

**A SYNTHESIS OF PYRROLOPHENANTHRIDONE ALKALOIDS
VIA CONSECUTIVE DIRECTED LITHIATION AND PALLADIUM-
CATALYZED CROSS-COUPPLING REACTIONS**

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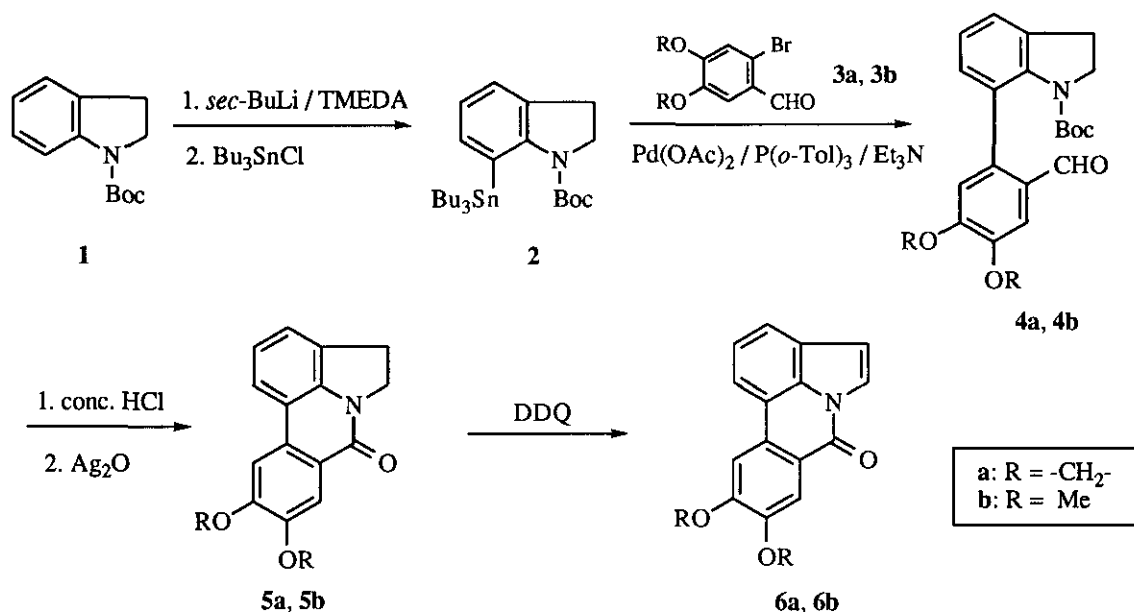
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Abstract- A short and convergent synthesis of pyrrolophenanthridone alkaloids, such as anhydrolycorin-7-one, oxoassoanine, hippadine, and pratosine, was developed by using directed lithiation and palladium-catalyzed cross-coupling as key reactions. Anhydrolycorin-7-one was converted to an antitumor alkaloid, kalbretorine, *via* directed lithiation and hydroxylation reactions.

A series of the pyrrolophenanthridone alkaloids¹ have been isolated from the bulbs of several *Crinum* species (*Amaryllidaceae*) and some of the alkaloids have been shown to exhibit significant biological activities. For examples, hippadine (**6a**) reversibly inhibits fertility in male rats² and kalbretorine (**8**) possesses antitumor activity.³ Due to such interesting activities, considerable synthetic efforts have been devoted to this type of compounds.⁴ The most common approaches involve the aryl-aryl cross-coupling reactions, which depend on the availability of 7-functionalized indolines or indoles at the starting point.^{4a,b,e,g} Recently we have developed a general method for the preparation of 7-substituted indolines *via* directed lithiation of 1-*tert*-butoxycarbonyl-indolines.⁵ In this paper, we wish to describe an application of this reaction for the synthesis of several pyrrolophenanthridone alkaloids.

1-*tert*-Butoxycarbonylindoline (**1**) was lithiated under the standard conditions⁵ (1.2 equiv. *sec*-BuLi / TMEDA / ether / -78 °C / 1 h) and then reacted with tributyltin chloride to give the 7-stannylated indoline (**2**) in 65% yield after purification by flash chromatography over alumina. The stannane (**2**)⁶ was coupled with 6-

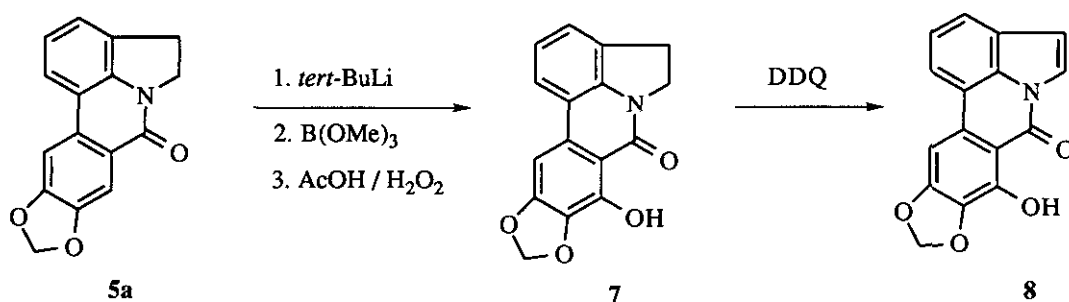
bromopiperonal (**3a**) under the Pd(0)-catalyzed conditions⁷ [Pd(OAc)₂-P(*o*-Tol)₃-Et₃N (1:2:2) (10 mol %)/DMF / 70 °C / 50 h] to give **4a** (mp 147 °C from CH₂Cl₂-hexane) in 63% yield. When the catalytic system was replaced by more common Pd(PPh₃)₄ or Pd(PPh₃)₂Cl₂, the yields of **4a** decreased to 8 or 14%, respectively. Deprotection of Boc group (conc. HCl / room temperature / overnight) followed by basification with 10% aqueous NaOH provided the cyclized hemiaminal, oxidation (10 equiv. Ag₂O / CH₂Cl₂ / overnight) of which, without isolation, gave anhydrolycorin-7-one (**5a**)⁸ (mp 245 °C from ether) in 80% overall yield. Dehydrogenation of **5a** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (2 equiv. / dioxane / reflux / 8 h) provided hippadine (**6a**)^{41,8,9,10} (mp 219-220°C from CH₂Cl₂-ether) in 84% yield. In a similar manner, oxoassoanine (**5b**)¹¹ and pratosine (**6b**)⁴¹ were synthesized from the stannane (**2**) and 6-bromoveratraldehyde (**3b**) via the coupling product (**4b**) (**4b**: 65% yield, mp 143-145 °C from pentane; **5b**: 86% yield, mp 276-277 °C from CH₂Cl₂-pentane; **6b**: 80% yield, mp 240 °C from CH₂Cl₂-hexane).



Scheme 1

The synthesis of kalbretorine (**8**)³ is of interest due to its antitumor activity. We expected that **8** could be synthesized from **5a** via the directed lithiation promoted by amide carbonyl¹² and subsequent hydroxylation.¹³ Thus, when **5a** was treated sequentially with *tert*-BuLi (2 equiv. / THF / -78 °C / 3 h), B(OMe)₃ (2 equiv. / -78

°C to room temperature / 3 h), AcOH (3 equiv.), and 30 % H₂O₂ (5 equiv. / room temperature / overnight), the C-8 hydroxylated compound (7) (mp 295 °C from CH₂Cl₂-ether) was obtained in 33% yield accompanied by the unreacted starting material (5a) (43%). This product was converted to kalbretorine (8) (mp 246-252 °C from CH₂Cl₂-ether) by DDQ dehydrogenation (2.5 equiv. / dioxane / reflux / 40 h) in 86% yield.



Scheme 2

In summary, we have developed a short and convergent synthesis of pyrrolophenanthridone alkaloids starting from easily available starting materials. This method should be applicable to the preparation of a variety of analogues, in which biological activity might be promised.

REFERENCES AND NOTES

- For reviews, see: a) S. F. Martin, 'The Alkaloids: The Amaryllidaceae Alkaloids,' Vol. 30, ed. by A. Brossi, Academic Press, Inc., San Diego, 1987, pp. 251-376; b) M. F. Grundon, *Natural Products Reports*, **1989**, *6*, 79.
- S. C. Chattopadhyay, V. Chattopadhyay, K. S. Mathur, K. S. Saini, and S. Ghosal, *Planta Med.*, **1983**, *49*, 252.
- S. Ghosal, R. Lochan, Ashutosh, Y. Kumar, and R. S. Srivastava, *Phytochemistry*, **1985**, *24*, 1825.
- a) T. Sakamoto, A. Yasuhara, Y. Kondo, and H. Yamanaka, *Heterocycles*, **1993**, *36*, 2597; b) A. I. Meyers and R. H. Hutchings, *Tetrahedron Lett.*, **1993**, *34*, 6185; c) D. St. C. Black, P. A. Keller, and N. Kumar, *Tetrahedron*, **1993**, *49*, 151; d) D. Pérez, E. Guitián, and L. Castedo, *Tetrahedron Lett.*,

- 1992, 33, 2407; e) R. Grigg, A. Teasdale, and V. Sridharan, *Tetrahedron Lett.*, **1991**, 32, 3859; f) D. P. Meirás, E. Guitián, and L. Castedo, *Tetrahedron Lett.*, **1990**, 31, 2331; g) M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, **1990**, 31, 1523; h) D. St C. Black, P. A. Keller, and N. Kumar, *Tetrahedron Lett.*, **1989**, 30, 5807; i) K. Hayakawa, T. Yasukouchi, and K. Kanematsu, *Tetrahedron Lett.*, **1987**, 28, 5895; j) S. Prabhakar, A. M. Lobo, and M. M. Marques, *J. Chem. Res. (S)*, **1987**, 167; k) B. S. Joshi, H. K. Desai, and S. W. Pelletier, *J. Nat. Products*, **1986**, 49, 445; l) S. Ghosal, K. S. Saini, and A. W. Frahm, *Phytochemistry*, **1983**, 22, 2305; m) T. Onaka, Y. Kanda, and M. Natsume, *Tetrahedron Lett.*, **1974**, 1179; n) H. Hara, O. Hoshino, and B. Umezawa, *Tetrahedron Lett.*, **1972**, 5031.
5. M. Iwao and T. Kuraishi, *Heterocycles*, **1992**, 34, 1031; *Idem*, *Org. Syn.*, submitted, **1993**.
 6. For a review of tin-based palladium-catalyzed cross-coupling reactions, see: T. N. Mitchell, *Synthesis*, **1992**, 803. See also: M. Iwao, H. Takehara, S. Furukawa, and M. Watanabe, *Heterocycles*, **1993**, 36, 1483.
 7. a) W. J. Thompson and J. Gaudino, *J. Org. Chem.*, **1984**, 49, 5237; b) N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez, and R. F. Heck, *J. Org. Chem.*, **1978**, 43, 2952.
 8. S. Ghosal, P. H. Rao, D. K. Jaiswal, Y. Kumar, and A. W. Frahm, *Phytochemistry*, **1981**, 20, 2003.
 9. A. A. Ali, M. K. Mesbah, and A. W. Frahm, *Planta Med.*, **1981**, 43, 407.
 10. We thank Professor K. Kanematsu, Kyushu University, for spectral data of hippadine.
 11. J. M. Llabrés, F. Viladomat, J. Bastida, C. Codina, and M. Rubiralta, *Phytochemistry*, **1986**, 25, 2637.
 12. For a review, see: V. Snieckus, *Chem. Rev.*, **1990**, 90, 879.
 13. For the directed lithiation-hydroxylation reaction, see: a) P. Beak and R. A. Brown, *J. Org. Chem.*, **1982**, 47, 34; b) M. Iwao, J. N. Reed, and V. Snieckus, *J. Am. Chem. Soc.*, **1982**, 104, 5531.
 14. All synthetic samples described in this paper were fully characterized by ^1H nmr, ir, and ms spectral, and elemental analyses.

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