

**Intramolecular Palladium-Catalyzed Cyclization of
Methyl 1-(2-Bromobenzyl)indole-2-carboxylates:
Synthesis of Pratosine and Hippadine**

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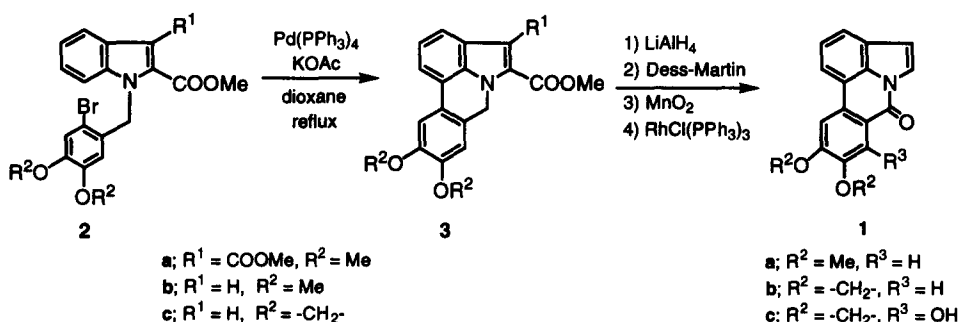
Abstract: Palladium-catalyzed cyclization of methyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2-carboxylate in the presence of potassium acetate in hot 1,4-dioxane gave a 7*H*-pyrrolo[3,2,1-*de*]phenanthridine derivative, which was converted to pratosine in four steps. In a similar manner, hippadine was also prepared.
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Pratosine (**1a**),¹ hippadine (**1b**),² and kalbretorine (**1c**)³ are 7*H*-pyrrolo[3,2,1-*de*]phenanthridine alkaloids, isolated from various species of *Amaryllidaceae*. This family has significant biological activities; for example, hippadine (**1b**)⁴ inhibits fertility in male rats and kalbretorine (**1c**)³ has antitumor activity. 7*H*-Pyrrolo[3,2,1-*de*]phenanthridine alkaloids were synthesized by allene intramolecular cycloaddition,⁵ intramolecular cycloaddition of α -pyrone,⁶ aryl-aryl cross-coupling reaction of 7-unsubstituted,^{7a} 7-halogeno,^{7b,c} 7-cuprated,^{7d} and 7-stanylated indolines,^{7e} and aryl-aryl cross-coupling reaction of 7-bromoindole derivatives.⁸ Attempts to synthesize 7*H*-pyrrolo[3,2,1-*de*]phenanthridine from radical cyclization of 1-benzyl-7-bromoindole resulted in low yields.⁹ In this paper we report a simple and useful synthesis of pratosine (**1a**) and hippadine (**1b**) by palladium-catalyzed intramolecular cyclization of methyl 1-(2-bromobenzyl)indole-2-carboxylate derivatives (**2**).

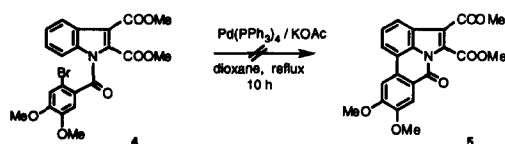
Treatment of dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**2a**) in hot dioxane in the presence of Pd(PPh₃)₄ and potassium acetate gave dimethyl 9,10-dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridine-4,5-dicarboxylate (**3a**) in 76% yield. In a similar manner, methyl 7*H*-pyrrolo[3,2,1-*de*]phenanthridine-5-carboxylates (**3b**) and (**3c**) were easily obtained from **2b** and **2c** in 96% and 91% yields, respectively.

LiAlH₄ reduction of methyl ester (**3b**) (95%) followed by the Dess-Martin oxidation (84%) gave the corresponding aldehyde, which was converted to pratosine (**1a**) by MnO₂ oxidation (76%), then decarbonylation using RhCl(PPh₃)₃ in hot xylene in the presence of dppp (Ph₂P(CH₂)₃PPh₂) in 84% yield. In a similar manner, hippadine (**1b**) was also obtained from **3c** by LiAlH₄ reduction (94%), Dess-Martin oxidation and MnO₂ oxidation (71%), and decarbonylation(79%).



References and Notes

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- Methyl 1-(2-bromobenzyl)indole-2-carboxylates (**2a-c**) were prepared from 2-bromobenzyl bromides and methyl indole-2-dicarboxylates in hot acetonitrile in the presence of potassium carbonate in 78%, 83%, and 85% yields, respectively.
- Attempts to obtain the 7*H*-pyrrolo[3,2,1-*de*]phenanthridone (**5**) from dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**4**) resulted in failure and the starting material was recovered.



- Pratosine (**1a**): mp 234-235°C (Et₂O-MeOH) (lit.,¹ 232-233°C); IR (Nujol) cm⁻¹: 1670; ¹H-NMR (CDCl₃) δ: 4.07 (3H, s, OMe), 4.12 (3H, s, OMe), 6.90 (1H, d, *J* = 4 Hz, H-4), 7.48 (1H, t, *J* = 7.5 Hz, H-2), 7.64 (1H, s, H-8), 7.75 (1H, dd, *J* = 7.5, 0.5 Hz, H-3), 7.96 (1H, dd, *J* = 7.5, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.05 (1H, d, *J* = 4 Hz, H-5). HRMS *m/z* (M⁺) calcd for C₁₇H₁₃NO₃: 279.0895. Found: 279.0891.
 Hippadine (**1b**): mp 215-216°C (*n*-hexane-acetone) (lit.,² 209-210°C, lit.,¹³ 217-218°C); IR (Nujol) cm⁻¹: 1673; ¹H-NMR (CDCl₃) δ: 6.17 (2H, s, CH₂), 6.90 (1H, d, *J* = 4 Hz, H-4), 7.48 (1H, t, *J* = 8 Hz, H-2), 7.66 (1H, s, H-8), 7.76 (1H, dd, *J* = 8, 0.5 Hz, H-3), 7.92 (1H, dd, *J* = 8, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.04 (1H, d, *J* = 4 Hz, H-5). HRMS *m/z* (M⁺) calcd for C₁₆H₉NO₃: 263.0582. Found: 263.0579.