would directly furnish **2** in excellent overall yield (50% from **25**). The latter alkaloid was readily transformed to pratosine (**3**) by oxidation with DDQ (55%).[16f]

With suitable conditions to effect the aryl coupling and cyclization sequence in hand, a series of simple pyrrol-

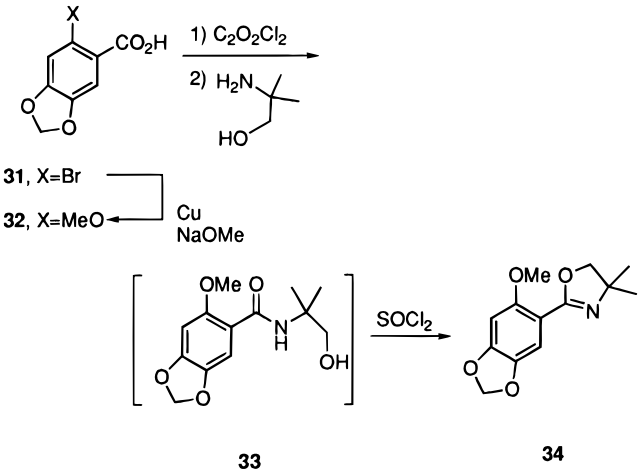
(36) 1,2-Dibromotetrafluoroethane is a well-recognized source of electrophilic bromine.

Table 1. Synthesis of the Pyrrolophenanthridone Analogs 30



Cpd.	Aryloxazoline, (R)	Biaryl **29** (% yield)	Pyrrolophenanthridone **30** (% yield)
a	**15a**, (H)	65	69
b	**15b**, (4-OMe)	74	70
c	**15d**, (3-Me)	83	82
d		78	57

Scheme 7

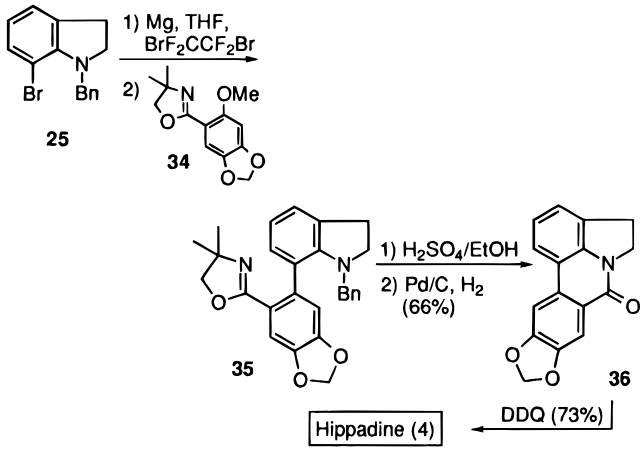


ophenanthridine analogs were synthesized in good yield from the corresponding aryloxazolines (Table 1).

In order to assess the versatility of this approach, a synthesis of the alkaloids hippadine (**4**) and kalbretorine (**5**) was next investigated. These presented an additional challenge since the requisite oxazoline precursors were not readily available from a commercial source. Furthermore, a synthesis of these compounds was of interest since they are also known to exhibit some biological activity (*vide supra*).

The aryloxazoline **34**, which could serve to reach both **4** and **5**, was prepared from piperonal by a series of steps described in Scheme 7. Bromination[37] and sodium chlorite oxidation[38] of piperonal furnished the acid **31**, which was transformed to the methoxy derivative **32** by copper-catalyzed methoxide ion displacement of bromine.[39] Conversion of the latter to the amide **33** and cyclization gave the oxazoline **34**.

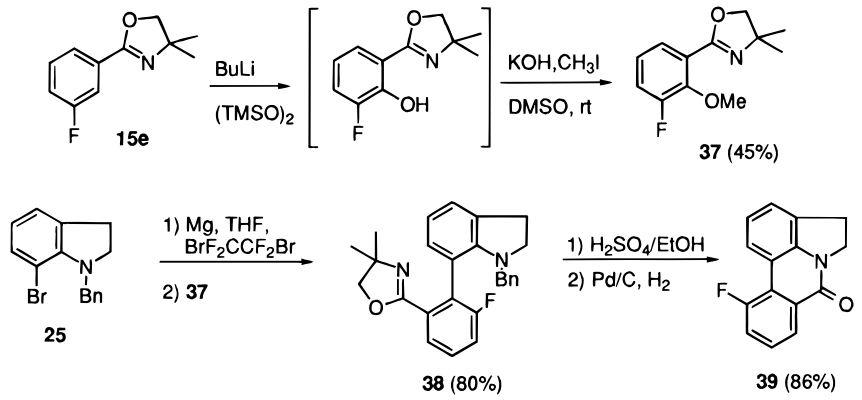
Coupling of the aryloxazoline with the magnesio derivative of **25** yielded the intermediate biaryl **35** in 68% yield. Subsequent hydrolysis and cyclization of **35** provided the pyrrolophenanthridone alkaloid anhydrolycorin-7-one (**36**), which was readily transformed to hippadine (**4**) in 73% yield by oxidation with DDQ.



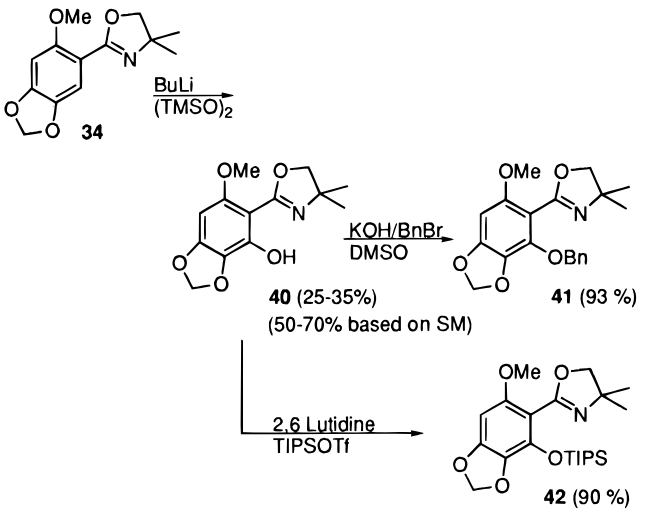
To further utilize this sequence to reach the pyrrolophenanthridone alkaloid kalbretorine (**5**), it was necessary to incorporate an additional oxygen substituent into the aryloxazoline **34**. This task represented some concern since it is not trivial to effect aromatic hydroxylations in a direct and regiospecific manner.[40] One promising solution to this problem involved the regioselective lithiation and hydroxylation of the aryloxazoline **34**[41,42] using bis(trimethylsilyl) peroxide as the electrophilic hydroxyl.[43] In a simple model study we found that the fluorooxazoline **15e** could be lithiated and hydroxylated with this reagent, affording the intermediate phenol which was transformed (KOH, CH_3I) to the *o*-(methoxyaryl)oxazoline **37** (Scheme 8). This compound was

(37) Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674.
(38) Pinnick, H. W.; Childers, W. E.; Bal, B. S. *Tetrahedron* **1981**, *37*, 2091.
(39) Mayer, W.; Fikentschen, R. *Chem. Ber.* **1958**, *91*, 1536.
(40) For a review of this subject, see: Wedemeyer, K.-F. In *Methoden der Organischen Chemie. Phenole*; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1976; Vol. IV/1C.
(41) (a) For a recent examples of aromatic hydroxylations, see: Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674. (b) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (c) For a procedure involving lithiation−boration−oxidation, see: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (d) For hydroxylation of aryl Grignards using oxodiperoxymolybdenum−pyridine−hexamethylphosphoric triamide (MoOPH), see: Lewis, N. J.; Gabhe, S. Y.; DeLaMater, M. R. *J. Org. Chem.* **1977**, *42*, 1479.

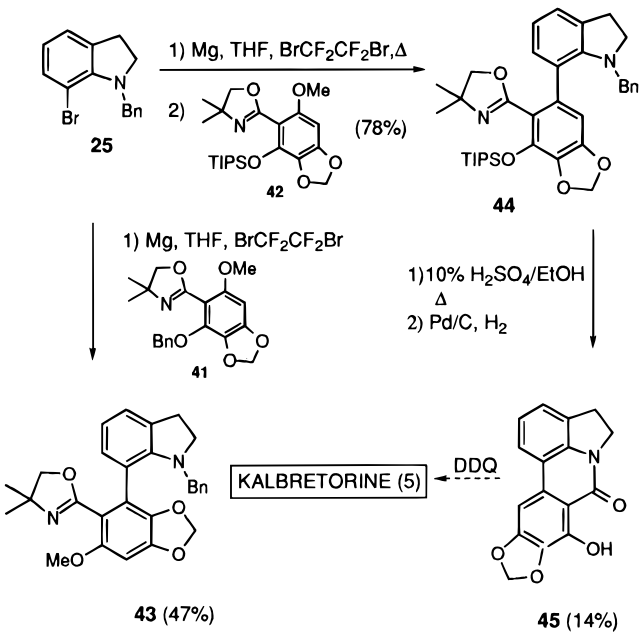
Scheme 8



Scheme 9



Scheme 10



subsequently transformed to the novel fluorine-containing pyrrolophenanthridone **39** via the biaryl **38** (68% over two steps).

The successful implementation of the latter sequence was next applied to the preparation of the aryloxazolines **41** and **42**. Thus, metalation and hydroxylation of **34** yielded the intermediate phenol **40** in 20−35% isolated yield (50−70% based on recovered starting material)[44] which was readily converted to the benzyl or silyl ether (**41** and **42**, respectively) under usual conditions (Scheme 9).

Interestingly, the coupling between the Grignard of **25** and the benzyl ether **41** resulted in regioselective displacement of only the benzyloxy group, thus providing the undesired methoxy biaryl **43** (Scheme 10). This may be the result of enhanced chelation between the benzyloxy group and the adjacent methylenedioxy substituent in **41**, thus making benzyloxy displacement more facile. It has been noted earlier[45a] that *o*-methoxy groups flanked by *m*-methoxy substituents are more readily displaced in the aryloxazolines. Thus, replacing the benzyloxy substituent with a bulkier triisopropylsilyl substituent (TIPS) appeared to have reduced[45b] the chelation of magnesio ion by the oxygens, thus allowing the *o*-methoxy substituent to be readily displaced, providing the correct biaryl, **44**. Desilylation and cyclization of **44** subsequently yielded the pyrrolophenanthridone **45** (14%),[45] which is a known precursor to the alkaloid kalbretorine (**5**).[20b]

Experimental Section

General. All NMR spectra (^{1}H, ^{13}C) were taken at 300 MHz in $CDCl_3$, CCl_4, or C_6D_6. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

Chromatography. TLC was performed on kieselgel 60, F254 aluminum plates (0.20 nm). Visualization was accomplished with ultraviolet (254 nm) or Dragendorff's reagent (on the oxazolines). Flash chromatography was performed using Amicon (200−400 mesh) silica gel or 135x catalyst support grade silica-alumina (Davidson). HPLC was carried out with a UV detector (254 nm). Solvents, ratios, flow rates are given in the individual procedures.

Reagents and Materials. Unless otherwise stated, all reagents were obtained from commercial suppliers and used without further purification. Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. THF and benzene were distilled from sodium benzophenone. Dichloromethane was distilled

(42) (a) Lithiation and hydroxylation of 4,4-dimethyl-2-(3-chlorophenyl)-2-oxazoline with molecular oxygen was previously attempted in this group, but in poor yield (20%): Meyers, A. I.; Gabel, R. A., unpublished results. (b) Lithiation and hydroxylation of 4,4-dimethyl-2-phenyl-2-oxazoline with MoOPh was reported by Avila (54%): Avila, W. B. Ph.D. Dissertation, Colorado State University, 1981.

(43) Ricci, A.; Taddei, M. *Synthesis* **1986**, 633.

(44) The undesired phenol resulting from lithiation at the 3-position was obtained in 15−20% yield.

(45) (a) Meyers, A. I.; Reuman, M. *Tetrahedron Rep.* **1985**, *41*, 837. (b) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, 3223. We thank the referee for pointing out this reference and suggestions for the regiochemistry observed.

from CaH_2. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and evacuated and then purged 3× with argon.

***N*-(Methoxymethyl)-7-bromoindole (9).** To an ice-cold suspension of oil free KH (1.2 g, 10.0 mmol) in THF (20 mL) was added 7-bromoindole[26] (1.10 g, 5.58 mmol) in THF (10 mL). The solution was stirred (15 min), TMEDA (0.926 mL, 6.13 mmol) was introduced, and stirring was continued for an additional 30 min. Chloromethyl methyl ether (465 μL, 6.13 mmol) was added, and the mixture was stirred (1 h), quenched with water, and warmed to rt. Extraction with ethyl acetate, drying (Na_2SO_4), and removal of the solvent *in vacuo* provided the crude amine which was purified by silica gel chromatography (hexanes/ethyl acetate/Et_3N 16:3:1) to give 1.14g (82%) of **9** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 1.2, 7.8 Hz, 1H), 7.41 (dd, J = 1.2, 7.8 Hz, 1H), 7.18 (d, J = 3.3 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 6.53 (d, J = 3.3 Hz, 1H), 5.80 (s, 2H), 3.28 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.0, 131.2, 127.6, 121.6, 120.6, 104.5, 102.8, 77.8, 54.8, 28.2.

General Procedure for Grignard Formation and Oxazoline−Biaryl Coupling (Entrainment Method). Synthesis of the Biaryl 20. To a suspension of the bromoindole **9** (478 mg, 2.00 mmol) and granular magnesium (96 mg, 4.00 mmol, 200 mesh) in THF (10 mL) was added 1,2-dibromotetrafluoroethane (120 μL, 1.00 mmol) in portions over the period of 1 h. The resulting Grignard reagent was added, via syringe, to a solution of the oxazoline **15a**[46] in THF (10 mL), and the reaction mixture was heated to reflux until TLC (hexanes/ethyl acetate/Et_3N, Dragendorff's stain) indicated the absence of starting material (3−12 h). The reaction was quenched with water, extracted with ethyl acetate (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give the crude biaryl which was purified by silica gel chromatography (hexanes/ethyl acetate/Et_3N 10:9:1) to give 438 mg (65%) of **20** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.2 Hz, 1H), 7.58 (dd, J = 1.2, 7.8 Hz, 1H), 7.41−7.51 (m, 3H), 7.10−7.15 (m, 2H), 6.99 (dd, J = 1.2, 7.2 Hz, 1H), 6.56 (d, J = 3.0 Hz, 1H), 4.85 (s, 2H), 3.49 (d, J = 8.0 Hz, 1H), 3.30 (d, J = 8.0 Hz, 1H), 2.78 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H); IR (thin film) 2966, 2928, 1654 cm^{-1}.

Biaryl 21. Following the procedure for **20**, the indole **9** (956 mg, 4.00 mmol) was converted to its Grignard reagent and allowed to react with the aryloxazoline **15c**[46] to give 1.18 g (71%) of the biaryl **21** as a viscous yellow oil, which was purified by silica gel chromatography (hexanes/ethyl acetate/Et_3N 10:9:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 0.9, 7.8 Hz, 1H), 7.31 (s, 1H), 6.95−7.15 (m, 4H), 6.54 (d, J = 3.3 Hz, 1H), 4.87 (ABq, J = 10.2 Hz, $\Delta\delta_{AB}$ = 16.8 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 3.46 (d, J = 8.1 Hz, 1H), 3.31 (d, J = 8.1 Hz, 1H), 2.85 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.2(s), 149.8(s), 147.9(s), 133.7(s), 132.6(s), 129.8-(s), 129.3(d), 125.4(s), 124.3(d), 121.3(s), 119.9(d), 119.5(d), 113.7(d), 111.6(d), 102.8(d), 79.0(t), 77.9(t), 66.5(s), 56.0(q), 55.8(q), 55.1(q), 27.8 (q). Further characterization was not attempted although this material was carried forward to pratosine, **5**.

Hypochlorite Oxidation of 21 to the Oxindole 22. According to the method of Weinreb,[32] the biaryl−oxazoline **21** (394 mg, 1.00 mmol) in ethyl acetate (10 mL) was treated with tetrabutylammonium bisulfate (34 mg, 0.1 mmol) and sodium hypochlorite (17 mL, 5.25%). The biphasic mixture was stirred at rt (6 h) at which time TLC (ethyl acetate) indicated the absence of **21** and the presence of a new less polar compound. The organic layer was separated, dried (Na_2SO_4), and concentrated to a crude oil which was characterized without further purification: ^{1}H NMR (300 MHz, C_6D_6) δ 7.55 (s, 1H), 7.50 (dd, J = 0.6, 6.9 Hz, 1H), 6.98 (dd, J = 1.9, 6.9 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H), 6.68 (s, 1H), 4.83 (d, J = 10.5 Hz, 1H), 4.56 (d, J = 10.5, 1H), 3.52 (d, J = 3.6 Hz, 2H), 3.42 (s, 3H), 3.38 (s, 3H), 2.85 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 170.3(s), 160.9(s), 150.9(s), 149.3(s), 138.0(s), 134.6(d), 130.7(s), 129.3,(s) 128.5(s), 127.1-(s), 123.9,(d) 123.5(d), 121.2(s), 114.5(d), 112.1(d), 78.6(t), 72.2-(t), 67.6,(s) 55.7(q), 55.5(q), 55.4(q), 28.1(q); IR (thin film) 2965, 2933, 1752, 1658 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 479 (1, M$^+$), 442 (21), 328 (8), 72 (33), 45 (100).

***N*-Benzyl-7-bromoindoline (25).** A solution of 7-bromoindoline[35] (1.8 g, 9.1 mmol) in THF (40 mL) was cooled to −78 °C and treated with *n*-BuLi (4.02 mL, 10.05 mmol, 2.5 M in hexanes). After 15 min benzyl bromide (1.19 mL, 10.1 mmol) was added and the mixture was allowed to warm to rt. After several hours the mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4), and concentrated to give a crude oil. Chromatography (hexanes/ethyl acetate/Et_3N 90:5:5) and Kugelrohr distillation (ot 250 °C, 0.5 mm) provided 2.6 g (99%) of **25** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.4 (m, 6H), 7.00−7.06 (m, 1H), 6.60 (dd, J = 7.2, 8.0 Hz, 1H), 4.82 (s, 2H), 3.41 (t, J = 8.8 Hz, 2H), 2.98 (t, J = 8.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.7(s), 138.9(s), 133.9(s), 132.7(d), 128.3(d), 127.8(d), 126.9(d), 123.6(d), 120.0(d), 103.4-(s), 54.6(t), 53.4(t), 28.5(t); low-resolution mass spectrum (GC−MS) m/z (rel abundance) 289:287 (M$^+$, 27:28), 206 (25), 117 (36), 91 (100). Anal. Calcd for $C_{15}H_{14}NBr$: C, 62.51; H, 4.89. Found: C, 62.60; H, 4.84.

General Procedure for Grignard Formation and Oxazoline−Biaryl Coupling (Single Addition Method). Synthesis of the Biaryl 26. A 50 mL round bottomed flask containing granular magnesium (96 mg, 4.00 mmol) was heated (110 °C) for ca. 1 h and then cooled to rt under an atmosphere of argon. *N*-Benzyl-7-bromoindoline (636 mg, 2.40 mmol) in 5 mL of THF and 1,2-dibromotetrafluoroethane (119 μL, 1.00 mmol) were introduced sequentially, and the resulting mixture was allowed to stir for 1 h (gas evolution). The Grignard reagent prepared in this manner was then transferred, via syringe, to a 50 mL two-necked round bottomed flask (equipped with a stir bar and reflux condensor) which contained a predried (NaH) solution of **15c**[46] (574 mg, 2.0 mmol) in THF (8 mL). The mixture was heated (50−60 °C) for 4−6 h during which time biaryl formation was followed by thin layer chromatography (R_f = 0.17; hexanes/ethyl acetate/Et_3N 80:15:5). When the absence of starting material was indicated by TLC, the mixture was cooled to rt, quenched with water (50 mL), and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give the crude biaryl which was purified by silica gel chromatography to give 673 mg (74%) of **26** as a light yellow glass: ^{1}H NMR (300 MHz, C_6D_6) δ 7.62 (s, 1H), 6.90−7.20 (m, 7H), 6.85 (s, 1H), 6.83 (t, J = 7.4 Hz, 1H), 4.08 (ABq, J_{AB} = 14 Hz, $\Delta\delta_{AB}$ = 50.2 Hz, 2H), 3.64 (brd, J = 7 Hz, 2H), 3.32 (s, 3H), 3.23 (s, 3H), 3.15−3.25 (brm, 1H), 2.85−2.95 (brm, 1H), 2.74 (t, J = 8.4 Hz, 2H), 1.19 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4(s), 149.8(s), 149.0(s), 147.3-(s), 138.9(s), 133.3(s), 130.5(s), 129.5(d), 127.8(d), 127.6(d), 126.4(d), 123.3(s), 123.2(d), 120.4(s), 117.7(d), 112.8(d), 112.0-(d), 79.2(t), 66.7(s), 55.8(q), 55.5(q), 55.1(t), 53.7(t), 28.4(t), 27.9-(q); IR (thin film) 1646 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 442 (M$^+$, 7), 342 (18), 266 (12), 207 (7), 178 (6), 91 (100).

Acid Hydrolysis of 26 to 27. The biaryl **26** (260 mg, 0.558 mmol) was dissolved in 10 mL of 10% H_2SO_4/ethanol (v/v) and heated to reflux overnight. After cooling to rt, the mixture was made basic with a 10% sodium hydroxide solution and extracted (2 × 20 mL) with dichloromethane. The organic layers were combined, dried (Na_2SO_4), and concentrated to the crude product which was purified by silica gel chromatography (hexanes/ethyl acetate/Et_3N 4:10:1) to give 152 mg (56%) of **27** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48, (s, 1H), 7.0−7.25 (m, 6H), 6.60−6.68 (m, 3H), 4.02 (d, J = 15 Hz, 1H), 3.87 (d, J = 15 Hz, 1H, partially obscured) 3.65 (s, 3H), 3.35−3.40 (m, 1H), 3.15 (apparent q , J = 8.7 Hz, 1H), 2.95−3.05 (m, 2H) 1.29 (br s, 1H), 0.94 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.9(s), 150.9(s), 148.5(s), 147.6(s), 138.8-(s), 134.8(s), 130.9(s), 129.7(d), 128.1(d), 127.3(d), 126.7(d) , 123.8(d), 123.7(s), 122.2(s), 117.9(d), 113.8(d), 75.2(t), 55.9(q), 55.7(q), 54.9(t), 53.9(t), 48.7(s), 28.3(t), 26.5 (q); IR (thin film) 3361, 2964, 2935, 2847, 1700, 1600 cm^{-1}; low-resolution mass

(46) Meyers, A. I.; Mihelich, E. D.; Gabel, R. *J. Org. Chem.* **1978**, *43*, 1372.

spectrum (GC−MS) *m/z* (rel abundance) 460 (M^+, 52), 280 (100), 91 (99), 72 (47).

Transesterification of 27 to 28. The biaryl **27** (50 mg, 0.108 mmol) was dissolved in 5 mL of methanol containing excess sodium methoxide and heated to reflux overnight. After cooling to rt, the mixture was quenched with water and extracted (2 × 20 mL) with dichloromethane. The organic layers were combined, dried (Na_2SO_4), and concentrated to the crude methyl ester which was purified by silica gel chromatography (hexanes/ethyl acetate/Et_3N 4:10:1) to give 24 mg (56%) of **28** as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 7.58 (s, 1H), 6.95−7.2 (m, 7H), 6.85 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 4.05 (ABq, J = 14.1 Hz, $\Delta\delta$ = 31 Hz, 2H), 3.43 (s, 3H), 3.32 (s, 1H), 3.21 (s, 3H), 2.9−3.2 (m, 2H), 2.79 (t, J = 8.0 Hz, 2H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 167.7, 152.1, 149.7, 148.6, 139.7, 135.9, 130.9, 130.3, 128.5, 128.4, 126.9, 124.7, 123.7, 123.1, 118.7, 114.4, 113.6, 55.8, 55.3, 55.1, 54.4, 51.3, 28.8; IR (thin film) 1725 cm^{-1}.

Cyclization of 28 to Oxoassoanine (2). A solution of the methyl ester **28** (24 mg, 0.06 mmol) in methanol (5 mL) containing a catalytic amount of acetic acid (0.1 mL) was hydrogenated (1 atm) in the presence of 10 mg of 10% Pd/C. After 2 h the absence of starting material was indicated by TLC (CH_2Cl_2/methanol 99:1) and the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with 3 N NaOH, dried (Na_2SO_4), and concentrated *in vacuo* to give 11 mg (66%) of the alkaloid **2** as a tan powder: mp 266−269 °C (lit.[16e] mp 260−270 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.77 (d, J = 8 Hz, 1H), 7.49 (s, 1H), 7.27 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 4.45 (apparent t, J = 8 Hz, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 3.40 (apparent t, 2H, J = 8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.62, 152.8, 149.5, 139.3, 130.8, 128.4, 123.5, 123.1, 121.3, 119.1, 116.6, 108.7, 102.9, 56.2, 56.0, 46.4, 27.3; IR (CCl_4) 1643, 1606 cm^{-1}.

General Procedure for the "One-Pot" Hydrolysis−Cyclization. Preparation of Oxoassoanine (2) from 26. The biaryl **26** (477 mg, 1.07 mmol) was dissolved in 10 mL of 10% H_2SO_4/ethanol (v/v) and heated to reflux overnight. After cooling to rt, the mixture was hydrogenated (1 atm) in the presence of 25 mg of 10% Pd/C (4 h) during which time the product precipitated. When the absence of starting material was indicated by TLC (CH_2Cl_2/methanol 99:1), the mixture was diluted with sufficient hot ethanol to redissolve the product then filtered through Celite. The filtrate was concentrated to one-quarter of its original volume, diluted with water (15 mL), neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo* to give 210 mg (70%) of the alkaloid **2** as a tan powder: mp, 268−269 °C (from EtOH). Spectral data were identical to those reported above.

Pratosine (3). According to the method of Black,[19k] a solution of oxoassoanine (**2**) (31 mg, 0.11 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (100 mg, 0.44 mmol) in benzene (50 mL) was heated to reflux for 12 h. Subsequent workup and silica gel chromatography (CH_2Cl_2) provided 17 mg (55%) of **3** as a tan powder: mp 234−235 °C (lit.[19k] mp 232−233 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 3.6 Hz, 1H), 7.93 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.70 (dd, J = 0.6, 7.5 Hz, 1H), 7.58 (s, 1H), 7.44 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 3.6 Hz, 1H), 4.10 (s, 3H), 4.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.3, 153.5, 149.5, 131.0, 129.4, 128.4, 123.8, 123.4, 122.3, 120.7, 117.9, 116.6, 110.6, 110.0, 103.6, 56.24, 56.20.

Biaryl 29a. Following the general procedure for **26**, the oxazoline **15a**[46] (450 mg, 2.19 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (540 mg, 1.87 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/Et_3N 85:10:5) provided 463 mg (65%) of the biaryl as a light yellow solid: mp 92−94 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.95 (dd, J = 1.5, 7.8Hz, 1H), 7.42 (dd, J = 1.5, 7.5 Hz, 1H), 6.80−7.20 (m, 9H), 6.78 (t, J = 7.5 Hz, 1H), 3.7−4.1 (m, 2H), 3.59 (s, 2H), 2.75−3.15 (m, 2H), 2.67 (t, J = 8.4 Hz, 2H), 1.13 (s, 6H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 162.8(s), 150.0(s), 141.0(s), 139.5(s), 131.1(s), 130.9(d), 130.3(d), 130.0(d), 129.2(s), 128.5(d), 128.3(d), 127.0(d), 126.9(d), 124.6(s), 123.8(d), 118.7(d), 79.2(t), 67.7(s), 56.4(t), 53.9(t), 28.8(t), 28.1(q); IR (thin film) 1650 cm^{-1}; low-resolution mass spectrum (GC−MS) *m/z* (rel abundance) 382 (M^+, 23), 282 (38), 219 (26), 206 (32), 91 (100), 65 (32). Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.46; H, 6.89; N, 7.28.

Biaryl 29b. Following the general procedure for **26**, the oxazoline **15b**[46] (376 mg, 1.6 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (500 mg, 1.74 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/Et_3N 80:15:5) provided 490 mg (74%) of **29b** as a light yellow glass: ^{1}H NMR (300 MHz, C_6D_6) δ 7.99 (d, J = 8.6 Hz, 1H), 7.00−7.20 (m, 8H), 6.79 (t, J = 7.4 Hz, 1H), 6.61 (dd, J = 2.7, 8.6 Hz, 1H), 4.01 (ABq, J = 11.5 Hz, $\Delta\delta_{AB}$ = 27 Hz, 2H), 3.61 (brs, 2H), 3.12 (s, 3H), 3.00−3.20 (m, 1H, partially obscured by s at 3.12), 2.80−3.00 (m, 1H), 2.70 (t, J = 8.4 Hz, 2H), 1.16 (s, 6H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 162.7(s), 161.1(s), 149.9(s), 142.9(s), 139.7(s), 132.0(d), 130.9(s), 130.2(d), 128.4(d), 128.3(d), 126.9(d), 124.7(s), 123.8(d), 121.7(s), 118.6(d), 115.8(d), 113.4(d), 79.0(t), 67.6(s), 56.4(t), 54.6(q), 54.1(t), 28.8(t), 28.2(q); IR (thin film) 1650 cm^{-1}; low-resolution mass spectrum (GC−MS) *m/z* (rel abundance) 412 (M^+, 7), 312 (17), 236 (12), 206 (14), 91 (100), 65 (20).

Biaryl 29c. Following the general procedure for **26**, the oxazoline **15d**[46] (350 mg, 1.58 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (500 mg, 1.74 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/Et_3N 18:1:1) provided 530 mg (83%) of **29c** as a light yellow glass: ^{1}H NMR (300 MHz, C_6D_6) δ 7.73 (dd, J = 2.0, 7.1 Hz, 1H), 6.90−7.20 (m, 9H), 6.75 (t, J = 7.4 Hz, 1H), 3.98 (ABq, J_{AB} = 14.1 Hz, 2H), $\Delta\delta_{AB}$ = 45.3 Hz), 3.55 (ABq, J_{AB} = 7.9 Hz, $\Delta\delta_{AB}$ = 1.5 Hz, 2H), 3.13 (dt, J = 7.4, 9.0 Hz, 1H), 2.86 (dt, J = 9.0, 10.3 Hz, 1H), 2.66 (t, J = 9.0 Hz, 2H), 2.22 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 163.0(s), 149.9(s), 140.3(s), 139.8(s), 138.0(s), 131.6(d), 130.6(s), 130.3(s), 130.0(s), 128.6(d), 128.3(d), 127.5(d), 127.3(d), 126.9(d), 123.8(d), 122.6(s), 118.4(d), 79.0(t), 67.7(s), 56.0(t), 54.3(t), 28.7(t), 28.1(q), 28.0(q), 20.6(q); IR (thin film) 1657 cm^{-1}; low-resolution mass spectrum (GC−MS) *m/z* (rel abundance) 396 (M^+, 7), 296 (13), 233 (18), 218 (12), 178 (9), 91 (100), 65 (21).

Biaryl 29d. Following the general procedure for **26**, 1-methoxy-2-naphthyloxazoline[13h] (306 mg, 1.20 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (300 mg, 1.04 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/Et_3N 85:10:5) provided 360 mg (78%) of **29d** as a light yellow solid: mp 115 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.80−7.87 (m, 4H), 7.45−7.55 (m, 2H), 7.17 (dd, J = 0.7, 7.2 Hz, 1H), 7.0−7.10 (m, 3H), 6.94 (dd, J = 0.7, 7.5 Hz, 1H), 6.75−6.82 (m, 3H), 3.82 (AB_q, J_{AB} = 7.9 Hz, $\Delta\delta_{AB}$ = 2.7 Hz, 2H), 3.54 (AB_q, J_{AB} = 13.7 Hz, $\Delta\delta_{AB}$ = 5.1 Hz, 2H), 3.15−3.25 (m, 1H), 2.95−3.15 (m, 3H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 163.8(s), 149.9(s), 138.7(s), 138.4(s), 134.0(s), 132.0(s), 130.4(d), 128.2(d), 127.9(d), 127.8(d), 127.7(d), 127.4(d), 126.8(d), 126.4(d), 126.2(s), 126.1(d), 123.7(d), 120.0(s), 117.6(d), 79.3(t), 67.2(s), 55.2(t), 53.6(t), 28.4(t), 28.0(q); IR (thin film) 1657 cm^{-1}; low-resolution mass spectrum (GC−MS) *m/z* (rel abundance) 432 (M^+, 12), 332 (19), 256 (21), 241 (12), 228 (10), 91 (100), 65 (21).

4,5-Dihydropyrrolo[3,2,1-*de*]phenanthridin-7-one (30a). Following the general procedure for **2**, cyclization of the biaryl **29a** (156 mg, 0.408 mmol) and purification by silica gel chromatography (ether/dichloromethane/Et_3N 10:5:1) provided 62 mg (69%) of the pyrrolophenanthridone **30a** as a tan solid: mp 89−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, J = 1.2, 8.1 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.69 (dt, J = 1.6, 7.2 Hz, 1H), 7.53 (dt, J = 1.2, 8.1 Hz, 1H), 7.24 (dd, J = 1.2, 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 4.37−4.42 (m, 2H), 3.34 (apparent t, J = 8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.8(s), 139.6(s), 133.6(s), 131.8(d), 130.6(s), 128.2(d), 127.6(d), 127.2(s), 124.3(d), 123.1(d), 121.9(d), 119.6(d), 116.6(s), 46.3(t), 27.1(t); IR (thin film) 1644, 1626 cm^{-1}; low-resolution mass spectrum (GC−MS) *m/z* (rel abundance) 221 (M^+, 82), 220 (100), 191 (22), 165 (15), 96 (25). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.38; H, 5.04; N, 6.23.

10-Methoxy-4,5-dihydropyrrolo[3,2,1-*de*]phenanthridin-7-one (30b). Following the general procedure for **2**, cyclization of the biaryl **29b** (350 mg, 0.850 mmol) and purification by silica gel chromatography (CH_2Cl_2/MeOH 95:5) provided 150

mg (70%) of the pyrrolophenanthridone **30b** as a tan solid: mp 217−218 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.63 (d, J = 8.9 Hz, 1H), 7.82 (dd, J = 0.8, 8.0 Hz, 1H), 7.55(d, J = 2.5 Hz, 1H), 7.31 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 2.5 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 4.37 (m, 2H), 3.96 (s, 3H), 3.38 (m, 2H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 163.0(s), 159.8(s), 140.8(s), 136.1(s), 131.4(s), 130.3(d), 124.9(d), 123.1(d), 121.4(d), 120.0(d), 116.6(s), 115.8(d), 105.1(d), 55.9(q), 46.5(t), 27.6(t); IR (CH_2Cl_2) 1645, 1604 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 251 (M^+, 87), 250 (100), 207 (39), 178 (34), 152 (30). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.27; H, 5.29.

11-Methyl-4,5-dihydropyrrolo[3,2,1-*de*]phenanthridin-7-one (30c). Following the general procedure for **2**, cyclization of the biaryl **29c** (300 mg, 0.757 mmol) and purification by silica gel chromatography (CH_2Cl_2/MeOH 97:3) provided 147 mg (82%) of the pyrrolophenanthridone **30c** as a tan solid: mp 187 °C (from MeOH); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 (dd, J = 1.3, 7.9 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.57 (dd, J = 0.8, 7.3 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.33 (dd, J = 0.8, 7.3 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.33 (dd, J = 0.8, 7.3 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.35−4.41 (m, 2H), 3.39 (apparent t, J = 8.4 Hz, 2H), 2.92 (s, 3H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 160.1(s), 148.6(s), 140.5(s), 136.2(d), 133.1(s), 131.3(s), 129.1(s), 127.4(d), 126.8(d), 124.9(d), 124.3(d), 122.9(d), 118.4(s), 46.3(t), 27.4(t), 25.7 (q); IR (thin film) 1643, 1591 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 235 (M^+, 94), 234 (100), 219 (15), 204 (13), 191 (14), 178 (9), 102 (18), 89 (16). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.44; H, 5.63.

30d. Following the general procedure for **2**, cyclization of the biaryl **29d** (200 mg, 0.46 mmol) and purification by silica gel chromatography (benzene/ethyl acetate 1:9) provided 72 mg (57%) of the pyrrolophenanthridone **30d** as a tan solid: mp 191−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90−9.00 (m, 1H), 8.51 (d, J = 8.7 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 7.90−8.00 (m, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.63 (m, 2H), 7.31 (dd, J = 1.0, 7.1 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 4.47 (m, 2H), 3.47 (apparent t, J = 8.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1(s), 140.5(s), 135.7(s), 132.1(s), 131.0(s), 129.5(s), 128.9(d), 128.4(d), 127.6(d), 126.9(d), 126.7(d), 126.0(s), 124.5(d), 124.1(d), 123.8(d), 123.1(d), 117.0(s), 46.2(t), 27.2(t); IR (thin film) 1642, 1610 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 271 (M^+, 100), 270 (75), 241 (32), 214 (11), 189 (13), 120 (12). Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.82; N, 5.16. Found: C, 83.91; H, 4.88; N, 5.10.

2-Methoxy-4,5-(methylenedioxy)benzoic Acid (32). To a stirred solution of 5.08 g (221 mmol) of Na metal dissolved in 400 mL of anhydrous methanol was added 2-bromopiperonylic acid (**31**)[47] (18.0 g, 73.7 mmol). Once the acid had dissolved, Cu powder (2.32 g, 36.5 mmol) was added and the mixture was heated at reflux for 18 h. The mixture was cooled, filtered through Celite, and concentrated to a white paste which was dissolved in 400 mL of water and acidified to pH 3 with concentrated HCl. The free acid was extracted with ethyl acetate, dried (Na_2SO_4), and concentrated to a white powder. Recrystallization (EtOH/water) provided 11.0 g (76%) of the pure acid **32** as a colorless solid: mp 152 °C (lit.[48] mp 148−149 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (brs, 1H), 7.49 (s, 1H), 6.57 (s, 1H), 5.99 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0, 155.3, 153.1, 142.5, 111.2, 110.1, 102.4, 94.2, 57.5; IR (thin film) 2500−3400 br, 1681 cm^{-1}.

4,4-Dimethyl-2-(2-methoxy-4,5-(methylenedioxy)-phenyl)-2-oxazoline (34). Following the procedure for **15a**,[46] the acid **32** (4.95 g, 25.2 mmol) provided 4.6 g (73%) of the oxazoline **34** as a colorless solid, which was recrystallized from hexanes: mp 74−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.51 (s, 1H), 5.92 (s, 2H), 4.02 (s, 2H), 3.79 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.8(s), 155.0(s), 150.5(s), 141.0(s), 110.2(d), 109.8(s), 101.6(t), 95.3(d), 78.7(t), 67.1(s), 57.2(q), 28.3(q); IR (thin film) 2966, 2888, 1638, 1505, 1485, 1430, 1263, 1194, 1032; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 249 (M^+, 71), 234 (61), 206 (55), 177 (79), 165 (100).

Biaryl 35. Following the general procedure for **26**, the oxazoline **34** (550 mg, 2.20 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (540 mg, 1.87 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/Et_3N 85:10:5) gave 540 mg (68%) of **35** as a white solid: mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.25 (m, 6H), 7.04 (dd, J = 1.1, 7.2 Hz, 1H), 6.86 (dd, J = 1.1, 7.2 Hz, 1H), 6.80 (s, 1H), 6.70 (t, J = 7.4 Hz, 1H), 5.92 (brs, 2H), 3.70−4.00 (m, 4H), 3.05−3.30 (m, 2H), 2.91 (t, J = 8.5 Hz, 2H), 1.25 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.2(s), 149.5(s), 149.1(s), 146.5(s), 139.1(s), 135.0(s), 130.9(s), 129.6(d), 128.2(d), 128.0(d), 126.6(d), 123.6(s), 123.4(d), 121.8(s), 118.1(d), 110.4(d), 109.6(d), 101.5(t), 79.4(t), 66.9(s), 55.8(t), 53.6(t), 28.5(t), 28.0(q); IR (thin film) 1648 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 426 (M^+, 11), 326 (23), 250 (29), 206 (9), 178 (13), 91 (100), 65 (24). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03 H, 6.14. Found: C, 76.00; H, 6.21.

Anhydrolycorin-7-one (36). Following the general procedure for **2**, cyclization of the biaryl **35** (380 mg, 0.89 mmol) and purification by silica gel chromatography (CH_2Cl_2/MeOH 97:3) gave 156 mg (66%) of the pyrrolophenanthridone **36** as a tan solid: mp 262−264 °C (lit.[16f] mp 260−270 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.27 (dd, J = 0.9, 7.2 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 6.11 (s, 2H), 4.45 (apparent t, J = 8.1 Hz, 2H), 3.40 (apparent t, J = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1(s), 151.5(s), 148.1(s), 139.1(s), 130.6(s), 130.3(s), 123.5(d), 122.9(d), 122.8(s), 119.1(d), 116.4(s), 106.5(d), 101.9(t), 100.6(d), 46.3(t), 27.2(t).

Hippadine (4). According to the method of Ghosal,[16a] a solution of anhydrolycorin-7-one (**36**) (49 mg, 0.184 mmol) and DDQ (125 mg, 0.550 mmol) in benzene (50 mL) was heated at reflux for 12 h. Subsequent workup and silica gel chromatography (CH_2Cl_2/ MeOH 97:3) provided 36 mg (73%) of **4** as colorless crystals: mp 217−218 °C (lit.[16a] mp 217−218 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 3.6 Hz, 1H), 7.95 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 6.14 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1, 152.5, 148.5, 131.6, 128.3, 123.9, 123.5, 122.5, 122.4, 121.3, 118.3, 116.6, 110.7, 108.0, 102.2, 101.6.

4,4-Dimethyl-2-(3-fluoro-2-methoxyphenyl)-2-oxazoline (37). A solution of (*m*-fluorophenyl)oxazoline **15e** (1.0 g, 5.18 mmol) in THF (50 mL) was cooled to −78 °C and treated with *n*-BuLi (2.36 mL, 5.4 mmol, 2.3 M in hexanes). The resulting yellow solution was maintained at −78 °C for 30 min, at which time neat bis(trimethylsilyl) peroxide[43] (1.15 g, 6.48 mmol) was added. The temperature bath was removed, and the mixture was allowed to warm to rt with stirring overnight. The deep purple solution was quenched with saturated NH_4Cl, the volatiles were removed *in vacuo*, and the crude material was dissolved in 5% HCl/MeOH (20 mL) and allowed to stir at rt (30 min). The mixture was then diluted with water (150 mL) and extracted (3 × 20 mL) with dichloromethane. The organic layers were combined, dried (Na_2SO_4), and concentrated to give the crude phenol which was directly dissolved in DMSO (10 mL) and treated with powdered KOH (1.6 g, 40 mmol) and methyl iodide (618 μL, 10 mmol). After several hours the mixture was diluted with water (300 mL) and extracted (3 × 20 mL) with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated to give the crude methoxyoxazoline. Silica gel chromatography (hexanes/ethyl acetate 9:1) provided 520 mg (45%) of the **37** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (apparent dt, J = 8.0, 1.3 Hz, 1H), 7.14 (ddd, J = 1.8, 8.0, 12 Hz, 1H), 7.00 (apparent td, J = 4.8, 8.0 Hz, 1H), 4.08 (s, 2H), 3.9 (d, J = 1.2 Hz, 3H), 1.35 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.3(s), 155.9 (d, J_{CF} = 247 Hz), 147.1 (d, J_{CF} = 13 Hz), 126.1 (d, J_{CF} = 3 Hz), 124.0 (s), 123.5 (d, J_{CF} = 8 Hz), 119.1 (d, J_{CF} = 19 Hz), 79.1 (t), 67.5 (s), 62.0 (d, J_{CF} = 4 Hz), 28.2 (q); IR (thin film) 1649 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 223 (M^+, 45), 208 (43), 180 (44), 151 (100), 137 (87), 109 (69).

(47) Dallacker, F. *Ann.* **1960**, *14*, 633.
(48) Arnold, R. T.; Bortnick, N. *J. Am. Chem. Soc.* **1945**, *67*, 1798.

Biaryl (38). Following the general procedure for **26**, the oxazoline **37** (400 mg, 1.80 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (574 mg, 2 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/ Et_3N 90:8:2) provided 580 mg (80%) of **38** as a light yellow oil: ^{1}H NMR (300 MHz, C_6D_6) δ 7.59−7.68 (m, 1H), 7.25 (brd, J = 7.2 Hz, 2H), 7.00−7.15 (m, 5H), 6.70−6.80 (m, 3H), 4.03 (ABq, J = 14.1 Hz, $\Delta\delta_{AB}$ = 23.6 Hz, 2H), 3.58 (ABq, J = 7.8 Hz, $\Delta\delta_{AB}$ = 0.3 Hz, 2H), 3.05−3.17 (m, 1H), 2.91 (apparent q, J = 9.0 Hz, 1H), 2.66 (apparent t, J = 9.0 Hz, 2H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 161.7 (d, J_{CF} = 3 Hz), 160.4 (d, J_{CF} = 245 Hz), 150.6, 139.4, 131.9 (d, J_{CF} = 3 Hz), 131.0, 130.6, 128.9 (d, J_{CF} = 18 Hz), 128.8 (d, J_{CF} = 8 Hz), 128.5, 128.3, 127.0, 125.7 (d, J_{CF} = 3 Hz), 124.4, 118.2, 117.3 (d, J_{CF} = 23 Hz), 116.3, 79.2 67.8, 55.7, 53.9, 28.6, 28.1, 28.0; IR (thin film) 1653 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 400 (M^+, 7), 300 (15), 237 (19), 224 (20), 183 (10), 91 (100), 65 (23).

11-Fluoro-4,5-dihydropyrrolo[3,2,1-*de*]phenanthridin-7-one (39). Following the general procedure for **2**, cyclization of the biaryl **38** (388 mg, 0.97 mmol) and purification by silica gel chromatography provided 200 mg (86%) of **39** as a tan powder: mp 167−169 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.29 (dd, J = 1.5, 7.8 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.40−7.60 (m, 2H), 7.34 (dd, J = 0.9, 7.5 Hz, 1H), 7.19 (t, 1H, J = 7.8 Hz), 4.36−4.41 (m, 2H), 3.39 (apparent t, J = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.6 (d, J_{CF} = 249 Hz), 158.9, 139.5, 130.4, 129.6 (d, J_{CF} = 5 Hz), 128.1 (d, J_{CF} = 9 Hz), 124.9, 124.6, 123.9 (d, J_{CF} = 32 Hz), 123.7 (d, J_{CF} = 1 Hz), 122.7 (d, J_{CF} = 11 Hz), 119.1 (d, J_{CF} = 22 Hz), 114.2 (d, J_{CF} = 3 Hz), 46.4, 27.2; IR (thin film) 1652 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 239 (M^+, 91), 238-(100), 209(14), 183(7), 105(3). Anal. Calcd for $C_{15}H_{10}NOF$: C, 75.30; H, 4.21. Found: C, 75.29; H, 4.24.

4,4-Dimethyl-2-(1-hydroxy-2-methoxy-4,5-(methylenedioxy)phenyl)-2-oxazoline (40). Following the procedure for **37**, the oxazoline **34** (2.49 g, 10.00 mmol) in THF was treated with *n*-BuLi (4.58 mL, 11.00 mmol, 2.4 M in hexanes) and bis(trimethylsilyl) peroxide[43] (2.67 mL, 15 mmol) to give, after workup and silica gel chromatography (hexanes/ethyl acetate/ benzene 70:25:5), 600 mg (23%) of **40** as light yellow needles: mp 149 °C (benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 14.49 (s, 1H), 5.90 (s, 1H), 5.37 (s, 2H), 3.54 (s, 2H), 3.68 (s, 6H), 0.98 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.5 (s), 157.0(s), 152.0(s), 147.0(s), 129.3(s), 101.5(t), 96.7(s), 85.9(d), 78.0(t), 64.2(s), 55.9(q), 27.8(q); IR (thin film) 2000−3500 (br), 1637 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 265 (M^+, 37), 193 (100), 178 (16), 150 (6).

4,4-Dimethyl-2-(1-(benzyloxy)-2-methoxy-4,5-(methylenedioxy)phenyl)-2-oxazoline (41). The phenol **40** (332 mg, 1.25 mmol) was combined with powdered KOH (200 mg, 5.00 mmol) and benzyl bromide (297 μL, 2.5 mmol) in DMSO (6 mL) and allowed to stir (8 h) at rt until TLC (hexanes/ethyl acetate/benzene) indicated the absence of starting material. The reaction mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated to give the crude material which was purified by silica gel chromatography to give 410 mg (92%) of **41** as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 7.50 (dd, J = 0.6, 8.0 Hz, 2H), 7.00−7.25 (m, 3H), 6.02 (s, 1H), 5.27 (s, 2H), 5.23 (s, 2H), 3.80 (s, 2H), 3.22 (s, 3H), 1.28 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.0(s), 154.8(s), 150.7(s), 141.8(s), 137.9(s), 131.1(s), 128.5-(d), 128.4(d), 128.0(d), 106.6(s), 101.1(t), 89.9(d), 78.6(t), 74.2-(t), 68.1(s), 56.4(q), 28.5(q); IR (thin film) 1666 cm^{-1}; low-resolution mass spectrum (GC−MS) m/z (rel abundance) 355 (M^+, 6), 194 (45), 91 (100), 65 (36).

4,4-Dimethyl-2-(1-((triisopropylsilyl)oxy)-2-methoxy-4,5-(methylenedioxy)phenyl)-2-oxazoline (42). The phenol **40** (270 mg, 1.02 mmol) was combined with 2,6-lutidine (128 μL, 1.1 mmol) and triisopropylsilyl triflate (295 μL, 1.10 mmol) in CH_2Cl_2 (5 mL). After stirring at rt (10 min), the solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (hexanes/ethyl acetate/ benzene 10:1:1) to give **42** as a colorless solid: mp 119 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 5.98 (s, 1H), 5.20 (s, 2H), 3.85 (s, 2H), 1.45 (m, 3H), 1.35 (s, 6H), 1.22 (d, J = 7.3 Hz, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1(s), 155.3(s), 149.8(s), 139.1(s), 130.8-(s), 107.4(s), 100.6(t), 89.0(d), 78.3(t), 68.2(s), 56.5(q), 28.6(q), 18.2(q), 13.9(d); IR (thin film) 1669 cm^{-1}.

Biaryl 43. Following the general procedure for **26**, the oxazoline **41** (200 mg, 0.56 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (287 mg, 1.00 mmol); workup and silica gel chromatography (hexanes/ethyl acetate/ Et_3N/benzene 10:3:1:1) provided 142 mg (47%) of **43** as a colorless foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.23 (m, 5H), 7.01(d, J = 7.2 Hz, 1H), 6.89 (d, J =7.2 Hz, 1H), 6.61 (t, J = 7.2 Hz, 1H), 6.40 (s, 1H), 5.81 (d, J = 0.6 Hz, 1H), 5.46 (d, J = 0.6 Hz, 1H), 4.35 (d, J = 15.3 Hz, 1H), 3.68−3.79 (m, 6H), 3.44 (apparent q, J = 7.5 Hz, 1H), 3.09 (apparent q, J = 8.7 Hz, 1H), 2.95 (apparent t, J = 7.5 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H).

Biaryl 44. Following the general procedure for **26**, the oxazoline **42** (421 mg, 1.00 mmol) was coupled with the Grignard of *N*-benzyl-7-bromoindoline (430 mg, 1.50 mmol); workup and silica gel chromatography (hexanes/Et_3N 19:1) provided 465 mg (78%) of **44** as a colorless foam: ^{1}H NMR (300 MHz, C_6D_6) δ 6.9−7.3 (m, 7H), 6.70 (t, J = 7.2 Hz, 1H), 6.59 (s, 1H), 5.07 (s, 2H), 4.43 (d, J = 15.0 Hz, 1H), 3.92 (d, J = 15.0 Hz, 1H), 3.70 (s, 2H), 3.15 (m, 1H), 2.83 (m, 1H), 2.64 (m, 2H), 1.41 (septet, J = 7.2 Hz, 3H), 1.19 (s, 3H, partially obscured), 1.18 (d, J = 7.2 Hz, 18H), 0.93 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 159.8(s), 150.2(s), 149.2(s), 140.2 (s), 138.6-(s), 136.7(s), 135.7(s), 131.0(s), 130.7(d), 128.7(d), 128.5(d), 128.2(d), 126.7(d), 123.8(d), 122.5(s), 118.2(s), 117.7(d), 104.6-(d), 100.7(t), 78.4(t), 68.0(s), 55.9(t), 54.1(t), 28.7(t), 28.0(q), 18.2(q), 13.9(s); IR (thin film) 1666 cm^{-1}; low-resolution mass spectrum (EI-DIP) m/z (rel abundance) 598 (M^+, 90), 555 (43), 499 (100), 422 (88).

8-Hydroxy-9,10-(methylenedioxy)-4,5-dihydropyrrolo-[3,2,1-*de*]phenanthridin-7-one (45). The biaryl **44** (380 mg, 0.635 mmol) was dissolved in 10 mL of 10% H_2SO_4/ethanol (v/v) and heated at reflux overnight. After cooling to rt, the reaction mixture was hydrogenated (1 atm) in the presence of 20 mg of 10% Pd/C (4 h). The debenzylated material was again heated to reflux, and the formation of **45** was followed by TLC ($CHCl_3$/MeOH 99:1). The reaction mixture was diluted with hot ethanol and filtered through Celite. The filtrate was concentrated to one-quarter of its original volume, diluted with water (15 mL), neutralized (pH = 7) with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo* to give a crude solid which was purified by silica gel chromatography ($CHCl_3$/MeOH 99.5:0.5) to give 24 mg (14%) of the pyrrolophenanthridone **45** as a tan solid: mp 294−295 °C (lit.[20b] mp 295 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.21 (s, 1H), 7.72 (dd, J = 8.1 Hz, 1H), 7.2−7.3 (m, 2H), 7.14 (s, 1H), 6.12 (s, 2H), 4.43 (apparent t, J = 8.4 Hz, 2H), 3.43 (apparent t, J = 8.4 Hz, 2H); low-resolution mass spectrum (GC−MS) m/z (rel abundance) 281 (M^+, 100), 252 (11), 195 (23), 167 (25).

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support of this work.

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JO951474X