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

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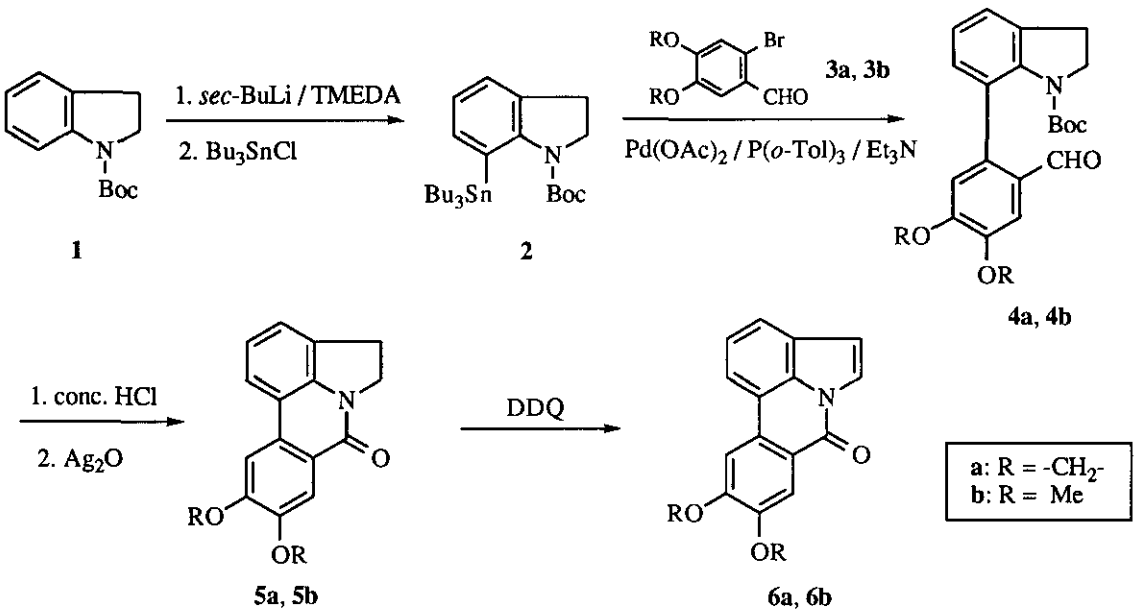
Abstract- A short and convergent synthesis of pyrrolophenanthridone alkaloids, such as anhydrolycorin-7-one, oxoassoanine, hippadine, and pratosine, was developed by using directed lithiation and palladium-catalyzed cross-coupling as key reactions. Anhydrolycorin-7-one was converted to an antitumor alkaloid,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

A series of the pyrrolophenanthridone alkaloids[1] 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 rats[2] and kalbretorine (**8**) posesses 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 conditions[5] (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-

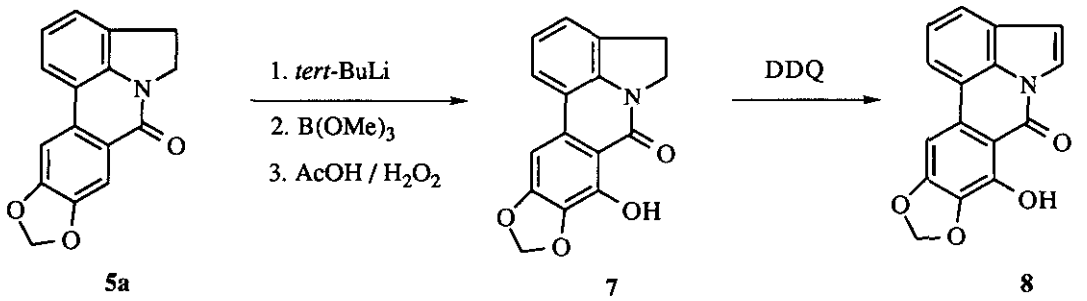
bromopiperonal (**3a**) under the Pd(0)-catalyzed conditions[7] [$Pd(OAc)_2$-P(*o*-Tol)$_3$-Et_3N (1:2:2) (10 mol %) / DMF / 70 °C / 50 h] to give **4a** (mp 147 °C from CH_2Cl_2-hexane) in 63% yield. When the catalytic system was replaced by more common $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$, the yields 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. Ag_2O / CH_2Cl_2 / 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**)[4l,8,9,10] (mp 219-220°C from CH_2Cl_2-ether) in 84% yield. In a similar manner, oxoassoanine (**5b**)[11] and pratosine (**6b**)[4l] 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 CH_2Cl_2-pentane; **6b**: 80% yield, mp 240 °C from CH_2Cl_2-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 carbonyl[12] 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 % H_2O_2 (5 equiv. / room temperature / overnight), the C-8 hydoxylated compound (**7**) (mp 295 °C from CH_2Cl_2-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 CH_2Cl_2-ether) by DDQ dehydrogenation (2.5 equiv. / dioxane / reflux / 40 h) in 86% yield.



5a **7** **8**

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.

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14. All synthetic samples described in this paper were fully characterized by ^{1}H nmr, ir, and ms spectral, and elemental analyses.

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