

First Total Synthesis of Trimeric Indole Alkaloid, Psychotrimine

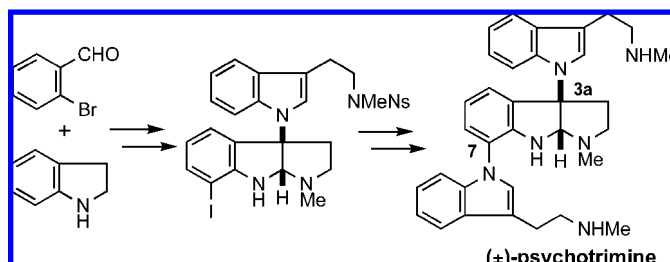
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Received October 30, 2007

ABSTRACT



The first total synthesis of (±)-psychotrimine, a novel trimeric indole alkaloid isolated from *Psychotria rostrata*, was achieved. In the total synthesis, the copper-mediated intramolecular and intermolecular aminations of halobenzenes, which respectively contributed to the construction of a pyrrolidinoindoline core and the installation of a third tryptamine unit, were used as key steps.

A number of polymeric-tryptamine-related alkaloids comprising two to eight pyrrolidinoindoline units have been isolated from rubiaceous plants,^{1,2} some of which show analgesic activity involving opioid or NMDA receptors.³ Our continuous chemical and pharmacological studies of indole alkaloids possessing analgesic activity⁴ have led to the isolation of a new trimeric-tryptamine-related alkaloid named psychotrimine from *Psychotria rostrata*, a rubiaceous plant indigenous to Malaysia.⁵ All hitherto known polymeric-tryptamine-related indole alkaloids are composed of pyrro-

lidinoindoline units linked at C3a-C3a' and/or C3a-C7' positions (Figure 1). In contrast, psychotrimine (**1**) is the first

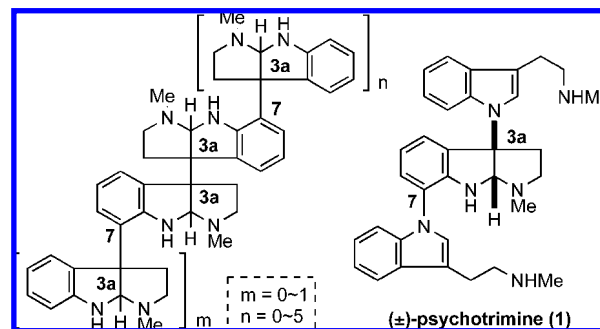


Figure 1. General structure of known polypyrrolidinoindoline alkaloids (left) and psychotrimine.

example of this class of alkaloid that contains tryptamine and pyrrolidinoindoline units in the same molecule as well as possesses new linkage modes between the *N*a function of tryptamine residue and the C3a and C7 positions of pyrro-

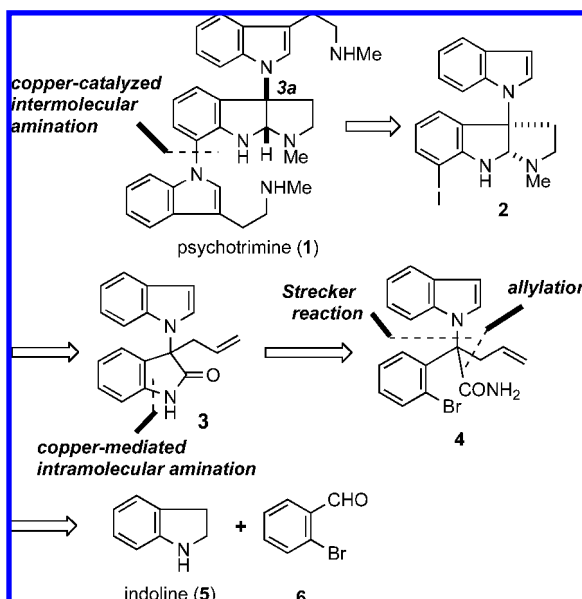
(1) For recent reviews, see: (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 163–236. (b) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2–23.

(2) For recent reports of the synthesis of pyrrolidinoindoline alkaloid, see: (a) Dounary, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. (b) Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2528–2531. (c) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *PNAS* **2004**, *101*, 5482–5487. (d) Monozzi, C.; Dalko P. I.; Cossy, J. *Chem. Commun.* **2006**, 4638–4640 and references cited therein.

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lidinoindoline core. In this paper, We report the first total synthesis of (±)-psychotrimine, thereby establishing the structure of this novel indole alkaloid.

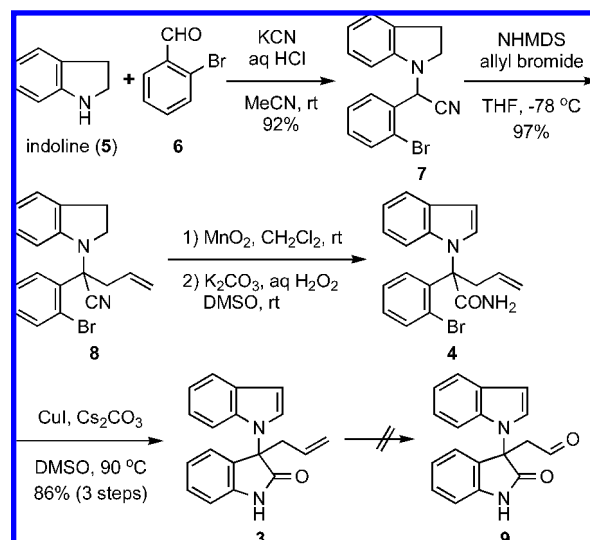
Scheme 1. Initial Retrosynthetic Analysis



Our initial synthetic plan is depicted in Scheme 1. Installation of a lower tryptamine segment in the last stage by copper-mediated intermolecular amination⁶ of pyrrolidinoindoline derivative **2** was expected to enable the total synthesis of **1**. Further, we envisioned that the pyrrolidinoindoline skeleton, the central part of this alkaloid, would be constructed by copper-mediated intramolecular amidation^{6a,c} of **4**, followed by appropriate transformation of resultant oxindole **3**. We anticipated that the quaternary carbon center in **4**, which corresponded to the characteristic C3a position in **1**, would be prepared from indoline (**5**) via the Strecker reaction and successive allylation at the α -position of the cyano function.

Initially, we attempted the copper-mediated intramolecular amidation to construct **3** using amide substrate **4**, which was prepared from indoline (**5**) and aldehyde **6** via a four-step operation (Scheme 2) that included the Strecker reaction, alkylation with allyl bromide, transformation of indoline to

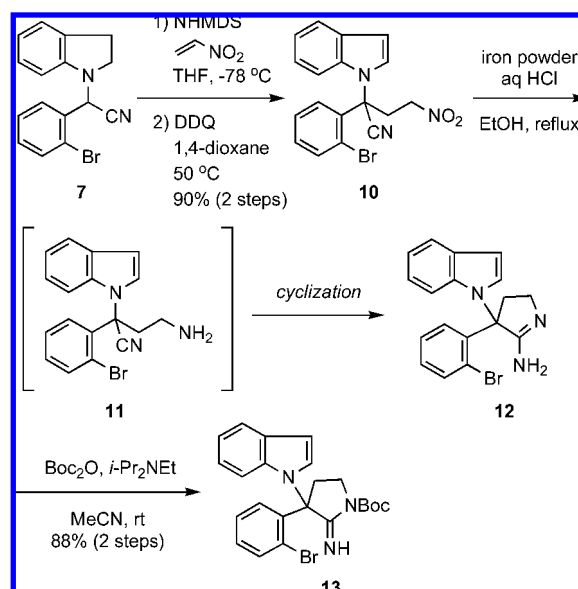
Scheme 2



indole by MnO_2 oxidation, and hydrolysis of the cyano group. By applying Fukuyama et al.'s conditions (CuI , Cs_2CO_3 , DMSO),^{6d} desired oxindole **3** was obtained in excellent yield. However, we could not obtain aldehyde **9** via oxidative cleavage of the allyl group, probably due to the instability of the indole moiety under the employed conditions.

Then, we embarked on the development of a new method to construct the pyrrolidinoindoline skeleton using amidine **13**. The conversion of α -amino nitrile **7** into amidine **13** is shown in Scheme 3. Here, conjugate addition reaction of **7**

Scheme 3



with nitroethylene⁷ followed by DDQ oxidation of the indoline moiety provided indole **10** in 90% overall yield. The nitro group was reduced with iron powder in aqueous

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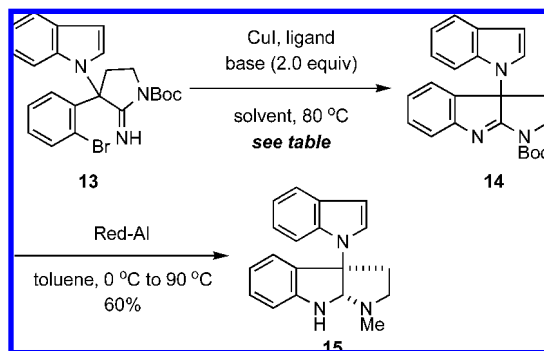
(5) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945–2948.

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hydrochloric acid and EtOH to give primary amine **11**, which was spontaneously cyclized to amidine **12**. Protection of pyrrolidine nitrogen with the *tert*-butoxycarbonyl (Boc) group gave amidine **13** in 88% overall yield from **10**.

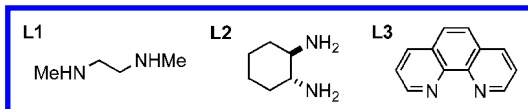
Having succeeded in the synthesis of amidine **13**, the stage was set for the copper-mediated intramolecular amination to construct the pyrrolidinoindoline core. As shown in Table 1, copper iodide was selected as the source of copper(I), and

Table 1. Copper-Mediated Intramolecular Amination



entry	CuI (mol %)	ligand ^a (mol %)	base	solvent ^b	time (h)	yield (%) ^c
1	20	L1 :40	K ₃ PO ₄	toluene	16	trace
2	20	L2 :40	K ₃ PO ₄	toluene	16	trace
3	10	L3 :40	Cs ₂ CO ₃	DME	41	10
4	100	—	Cs ₂ CO ₃	DMSO	2.5	decomp.
5	100	—	K ₂ CO ₃ ^d	DMSO	2.5	60
6	100	—	K ₃ PO ₄ ^d	DMSO	1.5	91

^a **L1**: *N,N'*-dimethylethylenediamine. **L2**: *trans*-*N,N'*-dimethylcyclohexanediamine. **L3**: 1,10-phenanthroline. ^b Degassed solvent was used. ^c Isolated yield. ^d 1.5 equiv of base was used.

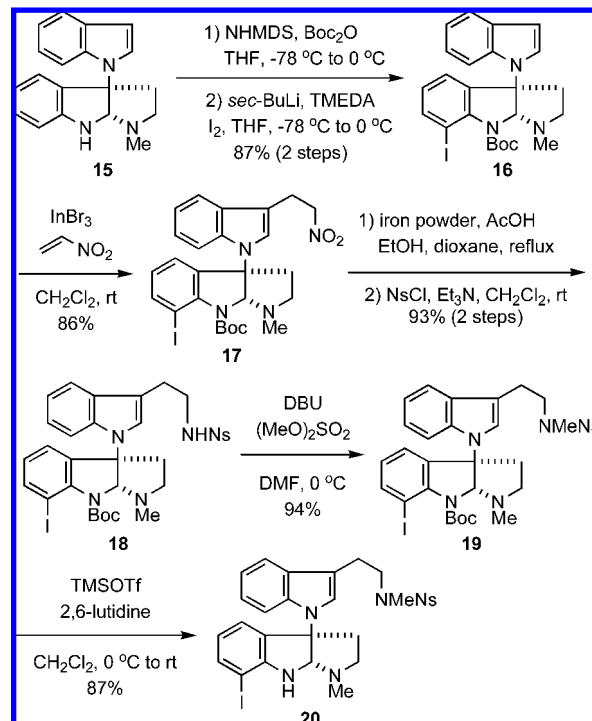


optimization of the other conditions (ligand, solvent, base) was undertaken. First, Buchwald's conditions using diamine compound (**L1**–**L3**) as ligand^{6a,b} were examined (entries 1–3). Under these conditions, the desired cyclization product was obtained in very low yield, probably due to the low reactivity of amidine nitrogen compared with aliphatic nitrogen.⁸ Then, we examined ligand-free conditions using a stoichiometric amount of copper iodide.^{6c,d} We tested several bases in DMSO at 80 °C and found that the choice of base was quite important for this transformation (entries 4–6): Cs₂CO₃ gave a complex mixture, while K₂CO₃ gave desired cyclization product **14** in 60% yield. The best result was obtained when K₃PO₄ was used as a base. Cyclization product **14** was transformed into pyrrolidinoindoline deriva-

tive **15** by reducing both imine and Boc groups with Red-Al. Thus, we have established a new method for the synthesis of pyrrolidinoindoline derivative using copper-mediated intramolecular amination.

Next, we turned our attention to the construction of the trimeric skeleton core using the copper-mediated intermolecular amination. To carry out this reaction, **15** was converted into iodide **20** as follows (Scheme 4). After

Scheme 4



protection of the aniline nitrogen with the Boc group, the resulting carbamate was treated with *sec*-BuLi and quenched with iodine to give iodide **16** in good yield.⁹ Side chain extension at the indole β-position in **16** was achieved by the conjugate addition reaction with nitroethylene in the presence of InBr₃ as a Lewis acid.¹⁰ After reduction of the aliphatic nitro group with iron powder and AcOH, the resulting primary amine was protected as *o*-nitrobenzenesulfonamide (Ns-amide),¹¹ followed by *N*-methylation via treatment with DBU and dimethyl sulfate¹² to give **19** in excellent yield. Finally, the Boc group was removed with TMSOTf and 2,6-lutidine to afford iodide **20**, the key substrate for the final conversion.

The final stage of the total synthesis of **1** was the copper-mediated intermolecular coupling of iodide **20** with tryptamine

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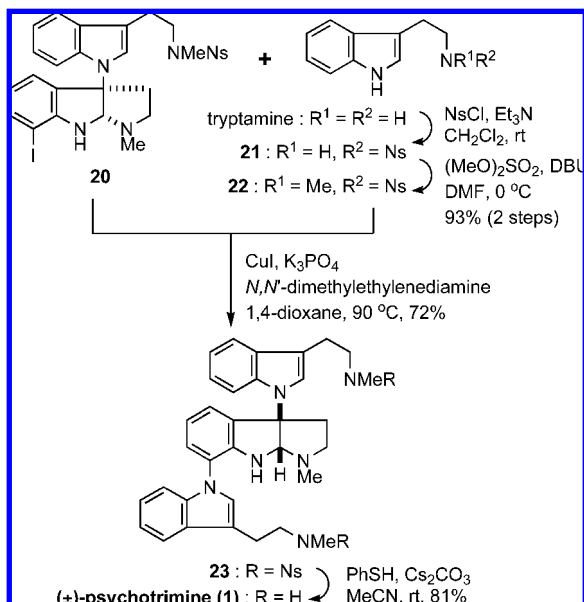
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derivative **22**, the latter of which was prepared from tryptamine via a two-step operation (Scheme 5):

Scheme 5



protection of primary amine with the Ns group and methylation with DBU and dimethyl sulfate. After several experiments, it was revealed that the ligand–base combination was an important factor for this coupling reaction. When the reaction was carried out using *N,N'*-dimethylethylene-

diamine as ligand and K_3PO_4 as base, the desired coupling product **23** was obtained in 72% yield.

Finally, the Ns group of both upper and lower tryptamine units was removed by conventional procedure to furnish the target molecule **1** in good yield. Synthetic **1** was completely identical in all respects (chromatographic behavior; mass; IR; UV; 1H and ^{13}C NMR) with natural psychotrimine except for the optical property. Hence, the structure of psychotrimine, which was proposed on the basis of spectroscopic analyses, was confirmed to be formula **1**.

In conclusion, we have achieved the first total synthesis of (±)-psychotrimine in 16 steps and 13.2% overall yield from indoline. The synthesis features the copper-mediated intramolecular amination of amidine substrate to form the pyrrolidinoindoline core, and the copper-mediated intermolecular amination to construct the trimeric skeleton. Further synthetic study of this class of alkaloids is underway in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures for **3**, **4**, **7**, **8**, **10**, **13–23**, **S1**, **S2**, and synthetic (±)-psychotrimine (**1**), and copies of 1H and ^{13}C NMR spectral data for **3**, **7**, **8**, **10**, **13–23**, synthetic (±)-psychotrimine (**1**), and natural psychotrimine. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702637R