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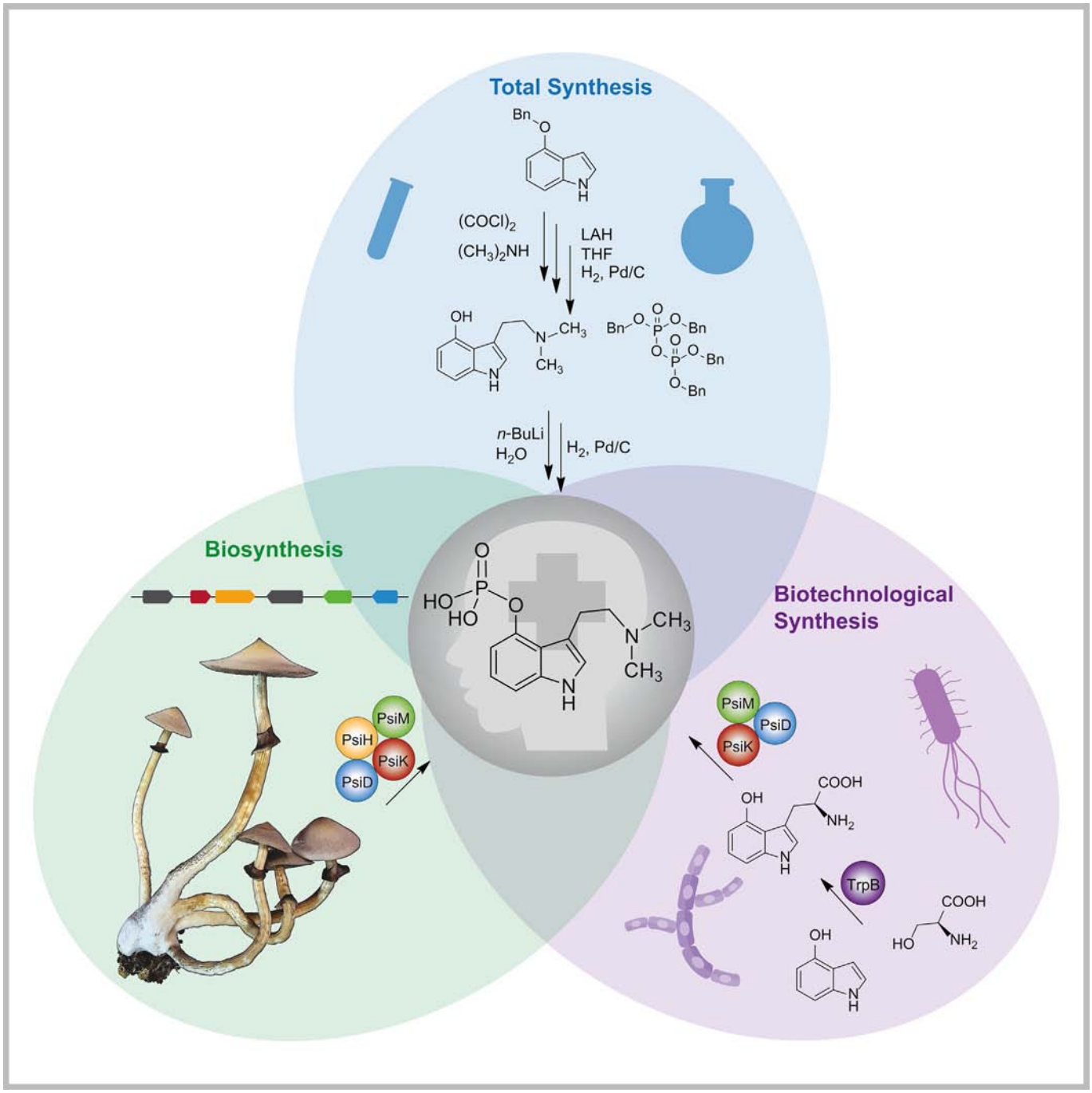
Natural Products |*Reviews Showcase*|

Production Options for Psilocybin: Making of the Magic

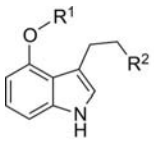
Janis Fricke, Claudius Lenz, Jonas Wick, Felix Blei, and Dirk Hoffmeister*[a]



Abstract: The fungal genus *Psilocybe* and other genera comprise numerous mushroom species that biosynthesize psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine). It represents the prodrug to its dephosphorylated psychotropic analogue, psilocin. The colloquial term "magic mushrooms" for these fungi alludes to their hallucinogenic effects and to their use as recreational drugs. However, clinical trials have recognized psilocybin as a valuable candidate to be developed into a medication against depression and anxiety. We here highlight its recently elucidated biosynthesis, the concurrently developed concept of enzymatic in vitro and heterologous in vivo production, along with previous synthetic routes. The prospect of psilocybin as a promising therapeutic may entail an increased demand, which can be met by biotechnological production. Therefore, we also briefly touch on psilocybin's therapeutic relevance and pharmacology.

Introduction

For decades, pharmaceutical chemistry has recognized microbial natural products as a valuable source for new drugs and drug leads.[1] Research has primarily been driven by the quest for new anti-infectives and anticancer compounds. Fungal metabolites have also served as immunosuppressants and lipid-lowering agents.[2] Depression and cancer-related anxiety are surely not among the conditions that would readily be associated with a fungal product as a promising treatment option. However, psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine, **1**, Figure 1), currently entering phase III clinical trials, is exactly



psilocybin (**1**):	$R^1 = PO_3H_2$	$R^2 = N(CH_3)_2$
psilocin (**2**):	$R^1 = H$	$R^2 = N(CH_3)_2$
norbaeocystin (**3**):	$R^1 = PO_3H_2$	$R^2 = NH_2$
baeocystin (**4**):	$R^1 = PO_3H_2$	$R^2 = NHCH_3$
norpsilocin (**5**):	$R^1 = H$	$R^2 = NHCH_3$
aeruginascin (**6**):	$R^1 = PO_3H_2$	$R^2 = N^+(CH_3)_3$

Figure 1. Chemical structures of psilocybin and related alkaloids from *Psilocybe* species and other "magic mushrooms".

that.[3] It is the major metabolite of the hallucinogenic so-called magic mushrooms and undoubtedly represents one of the most prominent natural products. We present the recently characterized biosynthesis enzymes of **1** and the concept of its biotechnological production in vitro and in a heterologous system in vivo. We also review synthetic routes to **1** and include a view back on the history of **1** and ahead to its future as a valuable therapeutic.

Spotlights on Psilocybin's History

"The first thing which they ate at the gathering was small, dark mushrooms (…). These are inebriating and induce visions to be seen and even provoke sensuousness."
(Bernardino de Sahagún, 1499–1590)

In his eminent *Historia general de las cosas de la Nueva Espana* (General History of the Things of New Spain), the Franciscan friar Bernardino de Sahagún provided an extraordinary ethnographic account on the indigenous people of today's Mexico, their culture, and their ceremonies. His report also documents the phenomenal pharmacological effects of psychotropic and hallucinogenic tryptamine-like alkaloids: psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine, **2**, Figure 1) is the actual psychotropic principle and unstable dephosphorylated follow-up product of **1**, which is more stable and the biosynthetically made metabolite. Minor mushroom alkaloids include norbaeocystin (**3**), baeocystin (**4**), norpsilocin (**5**), and the quaternary ammonium salt of **1**, aeruginascin (**6**) as non-, mono-, and trimethylated congeners.[4]

Botanist Richard E. Schultes (1915–2001) investigated the lost and misinterpreted identity of the "plant" that caused the effects described in the ancient reports from Central America[5] and the associated mushrooms of the genus *Panaeolus* (which includes species that produce **1**). Ethnomycologist R. Gordon Wasson (1898–1986) and his wife Valentina (1901–1958) collected specimens and had the opportunity to participate in a mushroom ritual of native Mexicans. The fungi were identified by mycologist Roger Heim (1900–1979) as members of the genera *Stropharia*, *Conocybe*, and *Psilocybe*.[6] He also provided chemist Albert Hofmann (1906–2008) at Sandoz Laboratories with *Psilocybe mexicana* fruiting bodies, who succeeded in isolating **1** and **2** and in elucidating their structures.[4a–c] Subsequently, close to 200 species, in the above genera and in *Gymnopilus*, *Pluteus*, and *Inocybe* species, have been confirmed as producers of **1**. The content of **1** depends on the extraction and workup method, as it may decompose to **2**.[4e] Reported values are typically about 0.85% of the dry mass for *Psilocybe serbica*, approximately 1.0% for *P. semilanceata*, and around 1.5–1.8% in *P. azurescens*.[7]

Structurally, these alkaloids are fairly simple and achiral, and they are closely related to the neurotransmitter serotonin (5-hydroxytryptamine). Compound **1** has a molecular mass of $m/z = 284.1$ ($C_{12}H_{17}N_2O_4P$), yet it uniquely combines two structural elements that are, each in their own way, unusual. First, a 4-hydroxyindole moiety is a very rare and distinctive structural feature among natural products. Second, **1** (and **3**, **4**, and **6** alike) features a phosphate ester, which is also comparatively rare in natural products, though is frequently found in energy metabolism and cellular signaling.

[a] *J. Fricke, C. Lenz, J. Wick, F. Blei, Prof. Dr. D. Hoffmeister*
Department Pharmaceutical Microbiology
Hans-Knöll-Institute Friedrich-Schiller-Universität
Beutenbergstrasse 11a, 07745 Jena (Germany)
E-mail: dirk.hoffmeister@leibniz-hki.de
The ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.201802758.

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Pharmacology of Psilocybin

A closer look at the pharmacology of **1** clarifies the reason behind the "magic" (i.e., the hallucinogenic effects) of the above fungi (Figure 2): after ingestion, cleavage of the phosphate ester occurs, which converts prodrug **1** into **2**.[7c] The latter compound interferes with serotonergic neurotransmission, as it agonistically acts on 5-hydroxytryptamine $(5\text{-HT})_{2A}$ and 5-HT_{2C} receptors (equilibrium dissociation constant, $K_i = 6$ nM for the 5-HT_{2A} receptor) and, to a lesser extent, on 5-HT_{1A} receptors of the human nervous system.[7c,8] The threshold dose for **1** is about 5 mg, and uptake of 12–20 mg per os (oral delivery) causes an altered state of consciousness.[8] A lethal dose can only be estimated theoretically.[7c] Somatic effects include dilated pupils, altered heart rate and blood pressure, among others. The perceptual effects become manifested in an altered sense of time (it appears to be virtually standing still), synaesthesia, and visual hallucinations, such as fractals and multicolored geometric objects.[7c,8a] Notable psychic effects are enhanced introspect, decreased depression, and mystical experiences, which is why native Central Americans considered these mushrooms divine and referred to them as "Flesh of the Gods".

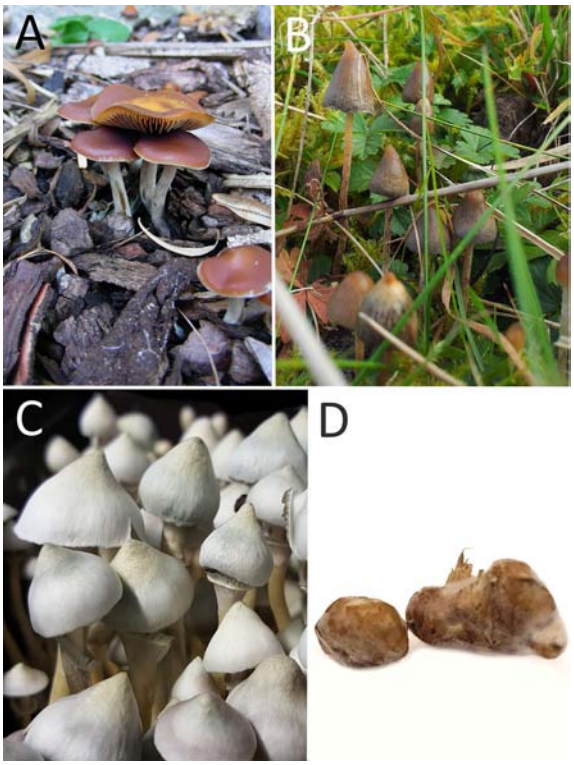


Figure 2. Mature fruiting bodies of a) *P. cyanescens* and b) *P. semilanceata* as producers of **1**. c) Cultivated mushrooms of an unpigmented *P. cubensis* strain. d) *Psilocybe* sclerotia containing **1**—Sclerotia are resilient fungal structures that withstand unfavorable environmental conditions.

How Mushrooms Make Psilocybin

The historically earliest and still popular—albeit now illicit—way for humans to have access to **1** is to ingest the producing organism, that is, to use its biosynthetic capacity, but how do mushrooms produce **1**?

Its origin from L-tryptophan (**8**) was established early on.[9] Today's knowledge on its biosynthesis is rooted in seminal work by pharmaceutical chemists Stig Agurell (1932–2018) and J. Lars Nilsson (1938–2014). They synthesized various ^{14}C- and ^{3}H-radiolabeled presumed precursors, fed them to fungal mycelium, and traced incorporation into **1**. In their work, these authors propose a five-step biosynthesis beginning with **8** that successively undergoes decarboxylation to tryptamine (**9**), repeated methylation to *N*,*N*-dimethyltryptamine (**10**), 4-hydroxylation to yield **2**, and 4-*O*-phosphorylation leading to the formation of **1** (Scheme 1).[10] On the basis of their results, these authors also hypothesize that alternative pathways to **1** may exist.

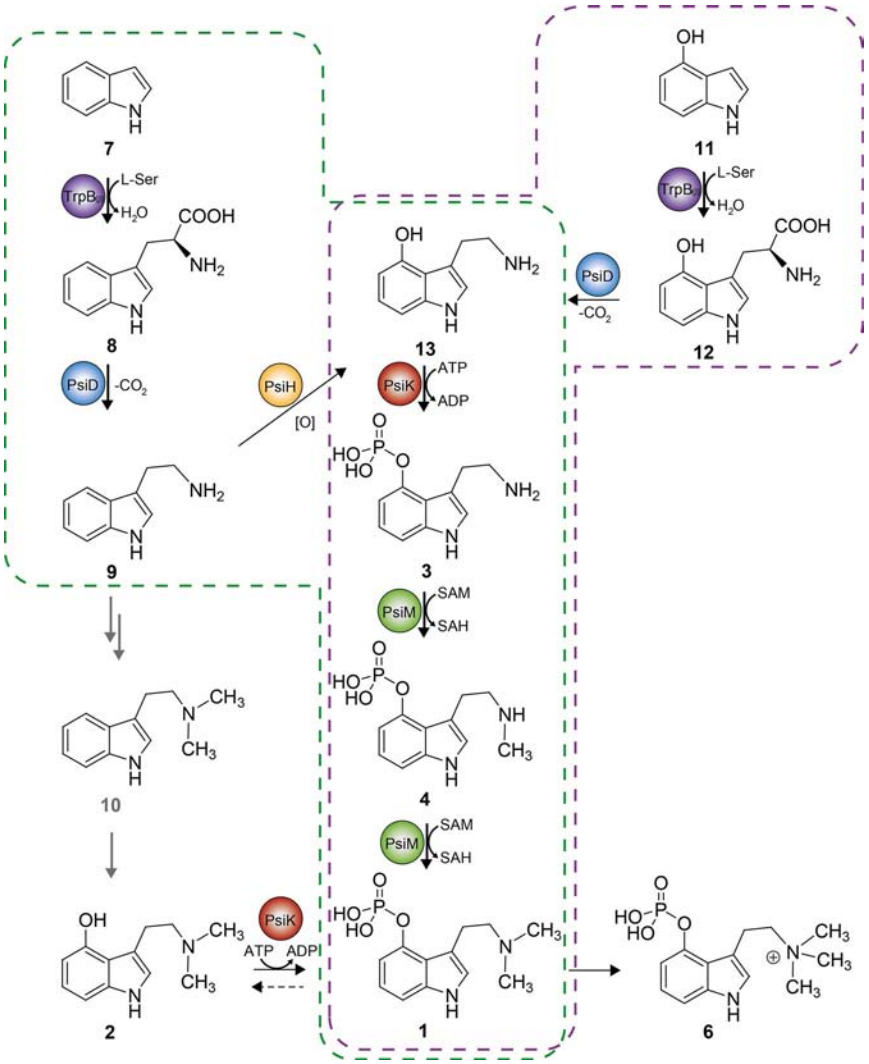
Half a century later, genomics greatly helped advance our understanding of the biosynthetic events. The genome sequences of various species producing **1**, including *P. cubensis*, a European isolate of the wider *P. cyanescens* species complex (*P. serbica*), a North American strain of *P. cyanescens* sensu stricto, *Panaeolus cyanescens*, and *Gymnopilus dilepis* have been reported.[11] These species share a set of genes in an approximately 11–22-kb portion in their genomes that encodes four biosynthesis enzymes along with transporters (Figure 3). Heterologous production of the putative decarboxylase PsiD, the kinase PsiK, and the methyltransferase PsiM in *Escherichia coli* and in vitro activity assays were performed. *Aspergillus niger* was used for in vivo characterization of PsiH, a putative P_{450} monooxygenase. The activities found confirmed the hypothesis that these enzymes catalyze the formation of **1**. Concurrently, the substrate specificity profiles revealed unexpected results regarding the order of biosynthetic events and the emerging option of the biotechnological production of **1**

PsiD catalyzes the decarboxylation of **8** into **9** as the initial step but is not strictly specific, as it also decarboxylates 4-hydroxy-L-tryptophan (**12**), which is advantageous for the in vitro production of **1**. Curiously, PsiD is entirely unrelated to known fungal and plant aromatic L-amino acid decarboxylases. Rather, it belongs to the family of pyridoxal 5′-phosphate (PLP)-independent phosphatidylserine decarboxylases.[11a]

PsiH is a P_{450} monooxygenase that selectively hydroxylates the 4-position of **9** to produce 4-hydroxytryptamine (**13**) as a second biosynthetic step (Scheme 1).[11a]

PsiK catalyzes the subsequent phospho-transfer step onto **13** to yield **3**. Opposite to the previous view, **2** is not the precursor of **1** but serves as a PsiK substrate as well. The reason and biosynthetic implications need to be viewed in the context of the methyltransferase PsiM.[11a]

The PsiM-catalyzed methyl-transfer steps convert **3** via **4** into **1**, which concludes the biosynthesis.[11a] The specificity of PsiM is remarkable. Aside from mere trace amounts of product **5**, detected with **13** as a methyl acceptor,[4e] PsiM seems to re-



Scheme 1. Biosynthesis of **1**. The green dashed frame indicates cellular biosynthesis, and the purple frame indicates enzymatic synthesis in vitro beginning from 4-hydroxyindole (**11**) or **12**. Gray arrows (left) symbolize the biosynthetic pathway initially proposed by Agurell and Nilsson,[10] who also assumed alternative routes toward **1**. Aeruginascin (**6**) has only been described from *Inocybe aeruginascens*, not from *Psilocybe* species. ATP = adenosine triphosphate, ADP = adenosine diphosphate, SAM = *S*-adenosylmethionine, SAH = *S*-adenosylhomocysteine.

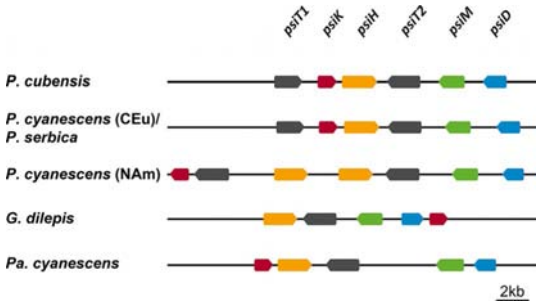


Figure 3. Genetic loci encoding enzymes for the biosynthesis of **1** in *Psilocybe cubensis*, a Central European (CEu) isolate of the *P. cyanescens* species complex (*P. serbica*), a North American (NAm) isolate of *P. cyanescens* sensu stricto, *Gymnopilus dilepis*, and *Panaeolus cyanescens*. The genes *psiK* (red) and *psiH* (gold) code for the kinase and the tryptamine monooxygenase, respectively, which modify the indole core. The genes *psiM* (green) and *psiD* (blue) code for the methyltransferase and the L-tryptophan decarboxylase, respectively, which initiate and conclude the biosynthesis of **1**. Putative transporter genes (e.g., *psiT1* and *psiT2* in *P. cubensis*) are shown in dark gray. Only the biosynthesis of **1** and transport genes are shown.

quire a 4-*O*-phosphoryloxy group for proper substrate recognition.

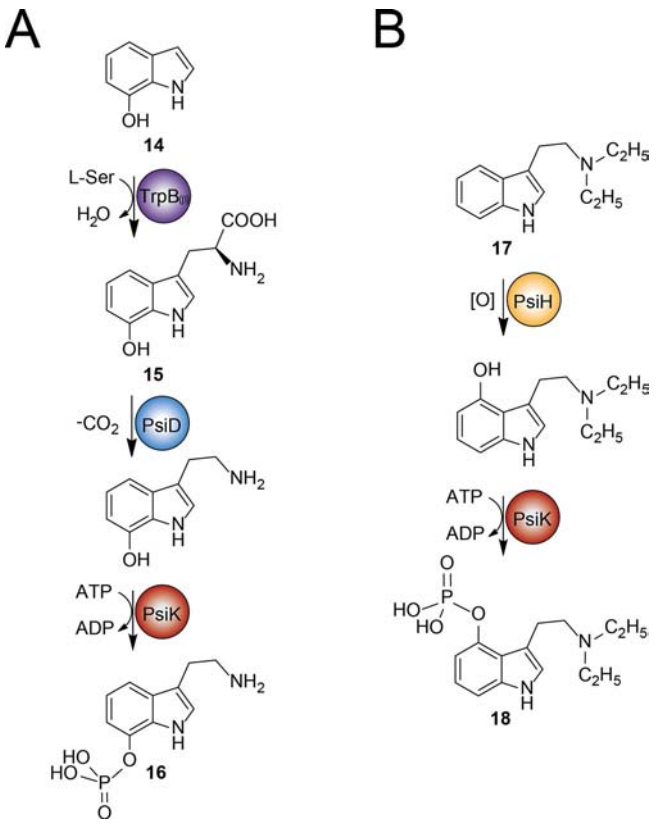
The above enzyme characteristics imply that neither **2** nor **10** is a pathway intermediate: the tight specificity of PsiM excludes the formation of **10** (which would precede **2** by only one step and become biosynthesized through hydroxylation by the substrate-flexible PsiH). Further, if **2** occurs, for example, by intracellular dephosphorylation, it is rephosphorylated by PsiK and is converted into **1**. Hence, the pathway is designed to prevent, rather than support, the formation of **2**. Still, **2** has been reported from *Psilocybe* species,[7c] yet the reported quantities represent an artifact generated during workup.[4e]

The identification of the biosynthetic enzymes toward **1** laid the foundation for its biotechnological synthesis, for which two different routes can be envisioned. The first option includes enzymatic synthesis in vitro, whereas the alternative route involves reconstitution of the pathway in vivo by introducing the biosynthesis genes into a suitable host.

Enzymatic Production In Vitro

As indicated above, PsiD accepts **12** as a substrate. This substrate has been used to initiate the in vitro process. Consequently, the PsiH-catalyzed hydroxylation can be eliminated, which helps to reduce the number of steps and, hence, the number of involved enzymes. Otherwise, the procedure would require a compatible P_{450} reductase as a redox partner to supply the monooxygenase with electrons. As proof of concept and without any further optimization, in a PsiD/PsiK/PsiM one-pot reaction (Scheme 1), amended with the respective co-substrates, 15 μmol of **12** was turned over into 3.9 μmol of **1**.[11a] Minor amounts of precursors **3** and **4** were also present after the reaction. For the first time, **1** was obtained neither from a mushroom nor synthetically.

Very recently, this procedure was extended by making use of the flexibility of the *P. cubensis* tryptophan synthase TrpB.[12] In fungi, tryptophan synthases are α/β-homodimers, and they catalyze the penultimate and terminal steps in the biosynthesis of **8**, which is the cleavage of 1-(indole-3-yl)glycerol phosphate in the first half reaction by the α subunit to release indole (**7**) for the second half reaction.[13] The latter is catalyzed by the β subunit and condenses **7** and L-serine into **8**. Precedence for flexible tryptophan synthases stems from bacterial representatives. Specifically, their β subunits are useful to generate halogenated tryptophan derivatives by offering the respective substituted indoles as substrate, whereas β-methylated tryptophan is produced upon replacing L-serine with L-threonine .[14] *P. cubensis* TrpB is the first mushroom tryptophan synthase to be characterized and is also flexible for substituted indoles. Particularly, it accepts 4-hydroxyindole (**11**), which allowed its integration into the production of **1** (Scheme 1). In a four-enzyme, one-pot reaction, **12** was produced by TrpB from L-serine and **11** as inexpensive building blocks and was further converted by PsiD, PsiK, and PsiM into **1**.[12] About 20% of added **11** was converted into **1**.



Scheme 2. a) In vitro enzymatic pathway to isonorbaeocystin (**16**).[12] b) Biotransformation of *N*,*N*-diethyltryptamine (**17**) into 4-phosphoryloxy-*N*,*N*-diethyltryptamine (**18**) by *P. cubensis*.[15] Catalysis by PsiH and PsiK has not yet been proven but is likely.

Enzymatic Production of Psilocybin Congeners

Intriguingly, *P. cubensis* TrpB accepts 7-hydroxyindole (**14**) as a substrate as well and, consequently, produces 7-hydroxy-L-tryptophan (**15**) in vitro. A combined TrpB/PsiD/PsiK/PsiM assay led to the formation of a new congener of **1**, isonorbaeocystin (**16**, 7-phosphoryloxytryptamine, Scheme 2), which proved that PsiD and PsiK were cooperative and accepted the respective intermediates.[12]

However, **16** was not methylated into the respective isomer of **1**. This is consistent with the previously observed specificity of the methyltransferase PsiM. As a perspective to develop further the concept of facile in vitro production of derivatives of **1**, future work may focus on directed evolution or site-specific engineering of *P. cubensis* PsiM to eliminate its gatekeeper role against the formation of **2** by relaxing its specificity.

An earlier approach included the biotransformation of *N*-alkyltryptamines, fed to fungal mycelia.[15] For example, *N*,*N*-diethyltryptamine (**17**) was hydroxylated and phosphorylated to 4-phosphoryloxy-*N*,*N*-diethyltryptamine (**18**) by *P. cubensis* (Scheme 2). This result adds to the notion of the flexible PsiH/PsiK enzyme pair, which are the most plausible candidates to have catalyzed this biotransformation.

Heterologous In Vivo Production

Detailed knowledge of the biosynthesis of **1** paved the way for the genetic engineering of a naïve microbial host for heterologous in vivo production. As a reliable and robust model organism, the *Aspergillus nidulans* mold was chosen.[16] To reconstitute the biosynthesis, all four biosynthesis genes needed to be inserted into the host genome. Further, concerted gene expression was critical. Briefly, a tetracyclin-inducible gene expression system (the so-called Tet-On cassette) was harnessed and combined with an advanced approach to produce the biosynthesis enzymes from a single transcript as a polycistron (i.e., expressing multiple genes as one mRNA molecule, which is still translated into discrete enzymes). In standard small-volume Erlenmeyer shake flasks and without further optimization of the culture conditions and media, **1** accumulated in the biomass, and titers reached $> 100\ mg\ L^{-1}$.[16]

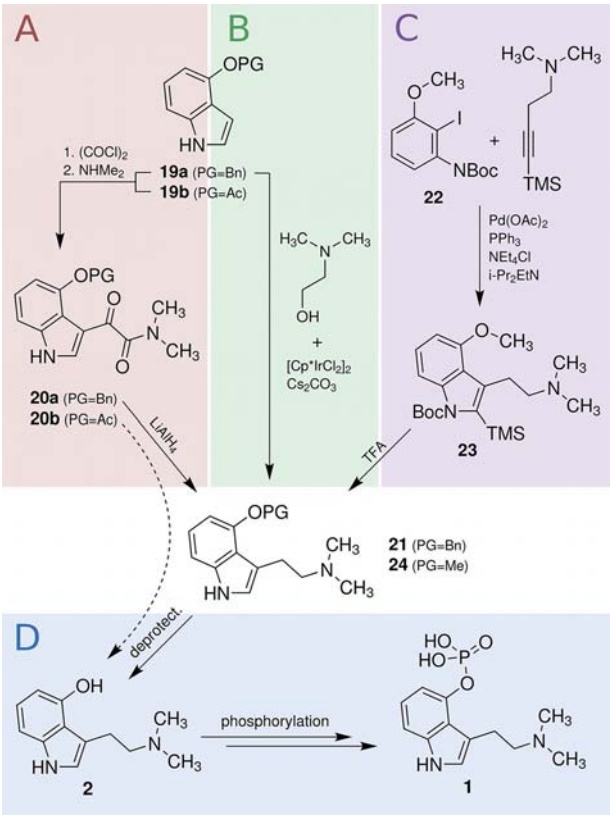
Synthetic Routes toward Psilocybin

Along with related tryptamines, **1** was first prepared chemically in the 1950s by Hofmann and co-workers.[4c,17] Since then, a couple of advances have been published (Scheme 3).

Traditionally, benzyl (Bn)-protected 4-hydroxyindole **19a** was first treated with oxalyl chloride and then with dimethylamine, which led to a dimethylaminooxalyl side chain in the 3-position of the indole nucleus (compound **20a**, Scheme 3a). This step was followed by $LiAlH_4$ reduction to **21** and finally deprotection to give **2**. Later, Hofmann's procedure[4c] was optimized (66% overall yields to **2**) by Nichols and Frescas.[18] In addition, Shirota et al.[19] replaced **19a** by **19b** to consolidate the reduction and deprotection steps of intermediate **20b** into a single step (Scheme 3, dashed arrow).

An alternative approach to build the side chain was published, by which indole-3-carbaldehyde was used for nucleophilic installation of a nitrile function that was then reduced and dimethylated.[20] Owing to the use of excess amounts of toxic reagents (thallium salt, cyanides) and low overall economy, this strategy can be considered inappropriate for large-scale synthesis.

The most recent contribution in the field (Scheme 3b) appears convincing with regard to its simplicity and atom and step economy, and it does not produce major quantities of toxic waste. Yields were comparable to those obtained by the traditional route (61% overall to **2**).[21] Bartolucci et al. succeeded in attaching a pretailored side chain to the desired position in one step by an iridium-catalyzed borrowing-hydrogen procedure to give formally only water as the byproduct.[21]



Scheme 3. Synthetic routes toward **2** and **1**. Ac = acetyl, Cp* = pentamethylcyclopentadienyl, Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid.

Beyond these methods, **2** was also synthesized by treating *ortho*-iodoanilin (**22**) derivatives with suitable unsaturated precursors.[22,23] Through this route, the indole core was formed directly by utilizing Pd catalysis (Scheme 3c). Whereas some of these methods still required subsequent multistep modifications on the sidechain,[22] Gathergood and Scammels accomplished this route via **23** and **24** with the final side chain generated prior to indole ring formation (Scheme 3c).[23] The yield from **22** to **2** was 24%.

The synthesis of **1** has been completed by phosphate-esterification of **2** (Scheme 3d). This terminal conversion has not yet received as much attention as the other steps, perhaps because **2** represents the actual bioactive compound and the synthesis of **1** requires additional steps. However, the synthesis of **1** as a less redox-sensitive but biocompatible storage form of the active alkaloid has likely been evolved in the biosynthesis to stabilize the fungal product and could serve the same purpose for the pharmaceutical chemist. To date, the most convenient phosphorylation of **2** uses *n*BuLi and tetrabenzyldiphosphate followed by deprotection by Pd-catalyzed hydrogenation,[19] which lead to **1** in acceptable yields (72% from **2**).

Presently, the demand for **1** for pharmaceutical purposes, that is, produced under current good manufacturing practice (cGMP) conditions for clinical studies, is met by organic synthesis. Currently, the cost to synthesize 1 g of **1** for phase III clinical studies, based on Hofmann's protocol, is estimated to be greater than 2000 USD.

Yet, in vitro biotechnologically produced compounds represent attractive alternatives. Cultures of an engineered fungal microorganism producing **1** can be relatively easily scaled up and grown in large fermenters. Compared with whole-cell catalysis, in vitro catalysis with isolated enzymes is usually advantageous for compound workup owing to a lower background. However, efforts to produce and purify the enzymes need to be taken into account, as well as enzyme stability, solubility, and supply of co-substrates (which in the case of whole-cell catalysis are provided by the host cells). Specific to P_{450} enzymes, electron-transfer partners need to be included in an in vitro approach.

Concluding Remarks: Psilocybin as a Future Therapeutic

The reason to produce—biotechnologically, synthetically, or biosynthetically—a psychotropic compound stems from its (re)discovered therapeutic value. The pharmaceutical usefulness of **1** was recognized soon after its discovery. Initially, synthetic **1** was distributed under the trade name Indocybin Sandoz for psychotherapeutic purposes.[8a] Moreover, its pharmacology earned **1** both a cult and a stigma. The mushrooms soon developed into a popular recreational drug. Prohibition began in the early 1970s, when **1** became a schedule I compound, according to the UN convention on drugs and similar national legislation in numerous countries.[24] Being legally

categorized as a highly addictive drug without medicinal usefulness, research on **1** was essentially abandoned.

Not until one generation of scholars later did research pick up momentum. Renewed interest in **1** as a prodrug of therapeutic agent **2** was accompanied by studies on its relative physiological and psychological safety in controlled and well-defined settings.[25] Studies showed promising outcomes in the therapy of cancer-related psychiatric distress and anxiety, treatment-resistant depression, and substance addiction.[26] However, a commonly acknowledged drawback of these studies is the low number of participants due to administrative barriers.[27] With the aim for the FDA to register **1** as a medication for psychological distress, phase III studies are currently being planned.[3] US-based nonprofit organizations, such as the Usona Institute in Madison, WI, and the Heffter Research Institute, support and promote research into the future clinical use of **1** on the basis of the highest clinical standards. These initiatives leave us with a cautiously optimistic view that **1** may return to pharmaceutical use in the not-too-distant future.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biosynthesis · biotechnology · depression · natural products · psilocybin

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