ORGANIC LETTERS

2008
Vol. 10, No. 1
125−128

First Total Synthesis of Trimeric Indole Alkaloid, Psychotrimine

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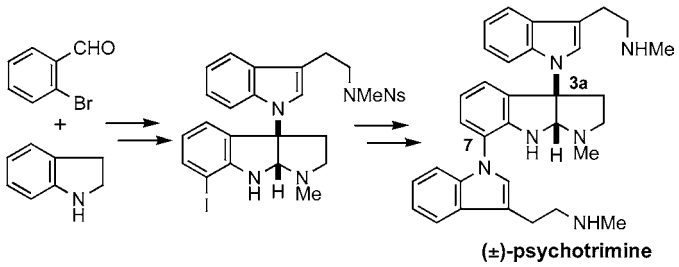
Received October 30, 2007

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 activity[4] 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 pyrrolidinoindoline units linked at C3a-C3a′ and/or C3a-C7′ positions (Figure 1). In contrast, psychotrimine (**1**) is the first 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-

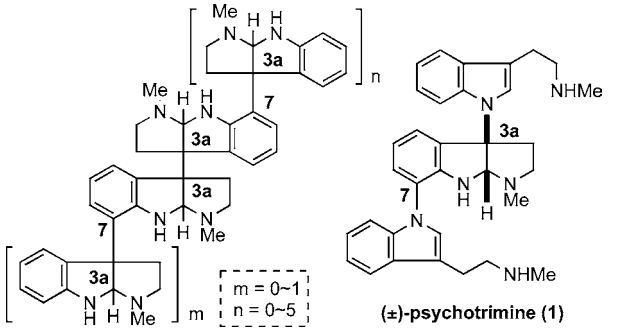


Figure 1. General structure of known polypyrrolidinoindoline alkaloids (left) and psychotrimine.

(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.

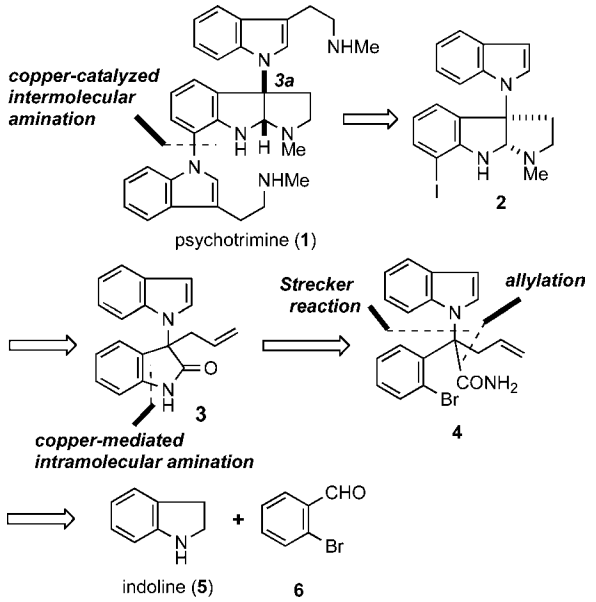
(2) For recent reports of the synthesis of pyrrolidinoindoline alkaloid, see: (a) Dounary, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964. (b) Kodanko, J. J.; Overman. L. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2528−2531. (c) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, 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.

(3) (a) Amador, T. A.; Verrota, L.; Nunes, D. S.; Elisabetsky, E. *Planta Med.* **2000**, *66*, 770−772. (b) Amador, T. A.; Verrota, L.; Nunes, D. S.; Elisabetsky, E. *Phytomedicine* **2001**, *8*, 202−206. (c) Verrota, L.; Orsini, F.; Sbacchi, M.; Scheildler, M. A.; Amador, T. A.; Elisabetsky, E. *Bioorg. Med. Chem.* **2002**, *10*, 2133−2142. (d) Kodanko, J. J.; Hiebert, S.; Peterson, E. A.; Sung, L.; Overman, L. E.; Linck, V. M.; Goerck, G. C.; Amador, T. A.; Leal, M. B.; Elisabetsky, E. *J. Org. Chem.* **2007**, *72*, 7909−7914.

10.1021/ol702637r CCC: $40.75
Published on Web 12/11/2007

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

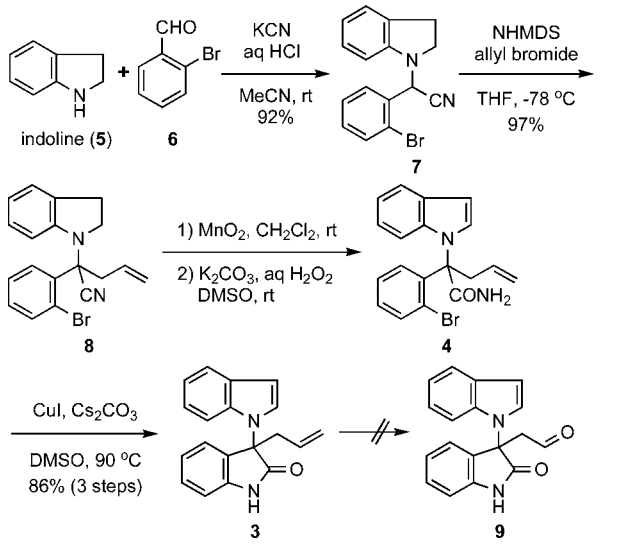
Scheme 1. Initial Retrosynthetic Analysis



Our initial synthetic plan is depicted in Scheme 1. Installation of a lower tryptamine segment in the last stage by copper-mediated intermolecular amination[6] 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 amination[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

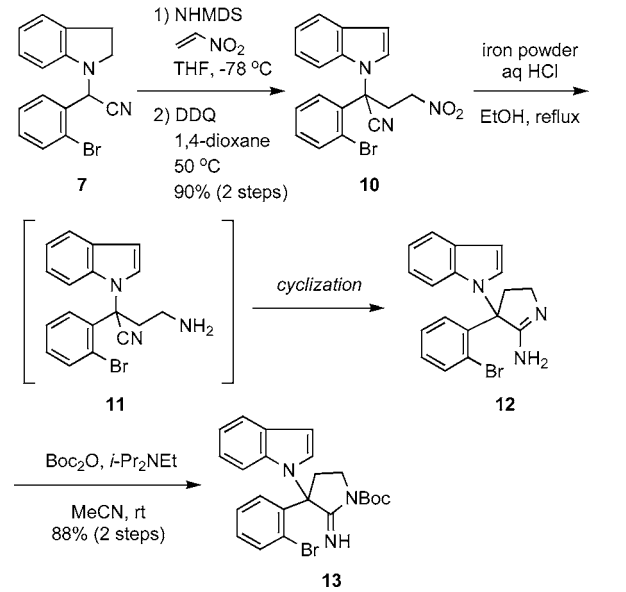
Scheme 2



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 nitroethylene[7] 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

(4) (a) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949−1956. (b) Matsumoto, K.; Horie, S.; Ishikawa, H.; Takayama, H.; Aimi, N.; Ponglux, D.; Watanabe, K. *Life Sci.* **2004**, *74*, 2143−2155. (c) Takayama, H.; Misawa, K.; Okada, N.; Ishikawa, H.; Kitajima, M.; Hatori, Y.; Murayama, T.; Wongseripipatana, S.; Tashima, K.; Matsumoto, K.; Horie, S. *Org. Lett.* **2006**, *8*, 5705−5708 and references cited therein.

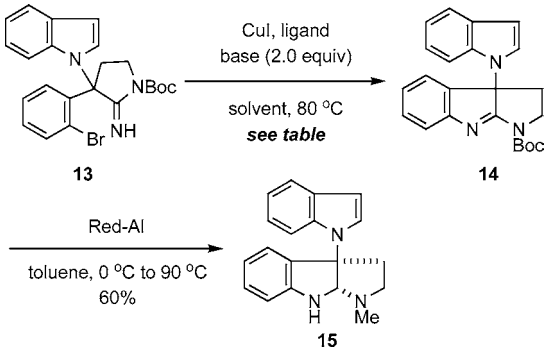
(5) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945−2948.

(6) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688. (c) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231−234. (d) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987−4990. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

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**.

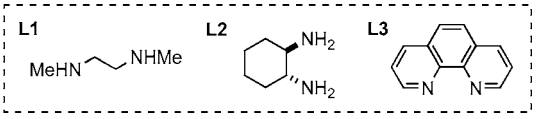
Having succeeded in the synthesis of amidine **13**, the stage was set for the copper-mediated intramolecular amination to construct the pyrrolidinoindoline core. As shown in Table 1, copper iodide was selected as the source of copper(I), and

Table 1. Copper-Mediated Intramolecular Amination



entry	CuI (mol %)	ligand[a] (mol %)	base	solvent[b]	time (h)	yield (%)[c]
1	20	**L1**:40	K_3PO_4	toluene	16	trace
2	20	**L2**:40	K_3PO_4	toluene	16	trace
3	10	**L3**:40	Cs_2CO_3	DME	41	10
4	100	–	Cs_2CO_3	DMSO	2.5	decomp.
5	100	–	K_2CO_3[d]	DMSO	2.5	60
6	100	–	K_3PO_4[d]	DMSO	1.5	91

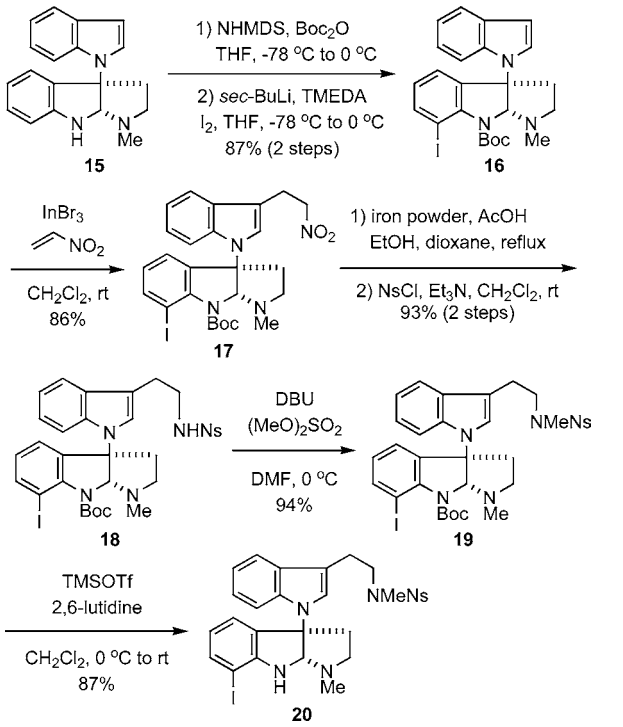
[a] **L1**: *N*,*N*′-dimethylethylenediamine. **L2**: *trans*-*N*,*N*′-dimethylcyclohexanediamine. **L3**: 1,10-phenanthroline. [b] Degassed solvent was used. [c] Isolated yield. [d] 1.5 equiv of base was used.



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): Cs_2CO_3 gave a complex mixture, while K_2CO_3 gave desired cyclization product **14** in 60% yield. The best result was obtained when K_3PO_4 was used as a base. Cyclization product **14** was transformed into pyrrolidinoindoline derivative **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 $InBr_3$ 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 sulfate[12] 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

(7) (a) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185−1189. (b) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3347−3358.

(8) Under these conditions, the coupling reaction between **13** and ligand (**L1** or **L2**) was observed. This type of *N*-arylation was reported by Buchwald's group. See ref 6b.

(9) (a) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008−9009. (b) Iwao, M.; Kuraishi, T. *Org. Synth.* **1996**, *73*, 85−93.

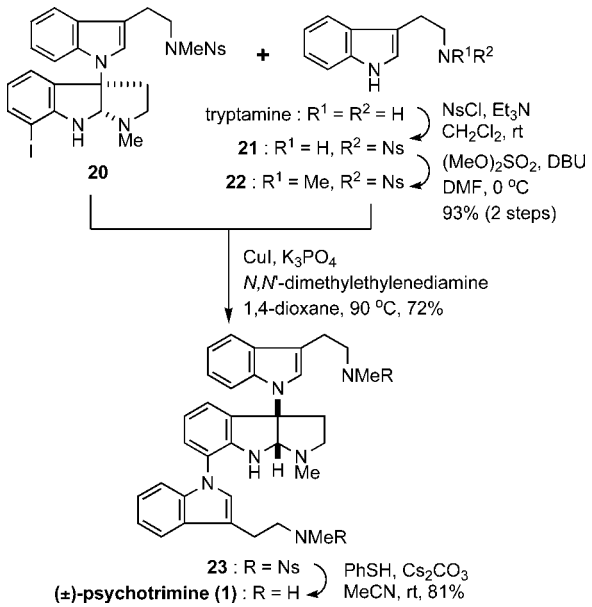
(10) (a) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110−1114. (b) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386−5389.

(11) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

(12) Biron, E.; Kessler, H. *J. Org. Chem.* **2005**, *70*, 5183−5189.

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*′-dimethylethylenediamine 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; ^{1}H 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 ^{1}H 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