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Palladium-catalyzed synthesis of tryptamines and tryptamine homologues: synthesis of psilocin

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ABSTRACT

A new Pd-catalyzed method for the synthesis of tryptamines is developed, and its applications to the synthesis of Corey's aspidophytine tryptamine **15** and psilocin **20** are also described.

1. Introduction

The tryptamines are an important class of compounds, whose structural motif is often embedded in naturally occurring molecules and pharmaceuticals.[1] Many of tryptamines and their derivatives possess potent biological activity, such as the neurotransmitter serotonin **1** [(3-(2-aminoethyl)-5-hydroxyindole, 5-hydroxytryptamine) (5-HT)],[2] toad poison dehydrobufotenine **2**,[3] and serotobenine **3** alkaloids (Fig. 1).[4]

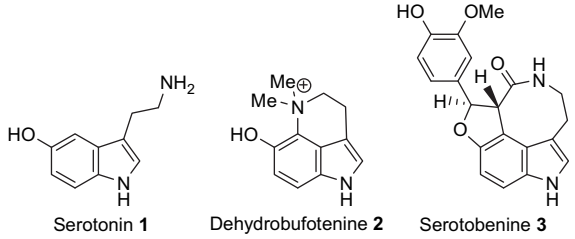

Figure 1. Examples of biologically active indoles.

A variety of well-documented traditional and modern methods for the synthesis of tryptamines with many possible substitution patterns on the benzene ring have been described, which can be divided into two broad categories. The first approach is to construct the pyrrole ring using an annulation method onto an appropriately substituted benzene precursor. Among these methods are the Fischer indole synthesis using 4-aminobutyraldehyde equivalent,[5] Abramovitch–Shapiro method,[6] and palladium-catalyzed tryptamine syntheses.[7] More recently, Nicolaou et al. reported an expedient and efficient cascade process based on metalation.[8] However, some of these reported methodologies suffer some disadvantages. For example, under traditional Fischer indole synthesis conditions, electron-deficient *p*-substituted phenylhydrazines cannot provide indoles, *m*-substituted phenylhydrazines usually yield a mixture of 4- and 6-substituted indoles, and the abnormal products were usually obtained during the Fischer indolization of *o*-methoxyphenylhydrazones.[9,5a]

The second approach is selective functionalization of the 3-position of benzene-substituted indole framework. Among the most successful methods in this category are gramine based approach,[10] reaction of indoles with oxalyl chloride followed by amination and reduction,[11] condensation of indoles with 2-nitroethyl acetate (or its equivalent) followed by hydrogenation.[12] However, these methods require a prefunctionalized indole unit, which can be either difficult to prepare or expensive.

Palladium-catalyzed transformations generally require only a catalytic amount of a metal complex and are tolerant of a large number of functional groups. Although the palladium-catalyzed reactions have had an important impact on indole synthesis,[13] there was few corresponding tryptamine synthesis was reported.[7] In 1997, the elegant work of Chen has demonstrated that indoles can be prepared by palladium-catalyzed one-pot annulation of *ortho*-iodoanilines and cyclic ketones.[14] Recently, Jia and Zhu have extended this method for the synthesis of highly benzene-substituted indoles by using aldehydes as starting materials.[15] In connection with a total synthesis project and due to the limitation of the current available synthetic approaches to benzene-substituted tryptamine derivatives, we now wish to report that this palladium-catalyzed method is also highly efficient for the preparation of tryptamines and tryptamine homologues. The application of this chemistry to the synthesis of 6,7-dimethoxy-1-methyltryptamine and total synthesis of the hallucinogenic psilocin is also documented.

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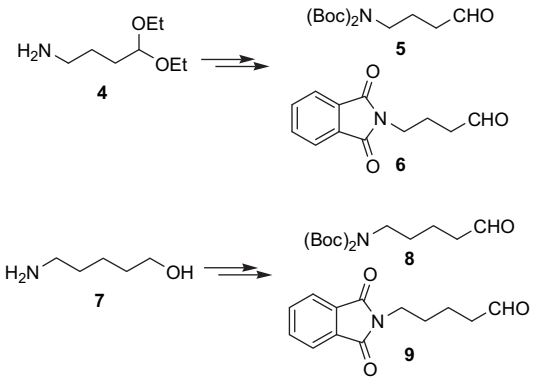
2. Results and discussions

In order to determine the influence of the nitrogen protecting groups, concerning the different deprotecting conditions for Boc and Phth, the Boc(or Phth)-protected 4-aminobutanal **5**, **6** and 5-aminopentanal **8**, **9** were synthesized in a few steps from commercially available aminoketal **4** or aminoalcohol **7** by the straightforward sequences (Scheme 1).[16]



Scheme 1. Synthesis of *N*-protected 4-aminobutanal and 5-aminopentanal.

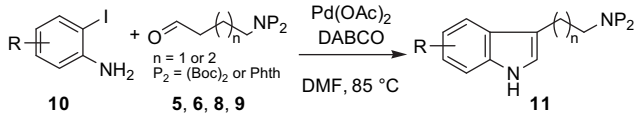
Reaction of *o*-iodoaniline **10a** with aldehyde **5** was examined as a model under standard condition (5% mol $Pd(OAc)_2$, DABCO, DMF, 85 °C). However, the two starting materials were not completely consumed even after 24 h. After several trials, we found that reaction of **10a** with **5** in the presence of 5% mol $Pd(OAc)_2$ and DABCO in DMF at 85 °C for 12 h, followed by the addition of 5% mol $Pd(OAc)_2$ and additional reaction for 12 h at the same temperature, afforded the desired tryptamine in 56% yield.

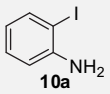
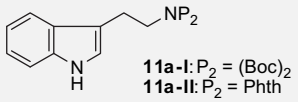
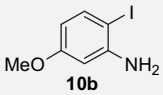
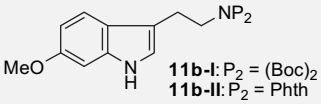
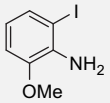
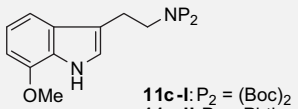
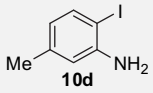
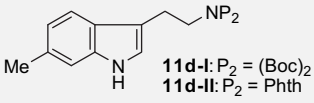
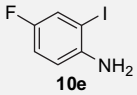
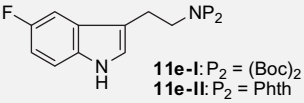
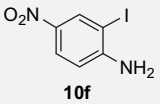
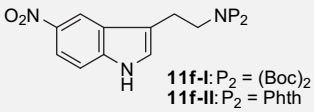
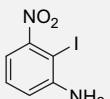
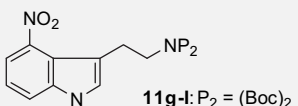
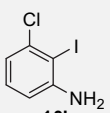
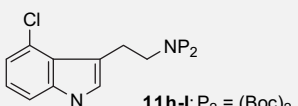
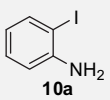
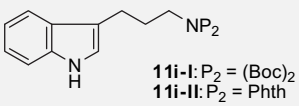
Once reliable conditions to synthesize tryptamines were established, we next investigated the scope of this reaction using various *o*-iodoanilines by varying systematically the electronic properties and substitution patterns of the aromatic ring (Table 1). The reaction worked well for *o*-iodoaniline with both electron-donating (entries 2–4), electron-withdrawing group (entries 5–8), and a diverse array of substitution patterns. Only **10h** gave the corresponding product **11h** in low yield. It is noteworthy that the tryptamine homologues **11i** can be readily synthesized starting from **8** or **9**.

In order to demonstrate the potential application of this methodology, we developed an alternative and expedient route for the synthesis of 6,7-dimethoxy-1-methyltryptamine **15**, a building block used by Corey in his elegant synthesis of aspidophytine (Scheme 2).[17,8b] Thus, reaction of the known 6-iodo-2,3-dimethoxy-aniline (**12**)[18] with aldehyde **6** provided the desired product **13** in 60% yield. Methylation of **13** (KOH, MeI) followed by deprotection gave 6,7-dimethoxy-1-methyltryptamine **15**.

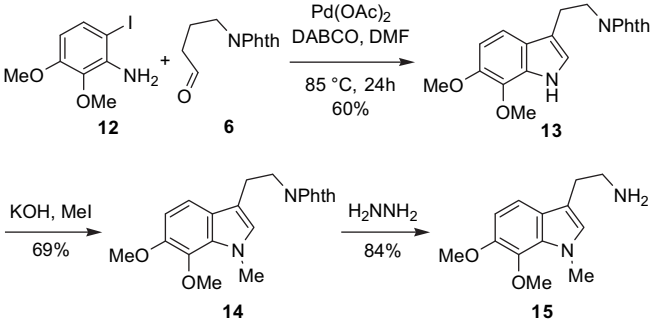
In order to explore its potential application in natural product total synthesis, we also developed an alternative and expedient entry into the synthesis of the hallucinogenic psilocin. Psilocin **20** was isolated from hallucinogenic fungi 'Magic mushrooms', which has received considerable attention from synthetic and medicinal chemists.[19] We adopted this chemistry to total synthesis of psilocin in a straightforward manner (Scheme 3). Thus, reaction of the known 2-iodo-3-methoxy-aniline **16** with aldehyde **6** provided the desired product **17** in 48% yield. Hydrolysis of **17** followed by reductive amination gave the desired product **19**, which was demethylated following the literature procedure to afford the psilocin.[19a]

Table 1
Synthesis of tryptamines.[a]

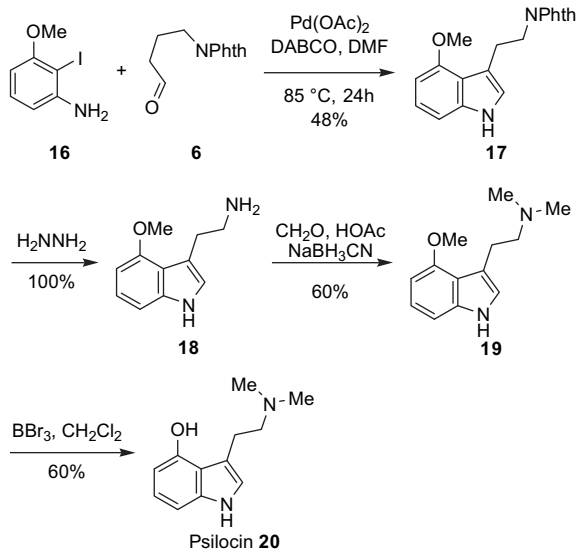


Entry	*O*-iodoaniline	Product	Yield[b] (%)
1	 **10a**	 **11a-I**: P_2 = $(Boc)_2$ **11a-II**: P_2 = Phth	56 52
2	 **10b**	 **11b-I**: P_2 = $(Boc)_2$ **11b-II**: P_2 = Phth	49 50
3	 **10c**	 **11c-I**: P_2 = $(Boc)_2$ **11c-II**: P_2 = Phth	79 66
4	 **10d**	 **11d-I**: P_2 = $(Boc)_2$ **11d-II**: P_2 = Phth	44 53
5	 **10e**	 **11e-I**: P_2 = $(Boc)_2$ **11e-II**: P_2 = Phth	56 49
6	 **10f**	 **11f-I**: P_2 = $(Boc)_2$ **11f-II**: P_2 = Phth	50 63
7	 **10g**	 **11g-I**: P_2 = $(Boc)_2$ **11g-II**: P_2 = Phth	50 60
8	 **10h**	 **11h-I**: P_2 = $(Boc)_2$ **11h-II**: P_2 = Phth	16 23
9	 **10a**	 **11i-I**: P_2 = $(Boc)_2$ **11i-II**: P_2 = Phth	52 77

[a] General reaction conditions: concentration 0.2 M in DMF, 0.10 equiv of $Pd(OAc)_2$, 1.0 equiv of *o*-iodoaniline **10**, 1.2 equiv of aldehyde, 3.0 equiv of DABCO, 85 °C.
[b] Isolated yield.



Scheme 2. Synthesis of Corey's aspidophytine tryptamine **15**.



Scheme 3. Total synthesis of psilocin.

3. Conclusion

In summary, we have developed a new and efficient palladium-catalyzed method for the synthesis of tryptamines and tryptamine homologues in a straightforward manner. The short synthesis of 6,7-dimethoxy-1-methyltryptamine and psilocin were also achieved by employing this chemistry. The present approach constitutes one of the most efficient accesses for benzene-substituted tryptamines and tryptamine homologues. We believe this chemistry will find wide applicability in organic synthesis.

4. Experimental section

4.1. Typical procedure

A mixture of *o*-iodoaniline (0.5 mmol), aldehyde (0.6 mmol), and DABCO (330.5 mg, 1.5 mmol) in dry DMF (2.5 mL) was degassed for 20 min. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) was added to the reaction, and the resulting reaction mixture was heated at 85 °C for 12 h followed by the addition of 5% mol $Pd(OAc)_2$, and stirred until the reaction was completed (usually 24–36 h; the progress of the reaction was monitored by TLC). The reaction mixture was cooled to room temperature and diluted with water. The aqueous phase was extracted with EtOAc (3×10 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of crude product by flash column chromatography provided the desired product.

4.2. Compound 11a–I (P_2=(Boc)$_2$)

A white solid; yielded 56%; mp 122–124 °C [lit.,[20] mp 122–124 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.68 (d, J=7.6 Hz, 1H), 7.36 (d, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H), 7. 00 (d, J=2.0 Hz, 1H), 3.88 (t, J=7.6 Hz, 2H), 3.05 (t, J=7.6 Hz, 1H), 1.47 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (2C), 136.3, 127.5, 122.2, 121.8, 119.2, 118.8, 112.7, 111.2, 82.1 (2C), 47.1, 28.0 (6C), 24.9; HRMS (ESI) m/z calcd for $C_{20}H_{28}N_2O_4Na$ $(M+Na)^+$ 383.1941; found 383.1939.

4.3. Compound 11a–II (P_2=Phth)

A yellow solid; yielded 52%; mp 164–166 °C [lit.,[21] mp 164–165 °C]; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.01 (br s, 1H), 7.85–7.83 (m, 2H), 7.74 (d, J=8.0 Hz, 1H), 7.71–7.69 (m, 2H), 7.35 (d, J=8.0 Hz, 1H), 7.19 (dt, J=8.0, 1.2 Hz, 1H), 7.13 (dt, J=8.0, 1.2 Hz, 1H), 7.10 (s, 1H), 4.01 (t, J=8.0 Hz, 2H), 3.16 (t, J=8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 136.3, 133.9, 132.2, 128.3, 127.4, 123.2, 122.1, 119.5, 118.8, 112.3, 111.1, 38.4, 24.3; HRMS (ESI) m/z calcd for $C_{18}H_{15}N_2O_2$ $(M+H)^+$ 291.1128; found 291.1126.

4.4. Compound 11b–I (P_2=(Boc)$_2$)[7a]

A white solid; yielded 49%; mp 162–164 °C; IR (KBr) ν_{max}: 3337, 2975, 1773, 1367, 1144, 1121, 1097, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.53 (d, J=8.8 Hz, 1H), 6.89 (d, J=2.0 Hz, 1H), 6.86 (d, J=2.0 Hz, 1H), 6.79 (dd, J=8.8, 2.0 Hz, 1H), 3,85 (t, J=7.2 Hz, 2H), 3.84 (s, 3H), 3.00 (t, J=7.2 Hz, 2H), 1.47 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 152.5 (2C), 137.0, 122.0, 120.9, 119.4, 112.9, 109.3, 94.7, 82.1 (2C), 55.7, 47.1, 28.0 (6C), 25.0; HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2O_5Na$ $(M+Na)^+$ 413.2047; found 413.2051.

4.5. Compound 11b–II (P_2=Phth)

A yellow solid; yielded 50%; mp 182–184 °C; IR (KBr) ν_{max}: 3382, 2947, 1763, 1708, 1627, 1397, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.84–7.82 (m, 2H), 7.71–7.69 (m, 2H), 7.59 (d, J=8.8 Hz, 1H), 6.97 (d, J=2.0 Hz, 1H), 6.83 (d, J=2.0 Hz, 1H), 6.79 (dd, J=8.8, 2.0 Hz, 1H), 3.99 (t, J=7.6 Hz, 2H), 3.83 (s, 3H), 3.12 (t, J=7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 156.6, 136.9, 133.8, 132.2, 123.2, 121.8, 120.7, 119.4, 112.4, 109.5, 94.6, 55.6, 38.5, 24.5; HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2O_3$ $(M+H)^+$ 321.1234; found 321.1228.

4.6. Compound 11c–I (P_2=(Boc)$_2$)

A white solid; yielded 79%; mp 106–108 °C; IR (KBr) ν_{max}: 3358, 2978, 1777, 1747, 1692, 1368, 1126, 1095, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.05 (t, J=8.0 Hz, 1H), 6.99 (d, J=2.0 Hz, 1H), 6.65 (d, J=8.0 Hz, 1H), 3.95 (s, 3H), 3.87 (t, J=8.0 Hz, 2H), 3.04 (t, J=8.0 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 (2C), 146.3, 129.0, 126.8, 121.7, 119.7, 113.4, 111.7, 101.8, 82.0 (2C), 55.2, 47.1, 27.9 (6C), 25.0; HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2O_5Na$ $(M+Na)^+$ 413.2047; found 413.2048.

4.7. Compound 11c–II (P_2=Phth)

A yellow solid; yielded 66%; mp 142–146 °C; IR (KBr) ν_{max}: 3340, 1769, 1696, 1398, 1085, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.84–7.81 (m, 2H), 7.71–7.68 (m, 2H), 7.35 (d, J=8.0 Hz, 1H), 7.06 (s, 1H), 7.05 (t, J=8.0 Hz, 1H), 6.64 (d, J=8.0 Hz, 1H), 4.01 (t, J=8.0 Hz, 2H), 3.94 (s, 3H), 3.14 (t, J=8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 146.1, 133.8, 132.1, 128.7, 126.7, 123.1, 121.6, 119.9, 112.7, 111.6, 101.9, 55.2, 38.5, 24.6; HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2O_3$ $(M+H)^+$ 321.1234; found 321.1233.

4.8. Compound 11d–I (P_2=(Boc)$_2$)

A white solid; yielded 44%; mp 152–154 °C; IR (KBr) ν_{max}: 3334, 2975, 1778, 1368, 1134, 1092, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.43 (s, 1H), 7.23 (d, J=8.0 Hz, 1H), 6.99 (dd, J=8.0, 2.0 Hz, 1H), 6.93 (d, J=2.0 Hz, 1H), 3.86 (t, J=7.6 Hz, 2H), 3.01 (t, J=7.6 Hz, 2H), 2.45 (s, 3H), 1.46 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (2C), 134.6, 128.3, 127.8, 123.4, 122.4, 118.4, 112.2, 110.8, 82.0 (2C), 47.2, 28.0 (6C), 25.0, 21.4; HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2O_4Na$ $(M+Na)^+$ 397.2098; found 397.2090.

4.9. Compound 11d–II (P_2=Phth)

A yellow solid; yielded 53%; mp 167–170 °C; IR (KBr) ν_{max}: 3375, 1767, 1701, 1432, 1396, 1355, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.94 (br s, 1H), 7.84–7.81 (m, 2H), 7.72–7.69 (m, 2H), 7.48 (s, 1H), 7.23 (d, *J*=8.4 Hz, 1H), 7.05 (d, *J*=1.6 Hz, 1H), 7.00 (d, *J*=8.4 Hz, 1H), 4.00 (t, *J*=8.0 Hz, 2H), 3.13 (t, *J*=8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 134.5, 133.8, 132.2, 128.7, 127.6, 123.7, 123.1, 122.1, 118.4, 111.9, 110.7, 38.6, 24.4, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}N_2O_2$ $(M+H)^+$ 305.1285; found 305.1283.

4.10. Compound 11e–I (P_2=$(Boc)_2$)

A white solid; yielded 56%; mp 158–160 °C; IR (KBr) ν_{max}: 3311, 2980, 1771, 1367, 1283, 1130, 1087, 936, 846, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (br s, 1H), 7.31 (dd, *J*=8.8, 4.8 Hz, 1H), 7.22 (dd, *J*=10, 2.4 Hz, 1H), 7.17 (d, *J*=2.4 Hz, 1H), 6.89 (dt, *J*=9.2, 2.4 Hz, 2H), 3.70 (t, *J*=7.2 Hz, 2H), 2.87 (t, *J*=8.0 Hz, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7 (d, *J*=230 Hz), 152.0 (2C), 132.9, 127.5 (d, *J*=9 Hz), 125.2, 112.3 (d, *J*=10 Hz), 111.1 (d, *J*=4 Hz), 108.9 (d, *J*=26 Hz), 102.7 (d, *J*=22 Hz), 81.5 (2C), 46.6, 27.5 (6C), 24.4; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}FN_2O_4Na$ $(M+Na)^+$ 401.1847; found 401.1841.

4.11. Compound 11e–II (P_2=Phth)

A yellow solid; yielded 49%; mp 122–124 °C; IR (KBr) ν_{max}: 3376, 1765, 1711, 1398, 1360, 1094, 1027, 991, 715 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (br s, 1H), 7.84–7.79 (m, 4H), 7.30 (dd, *J*=8.8, 4.4 Hz, 1H), 7.26 (dd, *J*=10.0, 2.4 Hz, 1H), 7.23 (d, *J*=2.0 Hz, 1H), 6.88 (dt, *J*=9.2, 2.4 Hz, 1H), 3.82 (t, *J*=7.6 Hz, 2H), 2.98 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 156.7 (d, *J*=230 Hz), 134.3, 132.9, 131.6, 127.3 (d, *J*=10 Hz), 125.1, 123.0, 112.4 (d, *J*=10 Hz), 110.9 (d, *J*=5 Hz), 109.1 (d, *J*=26 Hz), 102.6 (d, *J*=23 Hz), 38.0, 23.7. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}FN_2O_2$ $(M+H)^+$ 309.1034; found 309.1027.

4.12. Compound 11f–I (P2=$(Boc)_2$)

A yellow solid; yielded 50%; mp 180–182 °C; IR (KBr) ν_{max}: 3281, 2980, 1771, 1369, 1331, 1232, 1143, 1111, 1083, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 8.48 (d, *J*=2.0 Hz, 1H), 7.97 (dd, *J*=8.8, 2.0 Hz, 1H), 7.50 (d, *J*=8.8 Hz, 1H), 7.39 (s, 1H), 3.74 (t, *J*=6.8 Hz, 2H), 2.99 (t, *J*=6.8 Hz, 2H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.0 (2C), 140.3, 139.4, 127.2, 126.7, 116.4, 115.6, 114.1, 111.8, 81.5 (2C), 46.8, 27.4 (6C), 24.1; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}N_3O_6Na$ $(M+Na)^+$ 428.1792; found 428.1787.

4.13. Compound 11f-II (P_2=Phth)

A yellow solid; yielded 63%; mp 228–230 °C; IR (KBr) ν_{max}: 3432, 1768, 1708, 1398, 1327, 1122, 720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (br s, 1H), 8.51 (d, *J*=2.0 Hz, 1H), 7.94 (dd, *J*=8.8, 2.0 Hz, 1H), 7.82–7.79 (m, 4H), 7.48 (d, *J*=8.8 Hz, 1H), 7.44 (d, *J*=2.4 Hz, 1H), 3.86 (t, *J*=7.2 Hz, 2H), 3.10 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 167.8, 140.2, 139.4, 134.3, 131.5, 127.1, 126.4, 123.0, 116.4, 115.3, 113.9, 111.9, 38.2, 23.4; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}N_4O_4$ $(M+NH_4)^+$ 353.1244; found 353.1248.

4.14. Compound 11g–I (P_2=$(Boc)_2$)

A yellow solid; yielded 50%; mp 186–188 °C; IR (KBr) ν_{max}: 3269, 2985, 1766, 1521, 1367, 1328, 1138, 1103, 787 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.97 (br s, 1H), 7.93 (d, *J*=7.8 Hz, 1H), 7.92 (d, *J*=7.8 Hz, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 6.99 (d, *J*=2.4 Hz, 1H), 4.02 (t, *J*=5.4 Hz, 2H), 3.17 (t, *J*=5.4 Hz, 2H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (2C), 142.7, 139.8, 129.8, 119.8, 119.4, 118.4, 117.5, 110.6, 82.2 (2C), 47.3, 27.6 (6C), 27.0. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}N_3O_6Na$ $(M+Na)^+$ 428.1792; found 428.1785.

4.15. Compound 11g–II (P_2=Phth)

A red solid; yielded 60%; mp >250 °C; IR (KBr) ν_{max}: 3357, 1770, 1715, 1392, 1321, 1284, 1103, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (br s, 1H), 7.82–7.74 (m, 6H), 7.45 (s, 1H), 7.24 (t, *J*=8.0 Hz, 1H), 3.77 (t, *J*=6.8 Hz, 2H), 3.14 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 142.5, 139.3, 134.3, 131.4, 129.5, 122.9, 122.0, 118.3, 116.9, 110.2, 39.5 (in solvent peaks), 25.9; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}N_3O_4$ $(M+H)^+$ 336.0979; found 336.0973.

4.16. Compound 11h–I (P_2=$(Boc)_2$)

A pale yellow solid; yielded 16%; mp 184–188 °C; IR (KBr) ν_{max}: 3299, 2984, 1773, 1366, 1139, 1100, 742 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$) δ 9.42 (br s, 1H), 7.36 (t, *J*=4.4 Hz, 1H), 7.04 (s, 1H), 7.03 (s, 1H), 6.87 (d, *J*=2.4 Hz, 1H), 4.04 (t, *J*=6.4 Hz, 2H), 3.25 (t, *J*=6.0 Hz, 2H), 1.29 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (2C), 138.2, 126.2, 125.0, 124.4, 121.9, 119.8, 111.9, 110.5, 81.9 (2C), 47.6, 27.7 (6C), 25.8; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}ClN_2O_4Na$ $(M+Na)^+$ 417.1552; found 417.1555.

4.17. Compound 11h–II (P_2=Phth)

A yellow solid; yielded 23%; mp 220–222 °C; IR (KBr) ν_{max}: 3376, 1767, 1703, 1394, 1106, 716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (br s, 1H), 7.85–7.80 (m, 4H), 7.30 (dd, *J*=7.6, 1.2 Hz, 1H), 7.20 (d, *J*=2.4 Hz, 1H), 7.03 (t, *J*=7.6 Hz, 1H), 6.99 (dd, *J*=7.6, 1.2 Hz, 1H), 3.91 (t, *J*=7.2 Hz, 2H), 3.23 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.8, 137.9, 134.4, 131.6, 125.3, 124.6, 123.5, 123.0, 121.8, 119.2, 110.8, 110.7, 39.5 (in solvent peaks), 24.9; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}ClN_2O_2$ $(M+H)^+$ 325.0738; found 325.0730.

4.18. Compound 11i–I (P_2=$(Boc)_2$)

A white solid; yielded 52%; mp 115–116 °C; IR (KBr) ν_{max}: 3346, 2976, 1772, 1368, 1137, 1120, 1098, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.18 (dt, *J*=8.0, 1.2 Hz, 1H), 7.10 (dt, *J*=8.0, 1.6 Hz, 1H), 7.02 (d, *J*=2.0 Hz, 1H), 3.69 (t, *J*=7.6 Hz, 2H), 2.77 (t, *J*=7.6 Hz, 2H), 2.05–1.99 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 152.7 (2C), 136.3, 127.4, 121.9, 121.1, 119.1, 118.7, 115.8, 111.0, 82.1 (2C), 46.4, 29.3, 28.0 (6C), 22.4; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{30}N_2O_4Na$ $(M+Na)^+$ 397.2098; found 397.2090.

4.19. Compound 11i–II (P_2=Phth)

A yellow solid; yielded 77%; mp 130–132 °C [lit.,[22] mp 131–132]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.84–7.81 (m, 2H), 7.72–7.69 (m, 2H), 7.60 (d, *J*=8.0 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.17 (dt, *J*=8.0, 0.8 Hz, 1H), 7.11 (dt, *J*=8.0, 1.2 Hz, 1H), 7.08 (d, *J*=2.0 Hz, 1H), 3.81 (t, *J*=7.2 Hz, 2H), 2.84 (t, *J*=7.2 Hz, 2H), 2.18–2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 136.3, 133.8, 132.1, 127.3, 123.1, 121.9, 121.5, 119.1, 118.8, 115.1, 111.0, 37.8, 28.5, 22.4; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}N_2O_2$ $(M+H)^+$ 305.1285; found 305.1286.

4.20. Compound 13

A yellow solid; yielded 60%; mp 170–172 °C; IR (KBr) ν_{max}: 3382, 3358, 1767, 1702, 1398, 1082, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.85–7.83 (m, 2H), 7.72–7.69 (m, 2H), 7.38 (d, *J*=8.8 Hz, 1H), 7.02 (d, *J*=1.6 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 1H), 3.99 (t, *J*=8.0 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.10 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 147.2, 134.5, 133.8, 132.2, 130.8, 124.2, 123.1, 121.6, 113.8, 112.7, 108.4, 60.8, 57.5, 38.4, 24.5; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}N_2O_4$ $(M+H)^+$ 351.1339; found 351.1338.

4.21. Compound 14

To a solution of compound **13** (100 mg, 0.285 mmol) in dry THF was added KOH (32 mg, 0.57 mmol), (t-Bu)$_4$NI (11 mg, 0.0285 mmol), MeI (203 mg, 1.43 mmol), $MgSO_4$ (100 mg) at rt. The reaction mixture was stirred at rt for 1 day. Filtered by Celite, the solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (3×30 mL). The combined organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on Silica column chromatography (PE-EtOAc 5:1) to give compound **14** (72 mg) as a yellow powder. Yielded 69%; mp 151–153 °C; IR (KBr) ν_{max}: 1765, 1709, 1397, 1369, 1262, 1082, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.83 (m, 2H), 7.72–7.69 (m, 2H), 7.36 (d, J=8.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 6.79 (s, 1H), 3.95 (t, J=8.0 Hz, 2H), 3.94 (s, 6H), 3.92 (s, 3H), 3.06 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 148.0, 135.9, 133.8, 132.2, 130.4, 127.8, 125.5, 123.1, 113.9, 110.7, 108.0, 61.7, 57.5, 38.5, 35.1, 24.4; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_2O_4$ $(M+H)^+$ 365.1496; found 365.1490.

4.22. Compound 15[17a]

To a solution of compound **14** (52 mg, 0.143 mmol) in 5 mL of dry MeOH, 85% hydrazine hydrate (0.35 mL, 7.15 mmol) was added and the mixture was stirred at rt for 4 h. After addition of saturated $NaHCO_3$ solution (20 mL), MeOH was evaporated under reduced pressure. The aqueous phase was extracted with EtOAc (8×20 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on Silica column chromatography ($MeOH/CH_2Cl_2$–NH_4OH 10:100:1) to give compound **15** (28 mg) as a light yellow oil. Yielded 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J=8.8 Hz, 1H), 6.80 (d, J=8.8 Hz, 1H), 6.72 (s, 1H), 3.93 (s, 6H), 3.91 (s, 3H), 3.00 (t, J=6.8 Hz, 2H), 2.85 (t, J=6.8 Hz, 2H), 2.56 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 135.9, 130.5, 128.0, 125.5, 113.8, 111.5, 107.7, 61.7, 57.4, 42.0, 35.1, 28.4; HRMS (ESI) m/z calcd for $C_{13}H_{19}N_2O_2$ $(M+H)^+$ 235.1441; found 235.1446.

4.23. Compound 17

A yellow solid; yielded 48%; mp 164–166 °C; IR (KBr) ν_{max}: 3341, 1770, 1707, 1395, 1355, 1258, 1092, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.82–7.79 (m, 2H), 7.70–7.67 (m, 2H), 7.07 (t, J=8.0 Hz, 1H), 6.94 (d, J=8.0 Hz, 1H), 6.93 (d, J=8.0 Hz, 1H), 6.45 (d, J=8.0 Hz, 1H), 4.04 (t, J=7.2 Hz, 2H), 3.96 (s, 3H), 3.23 (t, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.6, 137.9, 133.7, 132.3, 123.0, 122.9, 121.1, 117.4, 113.0, 104.3, 99.3, 55.0, 39.9, 26.1; HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2O_3$ $(M+H)^+$ 321.1234; found 321.1241.

4.24. Compound 19[19c]

To a solution of compound **17** (100 mg, 0.31 mmol) in dry MeOH (10 mL), 85% hydrazine hydrate (775 mg, 15.5 mmol) was added and the mixture was stirred at rt for 4 h. After addition of saturated $NaHCO_3$ solution (20 mL), MeOH was evaporated under reduced pressure. The aqueous phase was extracted with EtOAc (6×10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by Silica column chromatography ($MeOH/CH_2Cl_2$–Et_3N 10:100:1) to give compound **18** (64 mg, 100%) as light yellow oil. To a solution of compound **18** (54 mg, 0.28 mmol), $NaBH_3CN$ (32 mg, 0.504 mmol), CH_3COOH (43 μL) in MeOH (1.5 mL) was added HCHO solution (37% HCHO; 0.5 mL HCHO in 1.5 mL MeOH) at 0 °C and the mixture was stirred at rt for 2.5 h. After addition of saturated $NaHCO_3$ solution (10 mL), MeOH was evaporated under reduced pressure. The aqueous phase was extracted with EtOAc (6×10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by Silica column chromatography ($MeOH/CH_2Cl_2$–Et_3N 5:100:0.5) to give compound **19** (37 mg as a light yellow solid). Yielded 61 %; mp 89–91 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 6.97 (t, J=8.0 Hz, 1H), 6.90 (dd, J=8.0, 0.8 Hz, 1H), 6.87 (s, 1H), 6.43 (d, J=7.6 Hz, 1H), 3.88 (s, 3H), 3.01 (t, J=8.0 Hz, 2H), 2.63 (t, J=8.0 Hz, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.8, 139.9, 123.2, 122.0, 118.5, 113.9, 105.8, 99.6, 62.9, 55.3, 45.4 (2C), 25.7; HRMS (ESI) m/z calcd for $C_{13}H_{19}N_2O$ $(M+H)^+$ 219.1492; found 219.1484.

4.25. Psilocin (20)[19]

To a solution of compound **19** (10 mg, 0.046 mmol) in dichloromethane (3 mL) was added BBr_3 (1 M in CH_2Cl_2; 0.18 mL, 0.18 mmol) at −78 °C and the mixture was stirred at rt for 9 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in dichloromethane (4 mL). $KHCO_3$ (7 mg, 0.07 mmol) and MeOH (2 mL) were added to the solution. After stirring for 30 min, the solvent was evaporated under reduced pressure and the residue was chromatographed on Silica column chromatography ($MeOH/AcOEt$–NH_4OH 20:80:2) to give compound **20** (5.6 mg) Yielded 60%; mp 173–176 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 6.86 (s, 1H), 6.86–6.74 (m, 2H), 6.32 (dd, J=7.2, 0.8 Hz, 1H), 3.01 (t, J=6.8 Hz, 2H), 2.74 (t, J=6.8 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.7, 140.7, 123.2, 122.1, 118.4, 114.0, 105.0, 104.2, 62.9, 45.3 (2C), 25.7; ESI $(M+H)^+$ 205.3.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.09.050.

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