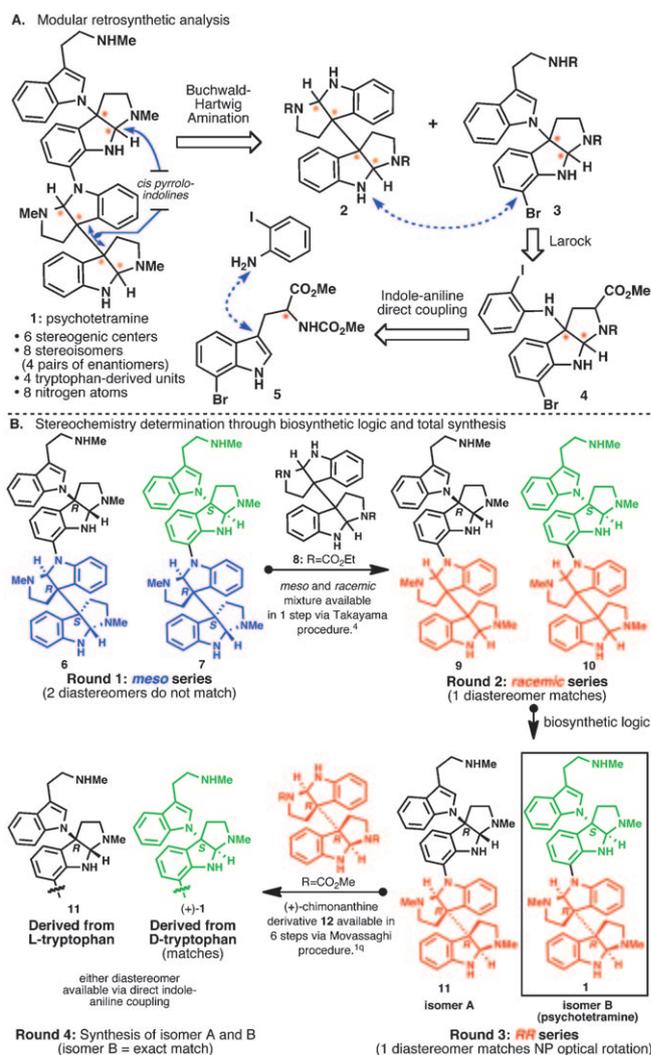


# Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine\*\*

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Polymeric tryptamine-based alkaloids belong to a structurally and biologically fascinating class of natural products.<sup>[1]</sup> Whereas the vast majority of such molecules are linked through C–C bonds, a small subset are linked from the C3 of one indole nucleus to the N1 of another. Psychotetramine (**1**, Scheme 1A) represents the curious case of a tryptamine tetramer containing both types of connectivity: a C3–C3 linked dimer bonded to a C3–N1 dimer through an unusual C7–N1 linkage. This interesting alkaloid was isolated in 2004,<sup>[2]</sup> but due to the limited quantity from nature and its complicated NMR spectra, a final chemical structure including stereochemistry was not determined. Here, a joint venture between our groups (H.T. and P.S.B.) is described, leading to the total synthesis and final structure elucidation of **1**. The pursuit of this complex natural product also led to an efficient enantioselective synthesis of the related alkaloid (+)-psychotrimine, an improved procedure for direct-indole aniline coupling, and one of the most complex and demanding contexts for a Buchwald–Hartwig amination.

Psychotetramine (**1**) was isolated from a rubiaceaceous plant, *Psychotria rostrata*, and exhibited  $[\alpha]_D^{25} = +82$  ( $c = 0.2$ , CHCl<sub>3</sub>). The molecular formula (C<sub>44</sub>H<sub>50</sub>N<sub>8</sub>), obtained by high-resolution FABMS analysis as well as the <sup>13</sup>C NMR spectrum (see Supporting Information), revealed 26 aromatic carbons and 18 sp<sup>3</sup> carbons, including three aminoacetal carbons, indicated that **1** composed of four tryptamine-related moieties containing one indole and three indoline chromophores. Detailed analyses of MS fragment pattern (Supporting Information) and 2D-NMR data indicated the presence of a chimonanthine unit, joined together by a N1–C7 and a C3–N1 linkage, respectively. This type of linkage at the chimonanthine aniline nitrogen is the first reported of hitherto known polymeric tryptamine-related alkaloids.<sup>[1]</sup> A final chemical structure including relative and absolute stereochemistry could not be determined by spectroscopic means.



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Psychotetramine (**1**) is a challenging target, especially without configurational assignment of its six stereogenic centers and the practical demands of molecules with high nitrogen content. Since the three pyrrolidine subunits of **1** must be *cis*-fused, there are eight possible stereoisomers (four pairs of enantiomers). The stereochemical determination and constitutional assignment of **1** was systematically accomplished through four “rounds” of total synthesis as graphically summarized in Scheme 1B.

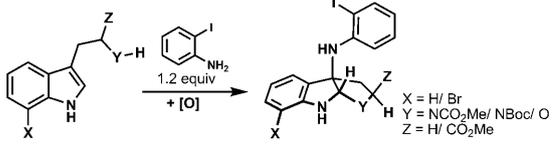
In order to systematically elucidate the structure of **1**, a modular retrosynthetic plan was devised (Scheme 1A). The

C7–N1 linkage was ruptured leading to two fragments of equal size and complexity (**2** and **3**). The union of fragments **2** and **3** was anticipated to test the limits of the Buchwald–Hartwig amination.<sup>[3]</sup> Fragment **2**, a chimonanthine derivative, could be fashioned rapidly as a mixture of isomers using Takayama's procedure for dimerization<sup>[4]</sup> or controllably in Movassaghi's elegant stepwise procedure.<sup>[14]</sup> Fragment **3**, an intermediate in the total synthesis of psychotrimine,<sup>[5]</sup> could be made in both racemic and enantiopure fashion by using the direct indole–aniline coupling of *o*-iodoaniline to **5**, followed by Larock annulation on adduct **4**.

In round 1, two diastereomers (**6** and **7**) were synthesized using a *meso*-chimonanthine fragment (in blue) and a racemic truncated psychotrimine fragment **3** (in green and black). However, neither of these structures matched the spectral data of psychotetramine (**1**). In round 2, the racemic D,L-chimonanthine series was coupled to the racemic truncated psychotrimine portion **3** to deliver diastereomers (**9** and **10**), one of which matched the spectral data of psychotetramine. Up until this point, the Takayama procedure for dimerization was employed since his rapid procedure allowed us to draw some conclusions quickly. In round 3, reasoning that the chimonanthine portion would correspond to the naturally occurring L-series, diastereomers **11** and **1** were synthesized by using Movassaghi's procedure to procure fragment **12**. Gratifyingly, one of those diastereomers matched psychotetramine (**1**), and thus, the final round involved the truncated psychotrimine fragments being synthesized in an enantiopure fashion leading to the finding that the structure of psychotetramine corresponds to **1** (see box, Scheme 1 B). Notably, the top portion of **1** has the same absolute configuration as that of psychotrimine (**23**) as determined by Takayama et al. in their enantiospecific synthesis.<sup>[5c]</sup> Albeit speculative, this may suggest similar biosynthetic pathways of the two natural products.

The total synthesis of (+)-**1** is illustrated in Scheme 2 and is representative (in terms of overall approach) of the syntheses of those preceding it (rounds 1–3, Scheme 1 B). Beginning with 7-bromo-D-tryptophan derivative ((–)-**13**, see Supporting Information for preparation), direct indole–aniline coupling with *o*-iodoaniline would furnish the required adduct (+)-**14**. However, previously reported conditions<sup>[5a,d]</sup> on (–)-**13** (see Table 1, entries 1–5) failed to give adduct (+)-**14** in reasonable yield. Drawing inspiration from our mechanistic studies and previous reports on electrophilic vicinal difunctionalizations of tryptamines,<sup>[6]</sup> it was found that Brønsted acids effectively promoted the reaction, affording (+)-**14**, even at temperatures as low as –35 °C with greater than 20:1 d.r. (entries 6–11). This contrasted with previously reported conditions<sup>[5a,d]</sup> wherein reasonable conversions did not proceed until above 0 °C (entries 4 and 5). The best result was obtained with the use of PPTS as an additive, delivering (+)-**14** in 66% yield (entry 6). Interestingly, these newly developed conditions also improved the yield on the non-brominated analog **25** (entries 12 and 13), brominated and non-brominated Boc-Trp-OME products **26** and **27** (entries 14–18), as well as the previously reported brominated tryptamine derivative product **28** (entries 19–21). The versatility of this new indole–aniline coupling procedure is further

**Table 1:** Optimization table for indole–aniline coupling.

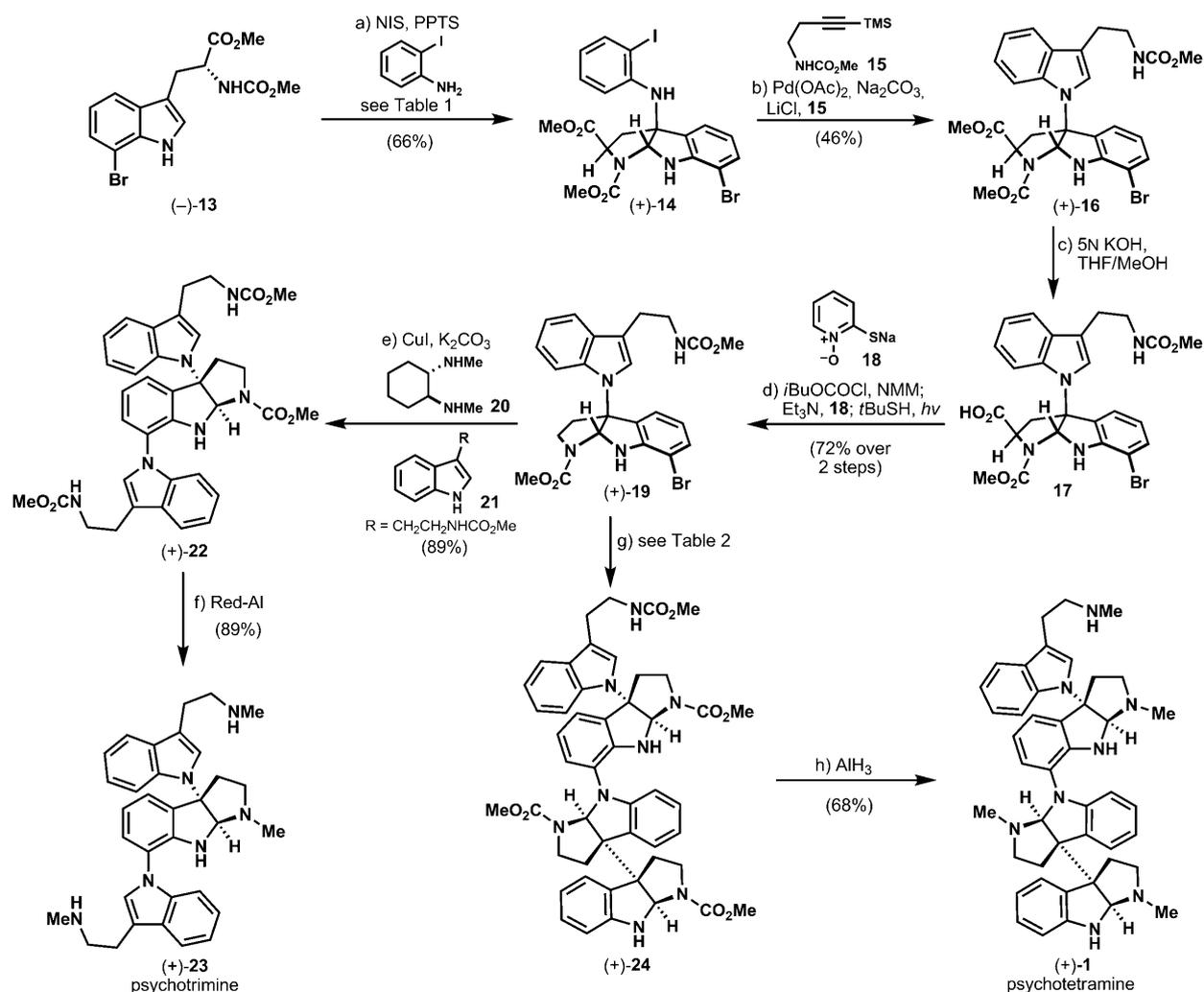


Product	No.	Conditions	% <sup>[a]</sup>
<b>14</b>	1	NIS (1.5 equiv), –45 to –35 °C	0
X = Br	2	NIS (1.1 equiv), EtNO <sub>2</sub> , –78 °C	0
Y = NCO <sub>2</sub> Me	3	Koser's reagent (3.0 equiv), 0 °C	0
Z = CO <sub>2</sub> Me	4	NIS (3.5 equiv), Et <sub>3</sub> N (1.2 equiv), 0 to 23 °C	32 <sup>[b]</sup>
	5	NIS (1.5 equiv), MeOH:MeCN (1:20), –45 to 3 °C	33 <sup>[b]</sup>
<b>6</b>		<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>66</b>
<b>7</b>		NIS (1.6 equiv), (±)-CSA (1.0 equiv), –45 to –35 °C	46
<b>8</b>		NIS (1.6 equiv), TsOH (1.0 equiv), –45 to –35 °C	30
<b>9</b>		NIS (1.6 equiv), TFA (1.0 equiv), –45 to –35 °C	23
<b>10</b>		NIS (1.6 equiv), Sc(OTf) <sub>3</sub> (1.0 equiv), –45 to –35 °C	58
<b>11</b>		NIS (1.6 equiv), AcOH (1.0 equiv), –45 to –35 °C	23
<b>25</b> , X = H	12	NIS (1.5 equiv), MeOH:MeCN (1:20), –45 °C	68
Y = NCO <sub>2</sub> Me	<b>13</b>	<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>75</b>
Z = CO <sub>2</sub> Me			
<b>26</b> , X = Br	14	NIS (3.5 equiv), Et <sub>3</sub> N (1.2 equiv), 0 to 23 °C	24 <sup>[b]</sup>
Y = NBoc	15	NIS (1.5 equiv), MeOH:MeCN (1:20), –45 °C	22 <sup>[c]</sup>
Z = CO <sub>2</sub> Me	<b>16</b>	<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>64</b>
<b>27</b> , X = H	17	NIS (1.5 equiv), MeOH:MeCN (1:20), –45 °C	79 <sup>[d]</sup>
Y = NBoc	<b>18</b>	<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>94</b>
Z = CO <sub>2</sub> Me			
<b>28</b>	19	NIS (3.5 equiv), Et <sub>3</sub> N (1.2 equiv), –45 to –35 °C	24
X = Br	20	NIS (3.5 equiv), Et <sub>3</sub> N (1.2 equiv), –45 to 23 °C	61–67 <sup>[d]</sup>
Y = NCO <sub>2</sub> Me	<b>21</b>	<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>70</b>
Z = H			
<b>29</b> , X = H	<b>22</b>	<b>NIS (1.6 equiv), PPTS (1.0 equiv), –45 to –35 °C</b>	<b>56</b>
Y = O, Z = H			

[a] Yield of isolated products. [b] No conversion was observed until warmed above 0 °C. [c] A d.r. of 1.2:1 was observed. [d] Best yields previously reported. All reactions were run on at least 20 mg scale and in MeCN as solvent, unless otherwise stated. A d.r. of >20:1 was observed unless otherwise stated. Either enantiomer of **13** was used in the optimization study to obtain **14**. NIS = *N*-iodosuccinimide, PPTS = pyridinium *p*-toluenesulfonate, CSA = camphorsulfonic acid.

exemplified by the successful transformation of tryptophol to give compound **29** in 56% yield.

Subsequent Larock annulation<sup>[7]</sup> of (+)-**14** led to tryptamine–tryptophan dimer (+)-**16** in 46% yield. Following saponification with aqueous KOH and Barton decarboxyla-



**Scheme 2.** Total synthesis of (+)-psychotetramine (**1**) and (+)-psychotrimine (**23**). Reagents and conditions: a) PPTS (1.0 equiv), *o*-iodoaniline (1.2 equiv), NIS (1.6 equiv), MeCN,  $-45^{\circ}\text{C}$  to  $-35^{\circ}\text{C}$ , 66%; b) Pd(OAc)<sub>2</sub> (0.21 equiv), LiCl (0.9 equiv), **15** (2.7 equiv), Na<sub>2</sub>CO<sub>3</sub> (2.6 equiv), DMF,  $102^{\circ}\text{C}$ , 1 h, 46%; c) 5 N aq KOH, THF/MeOH (1:2),  $23^{\circ}\text{C}$ , 1 h; d) THF/MeCN (2:1), *i*BuOCOCl (1.2 equiv), NMM (1.0 equiv),  $0^{\circ}\text{C}$  then  $23^{\circ}\text{C}$ , 15 min, then  $0^{\circ}\text{C}$ , **18** (1.2 equiv), Et<sub>3</sub>N (1.0 equiv), 15 min, then *t*BuSH (10 equiv), *h\nu*, 10 min,  $23^{\circ}\text{C}$ , 72% from **16**; e) CuI (0.32 equiv), K<sub>2</sub>CO<sub>3</sub> (7.0 equiv), **20** (0.60 equiv), **21** (3.0 equiv), 1,4-dioxane,  $101^{\circ}\text{C}$ , 9 h, 89%; f) Red-Al (16 equiv), toluene,  $110^{\circ}\text{C}$ , 5 min, 89%; g) [Pd<sub>2</sub>(dba)<sub>3</sub>] (5 mol% based on **19**), RuPhos (20 mol% based on **19**), NaOtBu (2.7 equiv), **12** (0.38 equiv), PhMe,  $100^{\circ}\text{C}$ , 5 h, 41% from **12**; h) AlH<sub>3</sub> (26 equiv), THF,  $60^{\circ}\text{C}$ , 5 min, 68%. MeCN = acetonitrile, DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran, NMM = *N*-methylmorpholine.

tion,<sup>[8]</sup> enantiopure (+)-**19** was in hand without any sign of debromination under the optimized conditions in 72% yield over two steps. The key subunit coupling of the truncated psychotrimine portion (+)-**19** with chimonanthine derivative (+)-**12**<sup>[19]</sup> was accomplished via an unusually complex Buchwald–Hartwig amination.<sup>[3]</sup> It is noteworthy that amination between two sterically congested coupling partners, in this case between an indoline nitrogen (of chimonanthine (+)-**12**) and an *ortho* substituted aryl halide (+)-**19**, in the presence of a total of four N–H’s, is a challenging task that required significant optimization; a selected listing of parameters that were screened is shown in Table 2.

Thus, it was found that RuPhos<sup>[3c]</sup> provided the best results as compared to that of other Buchwald ligands known to form C–N bonds such as XPhos and SPhos.<sup>[9]</sup> Buchwald’s recent modified procedure<sup>[10a]</sup> using LHMDS and the use of weaker bases<sup>[3f]</sup> such as Cs<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> in *t*BuOH or toluene as

solvent all proved to be less effective. The water-mediated catalyst preactivation protocol<sup>[10b]</sup> was also unsuccessful. Initially, it was hypothesized that the yield of the reaction was hampered by rapid debromination of the truncated psychotrimine fragment (+)-**19**. Means to reduce debromination, such as the slow addition of the [Pd<sub>2</sub>(dba)<sub>3</sub>], were unsuccessful. Using a large excess of the chimonanthine-derived fragment (+)-**12** also failed to improve the yield of the reaction. Gratifyingly, the yield of the reaction improved to 41% using an excess (2.6 equiv, 47% of which is recoverable) of (+)-**19** rather than the chimonanthine fragment (+)-**12**.

The total synthesis was completed using alane<sup>[11]</sup> to reductively convert the methylcarbamate groups into the methyl groups expressed in the natural product (+)-**1**. With a scalable route to enantiopure (+)-**19** in hand, an enantioselective total synthesis of psychotrimine (**23**) was also pursued.

**Table 2:** Optimization table for Buchwald–Hartwig amination of **19**.

$19 + 12 \xrightarrow[\text{ligand (20 mol \% to 19), 100 }^\circ\text{C, PhMe}]{[\text{Pd}_2(\text{dba})_3] (5 \text{ mol \% to 19), base,}}$		$24$		
Entry	Ligand	Base (equiv)	12/19 (equiv)	Yield <sup>[a]</sup>
1 <sup>[b]</sup>	RuPhos	NaOtBu (2.5)	1.5:1	30
2	SPhos	NaOtBu (2.5)	1.5:1	< 30
3	XPhos	NaOtBu (2.5)	1.5:1	< 20
4 <sup>[c]</sup>	RuPhos	LHMDS (3.0)	1.5:1	trace
5	RuPhos	K <sub>2</sub> CO <sub>3</sub> (5.0)	1.5:1	< 15
6 <sup>[d]</sup>	P( <i>t</i> Bu) <sub>3</sub> ·HBF <sub>4</sub>	NaOtBu (2.5)	1.5:1	trace
7 <sup>[e]</sup>	RuPhos	NaOtBu (2.5)	1.5:1	10–16
8 <sup>[e]</sup>	RuPhos	NaOtBu (4.0)	3.0:1	10
9 <sup>[e]</sup>	RuPhos	NaOtBu (4.0) <sup>[f]</sup>	1:3.0	32 <sup>[g]</sup>
10 <sup>[e]</sup>	RuPhos	NaOtBu (3.0) <sup>[f]</sup>	1:2.0	17 <sup>[g]</sup>
11 <sup>[e]</sup>	<b>RuPhos</b>	<b>NaOtBu (2.7)<sup>[f]</sup></b>	<b>1:2.6</b>	<b>41<sup>[g]</sup></b>

[a] Yield of isolated products. [b] Slow addition of [Pd<sub>2</sub>(dba)<sub>3</sub>] has no effect on yield. [c] Reaction was performed at 65 °C in THF.<sup>[10a]</sup> [d] Pd(OAc)<sub>2</sub> (5 mol%) was used with ligand (6 mol%). [e] Reaction was performed on at least 10 mg scale of **19**. [f] Base equivalents based on **12**. [g] Yield based on **12**. All reactions were run with 5 mg of **19** unless otherwise stated. Reactions were monitored with LC-MS for a maximum of 12 h. Other solvents (*t*BuOH, 1,4-dioxane), temperature, and amount of base (molar sum of **12** + **19**) were screened.

Thus, copper-mediated amination of (+)-**19** with the known tryptamine derivative **21**, followed by reduction of the methylcarbamate groups using Red-Al furnished psychotrimine (+)-**23** rapidly, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +193 (*c* = 1.0, CHCl<sub>3</sub>) (natural [ $\alpha$ ]<sub>D</sub><sup>18</sup> = +179 (*c* = 0.2, CHCl<sub>3</sub>)).<sup>[5c]</sup> This represents the shortest and highest yielding route to enantiopure psychotrimine (**23**) (9 steps, 7% overall from 7-bromoindole).

Synthetic psychotetramine (**1**) was spectroscopically similar to the spectra recorded in 2004 for *nat-1* but it was not identical. Although the <sup>1</sup>H NMR spectrum is a nearly exact match to that reported by Takayama et al., the <sup>13</sup>C NMR spectrum had several small differences (mainly in the N-Me region). It was found that the <sup>1</sup>H NMR spectrum displayed small differences as a function of concentration and solvent batch. The structure was finally secured and confirmed to be identical to *nat-1* upon repurification of the last remaining sample of *nat-1* followed by both co-HPLC and NMR with a synthetic sample.

In conclusion we have reported a solution to the stereochemical puzzle posed by psychotetramine (**1**) and the shortest and most efficient route thus far to access enantiopure psychotrimine (**23**). Along the way, a new general protocol was invented for the direct aniline–indole coupling that utilizes PPTS as a crucial additive. Overall, the described total synthesis showcases the utility of a modular approach to the synthesis of chimonanthine–psychotrimine hybrids through three powerfully simplifying assembly events: homodimerization of tryptophan,<sup>[14,4]</sup> heterocoupling of tryptophan with *o*-iodoaniline,<sup>[5a,d]</sup> and Buchwald–Hartwig amination.<sup>[3]</sup>

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