Determination of absolute configuration of trimeric indole alkaloid, psychotrimine, by first asymmetric total synthesis†

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The first asymmetric total synthesis of psychotrimine, a trimeric indole alkaloid, was accomplished *via* an asymmetric Ireland–Claisen rearrangement to construct a chiral quaternary carbon center, thereby establishing the absolute configuration of psychotrimine.

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] In our continuous chemical and pharmacological studies of indole alkaloids possessing analgesic activity,[4] we isolated psychotrimine, a new trimeric-tryptamine-related alkaloid, from a Malaysian rubiaceous plant, *Psychotria rostrata*.[5] All the hitherto known polymeric-tryptamine-related indole alkaloids are composed of pyrrolidinoindoline units linked at C3a–C3a′ and/or C3a–C7′ positions (Fig. 1). In contrast, psychotrimine (**1**) is the first example of this class of alkaloids that contains tryptamine and pyrrolidinoindoline units in the same molecule as well as possessing new linkage modes between the N_a function of the tryptamine residue and the C3a and C7 positions of the pyrrolidinoindoline core. Recently, we accomplished the first total synthesis of (±)-psychotrimine *via* copper-mediated intramolecular and intermolecular aminations of halobenzenes.[6] Although an elegant total synthesis of (±)-**1** was also reported by Newhouse and Baran,[7] its absolute configuration is still unknown.

We herein report the first asymmetric total synthesis of psychotrimine *via* an asymmetric Ireland–Claisen rearrangement,[8] which enabled us to determine the absolute configuration of the natural product.

Our synthetic plan is depicted in Scheme 1. Utilizing our previous work[6] on the synthesis of (±)-**1**, chiral pyrrolidinoindoline derivative **2** was synthesized for use as the key intermediate for the asymmetric synthesis of **1**. Pyrrolidinoindoline **2** would be transformed from chiral oxindole **3**, which could be prepared from an amide derivative of carboxylic acid **4** *via* the copper-mediated intramolecular amination of bromobenzene. The construction of a quaternary chiral carbon center in **4**, the key step in this synthesis, was expected by the asymmetric Ireland–Claisen rearrangement of chiral allylic ester **5** *via* a chirality transfer process. Compound **5** would be prepared from indoline (**6**), 2-bromophenylacetic acid (**7**), and known chiral allylic alcohol **8**.[9]

Chiral allylic ester **5** was prepared from 2-bromophenylacetic acid (**7**) in five steps (Scheme 2). Esterification of **7** followed by radical bromination at the benzylic position (NBS, AIBN, CCl_4) gave dibromo compound **9** in 98% yield. After alkaline hydrolysis of the methyl ester in **9**, the resulting carboxylic acid was coupled with chiral allylic alcohol **8** in the presence of pyridine-3-carboxylic anhydride (3-PCA)[10] and DMAP in CH_2Cl_2 to give **10** in 67% yield (2 steps). Next, indoline unit (**6**) was installed in **10** (TBAI, K_2CO_3, DMF) to afford Ireland–Claisen rearrangement precursor **5** in 73% yield as a diastereomeric mixture.

With chiral ester **5** in hand, the utility of the asymmetric Ireland–Claisen rearrangement in constructing a chiral quaternary carbon center at C3a in **1** was examined (Table 1). Amphoteric product **4** from the Ireland–Claisen rearrangement was converted without purification into amide **11** (HATU, *i*-Pr_2NEt, NH_4Cl, DMF) and the enantiomeric excess was determined by chiral HPLC analysis. Preliminary investigation suggested that the combination of KHMDS and THF as base and solvent is appropriate for this Ireland–Claisen rearrangement. Then, to realize chelation control (*vide infra*), such metal salts as LiCl, $ZnCl_2$, $MgCl_2$, $TiCl_4$, and $CoCl_2$ were investigated as additives. Among them, $ZnCl_2$ (entry 1) offered moderate chemical yield (58%) and enantiomeric excess (46% ee). By using ZnI_2 instead of $ZnCl_2$ and optimizing the reaction temperature and time (entry 2), the best result was obtained (79% yield, 74% ee). Interestingly, when LiCl was employed (entry 3), the product obtained in 43% yield contained the antipode predominantly (57% ee). The absolute configuration of the chiral product was determined as

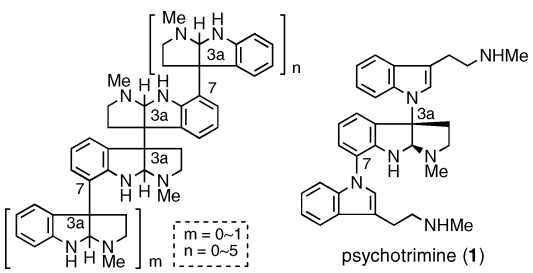

Fig. 1 General structure of known polypyrrolidinoindoline alkaloids (left) and the structure of psychotrimine (right).

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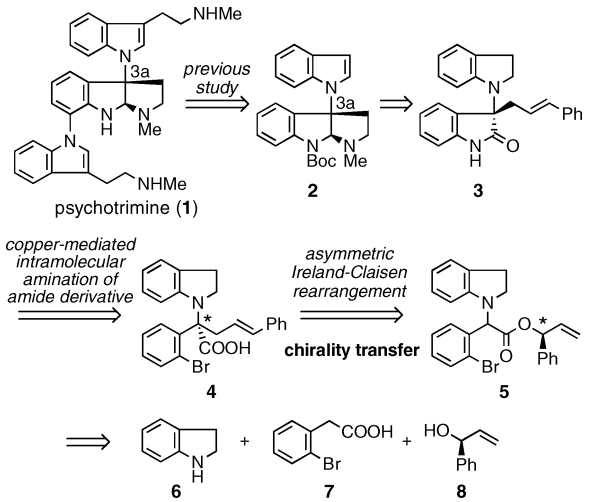
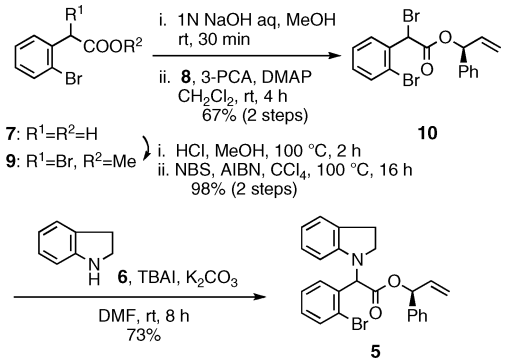


Scheme 1 Retrosynthetic analysis.

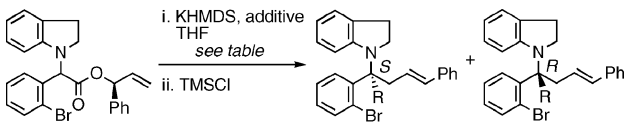


Scheme 2

follows. The product obtained in entry 2 (74% ee) was converted into nitrile derivative **13**, which was recrystallized from AcOEt–*n*-hexane to give an enantiomerically pure (99.9% ee as determined by chiral HPLC analysis) crystal (mp 155–157 °C). X-Ray crystallographic analysis revealed that this compound ($[\alpha]_D^{20}$ +150 (*c* 0.63, $CHCl_3$)) had the *S* configuration at the quaternary carbon center.†

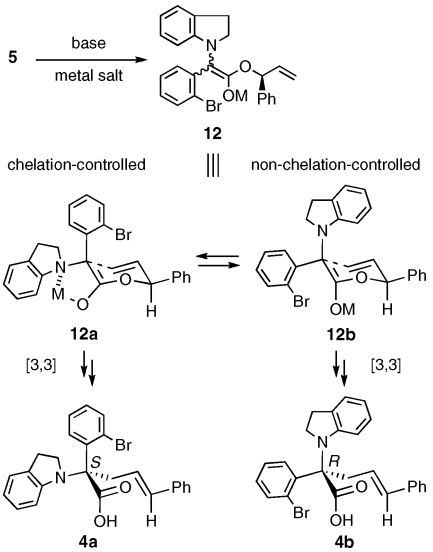
Based on the results described above, a possible mechanism for the asymmetric Ireland–Claisen rearrangement was considered, as shown in Scheme 3. Ketene acetal **12** generated

Table 1 Effects of additives on Ireland–Claisen rearrangement



Entry	Additive	Yield (%)	ee (%)[c]
1[a]	$ZnCl_2$	58	46 (*S*)
2[b]	ZnI_2	79	74 (*S*)
3[a]	LiCl	43	57 (*R*)

[a] Reaction conditions: (i) −78 °C, 30 min, (ii) −78 °C, 30 min, then rt, 1 h. [b] Reaction conditions: (i) −78 °C, 1 h, (ii) rt, 1 h. [c] Determined by chiral HPLC analysis.

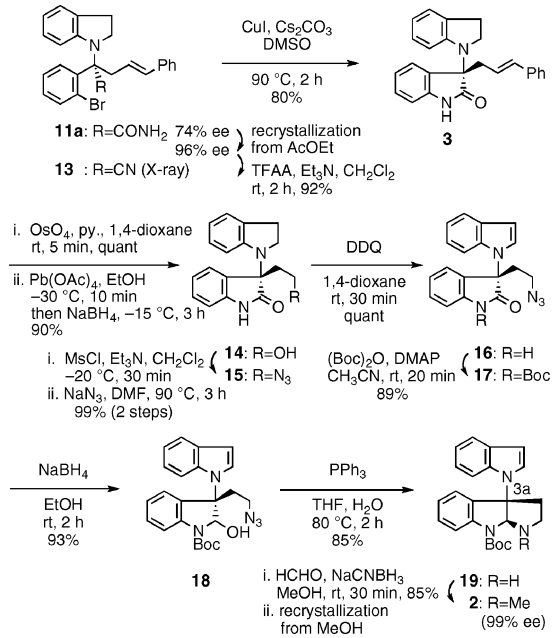


Scheme 3

by treating ester **5** with KHMDS and metal salt would have two chair-like transition states **12a** and **12b**, both of which favor the pseudo-equatorial position of the phenyl group. Using Zn salts, chelation between the nitrogen of the indoline part and the oxygen of the enolate would take place, producing the new chiral center (*S*) in high optical purity *via* the chirality transfer process. In case of entry 3, using LiCl as additive, the *R* enantiomer **4b** is produced dominantly, probably *via* a non-chelation-controlled transition state **12b**.[8]

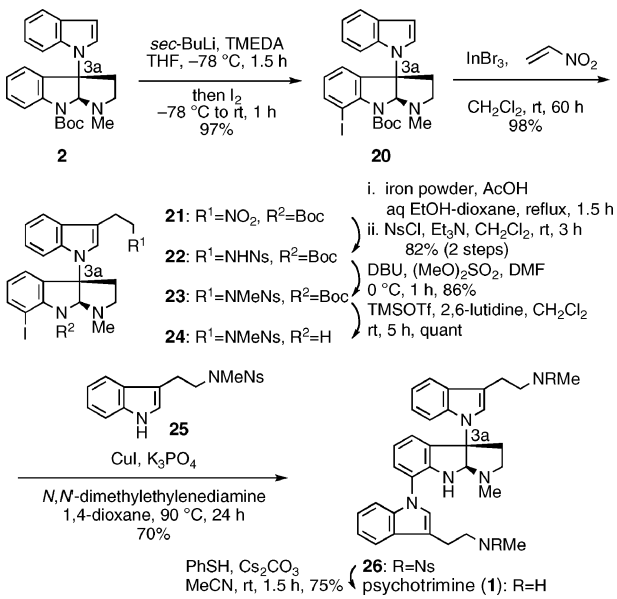
Next, amide **11a**, whose enantiomeric excess could be increased to 96% ee by recrystallization from AcOEt, was subjected to copper-mediated intramolecular amination of bromobenzene by treatment with CuI in the presence of Cs_2CO_3 in DMSO to give oxindole **3** in 80% yield (Scheme 4). Oxidative cleavage of the double bond and installation of a nitrogen function in the side chain were performed as follows. **3** was treated with OsO_4 to give a diol intermediate, which was cleaved with $Pb(OAc)_4$ and then reduced with $NaBH_4$ to afford primary alcohol **14** in 90% yield. Subsequently, an azide group was introduced to **14** in 99% yield in two steps ((i). MsCl, Et_3N, CH_2Cl_2, (ii). NaN_3, DMF) to give **15**. The indoline function in **15** was converted into indole in a quantitative yield by DDQ oxidation. The introduction of a Boc group to N_a of the oxindole unit in **16** and the subsequent partial reduction of the amide function in oxindole **17** with $NaBH_4$ provided hemiaminal **18** in 93% yield. Next, the azide group was reduced with PPh_3 in THF–H_2O to afford a primary amine, which spontaneously cyclized to give pyrrolidinoindoline **19** in 85% yield. Reductive methylation (HCHO, $NaCNBH_3$, MeOH) of N_b of the pyrrolidinoindoline unit furnished optically active key intermediate **2** in 85% yield.

Having succeeded in the synthesis of chiral intermediate **2**, we focused our energies on the completion of the asymmetric synthesis of psychotrimine by utilizing the method for the synthesis of racemic **1**[6] (Scheme 5). The seven-step transformation involved: (1) regioselective iodination of the benzene ring of the pyrrolidinoindoline unit to give **20**, (2) installation of the side chain at the β position of the indole ring using



Scheme 4

nitroethylene–$InBr_3$ to afford **21**, (3) reduction of the nitro group with Fe–AcOH, followed by protection of the resulting primary amine with nitrobenzenesulfonamide (Ns-amide), (4) *N*-methylation, (5) removal of the Boc group to yield **24**, (6) coupling with tryptamine derivative **25** by copper-mediated intermolecular amination to give trimeric product **26**, and (7) removal of the Ns group to furnish psychotrimine in 75% yield. Synthetic **1** ($[\alpha]_D^{24}$ +221 (*c* 0.3, $CHCl_3$)) with 3a*S* and 8a*R* stereochemistry was completely identical in all respects



Scheme 5

($[\alpha]_D$, NMR, mass) with the natural one ($[\alpha]_D^{18}$ +179 (*c* 0.2, $CHCl_3$)). Therefore, the absolute configuration of psychotrimine was established, as shown in formula **1**.

Synthetic (+)-psychotrimine was evaluated for its cytotoxic activity against three tumor cell lines, A549, HT29, and HTC116. As a result, **1** showed moderate cytotoxicity to only HT-29 (human colon adenocarcinoma grade II cell line; IC_{50} = 3.00 μg mL^{-1}).

In conclusion, we have achieved the first asymmetric total synthesis of cytotoxic psychotrimine (**1**) *via* an asymmetric Ireland–Claisen rearrangement to construct a chiral quaternary carbon center, which enabled us to determine the absolute configuration of the natural product.

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