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Total Synthesis of (±)-Psychotrimine

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Polymeric indole alkaloids have been a subject of intense synthetic investigation for the past 50 years, and progress in this area continues unabated.[1] In particular, oxidative (radical) dimerization of indole derivatives has provided a relatively simple solution to several classes of natural products, and it is believed that Nature uses a similar strategy.

Psychotrimine (**1**) is a recently isolated[2] alkaloid whose biosynthesis also appears to involve a tryptophan dimerization reaction. However, in this case, a rare example of N1−C3 (indole numbering system) tryptophan linkage is observed in contrast to the more common carbon−carbon linkages. The inherent preference of indoles to oxidatively dimerize at carbon, instead of at nitrogen, makes the construction of this bond uniquely challenging.[3] Unsurprisingly, there are currently no known methodologies to directly construct this type of C−N bond. Herein, we report the invention of such a method and demonstrate its power with an exceptionally concise synthesis of **1** that proceeds on a gram-scale with minimal use of protection chemistry and redox manipulations.

The simplest route to **1** would involve the merger of a dimeric tryptamine such as **2** with the hypothetical tryptamine cation **3** (Figure 1A). Since no such method for this construction existed, considerable efforts were devoted to inventing one. The direct union of prefunctionalized and activated tryptamine and indole subunits proved unsuccessful despite extensive experimentation.[4] Attention was turned to *o*-iodoaniline (**4**) as a potential surrogate for **3** (see Figure 1B). In principle, an activated (oxidized) form of **4** could react with a tryptamine derivative to furnish the desired N−C coupled product **A**. Unfortunately, products **B**−**F** are seemingly more likely to form if the tryptamine were to react with the oxidant or if the activated form of **4** were to act as an oxidant rather than an *N*-electrophile. For instance, products such as **B**,[5] **C**,[6] **D**,[7] **E**,[3a,c,d,f] and **F**[3b,e,g,h] are all known pathways during the oxidation of tryptamines, whereas **A** is not.

The proposed coupling reaction was explored using **4** and tryptophan derivative **5** (Table 1) with a variety of oxidants. Selected results are summarized in Table 1. Most oxidants (entries 1−3) led to complex mixtures from which the desired adduct **6** could be isolated.[8] The use of Koser's reagent[9] (entry 4), while slightly cleaner, required a lengthy purification, was not scalable, and required a 3-fold excess of **4**. Notably, simple halogenating agents such as NCS and NBS (entries 5 and 6) delivered **6** as the major diastereomer using only 1.2 equiv of **4**.[10] The key finding in rendering the reaction robust and scalable was using NIS (entry 7) to afford the C3 aminated product in 45% isolated yield along with ∼40% recovered **5**.

While an unambiguous mechanistic picture requires more extensive studies, order of addition experiments strongly suggest *initial aniline halogenation*.[11] Although the optimal procedure required addition of the oxidant to a mixture of the tryptamine and the aniline, significant product was obtained by preforming the *N*-haloaniline, whereas the inverse experiment (addition of aniline last) led to only trace formation of the desired product. The observed diastereoselectivity for the kinetically favored *exo* diastereomer is consistent with the indole 2,3-π bond reacting with aniline nitrogen, as has been observed with other electrophiles.[12] In line with these observations, the initially formed *N*-haloaniline is primed for nucleophilic attack by the tryptamine C-3 position, giving rise to a transient indolenine species, which after irreversible ring closure affords the desired product.

With an effective method for forging the hallmark feature of **1** in hand, its total synthesis was pursued. Beginning with the

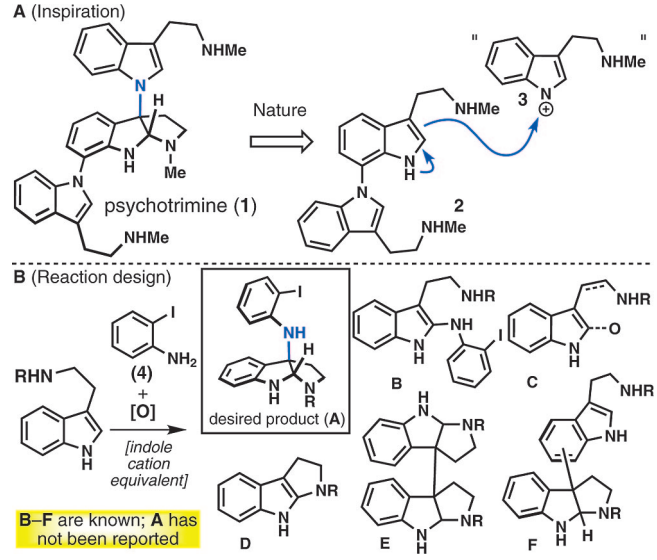
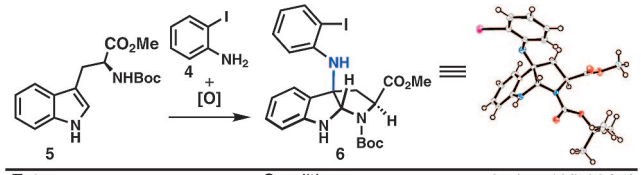


Figure 1. (A) Retrosynthetic analysis of **1** suggests the need to invent a direct coupling of indoles with anilines. (B) Potential products formed in the union of *o*-iodoaniline and a tryptamine derivative.

Table 1. Invention and Optimization of a Direct Indole−Aniline Coupling



Entry	Conditions	Isolated Yield (%)
1	**5** (1.0 eq), **4** (3.0 eq), CH_3CN, CAN (1.0 equiv), 0°C	–
2	**5** (1.0 eq), **4** (3.0 eq), $CHCl_3$, IBD (3.0 equiv), 23 °C	13
3	**5** (1.0 eq), **4** (3.0 eq), CH_3CN, PIFA (1.0 equiv), –30 °C	24
4	**5** (1.0 eq), **4** (3.0 eq), CH_3CN, Koser's reagent (3.0 equiv), 0 °C	46
5	**5** (1.0 eq), **4** (1.2 eq), CH_3CN, Et_3N (1.2 equiv), NCS (2.0 equiv), 0→23 °C	35[a]
6	**5** (1.0 eq), **4** (1.2 eq), CH_3CN, Et_3N (1.2 equiv), NBS (3.0 equiv), 0→23 °C	20[b]
7	**5** (1.0 eq), **4** (1.2 eq), CH_3CN, Et_3N (1.2 equiv), NIS (3.5 equiv), –45→23 °C	45[c,d]

[a] dr = 3:1. [b] dr = 10:1. [c] dr = 13:1 (major diastereomer is **6** in all entries). [d] ∼40% recovered **5**.

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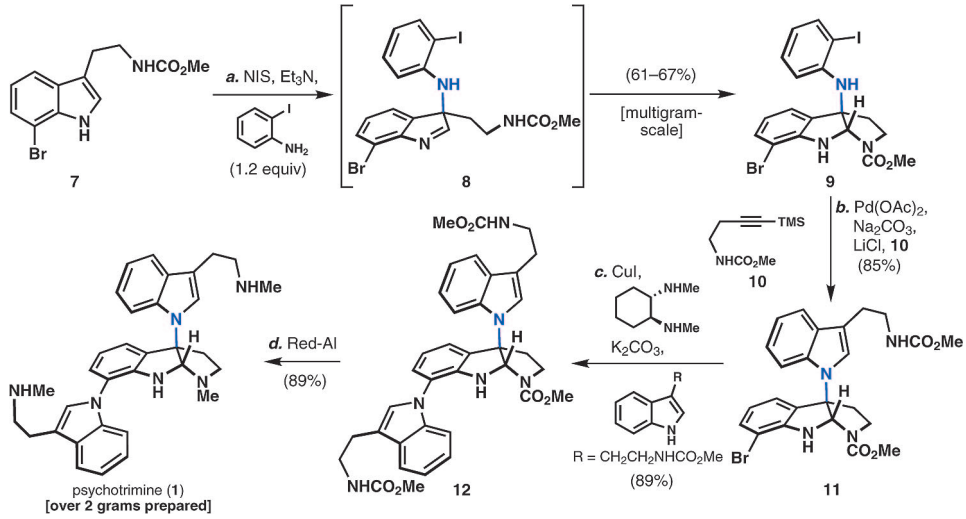
Scheme 1. Short Gram-Scale Total Synthesis of (±)-Psychotrimine (**1**)[a]



[a] Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (3.0 equiv), Et_3N (1.2 equiv), MeCN, −45 → 23 °C, 1 h, 61−67%; (b) $Pd(OAc)_2$ (0.21 equiv), Na_2CO_3 (2.6 equiv), LiCl (0.90 equiv), **10** (2.7 equiv), DMF, 102 °C, 20 min, 85%; (c) CuI (0.32 equiv), (±)-*trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (0.60 equiv), K_2CO_3 (7.0 equiv), N_b-(methoxycarbonyl)tryptamine (3.0 equiv), 1,4-dioxane, 101 °C, 9 h, 89%; (d) sodium bis(2-methoxyethoxy)aluminum hydride (22 equiv), toluene, 110 °C, 30 min, 89%.

methylcarbamate of 7-bromotryptamine (**7**; available by simple carbamoylation of the commercial amine in quantitative yield),[13] the direct aniline coupling was performed on multigram-scale to furnish adduct **9**, presumably via ring-chain tautomer **8** in 61−67% isolated yield along with ca. 30% recovered **7**. In step two of this sequence, a chemoselective Larock annulation[14] with known alkyne **10**[15] was performed, affording dimer **11** in 85% isolated yield (debromination not observed). Use of the Buchwald−Goldberg−Ullmann reaction[16] gave trimeric structure **12** with high chemoselectivity. Notably, *N*-arylation resulting from carbamate or indoline N−H coupling was not observed under these conditions, while palladium-mediated amination[17] led to complex mixtures. In the fourth step of the synthesis, Red-Al achieved triple conversion of the methyl carbamates[3g] in **12** to methyl groups, furnishing the natural product **1**, which was spectroscopically identical to that reported. Over 2 g of **1** has been easily prepared using this route. This compares favorably to the efficiency of both the isolation (21 mg isolated from 2 kg of plant material)[2] and a recently reported total synthesis of (±)-**1** (16 steps, 13.2% overall yield, milligram quantities).[18]

To summarize, the complex natural product psychotrimine (**1**) has been fashioned with a rare level of efficiency and practicality. From readily available **7**, only four steps (41−45% overall isolated yield) are necessary to procure multigram quantities of (±)-**1**. Functional group manipulations, protecting group chemistry, and unnecessary redox fluctuations have been minimized by initial strategy level considerations,[19] highly chemoselective transforms, and the invention of an operationally simple yet strategically powerful method for achieving the direct C-3 quaternization of tryptamine derivatives with *o*-iodoaniline. The high diastereoselectivity in the reaction of **5** + **4** (Table 1) bodes well for an enantioselective route to **1**. Studies along those lines, attempts to pin down the precise mechanism of this fascinating process, and further applications to natural product total synthesis are underway.

Acknowledgment. Financial support for this work was provided by Bristol-Myers Squibb. Dedicated to Prof. Larry Overman on the occasion of his 65th birthday.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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