

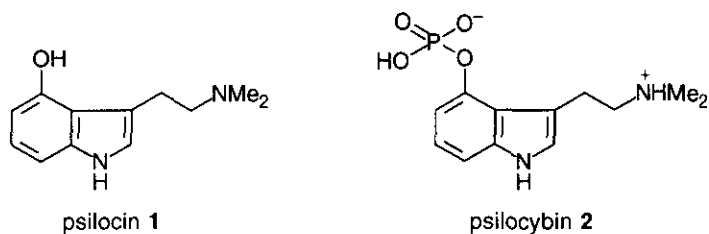
A NEW SYNTHESIS OF PSILOCIN

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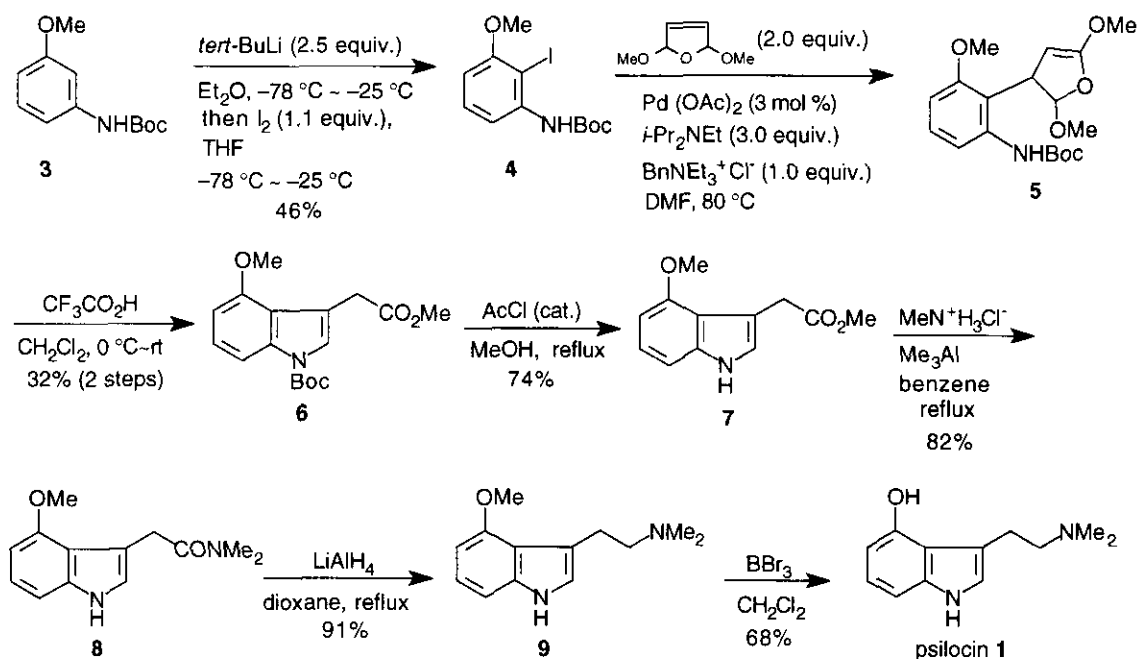
Abstract — A new route to the hallucinogenic alkaloid psilocin, isolated from the mushroom species *Psilocybe mexicana*, has been established.

Psilocin (**1**) is a minor hallucinogenic component isolated¹ from the mushroom species *Psilocybe mexicana* with the accompanying phosphorylation product psilocybin (**2**) and is the active species in the central nervous system (**Figure 1**).^{1,2} In spite of its interesting physiological activities and its rather simple structure, not many syntheses of psilocin (**1**) have been reported so far.³ In this paper, we wish to report a new synthesis of psilocin (**1**) employing our own procedure⁴ for the synthesis of indoleacetic acid.

**Figure 1**

Exposure of *N*-*tert*-butoxycarbonyl-3-methoxyaniline⁵ (**3**) to *tert*-butyllithium in ether allowed regioselective lithiation⁶ to give *N*-*tert*-butoxycarbonyl-2-iodo-3-methoxyaniline (**4**) in 46% yield on sequential treatment with iodine. When the iodide (**4**) was heated at 80 °C with 2 equiv. of 2,5-dihydro-2,5-dimethoxyfuran⁷ in DMF containing 3 equiv. of diisopropylethylamine and 1 equiv. of benzyltriethylammonium chloride in the presence of a catalytic amount of palladium(II) acetate⁴ (3 mmol %), the 3-aryl-2,3-dihydro-2,5-dimethoxyfuran⁷ (**5**) was generated as a mixture of diastereomers which, after filtration through silica gel column, was stirred with trifluoroacetic acid in dichloromethane at room temperature to furnish methyl *N*-*tert*-butoxycarbonyl-4-methoxyindoleacetate in 32% overall yield. In order to remove the *N*-carbamate functionality, **6** was refluxed with methanolic hydrogen chloride generated from acetyl chloride to give methyl 4-methoxyindoleacetate (**7**) in 74% yield. Transformation of

the ester (7) into the *N,N*-dimethylamide (8) by employing the Weinreb conditions,⁸ followed by reduction of the resulting amide (8) with lithium aluminum hydride in refluxing dioxane afforded *N,N*-dimethyl-4-methoxytryptamine (9) in 75% overall yield. Finally, 9 was exposed to boron tribromide⁹ in dichloromethane to give psilocin (1) in 68% yield.



Scheme 1

In summary, although the present synthesis requires some improvements, particularly, in the yields in the directed regioselective iodination step and the key Heck-type coupling step, the approach employed is novel and can be readily carried out.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hotstage instrument and are uncorrected. UV spectra were recorded on a HITACHI 320 spectrophotometer. IR spectra were recorded on a JASCO-IR 700 spectrophotometer. ¹H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer.

N-*tert*-Butoxycarbonyl-2-iodo-3-methoxyaniline (4)

To a stirred solution of *N*-*tert*-butoxycarbonyl-3-methoxyaniline (3) (200 mg, 0.9 mmol) in Et₂O (4 mL) was added *tert*-BuLi (1.64 M in hexane, 1.4 mL, 2.24 mmol) at -78 °C and the mixture was kept at -78 °C for 1 h and at -25 °C for 1.5 h. After cooling again to -78 °C, iodine (251 mg, 0.99 mmol) in THF (4 mL) was added to the mixture and the temperature, after kept at -78 °C for 30 min, was raised to rt. The mixture was diluted with Et₂O and washed successively with 10% Na₂SO₃, 5% NaHCO₃, and brine and

dried over MgSO_4 . After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel column (40 g, elution with 1:20 v/v AcOEt-hexane) to give the iodide (**4**) (146 mg, 46%) as colorless needles: mp 71.5-73.5 °C (hexane).

IR (Nujol): $\nu = 3386, 1731 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 7.74$ (1H, dd, $J = 8.2, 1.1$ Hz), 7.26 (1H, dt, $J = 8.2, 1.1$ Hz), 7.23 (1H, s), 6.53 (1H, dd, $J = 8.2, 1.1$ Hz), 3.88 (3H, s), 1.53 (9H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 158.5, 152.8, 140.5, 129.8, 112.7, 105.6, 81.0, 56.6, 28.3$, MS: $m/z = 349$ (M^+), 293, 249, 166, 57 (100 %); HRMS: Calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{I}$: 349.0134. Found: 349.0173, Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{I}$: C, 41.28; H, 4.62; N, 4.01; I, 36.35. Found: C, 41.30; H, 4.62; N, 3.96; I, 36.45.

Methyl *N*-tert-Butoxycarbonyl-4-methoxyindole-3-acetate (6)

A mixture of the iodide (**4**) (588 mg, 1.68 mmol), 2,5-dihydro-2,5-dimethoxyfuran (0.4 mL, 3.36 mmol), $\text{BnN}^+\text{Et}_3\text{Cl}^-$ (383 mg, 1.68 mmol), and *i*-Pr₂NEt (0.88 mL, 5.04 mmol) in DMF (11 mL) was heated at 80 °C for 19 h in the presence of $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mmol). After cooling, the mixture was diluted with Et₂O and washed successively with water, 5% NaHCO_3 , and brine, and dried over MgSO_4 . After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel column (20 g, elution with 1:6 v/v AcOEt-hexane) to give **5** (271 mg) as a diastereomeric mixture. Without separation, the mixture was then stirred with trifluoroacetic acid (0.1 mL, 0.1 mmol) in dichloromethane (5 mL) at rt for 30 min. The mixture was made basic by addition of 5% NaHCO_3 and was extracted with dichloromethane. The extract was washed with brine, dried over MgSO_4 , evaporated under reduced pressure, and chromatographed on silica gel column (30 g, elution with 1:8 v/v AcOEt-hexane) to give the indole carbamate (**6**) (173 mg, 32%) as a pale yellow oil.

IR (neat): $\nu = 1731 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 7.67$ (1H, d, $J = 8.1$ Hz), 7.26 (1H, s), 7.2 (1H, t, $J = 8.1$ Hz), 5.62 (1H, d, $J = 8.1$ Hz), 3.85 (3H, s), 3.85 (2H, s), 3.72 (3H, s), 1.60 (9H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 172.5, 154.2, 149.8, 137.2, 125.5, 123.3, 119.8, 113.4, 108.5, 103.3, 83.5, 55.2, 51.9, 32.5, 28.1$; MS: $m/z = 319$ (M^+), 263 (100 %), 169, 57; HRMS: Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: 319.1419. Found: 319.1421, Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.68; H, 6.63; N, 4.35.

Methyl 4-Methoxyindole-3-acetate (7)

To a solution of the carbamate (**6**) (331 mg, 1.04 mmol) in MeOH (7 mL) was added acetyl chloride (0.14 mL, 1.97 mmol) at 0 °C and, after 10 min at the same temperature, the mixture was refluxed for 30 min. After cooling, the mixture was made basic by addition of 5% NaHCO_3 and extracted with AcOEt. The extract was washed with brine, dried over MgSO_4 , evaporated under reduced pressure, and chromatographed on silica gel (20 g, elution with 1:4 v/v AcOEt-hexane) to give the ester (**7**) (168 mg, 74%) as colorless needles: mp 78-80.5 °C (AcOEt).

IR (Nujol): $\nu = 3406, 1721 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 8.03$ (1H, s), 7.08 (1H, t, $J = 8.0$ Hz), 6.98-6.86 (2H, m), 6.47 (1H, d, $J = 8.0$ Hz), 3.95 (2H, s), 3.87 (3H, s), 3.71 (3H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 173.8, 154.7, 138.0, 123.0, 122.1, 117.4, 108.6, 104.8, 99.6, 55.1, 51.8, 32.4$; MS: $m/z = 219$ (M^+), 160 (100 %), 130; HRMS: Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$: 219.0895. Found: 219.0873.

3-(*N,N*-Dimethylaminocarbonylmethyl)-4-methoxyindole (8)

To a stirred suspension of methylamine hydrochloride (87 mg, 1.07 mmol) in benzene (3 mL) was added Me_3Al (1 M in hexane, 1.1 mL, 1.1 mmol) at rt and, after 1 h at the same temperature, a solution of the

ester (**7**) (78 mg, 0.36 mmol) in benzene (2 mL) was added and the mixture was refluxed for 50 min. The mixture, after cooling, was made basic with 25% NH_4Cl and, after 30 min, 5% aqueous sodium potassium tartrate was added. The mixture was extracted with Et_2O and the extract was washed with brine, dried over MgSO_4 , evaporated under reduced pressure, and chromatographed on silica gel column (12 g, elution with 3:97 v/v MeOH-AcOEt) to give the amide (**8**) (69 mg, 82%) as colorless needles: mp 169-171 °C (acetone).

IR (Nujol): $\nu = 3248, 1632 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 8.32$ (1H, s), 7.05 (1H, t, $J = 8.0$ Hz), 6.96-6.89 (2H, m), 6.47 (1H, d, $J = 8.0$ Hz), 4.05 (2H, s), 3.89 (3H, s), 3.07 (3H, s), 3.00 (3H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 173.2, 154.7, 138.0, 122.5, 121.9, 109.1, 105.0, 99.4, 55.1, 37.7, 35.6, 32.0$; MS: $m/z = 232$ (M^+), 160 (100%), 130; HRMS: Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$: 232.1211. Found: 232.1211.

***N,N*-Dimethyl-4-methoxytryptamine (**9**)**

A solution of the amide (**8**) (54.3 mg, 0.23 mmol) in dioxane (4 mL) was refluxed with LiAlH_4 (36 mg, 0.94 mmol) for 30 min. After cooling, the mixture was diluted with Et_2O and the excess LiAlH_4 was decomposed by addition of several drops of 5% NaOH . After stirring for 30 min, the mixture was dried over MgSO_4 and evaporated under reduced pressure. The residue was taken into 5% HCl and the solution was made basic with 5% NaHCO_3 and extracted with AcOEt. The extract was washed with brine, dried over K_2CO_3 and evaporated under reduced pressure to give the amine (**9**) (47 mg, 91%) as a colorless needles: mp 89-92 °C (benzene) (lit.,³ mp 89-92 °C).

IR (Nujol): $\nu = 3408 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 8.16$ (1H, s), 7.07 (1H, t, $J = 8.0$ Hz), 6.92 (1H, dd, $J = 8.0, 1.0$ Hz), 6.85 (1H, d, $J = 1.0$ Hz), 6.47 (1H, d, $J = 8.0$ Hz), 3.76 (3H, s), 3.09-3.03 (2H, m), 2.66-2.60 (2H, m), 2.34 (6H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): $\delta = 155.0, 138.2, 122.8, 120.5, 117.6, 114.9, 104.6, 99.4, 61.8, 55.0, 45.4, 29.7, 25.0$; MS: $m/z = 218$ (M^+), 58 (100%); HRMS: Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$: 218.1419. Found: 218.1415.

Psilocin (1**)**

To solution of the amine (**9**) (28 mg, 0.13 mmol) in dichloromethane (8 mL) was added BBr_3 (1M in CH_2Cl_2 ; 0.52 mL, 0.52 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 (10 mL) and made basic by addition of KHCO_3 (20 mg, 0.2 mmol) and MeOH (5 mL) was added to the solution. After stirring for 30 min at rt, the solvent was evaporated under reduced pressure and chromatographed on alumina column (neutral, activity I, 12 g, elution with 20:80:2 v/v/v MeOH-AcOEt- NH_4OH) to give psilocin (**1**) (17.8 mg, 68%) as colorless crystals; mp 171-173 °C (lit.,^{1b,3} mp 173-176 °C).

IR (Nujol): $\nu = 3396, 3275 \text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3): $\delta = 7.88$ (1H, s), 7.05 (1H, t, $J = 8.0$ Hz), 6.88-6.82 (2H, m), 6.56 (1H, d, $J = 8.0$ Hz), 2.98-2.92 (2H, m), 2.72-2.67 (2H, m), 1.26 (6H, m); MS: $m/z = 204$ (M^+), 58 (100%); HRMS: Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$: 204.1262. Found: 204.1269.

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