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A Total Synthesis of the Pyrrolophenthridone Alkaloid Oxoassoanine

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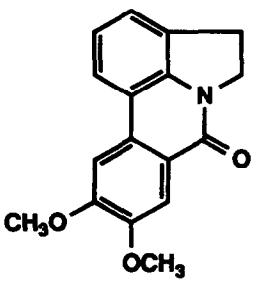
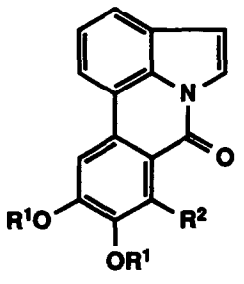
Abstract: *Coupling of the Grignard derived from N-Benzyl-7-bromoindoline with an aryl oxazoline leads to the title compound in good yield (Scheme 3). This methodology provides a versatile route to the Pyrrolophenthridone class of alkaloids.*

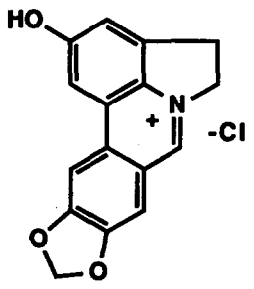
Oxoassoanine **1** and Pratosine **2a** are representative members of the Pyrrolophenthridone class of alkaloids. Isolated from various species of *Amarilidacea*,[1] several of these indole alkaloids have been shown to possess significant biological activity. The best known of these is Hippadine **2b** which was shown to reversibly inhibit fertility in male rats.[2a] Other examples include Kalbretorine **2c** which exhibits antitumor activity[2b] and a related compound Ungeremine **3** that was shown to be active against some types of carcinoma.[2c]



1



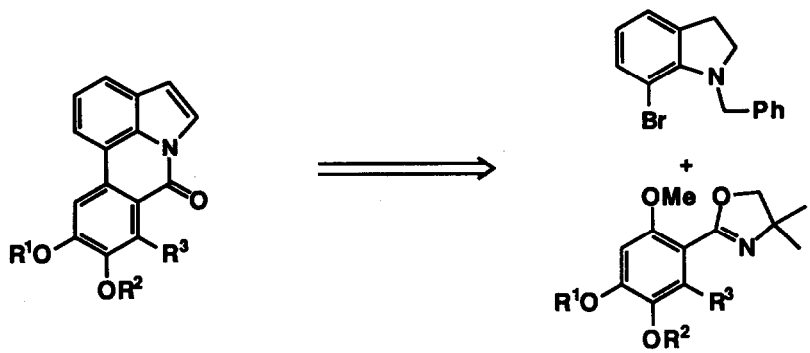
2a $R^1 = CH_3$, $R^2 = H$
2b $R^1 = -CH_2-$, $R^2 = H$
2c $R^1 = -CH_2-$, $R^2 = OH$



3

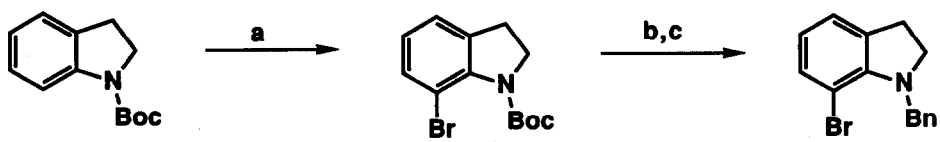
The Pyrrolophenthridones have previously been reached through a variety of synthetic strategies,[3] the most common involving formation of the aryl aryl bond through an inter or intramolecular coupling reaction. Examples of this include use of a modified Suzuki coupling,[3e]

Pschorr cyclization,[3g] and oxidative or reductive palladium catalyzed couplings.[3a,3c] Although many of these methods are chemically succinct they typically suffer from low yields (10-50%) and, in some cases, from a lack of versatility. Previous work in this group has demonstrated that aryl oxazolines can be coupled with a wide range of aryl Grignards to give the corresponding biaryls in good yield and with excellent regioselectivity.[4] Based on this precedent, we felt that a mild oxazoline coupling to a 7-bromoindole derivative could provide a versatile entry into this class of compounds (Scheme 1). We now report our initial findings which support our contention concerning this sequence.



Scheme 1

Lithiation of the Boc-protected indoline **4** and bromination with 1,2-ethylenedibromide provided the 7-bromo compound **5** in ~ 60% yield (Scheme 2).[5] It was found, however, that a 5 to 10% increase in yield could be obtained if 1,2-dibromotetrafluoroethane was used as the source of electrophilic bromine. Removal of the Boc group with trifluoroacetic acid furnished the free amine which was directly converted to the *N*-benzyl indoline **6** by butyllithium and benzyl bromide.

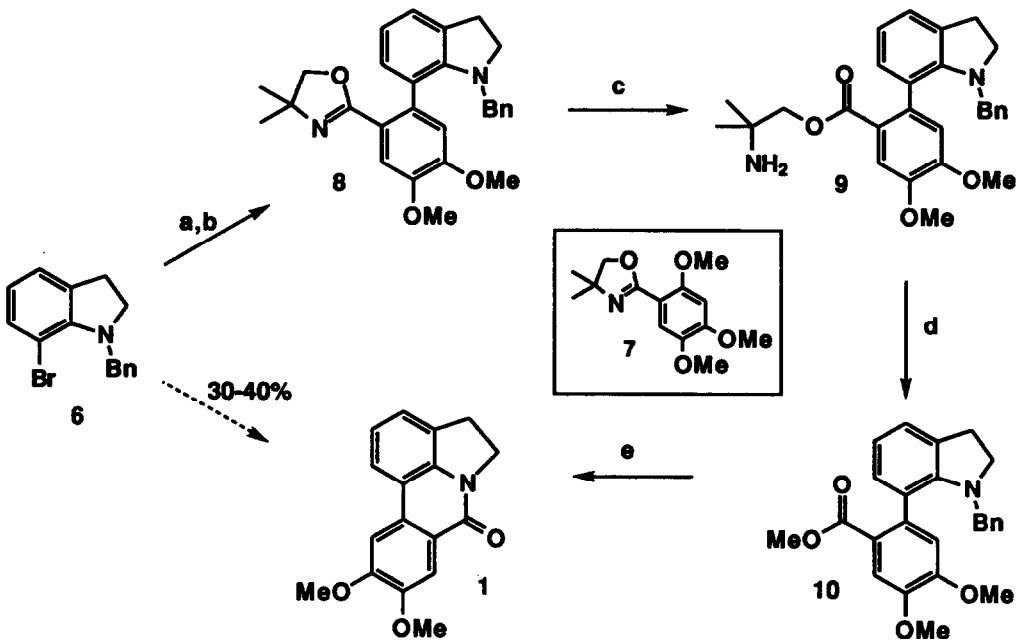


4 **5** **6**

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

Scheme 2

The corresponding Grignard of bromoindoline **6** was then generated by treating **6** with magnesium turnings in THF containing 1,2-dibromotetrafluoroethane as an entrainer.[6] Grignard formation was complete after 1 h as evidenced by VPC showing complete consumption of the starting material. Addition of the oxazoline **7** followed by heating overnight led to the coupled product **8** in a 71% yield.[7] Heating a solution of the biaryl **8** in 10% ethanolic H_2SO_4 resulted in partial hydrolysis of the oxazoline to the aminoester **9**, which was trans-esterified to the methyl ester **10** by treatment with methanolic sodium methoxide. In order to prepare for the final ring closure to **1**, the benzyl indoline **10** was hydrogenated using Pd/C and H_2 (1 atm). At this point the intermediate free amine spontaneously underwent acylation by the adjacent carbomethoxyl group affording Oxoassoanine **1**.[8] Previous work has already shown that Oxassoanine can be converted to Pratosine **2a** by oxidation with DDQ,[9] thus a route to the latter is now quite accessible. Simple substituent variation of the starting oxazoline **7** should provide access to further derivatized Pyrrolophenthridone alkaloids. Work in this area is in progress.



a) Mg, THF, BrF_2CCF_2Br, rt, 1h; b) 7, Δ, 12-15h (71%); c) 10% H_2SO_4/EtOH, Δ, 24h; d) NaOMe/MeOH, Δ, 3h; e) Pd/C, HOAc, MeOH, H_2 (1atm).

Scheme 3

Acknowledgement. The authors are grateful to the National Institutes of Health for financial support.

References and Notes

1. a) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637; b) Grundon, M. F. Natural Product Reports,1989, *6*, 85.
2. a) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003; b) Ghosal, S.; Lochan, R.; Shutosh, A.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825; c) Xu, B.; Chen, J. T.; Yang, J. L.; Chang, S. Y.; Yueh H. F.; Wang T. W.; Chou C. H. in *US-China Pharmacology Symposium*; Burns, J. J.; Tsuchitani, P. J. Eds; National Academy of Sciences: Washington D. C., 1980; p. 151.
3. a) Black, D. St. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151 and refs therein; b) Castedo, L.; Guitian, E.; Perez, D. *Tetrahedron Lett.* **1992**, *33*, 2407; c) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859; d) Castedo, L.; Guitian, E.; Meiras, D.P.*Tetrahedron Lett.* **1990**, *31*, 2331; e) Snieckus, V.; Siddiqui, M. A. *Tetrahedron Lett.* **1990**, *31*, 1523 and refs therein; f) Kanematsu, K.; Yasukouchi, T.; Hayakawa, K. *Tetrahedron Lett.* **1987**, *28*, 5895; g) Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry* **1983**, 22, 2305; h) For a recent review on these alkaloids see: Black, D. St. C. *Synlett* **1993**, 246.
4. Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.
5. Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.
6. Lai, Y.-H. *Synthesis* **1981**, 585.
7. All new compounds gave spectroscopic data in agreement with the assigned structures. **8**: ^{1}H NMR (300 MHz, C_6D_6) δ 7.63 (s, 1H); 6.9-7.2 (m, 7H); 6.82-6.87 (m, 2H); 4.32 (br d, J = 14 Hz, 1H); 3.88 (br d, J = 14 Hz, 1H); 3.64 (br d, J = 7 Hz, 2H); 3.29 (s, 3H); 3.21 (s, 3H); 3.17 (m, 1H); 2.91 (m, 1H); 2.73 (t J = 7 Hz, 2H); 1.19 (s, 6H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 163.1 (s), 151.2 (s), 149.9 (s); 148.6 (s); 139.8 (s); 134.2 (s); 130.9 (s); 130.7 (d); 128.3 (d); 126.9 (d); 124.8 (s); 123.6 (d); 121.0 (s); 118.5 (d); 114.1 (d); 113.6 (d); 79.2 (t); 67.4 (s); 56.1 (t); 55.3 (q); 55.1 (q); 54.2 (t); 28.9 (t); 28.3 (q); IR (thin film) 2964, 2930, 2847, 1650, 1602, 1512, 1402, 1359, 1206, 1045, 993 cm^{-1}. Low resolution nass spectrum (DIP-EI) *m/e* (rel abundance) 442 (M^+, 12), 384 (5), 342 (19), 91 (100).
8. Mp 268-269 °C (Lit. 260-270, 247-250 °C)[3g], ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H); 7.77 (d, 1H, J = 8 Hz); 7.49 (s, 1H); 7.27 (d, 1H, J = 8 Hz); 7.17 (t, 1H, J = 8 Hz); 4.45 (t, 2H, J = 8 Hz) 4.05 (s, 3H); 4.01 (s, 3H); 3.40 (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) 2966, 2940, 2909, 1643, 1606, 1518, 1479, 1265, 1210 cm^{-1}.
9. Black, D. St. C.; Keller, P. A.; Kumar, N. *Tetrahedron Lett.* **1989**, *30*, 5807.

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