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Communication

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Biosynthesis of an Anti-Addiction Agent from the Iboga Plant

Scott C. Farrow[1], Mohamed O. Kamileen[1], Lorenzo Caputi[1], Kate Bussey[2], Julia E. A. Mundy[2], Rory C. McAtee[3], Corey R. J. Stephenson[3], Sarah E. O'Connor[1*]

AUTHOR ADDRESS

[1] Max Planck Institute of Chemical Ecology, Department of Natural Product Biosynthesis, Hans-Knöll-Straße 8, 07745 Jena, Germany

[2] John Innes Centre, Department of Biological Chemistry, Norwich Research Park, Norwich, NR4 7UH, UK

[3] Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA

Supporting Information Placeholder

ABSTRACT: (–)-Ibogaine and (–)-voacangine are plant derived psychoactives that show promise as treatments for opioid addiction. However, these compounds are produced by hard to source plants, making these chemicals difficult for broad-scale use. Here we report the complete biosynthesis of (–)-voacangine, and de-esterified voacangine, which is converted to (–)-ibogaine by heating, enabling biocatalytic production of these compounds. Notably, (–)-ibogaine and (–)-voacangine are of the opposite enantiomeric configuration compared to the other major alkaloids found in this natural product class. Therefore, this discovery provides insight into enantioselective enzymatic formal Diels-Alder reactions.

Treatment of opiate addiction remains challenging, with over 45-thousand people in the United States dying in 2017 and a 500% increase in yearly opioid overdose deaths since the year 2000 [1]. (–)-Ibogaine (**1**) (Figure 1A), a plant-derived iboga-type alkaloid, has anti-addictive properties that were discovered by Howard Lotsof in 1962 when he noticed that ingesting this compound mitigated heroin cravings and acute opiate withdrawal symptomatology [2,3]. Although the toxicity of (–)-ibogaine (**1**) has slowed its formal approval for addiction treatment in many countries, increased knowledge of its mode of action, side-effects and the discovery of (–)-ibogaine (**1**) analogs clearly indicate its potential as an anti-addictive agent [2–4]. The plant that synthesizes (–)-ibogaine (**1**), *Tabernanthe iboga* (Iboga), is difficult to cultivate, prompting interest in developing biocatalytic methods for (–)-ibogaine (**1**) production.

While the biosynthesis of the (+)-iboga type alkaloid scaffold was recently elucidated [5], biosynthesis of the antipodal (–)-ibogaine (**1**) remained unknown. Here we show that (–)-ibogaine (**1**) biosynthesis uses the same starting substrate as observed in (+)-iboga biosynthesis, but the key formal Diels-Alder cyclization step proceeds *via* a distinct mechanism to generate the reduced iboga alkaloid (–)-coronaridine (**2**) (Figure 1A). We further demonstrate that enzymatically generated (–)-coronaridine (**2**) can be 10-hydroxylated and 10-*O*-methylated [6] to form (–)-voacangine (**3**), and treatment of (–)-voacangine (**3**) with a *T. iboga* esterase reported here, followed by heating, yields (–)-ibogaine (**1**). This biocatalytic production strategy may facilitate sustainable and enhanced production of (–)-ibogaine (**1**) along with less toxic analogs, and moreover, reveals how two closely related enzyme systems generate two optical series *via* a formal Diels-Alder reaction.

A transcriptome of *T. iboga* was previously obtained using seeds gifted by the Ibogaine Alliance [6]. Upon discovery of the pathway for the structurally related, antipodal iboga alkaloid (+)-catharanthine (**4**) from the plant *Catharanthus roseus* (Figure 1A) [5], we hypothesized that *T. iboga* homologs of these *C. roseus* enzymes were responsible for biosynthesis of the (–)-iboga scaffold. (+)-Catharanthine (**4**) is synthesized by oxidation of stemmadenine acetate (**6**) by PAS (Precondylocarpine Acetate Synthase) to yield precondylocarpine acetate (**7**), which is reduced by DPAS (DihydroPrecondylocarpine Acetate Synthase) to give dihydroprecondylocarpine acetate (**8**). Dihydroprecondylocarpine acetate (**8**) undergoes elimination of acetic acid to yield the iminium form of dehydrosecodine (**9a**), which then undergoes isomerization to its enamime form (**9b**), followed by a formal Diels-Alder cyclization catalyzed by CS (Catharanthine Synthase), an α/β hydrolase homolog, to yield (+)-catharanthine (4) (Figure 1B, red box). We identified, cloned and heterologously expressed three homologs of PAS (flavin dependent oxidases), two of DPAS (medium chain alcohol dehydrogenases) and two of CS (α/β hydrolase homologs) from the *T. iboga* transcriptome.

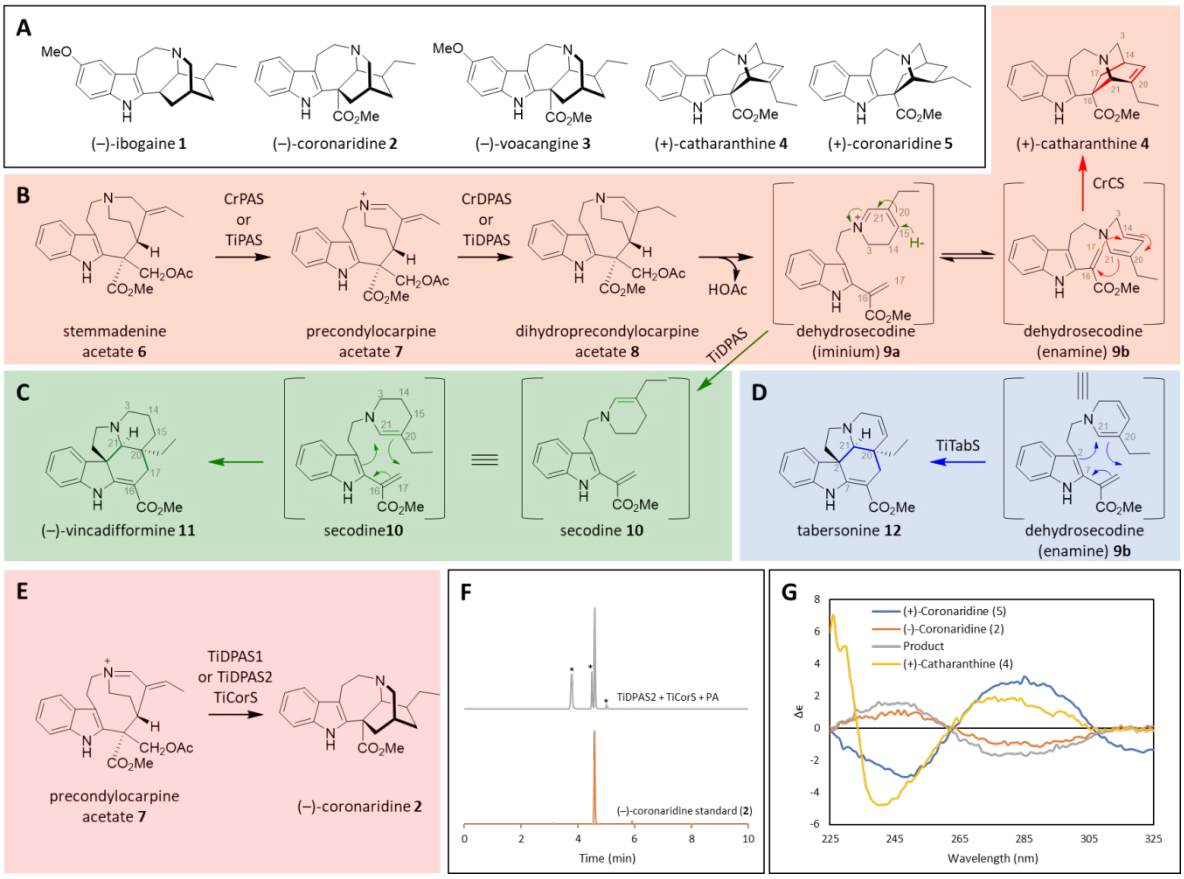

Figure 1. (+) and (–) iboga alkaloids. **A.** Anti-addiction agents (–)-ibogaine (**1**) and (–)-voacangine (**3**) are antipodal to (+)-catharanthine (**4**), a precursor to the anti-cancer drug vincristine. **B.** Biosynthesis of (+)-catharanthine (**4**). It is assumed that dehydrosecodine iminium **9a** is initially formed, and it then tautomerizes to the enamine form **9b**. **C.** Biosynthesis of (–)-vincadifformine (**11**). **D.** Biosynthesis of (–)-tabersonine (**12**). **E.** Biosynthesis of the reduced iboga alkaloid (–)-coronaridine (**2**) directly from precondylocarpine acetate (**7**). **F.** LC-MS chromatogram showing formation of (–)-coronaridine (**2**) after incubation of precondylocarpine acetate (**7**) (50 μM) with TiDPAS2 (1 μM), TiCorS (5 μM) and NADPH (8 equivalents). Peaks marked with an asterisk are uncharacterized side products (*m/z* 339) that decomposed during isolation attempts. **G.** CD spectra of enzymatically produced coronaridine compared to authentic standards.

The three PAS enzymes (TiPAS1, TiPAS2, TiPAS3) each had the same biochemical function as the homolog involved in (+)-catharanthine (**4**) biosynthesis, CrPAS, namely oxidation of stemmadenine acetate (**6**) to precondylocarpine acetate (**7**) (Figure 1B, Figure S1) [5]. All subsequent experiments were performed with CrPAS, for which an optimized expression system had been developed [5]. Next, TiDPAS1 (76.3% sequence identity to CrDPAS involved in catharanthine biosynthesis) and TiDPAS2 (86.3% sequence identity to CrDPAS) were tested with CrPAS and stemmadenine acetate (**6**). The expected reduced product, dihydroprecondylocarpine acetate (**8**) (Figure 1B), is unstable and is not directly observed. In the presence of limiting amounts of the NADPH cofactor required by DPAS (1 substrate equivalent), a compound with *m/z* 337 was instead detected (Figure S2). This product, which had been previously observed with CrDPAS [5], is likely an isomer of dehydrosecodine which forms after desacetoxylation of dihydroprecondylocarpine acetate (**8**) (Figure 1B). Surprisingly, in the presence of excess NADPH cofactor (>8 substrate equivalents), addition of either TiDPAS1 or TiDPAS2 generated the alkaloid vincadifformine (**11**) (Figure S3-6), which is formed through Diels-Alder cyclization of reduced dehydrosecodine (secodine (**10**)) (Figure 1C, green box). We hypothesize that with excess NADPH, TiDPAS1/2 over-reduces precondylocarpine acetate (**7**) to form secodine (**10**), which, in the absence of a dedicated cyclase enzyme, cyclizes spontaneously *via* a Diels-Alder mechanism to form vincadifformine (**11**). Biomimetic syntheses have shown that a (±)-vincadifformine analog readily forms from secodine (**10**), potentially due to the propensity of secodine (**10**) to adopt the conformation required for this Diels-Alder cyclization [7,8]. The vincadifformine (**11**) observed in the CrPAS/TiDPAS reactions could be the result of a non-enzymatic cyclization, though surprisingly, CD spectra indicate that this reaction product is enantiomerically enriched (–)-vincadifformine (**11**) (Figure S7). Thus, binding of secodine (**10**) to TiDPAS1/2 may provide an enantiomerically enriched cyclization product [9].

Finally, we tested the function of the two observed *T. iboga* CS homologs, which could be responsible for the key cyclization step to the (–)-iboga enantiomer. Addition of one of these homologs to assays containing stemmadenine acetate (**6**), CrPAS and TiDPAS1/TiDPAS2 and varying amounts of NADPH, yielded the alkaloid tabersonine (**12**), which forms through an alternative Diels-Alder cyclization mode of dehydrosecodine (**9**) [5] (Figure 1D, blue box, Figure S8), and this enzyme was thus named TiTabS (Tabernanthe iboga Tabersonine Synthase, 72.5 % sequence identity to previously

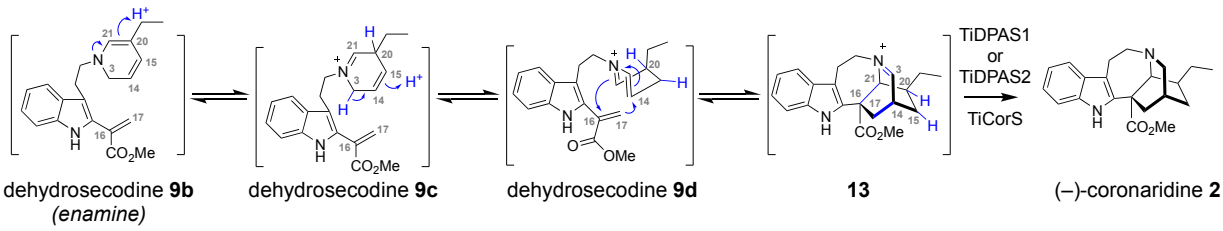

Figure 2. Biosynthesis of (–)-coronaridine (**2**) by TiDPAS1/2 and TiCorS. One plausible chemical mechanism for formation of the (–)-coronaridine (**2**) scaffold that is consistent with experimental evidence.

identified tabersonine synthase from *C. roseus*, CrTS). *T. iboga* contains tabersonine (**12**) and numerous tabersonine derived alkaloids [10], so identification of this enzyme activity, which has previously been observed in *C. roseus*, was expected. Incubation of stemmadenine acetate (**6**) with CrPAS, TiDPAS1/TiDPAS2 or precondylocarpine acetate (**7**) with TiDPAS1/TiDPAS2, excess NADPH and the second CS homolog from *T. iboga* led to the formation of the reduced iboga alkaloid coronaridine (**2**) (Figure 1E), as evidenced by mass fragmentation and comparison to an authentic standard (Figure 1F, Figure S9-13). Although several side products were also observed in this *in vitro* enzymatic reaction (Figure 1F), coronaridine (**2**) was the major product. This *T. iboga* CS homolog was thus named TiCorS (Coronaridine Synthase, 71.9 % sequence identity to CrCS). To assign the stereochemistry of coronaridine (**2**), the enzymatic product was isolated and subjected to CD analysis, which upon comparison to previous literature reports as well as authentic standards of (–)-coronaridine (**2**) (isolated from *Tabernaemontana divaricata*) [6] and (+)-coronaridine (**5**) (obtained from total synthesis, [11]) (Figure 1G), indicated that the enzymatic product is (–)-coronaridine (**2**). Therefore, the biosynthetic pathways for both (+) and (–) iboga alkaloid scaffolds have now been elucidated.

We hypothesized how the (–)-coronardine enantiomer might form in this system. (–)-Catharanthine could be formed from dehydrosecodine (**9**), analogous to (+)-catharanthine (**4**) biosynthesis in *C. roseus* (*e.g.* Figure 1B), and then subsequently reduced to form (–)-coronaridine (**2**). However, (–)-catharanthine is not observed as an intermediate in these enzymatic assays, nor has (–)-catharanthine been identified from natural sources. Alternatively, while it is obvious how vincadifformine (**11**) can be formed directly from secodine (**10**) (Figure 1C), there is no logical mechanism by which any secodine (**10**) isomer can be cyclized to form (–)-coronaridine (**2**). Therefore, we hypothesize that secodine (**10**) also does not act as an intermediate in (–)-coronaridine (**2**) biosynthesis. To gather evidence for an alternative mechanism, we isolated the dehydrosecodine-like product of precondylocarpine acetate (**7**) and TiDPAS1/2 that is formed under limiting NADPH conditions (**9**, *m/z* 337), which was also observed with DPAS from *C. roseus* [5]. This compound **9** can be incubated with TiTabS to generate tabersonine (**12**), thus confirming it to be the dehydrosecodine substrate for the cyclases (Figure S14). We incubated **9** with TiCorS, and, instead of observing the coronaridine product directly, we observed an intermediate product, **13** (*m/z* 337). This product was isolated in partially purified form and was then added to TiDPAS1/2 and NADPH (8 equivalents), resulting in the formation of (–)-coronaridine (**2**) (Figure S15). Although **13** was too unstable to be structurally characterized, this experiment nevertheless suggests a reaction order and mechanism in which TiDPAS1/2 initially reduces precondylocarpine acetate (**7**) to generate dehydrosecodine (**9b**) , which undergoes tautomerization (**9c-d,** [12,13]), followed by a formal [4+2] cyclization [14] to yield iminium **13**. Iminium **13** would then be reduced by TiDPAS1/2 to form (–)-coronaridine (**2**) (Figure 2). In further support of this mechanism, when assays with **9**, TiCorS, TiDPAS2 and NADPH (8 equivalents) were performed in D_2O, a compound co-eluting with (–)-coronaridine (**2**) with two additional atomic mass units was observed (Figure S16). Notably, when CS and TS were assayed in D_2O, no isotopic label was incorporated (Figure S16). This provides further support that the mechanism of TiCorS, which requires tautomerization of the dihyropyridine ring, is distinct from the mechanism of CS and TS, which proceeds directly from dehydrosecodine (**9b**). This highlights that isomerization of dehydrosecodine provides the capacity for generating further structural diversity beyond (+)-catharanthine (**4**) and (–)-tabersonine (**12**). In short, this combination of cyclase, tautomerization and reductase activity generates an additional scaffold beyond the previously reported (+)-catharanthine (**4**) and (–)-tabersonine (**12**).

We next tested whether enzymatically synthesized (–)-coronaridine (**2**) could be used to generate (–)-voacangine (**3**) and (–)-ibogaine (**1**). We incubated the TiCorS/TiDPAS product with the previously identified ibogaine enzymes I10H and N10OMT, which respectively 10-hydroxylate and 10-*O*-methylate (–)-coronaridine (**2**) to generate (–)-voacangine (**3**)[6]. Consistent with our structural assignment of (–)-coronaridine (**2**), incubation of the TiCorS/TiDPAS enzymatic product with these downstream enzymes yielded a product that was identical to an authentic standard of (–)-voacangine (**3**) (Figure 3, Figure S17). Not surprisingly, incubation of I10H and N10OMT with synthetic (+)-coronaridine (**5**) gave only trace amounts of product (Figure S18), highlighting the selectivity of the downstream enzymes to the stereochemistry of the substrate. In a well-established semi-synthetic process, (–)-voacangine (**3**) is subjected to a basic saponification to remove the methyl ester, and then heated to facilitate decarboxylation [15]. The *T. iboga* transcriptome revealed three homologs of PNAE (Polyneuridine Aldehyde Esterase), an enzyme involved in the de-esterification and decarboxylation of ajmalan-type alkaloids found in other Apocynaceae plants [16], which had a similar co-expression profile as TiPAS1, TiDPAS2 and TiCorS. Incubation of TiPNAE1 with (–)-voacangine (**3**) yielded a product with a mass consistent with the de-esterified compound **15**, which then slowly converted to (–)-ibogaine (**1**) (Figure 3). Heating of the de-esterified (–)-

voacangine (**15**) product increased the efficiency and speed of this conversion (Figure S19), suggesting that this decarboxylation is non-enzymatic, and a dedicated decarboxylase may be involved *in planta*. Regardless, enzymatic (–)-voacangine (**3**) provides an effective semi-synthetic starting material for (–)-ibogaine (**1**). Although TiPNAE1 could also de-esterify (–)-coronaridine (**2**), decarboxylation did not occur even after heating, suggesting that the electron donating methoxy group on the indole of (–)-voacangine (**3**) is required for spontaneous decarboxylation (Figure S20).

(–)-Ibogaine (**1**) has a storied history dating back hundreds of years to the Congo Basin and the Bwiti religion, though it was the serendipitous discovery of the anti-addictive properties of (–)-ibogaine (**1**) that captured the attention of modern medicine. Here we report the biosynthesis of (–)-voacangine (**3**), and also report an esterase that may improve semi-synthesis of (–)-ibogaine (**1**). In addition to its extraordinary bioactivity, (–)-ibogaine (**1**) provides an opportunity to compare the formal Diels-Alder enzymatic synthesis of (–) and (+)-iboga enantiomers. The discovery and initial investigation of TiCorS suggest a possible mechanism for this cyclization and a basis for future enzyme engineering for this emerging class of cyclases. There are approximately 100 iboga alkaloids identified in nature [10], both of + and – optical series, and discovery of this pathway now provides full access to both medicinally important scaffolds [17], in addition to providing the first biocatalytic method for production of the anti-addictive alkaloid (–)-ibogaine (**1**)

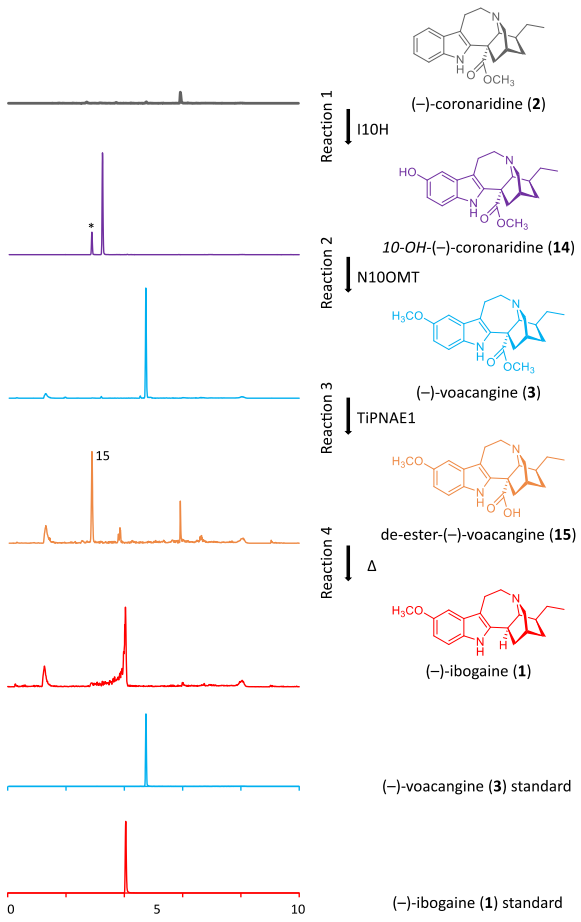

Figure 3. Formation of (–)-ibogaine (**1**) from enzymatically generated (–)-coronaridine (**2**). Peaks marked with an asterisk were products of endogenous yeast enzymes present in cultures expressing I10H.

ASSOCIATED CONTENT

Supporting Information. Materials and Methods, Figures S1-S20, Tables S1-S3, Data S1, References (1-6). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Correspondence to: oconnor@ice.mpg.de

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Notes

Authors declare no competing interests. All data is available in the main text or the supplementary materials. Genbank accession numbers: MK840850 (TiPAS1); MK840851 (TiPAS2); MK840852 (TiPAS3); MK840853 (TiTabS); MK840854 (TiCorS); MK840855 (TiDPAS1); MK840856 (TiDPAS2); MK840857 (TiPNAE1); MK840858 (TiPNAE2); MK840859 (TiPNAE3).

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ABBREVIATIONS

Catharanthus roseus catharanthine synthase, CrCS; Tabernanthe iboga coronaridine synthase, TiCorS; *Tabernanthe iboga* dihydroprecondylocarpine acetate synthase 1, TiDPAS1; *Tabernanthe iboga* dihydroprecondylocarpine acetate synthase 2, TiDPAS2; flavin adenine dinucleotide, FAD; nicotinamide adenine dinucleotide phosphate, NADPH; *Tabernanthe iboga* polyneudridine aldehyde esterase like 1, TiPNAE1; *Tabernanthe iboga* polyneudridine aldehyde esterase like 2, TiPNAE2; *Tabernanthe iboga* polyneudridine aldehyde esterase like 3, TiPNAE3*; Tabernanthe iboga* precondylocarpine acetate synthase 1, TiPAS1; *Tabernanthe iboga* precondylocarpine acetate synthase 2, TiPAS2; *Tabernanthe iboga* precondylocarpine acetate synthase 3, TiPAS3; *Tabernanthe iboga* tabersonine synthase, TiTabS; *Catharanthus roseus tabersonine synthase, CrTS*.

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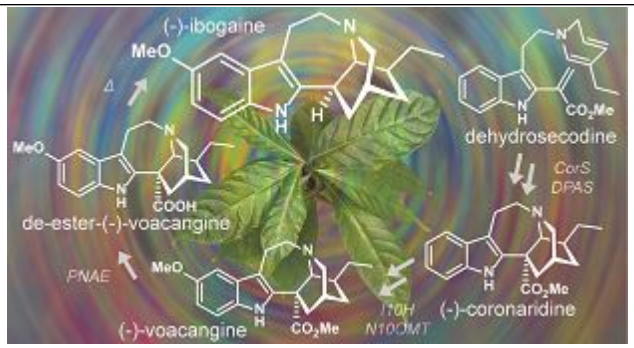
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CO2Me
CorS
DPAS
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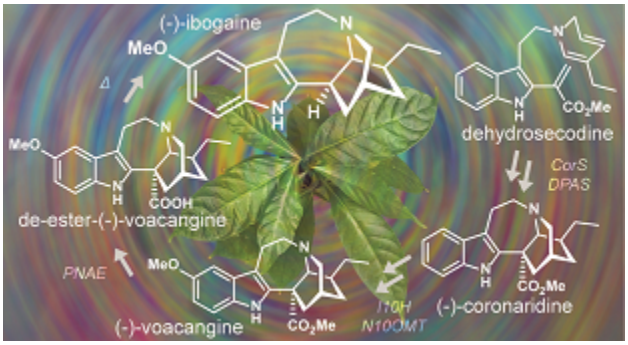

Graphical abstract