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Permalink

https://escholarship.org/uc/item/3r39h1b7

Journal

Natural Product Reports, 38(2)

ISSN

0265-0568

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Publication Date

2021-03-04

DOI

10.1039/d0np00033g

Peer reviewed

The Iboga Enigma: The Chemistry and Neuropharmacology of Iboga Alkaloids and Related Analogs

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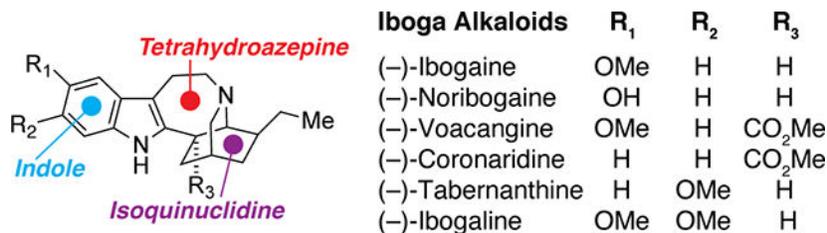[1]Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA

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Abstract

Few classes of natural products have inspired as many chemists and biologists as have the iboga alkaloids. This family of monoterpenoid indole alkaloids includes the anti-addictive compound ibogaine as well as catharanthine, a precursor to the chemotherapeutic vinblastine. Despite being known for over 120 years, these small molecules continue to challenge our assumptions about biosynthetic pathways, catalyze our creativity for constructing complex architectures, and embolden new approaches for treating mental illness. This review will cover recent advances in both the biosynthesis and chemical synthesis of iboga alkaloids as well as their use as next-generation neurotherapeutics. Whenever appropriate, we provide historical context for the discoveries of the past decade and indicate areas that have yet to be resolved. While significant progress regarding their chemistry and pharmacology has been made since the 1960s, it is clear that the iboga alkaloids will continue to stoke scientific innovation for years to come.

toc

Iboga Alkaloids	R_1	R_2	R_3
(−)-Ibogaine	OMe	H	H
(−)-Noribogaine	OH	H	H
(−)-Voacangine	OMe	H	CO_2Me
(−)-Coronaridine	H	H	CO_2Me
(−)-Tabernanthine	H	OMe	H
(−)-Ibogaline	OMe	OMe	H

INTRODUCTION

Ibogaine was first isolated in 1901,[1] and its structure was deduced by Bartlett, Dickel, and Taylor in 1958.[2] In 1960, its absolute stereochemistry was unambiguously assigned by X-ray crystallography.[3] The defining features of the iboga architecture include an indole, a 7-membered tetrahydroazepine, and a bicyclic isoquinuclidine (Figure 1). Since ibogaine's initial discovery, hundreds of alkaloids bearing structural and/or biosynthetic similarities to ibogaine have been identified. The chemical structures of some of the more common iboga alkaloids are highlighted in Figure 1 with the Le Men and Taylor numbering convention indicated.[4] While this review will primarily focus on monomeric iboga alkaloids, dimeric structures containing at least one iboga component are also common and include the notable chemotherapeutics vincristine and vinblastine (Figure 1). For information on the chemistry and/or biology of this class of bisindole alkaloids, we point the reader to a recent review.[5]

The unique structures of iboga alkaloids have captured the imagination of chemists for decades, while their unusual effects on the brain have challenged conventional ideas about treating substance use disorder. Though substantial progress has been made concerning the chemistry and neuropharmacology of these alkaloids, many unresolved problems and unanswered questions remain. Ibogaine—the prototypical iboga alkaloid with the most neurobiological data—still lacks a truly robust, scalable, enantioselective total synthesis. Moreover, its biological mechanism of action is completely opaque, pushing the limits of what traditional neuropharmacology is capable of explaining. Here, we summarize the history of iboga alkaloid isolation, biosynthesis, total synthesis, analog development, and neuropharmacology with particular emphasis placed on advances made in the past decade.

ISOLATION

Monoterpenoid indole alkaloids (MIA) of the iboga-type are found in a variety of plant species around the world, though historically, isolation of iboga alkaloids has generally been restricted to regions of West Africa.[6] There are hundreds of iboga alkaloids, but the compounds shown in Figure 1 represent some of the most commonly reported in natural product isolation and total synthesis literature. Of these alkaloids, ibogaine has attracted significant attention due to its therapeutic potential (vide infra). However, the isolation of ibogaine from natural sources has been plagued by ethical and environmental challenges,[7] as it only accounts for approximately 0.3% of the root bark weight in *Tabernanthe iboga* (Table 1). In contrast, significantly larger amounts of voacangine can be extracted from the root bark of *Voacanga africana* (~1.7% of the root bark). As a result, ibogaine is often produced via semi-synthesis starting from voacangine.[10] Conversion of voacangine to ibogaine generally requires a two-step protocol involving saponification of the C16 methyl ester followed by acidification and heating to induce decarboxylation.[7,8] In addition to ibogaine, Table 1 details several other common iboga alkaloids found in the *Tabernanthe* and

Voacanga genera. Interestingly, catharanthine belongs to the opposite optical series compared to other reported iboga alkaloids and is exclusively found in the *Catharanthus roseus* plant species. The isolated compounds in Table 1 have sparked interest in more recent efforts to determine the alkaloid profiles of plants in the broader Apocynaceae family.

NEWLY ISOLATED IBOGA ALKALOIDS (2010–2019)

Prior to 2010, iboga alkaloids were primarily isolated from plant species found in western parts of Africa.[6] However, recent reports have noted the discovery of these alkaloids in plants from other regions of the world including Mexico, China, and Malaysia (Figure 2 and Table S1).[15] Belonging to the Apocynaceae family, the *Ervatamia* genus (also called *Tabernaemontana*) has been found to produce a wide array of interesting iboga-type alkaloids with unique oxidation patterns and complex polycyclic frameworks. In 2014, Ye and co-workers isolated seven new iboga alkaloids from the *Ervatamia officinalis* plant species (**9**, **10**, **11**, **14**, **18**, **37**, **49**) along with ten previously known compounds including ibogaine, voacangine, and ibogaline.[16] Primarily found in the Guangdong and Hainan Provinces of China, *Ervatamia officinali*s is rich in MIAs.[17] Isolated ervaoffines A and B (**9** and **10**) were characterized using X-ray diffraction and electronic circular dichroism (ECD), and they represent the first iboga-type pseudoindoxyl alkaloids with a C2 spiro carbon configuration opposite that of known members of this class, such as iboluteine (**177**).

In addition to ervaoffines A–D (**9**, **10**, **11**, **49**), **14** and **37** were also isolated from *Ervatamia officinalis* (Figure 2).[18] These newly isolated alkaloids are likely derived from ibogaine (**1**), which is a major constituent of *Ervatamia* plants. Indole oxidation would lead to intermediate **50**, which could lose an equivalent of water through either Path A or Path B (Scheme 1). Subsequent pinacol rearrangements would ultimately lead to **9** and **11**, respectively. In 2017, Ye and co-workers isolated several additional ervaoffine alklaoids (**33**, **34**) from *E. officinalis*.[19] The proposed biosynthesis of **33** and **34** involves the generation of a C5–C6 olefin in either ibogaine or coronaridine. Oxidative cleavage of the C5–C6 olefin to the corresponding dicarbonyl would produce an intermediate that could be transformed to **33** and **34** through oxidation followed by amidation or decarboxylation.

The *Ervatamia* genus consists of approximately 120 species, which are primarily distributed in the subtropical and tropical regions of Australia and Asia. Phytochemical studies of this genus have led to the discovery of MIAs and bisindole alkaloids of various skeletal types.[20,21] In 2015, Gao and co-workers isolated **12**, **22**, **23**, and **43** from *Ervatamia hainanensis* (Figure 2).[22] Absolute configurations were determined by various methods including X-ray diffraction and ECD spectroscopy. Interestingly, compounds **12**, **22**, and **23** contain an alcohol at C19, suggesting that 19-hydroxycoronaridine is likely a common precursor. Conodusine E (**31**) was also isolated and its biosynthesis likely involves oxidation of 19-hydroxycoronaridine. The newly isolated alkaloid **31** was shown to possess mild anti-inflammatory properties. In 2016, several additional alkaloids from *E. hainanensis* were isolated by Ye and co-workers (Figure 2).[23] Similar to ervatamine G, **38**, **39**, **40**, **47** are all substituted at the C3 position of the isoquinuclidine, with **39** representing the first example of a cyano-substituted oxindole alkaloid.

In 2016, Kam and co-workers mined the Malaysian plant *Tabernaemontana corymbosa* for iboga-type alkaloids.[24] Using NMR, mass spectrometry, and X-ray diffraction analysis, they isolated and characterized the conodusine alkaloids (**27**, **29**, **30**, **31**, **32**) (Figure 2). Since then, other groups have reported the isolation of additional iboga alkaloids (**21**, **28**, **25**, **26**, **10**, **35**) from *T. corymbose*.[25,26,27] The biosynthetic origin of the unusual pyrrolidinone-containing compound **35** is still largely unknown.[27] Alkaloids **25** and **26** possess unprecedented skeletons, possibly derived from a cleavamine precursor (Scheme 2).[25] The proposed biosynthetic pathway to produce **25** and **26** likely starts from the oxidation of conodusine A (**27**) to **53**. Next, fragmentation of the isoquinuclidine would produce **54**. Hydrolysis of the iminium followed by enamine attack of the resulting aldehyde would produce **56**. Nitrogen attack at the iminium and dehydration would yield **26** (Path A), while tautomerization followed by S_N2' reaction and dehydration (Path B) would yield **25**. Though tabertinggine was only just recently discovered as an optically active natural product, the skeletal framework has been known since 1966 when Büchi inadvertently produced a related compound through an undesired rearrangement.[28] Ultimately, he was able to use this intermediate to complete the first ever total synthesis of ibogaine (vide infra).

The plant species *Tabernaemontana divaricata* is yet another member of the Apocynaceae family that is rich in iboga alkaloids. Commonly found in the Yunnan and Guangxi Provinces of China, phytochemical investigations of *T. divaricata* have led to the isolation and characterization of **13**, **36**, **42**, **44**, **45**, **46**, and **48** (Figure 2 and Table S1).[29,30,31] Most of these newly isolated alkaloids possess substitution at the C3 position of the isoquinuclidine. The biosynthesis of these compounds is likely to proceed through oxidation of simpler iboga alkaloids at C3 followed by C–C bond formation.

Initially believed to be found only in plants native to western Africa, iboga alkaloids are being discovered in a wide variety of Apocynaceae family members found around the world. These new sources may help to ensure that sufficient quantities of iboga alkaloids can be produced for future biological testing. In addition, the isolation of new iboga alkaloids provides important insight into novel biosynthetic pathways.

BIOSYNTHESIS OF IBOGA ALKALOIDS

Unlike in prokaryotes, the genes encoding metabolic pathways in plants are not typically clustered, making the full elucidation of alkaloid biosynthesis quite challenging. Typically, each individual plant-derived enzyme must be identified, cloned, and isolated to firmly establish a role in the synthesis of a particular alkaloid. Though several enzymes in the production of iboga alkaloids still remain elusive, our knowledge of iboga alkaloid biosynthesis has improved drastically over the past 15 years due in large part to the pioneering work of Sarah O'Connor, Vincenzo De Luca, and others.

Like all MIAs, the iboga alkaloids are derived from tryptamine (**59**), which is produced from the enzymatic decarboxylation of tryptophan (**58**) by tryptophan decarboxylase (TDC) (Scheme 3).[32,33,34] The remainder of the iboga carbon skeleton can trace its origins to secologanin (**62**), an iridoid synthesized from isopentenyl pyrophosphate (**60**) and dimethylallyl pyrophosphate (**61**) via the non-mevalonate pathway (Scheme 3).[35] Ten

enzymes are required to produce **62**,[36,37,38,39,40,41,42] which subsequently reacts with **59** to form strictosidine (**63**). This critical Pictet-Spengler reaction is catalyzed by strictosidine synthase (STR),[43,44] producing **63** as a single enantiomer (Scheme 3). Strictosidine (**63**) is a key intermediate en route to a number of indole alkaloids including those of the ajmalan, corynanthe, aspidosperma, quinoline, and iboga families.[35]

Many of the enzymes in *T. iboga* and *C. roseus* share a high degree of sequence homology, and thus, the biosynthetic pathways leading to ibogaine and catharanthine are quite similar until their late-stage divergence from dehydrosecodine (**77**). A number of the compounds en route to the iboga alkaloids are short-lived or produced in such small quantities that characterization via LC-MS has been challenging. As a result, many of the intermediates in the biosynthetic pathway to iboga alkaloids have been proposed based on the structures of their precursors and products. Whenever possible, we indicate which intermediates have actually been isolated.

The first step in the biosynthesis of iboga alkaloids from strictosidine (**63**) involves glycosidic bond cleavage catalyzed by strictosidine β-deglucosidase (SGD) to produce the six-membered lactol **64** (Scheme 4).[45,46] Opening of the lactol produces aldehyde **65**, which rapidly condenses with the secondary amine to yield iminium **66**. Isomerization to the more conjugated system produces **67**, which is immediately reduced by geissoschizine synthase 1 (GS1) to produce **68**.[47] Oxidation of the indole by geissoschizine oxidase (GO) yields **69**, which immediately undergoes intramolecular Mannich reaction followed by Grob fragmentation to yield preakuammicine (**71**).[48] As **71** is unstable, the iminium is rapidly reduced by REDOX1. The identification of REDOX1 was made possible due to its sequence homology to GS1, another iminium reductase.[48] Subsequent reduction of the aldehyde by REDOX2 produces the stable intermediate stemmadenine (**72**).[48]

The conversion of stemmadenine (**72**) to dehydrosecodine (**77**) is a common pathway en route to both iboga and aspidosperma alkaloids (Scheme 5). First, stemmadenine (**72**) is acetylated by stemmadenine O-acetyltransferase (SAT) to afford stemmadenine acetate (**73**).[48] Oxidation by precondylocarpine acetate synthase (PAS) produces iminium **74**, which is reduced by dihydroprecondylocarpine acetate synthase (DPAS) in the presence of NADPH to yield the key enamine intermediate **75**.[49] Fragmentation produces iminium **76**, which tautomerizes to the critical intermediate dehydrosecodine (**77**).[49] Dehydrosecodine (**77**) represents the point of divergence for the aspidosperma and iboga biosynthetic pathways. However, it has never been isolated, presumably due to the unstable nature of the *N*-alkyl dihydropyridine. When O'Connor and co-workers subjected **73** to PAS and DPAS, they were able to isolate angryline (**82**) as a mixture of enantiomers (Figure 3).[53] Angryline represents a stable precursor to dehydrosecodine (**77**) and is produced from an intramolecular Diels-Alder reaction between the iminium group of **77** and the vinylindole (Figure 3).

In the presence of tabersonine synthase (TS), dehydrosecodine (**77**) can undergo a Diels-Alder-like reaction to produce tabersonine (**78**).[50] However, it is currently unclear if natural enzymes like TS are capable of catalyzing truly concerted Diels-Alder reactions.[51] Reorientation of dehydrosecodine (**77**) reveals that it has the potential to undergo a second Diels-Alder-like reaction to form (+)-catharanthine (**7**) (Scheme 5). This reaction is likely to

occur through a stepwise mechanism. When (+)-catharanthine (**7**) was incubated with catharanthine synthase (CS), the product of a retro Mannich reaction was observed, indicating that the forward reaction is likely to proceed through conjugate addition of the vinylogous enamine followed by Mannich reaction.[52,53] Such stepwise formal Diels-Alder reactions are known to be favored with very electron-rich dienes, very electron-deficient dienophiles, or under conditions that stabilize the zwitterionic intermediate.[54] In this case, the reaction must be templated by CS, as only one enantiomer is formed.[49]

One of the most intriguing aspects of iboga alkaloid biosynthesis is the fact that *C. roseus* and *T. iboga* produce natural products of the opposite enantiomeric series (e.g., (+)-catharanthine and (–)-coronaridine, respectively). One might assume that *T. iboga* generates (–)-catharanthine, which in principle could be reduced to yield (–)-coronaridine (**7**). However, (–)-catharanthine has never been isolated, suggesting that this pathway does not exist in nature. Instead, deuterium labeling studies have shown that coronaridine synthase (CorS) catalyzes the isomerization of **77** to **79** followed by a very unusual [4+2] cycloaddition to produce **80** (Scheme 5).[50,53] While imino Diels-Alder reactions are well known,[55]the product **80** is formally an anti-Bredt olefin when drawn as the iminium resonance structure. This reactive species is immediately reduced by DPAS to afford (–)-coronaridine (**4**).[50]

When angryline (**82**) is exposed to TS, CS, or CorS/DPAS it produces tabersonine (**78**), (+)-catharanthine (**7**), and (–)-coronaridine (**4**), respectively.[53] The formation of three distinct chiral natural products from a common achiral intermediate is a hallmark of iboga/aspidosperma biosynthesis (Figure 3)

Conversion of **4** to 10-hydroxycoronaridine is accomplished by the P450 enzyme ibogamine-10-hydroxylase (I10H) (Scheme 5).[56] Methylation by noribogaine-10-*O*-methyltransferase (N10OMT) produces (–)-voacangine (**3**).[56] Polyneudridine aldehyde esterase-like 1 (PNAE1) has been shown to convert both **3** and **4** to their corresponding carboxylic acids.[50,57] However, the pathways converting these acids to ibogaine and ibogamine still have not been fully elucidated. The O'Connor group reported that the hydrolysis product of **3** does spontaneously decarboxylate to produce ibogaine.[50] However, this reaction is slow, and heating is required to increase its rate. Furthermore, this transformation does not proceed when the hydrolysis product of **4** is heated. Therefore, it is likely that an unidentified decarboxylase(s) is responsible for the final step in the biosynthesis of ibogaine and ibogamine. Furthermore, ibogamine can be converted to ibogaine via I10H-mediated hydroxylation followed by N10OMT-catalyzed *O*-methylation.[56] However, when noribogaine (**2**) is used as a substrate, N10OMT exhibits a low turnover rate suggesting that this transformation might actually be mediated by a currently unidentified *O*-methylase.

Tabersonine (**78**) is known to be hydroxylated at the C11 position by tabersonine 16-hydrolase (T16H); however, a similar hydroxylase(s) acting on the iboga scaffold to produce tabernanthine (**5**) or ibogaline (**6**) has not been identified. Through sequence homology, five additional P450s related to T16H and I10H were identified in *T. iboga*. These enzymes were cloned, but they did not catalyze the C11-hydroxylation of either coronaridine or ibogamine.

[56] Therefore, it is possible that tabernanthine (**5**) and ibogaline (**6**) are produced from an oxidase unrelated to the P450 family.

The enzymes that produce iboga and aspidosperma alkaloids have been shown to be somewhat promiscuous. An interesting study by the O'Connor group involved feeding substituted tryptamines to a *C. roseus* hairy root culture.[58] Using LC-MS, they concluded that the unnatural tryptamine derivatives were incorporated into the scaffolds of the natural products. Feeding studies are only one approach for producing "unnatural" natural products. The O'Connor group has also expressed several prokaryotic halogenases or engineered halogenases, such as RebH, in *C. roseus*, leading to the production of chlorinated tabersonine analogs.[59,60]

HISTORICAL SYNTHESES OF IBOGA ALKALOIDS

Since Büchi's pioneering synthesis of ibogaine in 1966,[28] there have been numerous synthetic approaches to iboga alkaloids. For a comprehensive analysis of strategies prior to 2011, we refer the reader to an excellent review by Sinha and co-workers.[61] Here, we focus on historical strategies for constructing the isoquinuclidine, tetrahydroazepine, and indole ring systems characteristic of this alkaloid family.

Construction of the Isoquinuclidine

The isoquinuclidine ring system represents a structural focal point for the iboga alkaloids.[62] Methods to construct this [2.2.2] bicycle have centered around three fundamental strategies —cycloaddition, transannular cyclization, and radical rearrangement (Figures 4–6). The cycloaddition strategy was first successfully utilized by Büchi and co-workers (Figure 4). [63,28] Their approach involved the reduction of nicotinamide pyridinium **83** with sodium borohydride to give a regioisomeric mixture of dienes **84** and **85**. When this mixture was subjected to a Diels-Alder reaction with methyl vinyl ketone (MVK), only dihydropyridine **85** underwent cycloaddition, yielding isoquinuclidine **86** in 13% yield as a mixture of epimers over two steps. The authors postulated that the greater electron delocalization of **84** prevents cycloaddition with MVK.

Most syntheses that have adopted this approach have opted to transform the substituent on the dienophile into the exo C20 ethyl group of the iboga alkaloids.[28,64,65] This poses an obvious challenge given the inherent endo selectivity of most Diels-Alder reactions. To overcome this issue, Sames and co-workers took advantage of the acidic protons alpha to the carbonyl (Figure 4).[65] By treating a 3:1 endo:exo mixture of the Diels-Alder adducts with base, they achieved epimerization to a thermodynamic ratio (2:3) of **88** and **89**. After exo enrichment, conversion to the tosylhydrazones **90** and **91** allowed for separation via crystallization. Fukuyama and co-workers sought to avoid endo/exo diastereoselectivity issues altogether by performing the Diels-Alder reaction with a symmetrical dienophile (Figure 4).[66] Treatment of trans-dibromide **92** with DABCO afforded the requisite dihydropyridine **93**, which was then reacted with dimethyl methylenemalonate to give isoquinuclidine **94** in 94% yield over two steps.

In the approaches described above, the Diels-Alder reactions were uncatalyzed, leading to racemic mixtures of isoquinuclidines. Recently, Batey and co-workers reported an enantioselective Diels-Alder reaction of dihydropyridine **87** with acrolein in the presence of a valine-derived organocatalyst (Figure 4),[67] leading to a formal synthesis of (+)-catharanthine. In 2006, Borschberg and co-workers reported another enantioselective synthesis of an iboga alkaloid, although their approach involved an intramolecular nitrone-olefin [3+2] cycloaddition (Figure 4).[68,69] Key intermediate **96** was synthesized from L-glutamic acid and (2*S*)-but-3-en-2-ol. A crucial chirality transfer in the Ireland-Claisen rearrangement of a silyl ketene acetal afforded intermediate **96** in high diastereoselectivity. The subsequent 1,3-dipolar cycloaddition produced **97** in 67% yield.

Another common approach to accessing the isoquinuclidine framework of iboga alkaloids involves the transannular cyclization of an amine derivative. Huffman and co-workers were the first to employ this strategy in 1965.[70,71] Ring opening of cyclic epoxy ester **98** followed by transannular amidation produced the isoquinuclidine in a single step. Subsequent tosylation of the C16 alcohol afforded intermediate **100** in 57% yield over two steps (Figure 5). However, when this strategy was applied to the synthesis of ibogamine, the yields were greatly reduced owing to the complex mixture of diastereomeric products obtained during the synthesis of epoxide **99**.[72]

Variants of the transannular cyclization strategy have involved the preassembly of the indole and/or tetrahydroazepine rings prior to formation of the isoquinuclidine (Figure 5). The approach taken by Grieco and co-workers mirrored that of Huffman and produced **103** in excellent yield.[73] A hallmark of both of the Huffman and Grieco syntheses is the incorporation of an enolizable proton at what will become the bridgehead position, enabling both diastereomers to be converted to the desired isoquinuclidine.

A related approach pioneered by Sallay established what would become the tetrahydroazepine of ibogamine prior to transannular alkylation forming **105**.[74] White and co-workers improved upon the racemic Sallay synthesis by constructing **104** using an asymmetric Diels-Alder reaction as the key step (Figure 5). Base-mediated cyclization afforded **105** in high yield, which was converted to (–)-ibogamine.[75]

In addition to classic acylation and alkylation reactions, several other transannular cyclizations have been utilized to access the isoquinuclidine core of iboga alkaloids. For example, Nagata and co-workers favored the use of a transannular aziridination reaction,[76,77,78] while Trost and co-workers relied on Pd-catalyzed allylic alkylation.[79,80] Trost's 1978 synthesis of (+)-ibogamine was a landmark paper for the field (Figure 5). Use of a chiral auxiliary enabled an asymmetric Diels-Alder reaction (60% ee), and the product was subjected to reductive amination to produce **106**. Treatment of **106** with Pd[0] led to **107**, which was converted to the natural product through a metal-mediated olefin arylation. Trost's synthesis was the first to use a transition metal to access an iboga alkaloid, and it set precedent for many similar strategies to follow.

Generally, methods to form the isoquinuclidine of iboga alkaloids have started from either an acyclic, cyclic, or fused cyclic precursor. In 2005, Hodgson developed an alternative

strategy starting from an existing bridged bicycle (Figure 6).[81] An enantioselective desymmetrization of meso tropenone **108** gave radical precursor **109** in 46% yield over four steps. Reduction of the ketone with $NaBH_4$ gave the corresponding bromohydrin, which was then transformed into **113** via homoallylic radical rearrangement. This one-pot procedure led to an efficient formal synthesis of (+)-ibogamine.

Construction of Tetrahydroazepine

The 7-membered tetrahydroazepine is a crucial structural element linking the indole and isoquinuclidine rings of the iboga alkaloids. Most syntheses have relied on one of three strategies for its construction—formation of the C2–C16 bond, C7–amine linkage, or ring-expansion. The C2–C16 bond disconnection was first explored by Nagata in 1968[76] and later exploited by Imanishi.[82] The cyclization of **114** was achieved by refluxing in a stoichiometric amount of *p*-TsOH for a short duration. Treatment of the resulting tosylate with *in situ* generated AlH_3 produced ibogamine (**81**) in reasonable yields (Figure 7). In 1985, Huffman employed an alternative strategy using tosylate **115**. Lewis acid-mediated cyclization of **115** followed by reduction of the lactam gave **81** in 32% yield over two steps (Figure 7).

The C2–C16 bond disconnection was also key feature of Trost's 1978 synthesis.[79] Using a novel olefin arylation, Trost and co-workers were able to forge the C2–C16 bond from **107** using a mixture of palladium and silver (Figure 7). Reduction of the resulting organopalladium species afforded (+)-ibogamine in 43% yield. In 2015, Sames applied a slight modification of this C–H activation strategy by using a preformed palladium tetrafluoroborate catalyst instead of a combination of $PdCl_2(CH_3CN)_2$ and $AgBF_4$.[65] This result suggests that silver is not directly involved in cyclization and serves merely to facilitate chloride exchange for a noncoordinating tetrafluoroborate, thus generating a more active catalyst. Though interesting, the methods developed by Trost and Sames suffered several drawbacks such as low yields and the need for stoichiometric or supra-stoichiometric amounts of palladium (1–2 eq). In 2012, Sinha employed a modified strategy using only catalytic amounts of palladium catalyst (Figure 7).[64,83] Pre-functionalization of the indole C2 position with an iodide (**116**) enabled a reductive Heck reaction to be performed using only 10 mol% of $Pd(OAc)_2$. This more economical approach towards the tetrahydroazepine ring system enabled the synthesis of ibogaine (**1**) in 66% yield.

Another popular strategy for constructing the tetrahydroazepine involves the introduction of a linker between the nitrogen of the isoquinuclidine and the C3 position of the indole (C7 based on the Le Men and Taylor numbering). Using a method developed by Kutney,[84] Das and co-workers performed a debenzylation of a quaternary ammonium salt derived from **117** (Figure 8).[85] Though they were able to isolate catharanthine, the route was low yielding as formation of the quaternary ammonium salt was challenging. Fukuyama and co-workers took a slightly different approach by deprotecting the isoquinuclidine prior to alkylation.[66] They noticed that hydrogenolysis of **118** also resulted in the reduction of the endocyclic olefin. Instead, a mild and chemoselective deprotection using triethylsilane and palladium acetate afforded catharanthine in a single step. Interestingly, the desired intramolecular S_N2

alkylation occurred readily following carbamate deprotection, presumably due to the highly rigidified nature of the intermediate amine.

Sundberg and co-workers also chose to construct the tetrahydroazepine after the indole and isoquinuclidine rings had already been established (Figure 8).[86] However, their approach involved the generation of a radical through irradiation of chloroacetamide **119**. Radical cyclization afforded **120** in modest yield.

The final strategy used to construct the tetrahydroazepine involves ring expansion, and this was the method by which Büchi first synthesized ibogaine (Figure 9).[28,63] Treatment of **121** with a mixture of Zn and AcOH resulted in reductive opening of the 6-membered ring. Following protonation at the γ-position, conjugate addition of the amine produced ibogaine in 57% yield. White and co-workers also synthesized the 7-membered ring through ring expansion. Beckman rearrangement of **124** yielded **125** in good yield.

Construction of the Indole

The indole ring system of the iboga alkaloids is biosynthetically derived from tryptophan, and most synthetic efforts toward the iboga alkaloids have started from tryptamine derivatives. For example, Büchi's 1966 synthesis of ibogaine involved the coupling of an isoquinuclidine with indole acetic acid.[28] More recently, alternative approaches to generating the indole have been explored (Figure 10). In 2000, White and co-workers installed the indole at a late-stage through a Fischer indole cyclization of **105** to afford **126** in 66% yield over two steps.[75] Fukuyama and co-workers built the indole through radical cyclization of thioanilide **127**.[66] They noticed that standard tin hydride conditions failed to produce the desired product in acceptable yields. Instead, they found that a phosphorus-based hydrogen atom donor afforded the desired cyclization. Recently, Sinha and co-workers decided to synthesize the indole very early in their synthesis.[64] Larock annulation of aniline **129** and alkyne **130** provided **131** in modest yield. Very few synthetic strategies towards iboga alkaloids have made the construction of the indole a focal point for the synthesis, perhaps because the 7-membered tetrahydroazepine and bicyclic isoquinuclidine ring systems are viewed as being more challenging to access.

RECENT SYNTHETIC APPROACHES TO IBOGA ALKALOIDS (2010–2019)

In the past decade, several groups have focused on developing innovative methods to construct the isoquinuclidine ring system.[87,88,89] Coldham and coworkers previously employed a tandem oxime alkylation/nitrone cycloaddition to access both the aspidosperma[90,91] and daphniphyllum alkaloids.[92] In 2019, they extended their methods for constructing bridge bicyclic [3.3.1] systems to the iboga alkaloids simply by adjusting the positions of the branch point (C5 vs C4) and the dipolarophile (internal vs terminal olefin) (Figure 11).[87] Following hydrolysis of the dithiane in **137** and N–O bond reduction, Coldham and co-workers were able to intercept an intermediate previously accessed by Borschberg,[69] completing a formal synthesis of 19-hydroxyibogamine.

Asymmetric Syntheses of Iboga Alkaloids

Prior to 2010, most synthetic strategies to iboga alkaloids led to racemic mixtures, while the more modern approaches of the past decade have taken advantage of recent developments in asymmetric synthesis. Most asymmetric syntheses of iboga alkaloids focus on the enantioselective construction of the isoquinuclidine ring system. In 2019, Nemoto and coworkers showcased an elegant strategy focused on the desymmetrization of meso isoquinuclidine **143**.[88] To access the meso compound, they employed chemistry that they first reported in 2015[93] involving the formal insertion of a rhodium carbenoid into an amide C–N bond (Figure 12). Attack of the PMB-protected nitrogen in **138** on the rhodium carbenoid produced Rh-associated N-ylide **139**. Subsequent Stevens rearrangement produced isoquinuclidine **141**. Using computational chemistry, Nemoto and co-workers ruled out a step-wise mechanism for the Stevens rearrangement in favor of a concerted, asynchronous process.

Upon generation of diketone **141**, an *in situ* reduction with DIBAL-H afforded 1,3-diol **142** with high diastereoselectivity. Desymmetrization of **142** with a chiral phosphoric acid catalyst proved unsuccessful due to a background reaction involving the basic nitrogen (Figure 12). While Boc protection of **143** showed slight improvement in enantioselectivity, protection with a strong electron withdrawing sulfonamide (i.e, Ns) afforded the desymmetrized product **144** in 40% yield and 78% ee. By optimizing the catalyst, solvent, and temperature, they were eventually able to obtain the nosyl-protected **144** in 74% yield and 94% ee, which they took on to complete a formal synthesis of (+)-catharanthine.

A similar enantioselective approach to the isoquinuclidine using an N-ylide intermediate was taken by Luo and coworkers in 2016 (Scheme 6).[89] Their route started with **145**, which was prepared from tryptamine in 3 steps (98% ee) via an asymmetric organocatalytic Pictet-Spengler reaction.[94] Protection of the indole nitrogen, propargylation, and deprotection afforded diastereomers that were readily separated. Reduction of the desired diastereomer **146** produced **147**, which was subjected to a one-pot procedure involving the gold-catalyzed conversion of the terminal alkyne to an α-chloromethyl ketone[95] followed by intramolecular alkylation to yield **149** in 73% yield. The basicity of the tertiary amine poisoned the gold catalyst making acidification with TFA/MsOH necessary. Gram scale preparation of **149** was improved significantly by adding one equivalent of AgOTf, which promoted transannular alkylation of **148**. The key Stevens rearrangement was accomplished through initial formation of enamine **150**, furnishing the isoquinuclicine in modest yield. Interestingly, the use of N-methylmorpholine in place of piperidine failed to produce **153**, suggesting that formation of the enamine was critical to the success of the Stevens rearrangement.

Next, exocyclic olefin **154** was accessed through a Wittig reaction, and the (*Z*)-configuration was assigned by NOESY NMR. Hydrogenation of **154** with H_2 and Pd/C gave (+)-epiibogamine (**155**) exclusively (97% yield). To solve this issue, Luo and co-workers employed hydrogen atom transfer (HAT) conditions originally developed by Baran and Shenvi,[96,97,98] which produced a separable mixture of (+)-epiibogamine (**155**) and (+)-ibogamine (**81**) in 34% and 26% yield, respectively.

In 2012, Takayama and coworkers utilized an asymmetric Diels-Alder reaction to complete an enantioselective synthesis of voacangalactone (Scheme 7).[99] Takayama's approach incorporated elements from several previous strategies towards iboga alkaloids. First, **156** was synthesized through vinyl iodide coupling with a chiral oxazolidinone using Buchwald's method.[100] A highly diastereoselective Diels-Alder reaction with dimethyl methylenemalonate produced **157** in 97% yield. Removal of the oxazolidinone and TBS group followed by Cbz protection of the nitrogen yielded alcohol **158**, which was mesylated and subjected to transannular alkylation. Using a strategy pioneered by Fukuyama and co-workers, **160** was converted to **161** through ester hydrolysis and subsequent iodolactonization.[66] Reduction to the corresponding alcohol followed by radical-mediated deiodination and oxidation with DMP produced aldehyde **163**, which was converted to the desired alkyne **164** through Seyferth-Gilbert homologation using the Ohira-Bestmann reagent. Sonagashira cross-coupling of **164** with 2-iodo-4-methoxyaniline produced **165** in 60% yield. Alkyne **165** was transformed into indole **166** using a Au-catalyzed cyclization first developed by Utimoto.[101] The 7-membered ring was constructed through a series of steps that included indole acylation with oxalyl chloride, ester formation, Cbz-deprotection, and amide bond formation. Reduction of **168** with borane produced (−)-voacangalactone (**169**) in 56% yield. Takayama's approach afforded optically pure voacangalactone in 3% overall yield and highlights the power of diastereoselective Diels-Alder reactions for the asymmetric construction of 6-membered rings.

Synthesis of Post Iboga Alkaloids

In 1966, Büchi and coworkers isolated an unusual rearrangement product (**121**) en route to ibogaine.[28] It wasn't until 2013 when it was realized that Büchi's rearrangement product resembled the structure of the newly isolated natural product tabertinggine (**25**).[25] Büchi's pioneering efforts inspired a more recent strategy by She and co-workers enabling ibogamine to be accessed from tabertinggine (**25**).[102] Moreover, they were able to access several additional iboga alkaloids from Büchi's intermediate **121**. Their synthesis commenced with the preparation of **172** via a one-pot sequence involving Pictet-Spengler reaction and intramolecular amidation of 5-MeO-tryptamine (**170**) (Scheme 8). After protection of the indole nitrogen with Boc$_2$O, an aldol condensation with **173** produced **174** in excellent yield. The secondary alcohol was mesylated and eliminated to afford an α,β-unsaturated lactam that underwent diastereoselective hydrogenation. Treatment with LiAlH$_4$ followed by HCl effectively reduced both the amide and ester while also removing the Boc group and hydrolyzing the ketal. Oxidation of primary alcohol **176** followed by intramolecular aldol condensation gave **121** in 75% yield over two steps. Reduction with zinc in acetic acid followed by Wolff-Kishner reduction gave (±)-ibogaine (**1**) in low yield (11%).

With the exception of the final step, this route to ibogaine was relatively high yielding, providing sufficient material to access several "post-iboga alkaloids"[103] (e.g., **37**, **49**, **51**, and **177**) via oxidation of ibogaine (**1**) (Scheme 8). Ibogaine was successfully oxidized with DMDO from the less hindered face to produce **51**. Base-mediated ring-contraction gave iboluteine (**177**) with the desired spiro configuration. An alternative oxidation of ibogaine with I$_2$/NaHCO$_3$ produced lactam **37**. Further oxidation with H$_2$O$_2$ led to ring cleavage

affording ervaoffine D (**49**) in excellent yield. She's strategy not only enabled an efficient route to tabertinggine (**25**) and Büchi's intermediate (**121**), it provided the first syntheses of compounds **37**, **49**, and **51**.

In 2018, Han and coworkers reported a biosynthetically inspired conversion of (+)-catharanthine to various post-iboga alkaloids including (–)-voatinggine (**26**), (–)-tabertinggine (**25**), and (+)-dippinine B.[104] A hallmark of Han's strategy was the utilization of oxidative rearrangements to acquire structural diversification. Additionally, this pioneering work showcased a unique method for accessing the challenging pentacyclic core found in the chippiine and dippinine alkaloids.

Biosynthetic Approach to Iboga Alkaloids

A defining feature of iboga biosynthesis is the formation of multiple alkaloid families from a common dehydrosecodine (**77**) intermediate (Scheme 5). However, the dihydropyridine of dehydrosecodine is very unstable, making the implementation of a truly biomimetic synthesis quite challenging. In 2014, Oguri and co-workers found an elegant solution to this problem (Scheme 9).[105] Their synthesis began with a Pictet-Spengler reaction between tryptamine and **178**, followed by ring expansion[106] to give **179** in 68% yield. Reduction of **179** with sodium cyanoborohydride and subsequent N-propargylation produced **180**. Reaction of **180** with chiral oxazolidinone **181** gave a zwitterionic intermediate that underwent a regioselective Hoffmann elimination to afford dihydropyridine precursor **182**. Upon treatment with a Cu(I) catalyst, a cascade transformation first produced dihydropyridine **183**, which immediately underwent a diastereoselective Diels-Alder reaction to produce **184**. An additional 4 steps were required to convert the C20 substituent into the ethyl group of (–)-catharanthine (**7**).

Of all the syntheses of iboga alkaloids (Table 2), the Oguri Group's synthesis stands out because their biomimetic approach enabled them to access several alkaloid families from a common intermediate (Figure 13). Simply by changing R_1, R_2, and the reaction conditions, Oguri and co-workers could access either iboga-type (e.g., **186**), ngouniensine-type (e.g., **187**), aspidosperma-type (e.g., **188**), or andranginine-type structures (e.g., **189**) from **185**. This landmark paper showcases how powerful biomimetic approaches can be for alkaloid total synthesis.

BIOLOGICAL ACTIVITY OF IBOGAINE

The anti-addictive properties of ibogaine have been known since the 1960s, though this initial information was based entirely on anecdotal reports from heroin users. Since that time, several open-label and/or retrospective studies have suggested that ibogaine might be useful for treating substance use disorder (SUD) as it appears to reduce drug cravings, decrease symptoms of withdrawal, and prevent relapse.[107,108,109,110,111] Moreover, rodent studies have confirmed the anti-addictive potential of ibogaine by demonstrating the natural product reduces drug self-administration, prevents drug-induced dopamine release in several brain regions, attenuates drug-induced conditioned place preference, and decreases signs of withdrawal.[112,113,114] However, double-blind, placebo-controlled clinical trials firmly establishing the efficacy of ibogaine are still lacking. It is illegal to possess ibogaine in the

United States, as it is classified as a schedule I drug. As a result, many people have sought treatment from informal clinics in countries where ibogaine is not regulated.[115] For information on the history and pharmacology of ibogaine, we point the reader to several excellent reviews on these subjects.[116,117,118,119]

Despite ibogaine's promising therapeutic efficacy, major safety concerns have tempered excitement for its clinical development. First and foremost, ibogaine is known to cause long-lasting hallucinations,[118] and at very high doses it can lead to tremors and Purkinje cell death in rats.[120] However, its cardiotoxicity has been the biggest concern. Ibogaine inhibits hERG potassium channels in the heart,[121,122] with several deaths being linked to its adverse effects on heart function.[123,124] Ibogaine is very nonpolar, as evidenced by the fact that it readily accumulates in adipose tissue,[125] and it is well known that hERG inhibition is a major liability for many non-polar, basic amines.[126] Previously, ibogaine was sold in France as a neurotherapeutic, however its adverse effects led to its removal from the market.[116] Since that time, a major goal for the field has been to identify ibogaine congeners with similar therapeutic efficacies, but improved safety profiles.

SYNTHESIS OF IBOGALOGS

Ibogaine's mechanism of action is poorly defined, which has severely inhibited drug discovery efforts using it as a lead structure. Ibogaine and its active metabolite noribogaine bind to a number of targets with only modest affinities including serotonin, opioid, acetylcholine, sigma, and NMDA receptors as well as serotonin, dopamine, and norepinephrine transporters (Table S2).[116] Without an obvious target-based assay to drive structure-activity relationship (SAR) studies, medicinal chemistry efforts have focused on producing antiaddictive ibogaine analogs (i.e., ibogalogs) lacking major side effects. As in vivo addiction assays are costly and time consuming, very few ibogalogs have been tested in these models. However, a number of compounds with interesting structures and/or preliminary biological data have been reported (Figure 14 and Table S2).
64,65,120,149,154,161,162,163,172,127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144. 145, 146, 147, 14

Early efforts focused on comparing the properties of ibogaine to those of other iboga alkaloids. With the exception of very bulky substituents (e.g., **192**), indole substitution appears to have very little effect on NMDA receptor binding affinity (Table S2, **1–5**).[149] However, reducing the size of the C18 ethyl group decreases the NMDA receptor binding affinity substantially (Table S2, **190** and **191**). While **192** is a weak NMDA receptor ligand, it displays comparable potency to ibogaine at the KOR. In contrast, the affinity of noribogaine for the KOR is nearly two orders of magnitude greater than that of ibogaine (Table S2),[149] and it appears to be a G protein biased ligand.[150] As noribogaine is a long-lived metabolite of ibogaine,[151] and kappa ligands are known to have anti-addictive properties,[152] noribogaine might play an important role in the anti-addictive properties of ibogaine.

The majority of iboga alkaloid SAR studies were made possible by the synthetic efforts of Martin Kuehne and co-workers. Perhaps the most exciting analog that they discovered was 18-methoxycoronaridine (18-MC, **193**), which was synthesized in 13 steps.[153] In

collaboration with Stanley Glick's pharmacology group, 18-MC was found to possess many of the same anti-addictive properties as ibogaine without causing tremors, cerebellar neurotoxicity, or inhibiting hERG channels[154] (Table S2). By varying the ester or exchanging it for an amide, a number of 18-MC derivatives were synthesized.[155] The binding affinities of these analogs for the α3β4-nicotinic receptor correlated to their effects on morphine self-administration, leading to the hypothesis that α3β4-nicotinic receptors are important for the anti-addictive properties of 18-MC.[156] Few ibogalogs have demonstrated ibogaine-like therapeutic properties with minimal toxicity issues, making 18-MC quite unique.[157,158] Currently, 18-MC is being tested in phase II clinical trials for treating opioid use disorder.

The majority of the analogs developed by Kuehne and co-workers contained all of the major structural features of iboga alkaloids—isoquinuclidine, tetrahydroazepine, and indole rings. As a result, they are quite difficult to synthesize. Thus far, relatively few function-oriented synthesis (FOS)[159] efforts toward simplified iboga scaffolds have emerged. A few studies have disclosed biological data for ibogalogs lacking the tetrahydroazepine (Figure 14, Table S2, **195–197**), while only a single report describes biological data for ibogalogs lacking the isoquinuclidine (Figure 14, Table S2, **198–202**). To the best of our knowledge, none of these simplified ibogalogs have been tested using in vivo models of addiction.

In addition to 18-MC and the other iboga congeners described above, a number of very interesting analogs related to iboga alkaloids have been synthesized, but not tested for biological activity. These include 1) analogs developed by Sundberg where the tetrahydroazepine is contracted (**203**),[160] expanded (**204**),[161] or removed completely (**205**),[160] 2) ibogaine analogs developed by Sames and co-workers that lack the C2–C16 bond (**206–207**),[65] and compounds developed by Sinha with C2 and C7 transposed (**208–209**).[162,64]

With the exception of one report in 1994,[163] all of the SAR studies described above utilized the natural products or synthetic racemates. This single report claims to have tested the "R- and S-enantiomers" of ibogamine and coronaridine and found that these compounds produced similar effects on morphine self-administration. However, no asymmetric syntheses of (+)-coronaridine or (+)-ibogamine had been reported prior to this publication. In fact, the first asymmetric syntheses of (+)-coronaridine[164] and (+)-ibogamine[81] were reported by Kuehne and Hodgson in 2001 and 2005, respectively. Furthermore, ibogamine and coronaridine contain multiple stereogenic centers, making the designation of "R- and S-enantiomers" ambiguous (no description of their optical rotations was provided). We think that the "R- and S-enantiomers" described in this study are more likely the exo and endo epimers of the C20 position, both of which would be racemic compounds. If we are correct, then to the best of our knowledge, it is unknown if alkaloids from ibogaine's antipodal series (e.g., catharanthine) have anti-addictive properties.

ADVANCES IN IBOGA NEUROBIOLOGY

In standard assays, ibogaine appears to have weak affinity for a large number of neuroreceptors, which has hindered efforts to define its mechanism of action.[165,166]

Moreover, its therapeutic effects are relatively long-lasting,[167,168] which implicates neural plasticity mechanisms leading to the re-wiring of addiction-related neural circuitry. The first piece of evidence suggesting that ibogaine might promote neural plasticity was provided by Dorit Ron and co-workers. They demonstrated that ibogaine increases glial cell line-derived neurotrophic factor (GDNF) expression in the ventral tegmental area (VTA), and that infusion of ibogaine into the VTA of rodents decreases alcohol consumption.[169] Recently, a study by Carrera and co-workers showed that ibogaine can impact brain-derived neurotrophic factor (BDNF) and GDNF signaling in several brain regions that play key roles in the pathophysiology of addiction.[170] Neurotrophic factor signaling is well known to promote structural neural plasticity—the physical re-wiring of the brain.

Compounds capable of rapidly promoting structural neural plasticity are known as psychoplastogens.[171] Recently, our group demonstrated that noribogaine, an active metabolite of ibogaine,[172] is a potent psychoplastogen that increases cortical neuron dendritogenesis.[173] Other psychoplastogens, including several psychedelic compounds, possess anti-addictive properties in the clinic that mirror the effects of ibogaine.[174] By modifying addiction-related circuitry instead of simply blocking the targets of addictive substances, psychoplastogens like ibogaine have the potential to produce long-lasting anti-addictive effects across a wide range of substances (e.g., opioids, alcohol, stimulants, etc.) and represent a new approach to treating substance use disorders.

Currently, it is unknown if ibogalogs like 18-MC are psychoplastogenic. However, unlike ibogaine, 18-MC does not increase *GDNF* expression in SH-SY5Y cells or reduce alcohol self-administration following direct infusion into the VTA, suggesting that the mechanisms of the two compounds are likely different.[175] Given the fact that a large number of novel ibogalogs have been developed (Table 4), these compounds should be re-evaluated using phenotypic neural plasticity assays[173] in an effort to identify safer and more efficacious ibogaine analogs.

CONCLUSION

A number of advances have been made in the past 10 years regarding iboga chemistry and biology. We now know how the antipodal series of these alkaloids are generated from a common achiral precursor, and biomimetic approaches are enabling the rapid synthesis of several iboga family members. Furthermore, new clues have emerged regarding how iboga alkaloids might produce long-lasting neurotherapeutic effects. However, there are still a number of chemical and biological challenges that need to be addressed if we are to rationally engineer safe and effective medicines for treating neuropsychiatric disorders based on the iboga core structure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

BIOGRAPHIES

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David E. Olson studied chemistry and biology at Union College and received his Ph.D. in chemistry from Stanford University. After his graduate work, he completed postdoctoral training in neuroscience at the Broad Institute of MIT and Harvard. He is currently an assistant professor in the Department of Chemistry and the Department of Biochemistry & Molecular Medicine at the University of California, Davis as well as the president and chief scientific officer of Delix Therapeutics. His research interests broadly encompass the area of chemical neuroscience and include the synthesis of psychoactive natural products, the development of novel neurotherapeutics, and mechanistic neuropharmacology.

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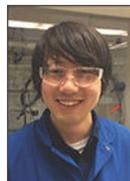
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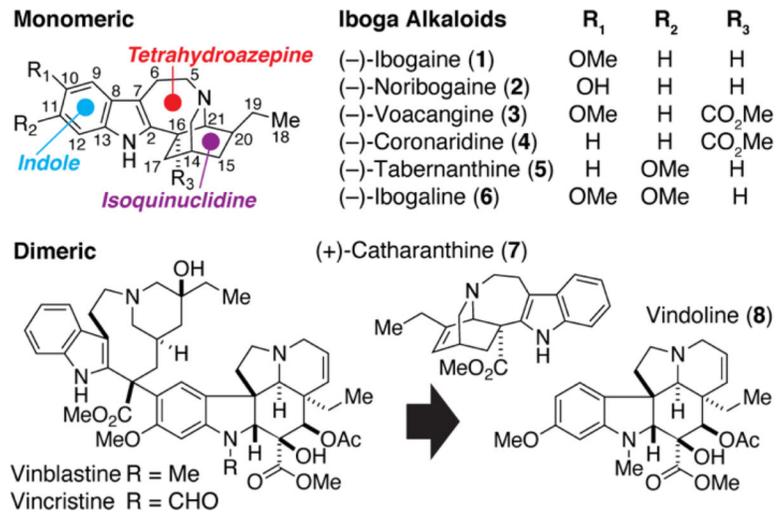
Figure 1.
Structures of iboga alkaloids and related compounds
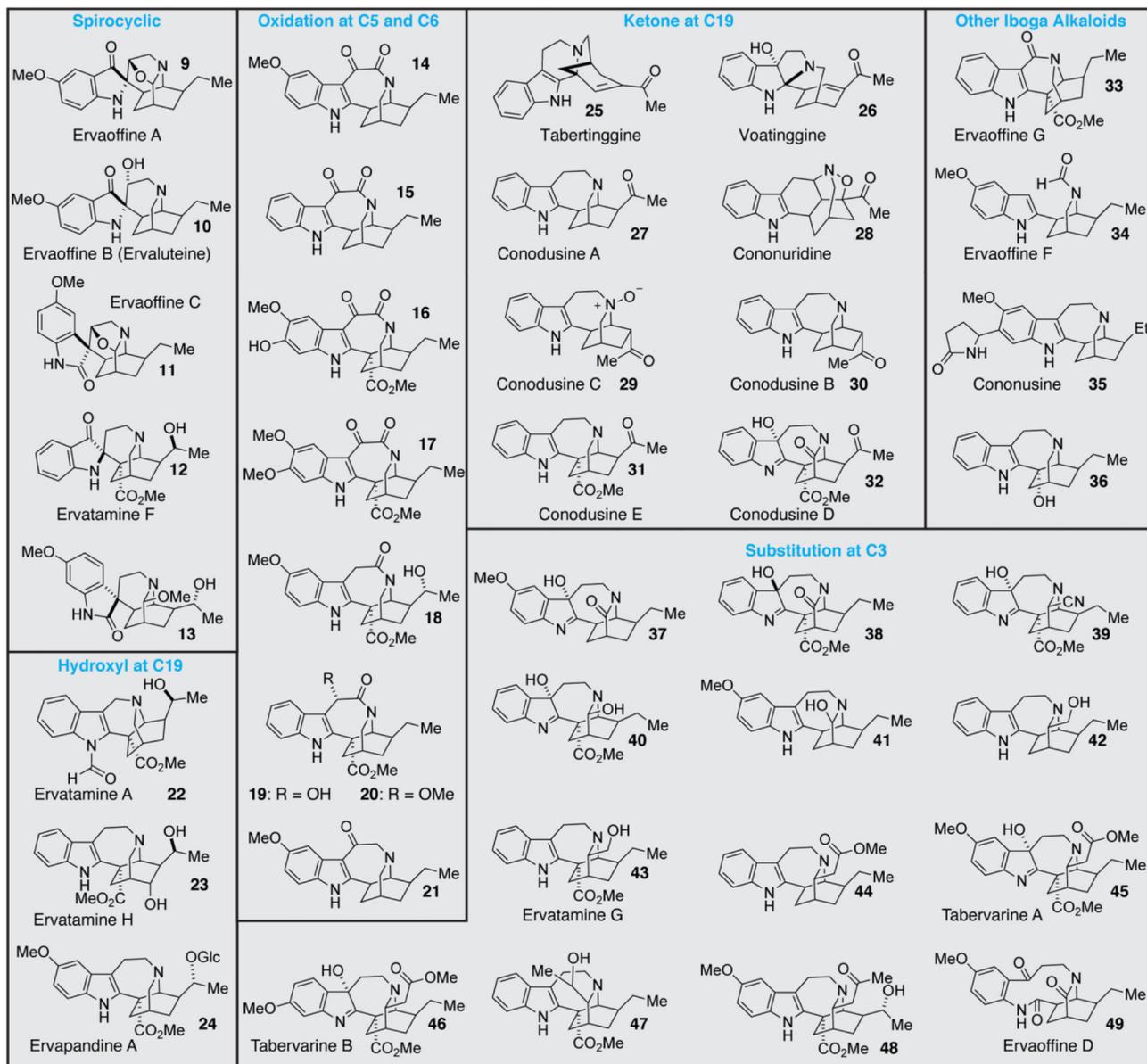
Figure 2.
Newly isolated iboga alkaloid during the period 2010–2020
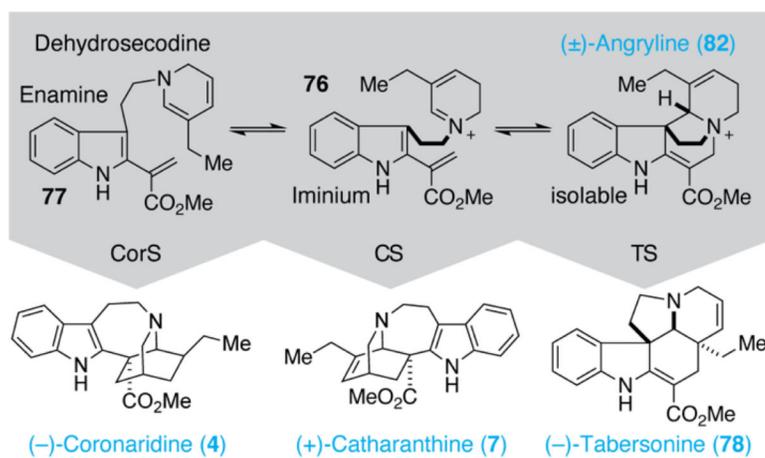
Figure 3.
Racemic angryline gives rise to three chiral natural products through the intermediacy of achiral dehydrosecodine. Isolable compounds are highlighted in blue.
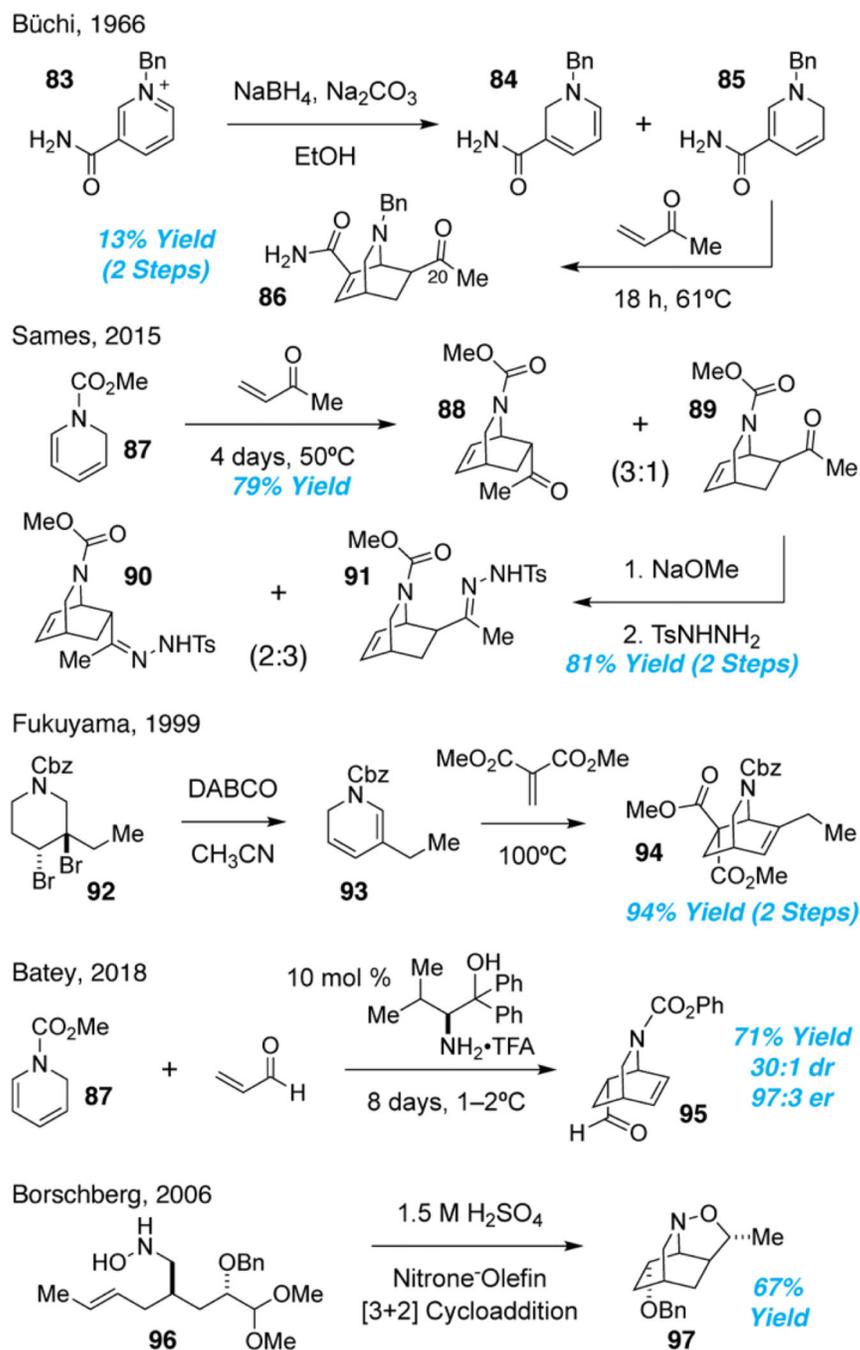
Figure 4.
Cycloaddition approaches to the isoquinuclidine of iboga alkaloids
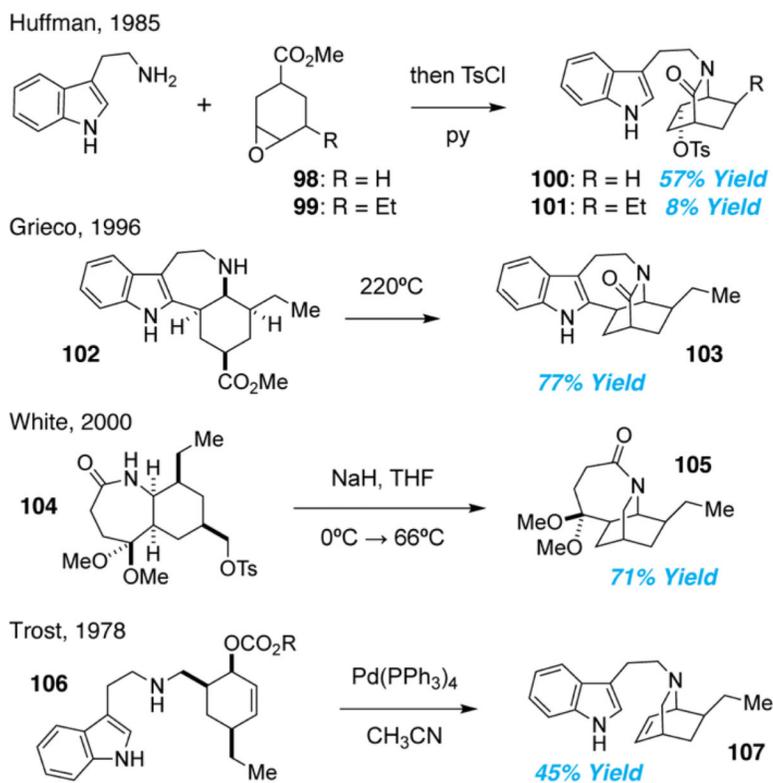
Figure 5.
Transannular cyclization approaches to the isoquinuclidine of iboga alkaloids
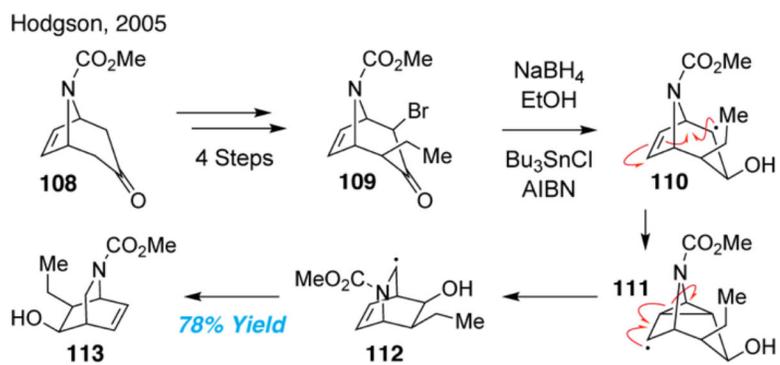
Figure 6.
Hodgson's radical rearrangement approach to the isoquinuclidine cyclization approaches to the isoquinuclidine of iboga alkaloids
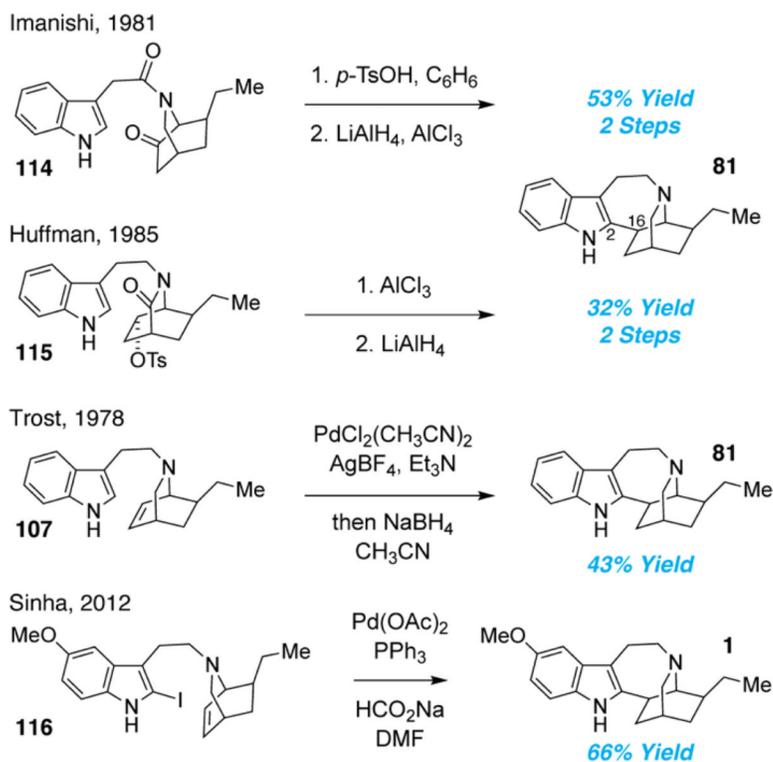
Figure 7.
Construction of the tetrahydroazepine through C2–C16 bond formation. Though Trost and co-workers did not report the number of equivalents of Pd that were used to effect cyclization, subsequent work by Sames and co-workers suggests that > 1 equivalent of Pd was likely necessary.
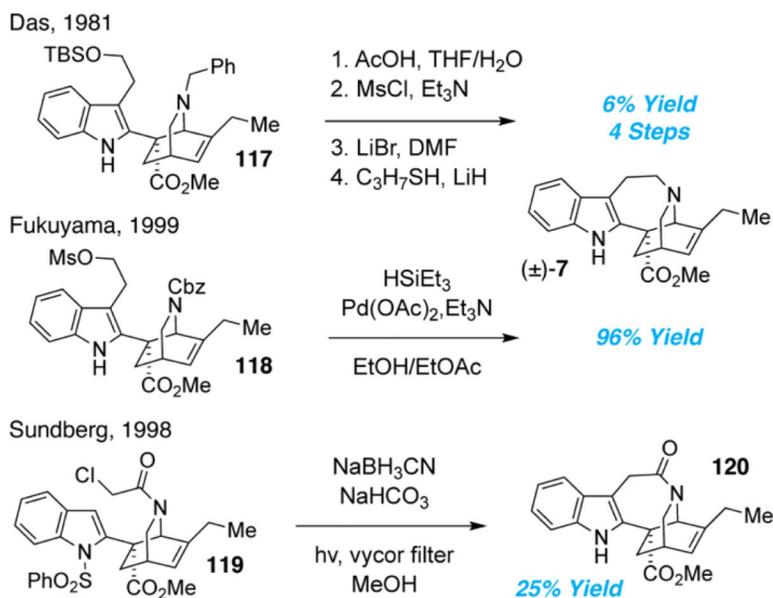
Figure 8.
Construction of the tetrahydroazepine through C7–amine linkage
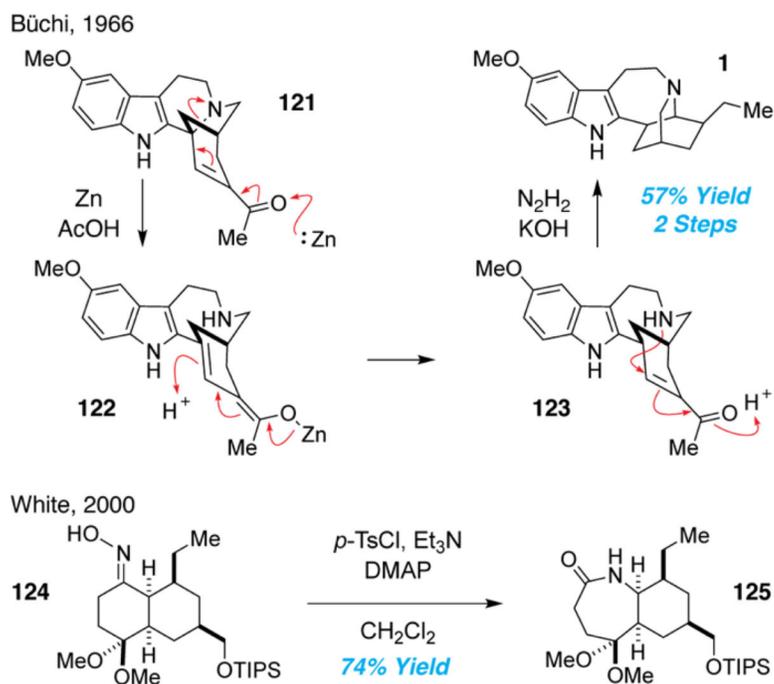
Figure 9.
Construction of the 7-membered ring through ring expansion
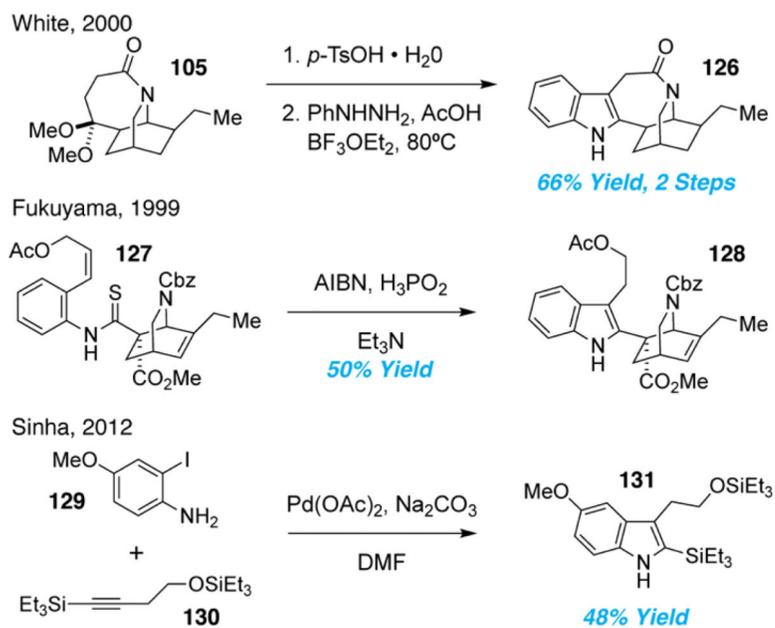
Figure 10.
Construction of the indole
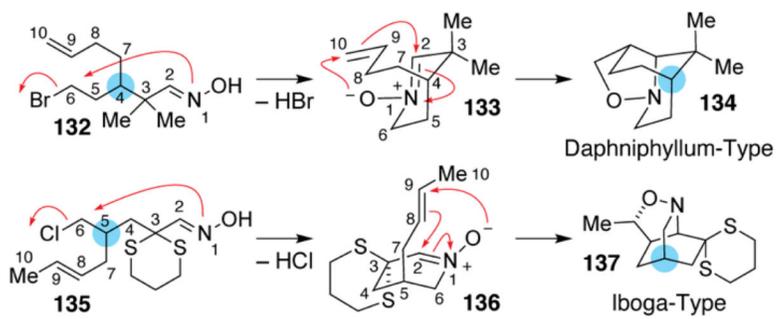
Figure 11.
Coldham's alkylation/cycloaddition strategy to iboga alkaloids
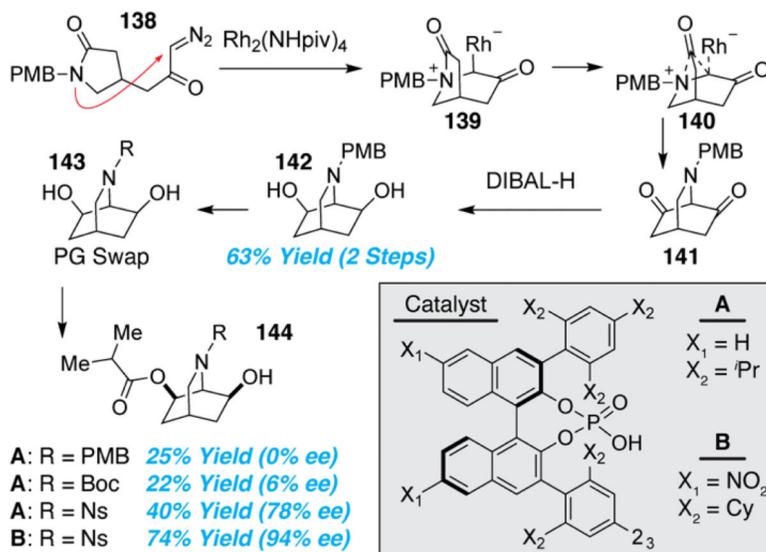
Figure 12.
Nemoto's asymmetric synthesis of 144. PG = protecting group.
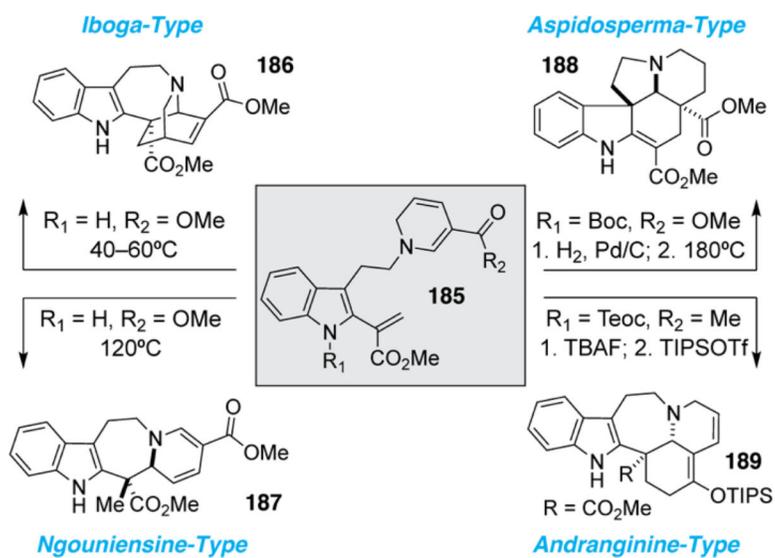
Figure 13.
Oguri's intermediate **185** enables access to multiple families of alkaloids
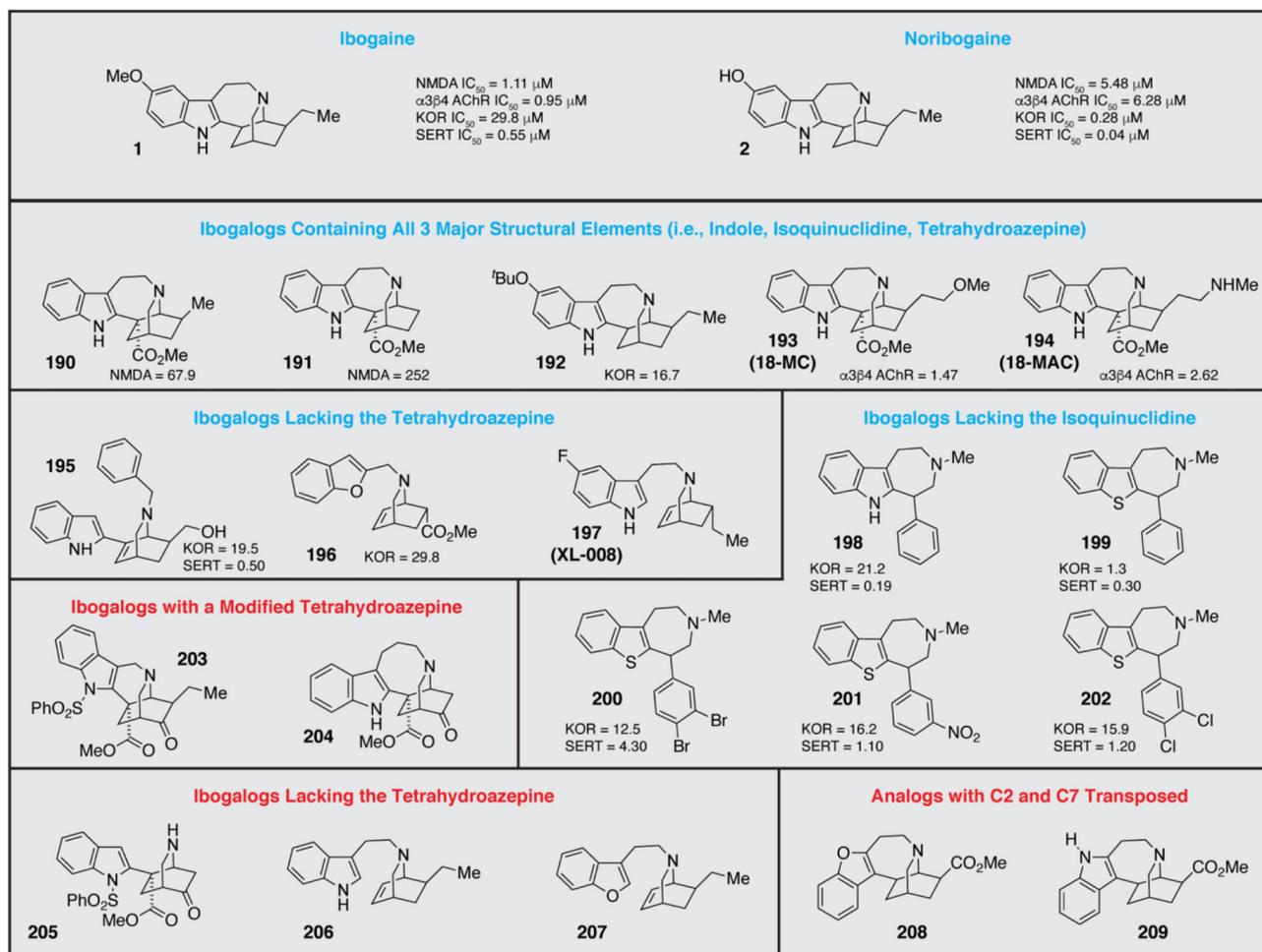
Figure 14.
Structures of several iboga analogs. Blue headings indicate analogs that have been tested in biological assays. Red headings indicate analogs that have not yet been tested in biological assays. Select IC$_{50}$ values are indicated (μM). For complete biological testing details, see Table S2.
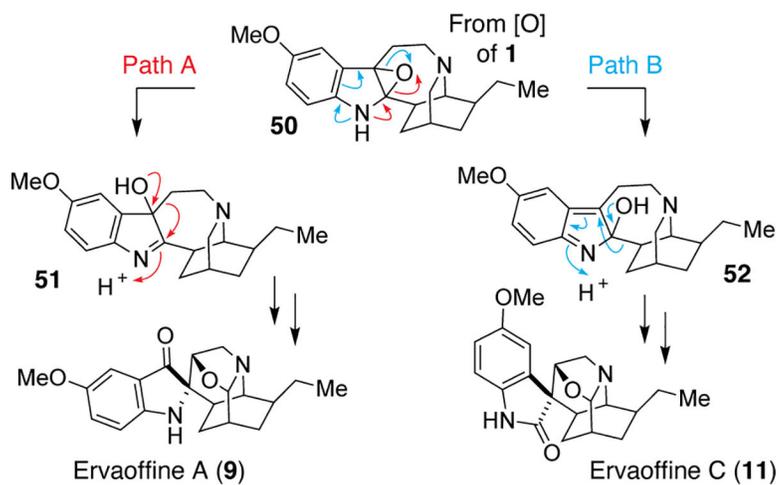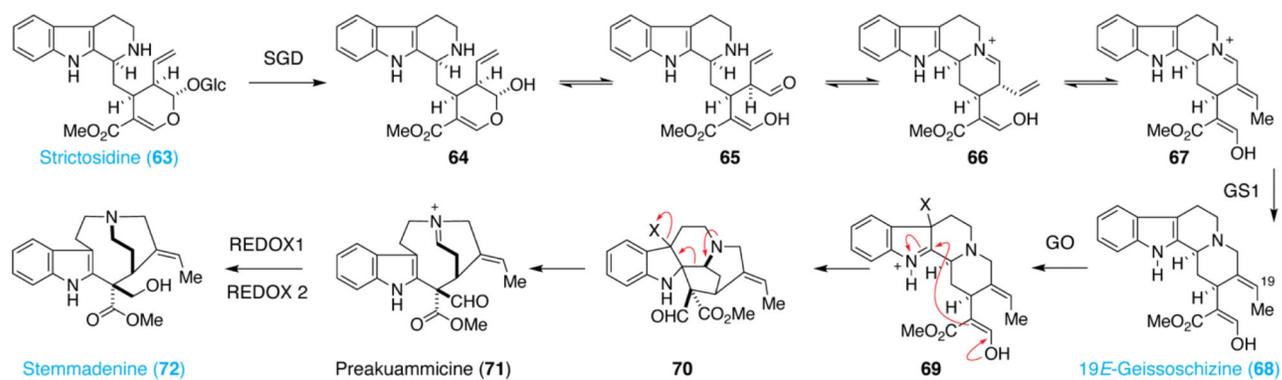
Scheme 1.
Proposed mechanism for the oxidative rearrangement of ibogaine to form ervaoffine A and C
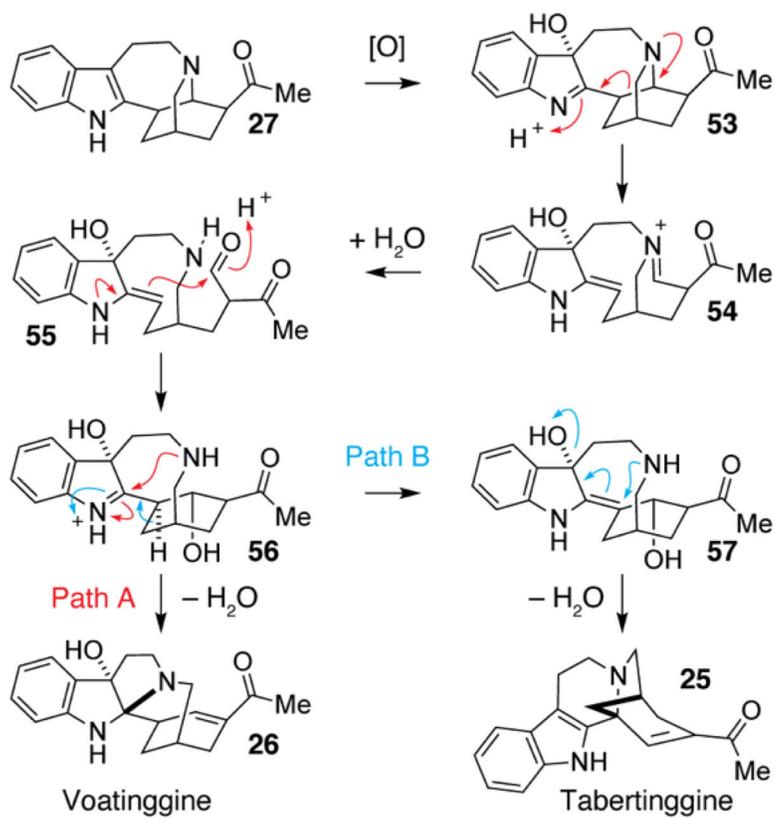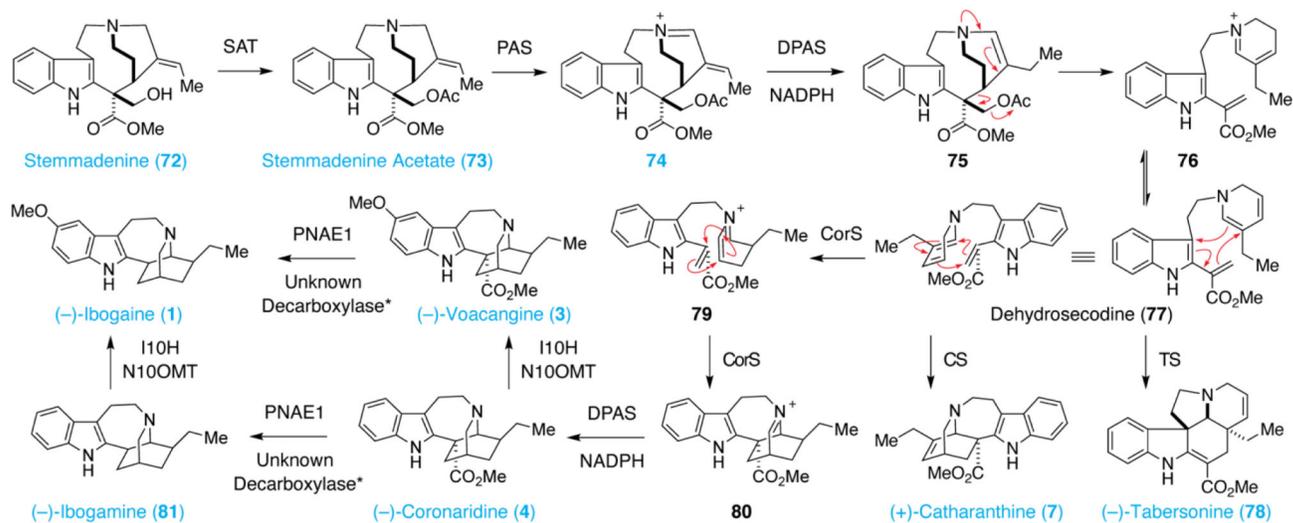
Scheme 2.
Proposed mechanism for the formation of tabertinggine and voatinggine
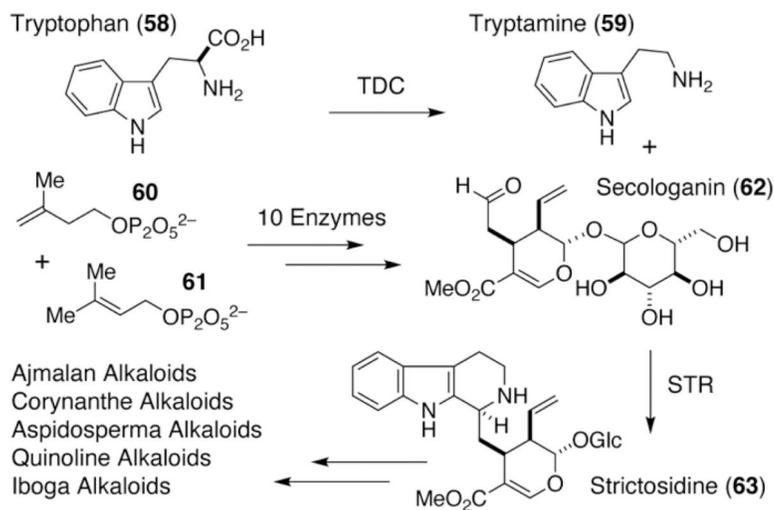
Scheme 3.
Biosynthesis of strictosidine

Scheme 4.
Biosynthesis of stemmadenine. Compounds that have been isolated are highlighted in blue.

Scheme 5.
Biosynthesis of iboga and aspidosperma alkaloids. Compounds that have been isolated are highlighted in blue. *Compound **1** can be produced from **3** following slow, spontaneous decarboxylation. This reaction can be accelerated with heat. No spontaneous decarboxylation of **4** was observed even after heating.
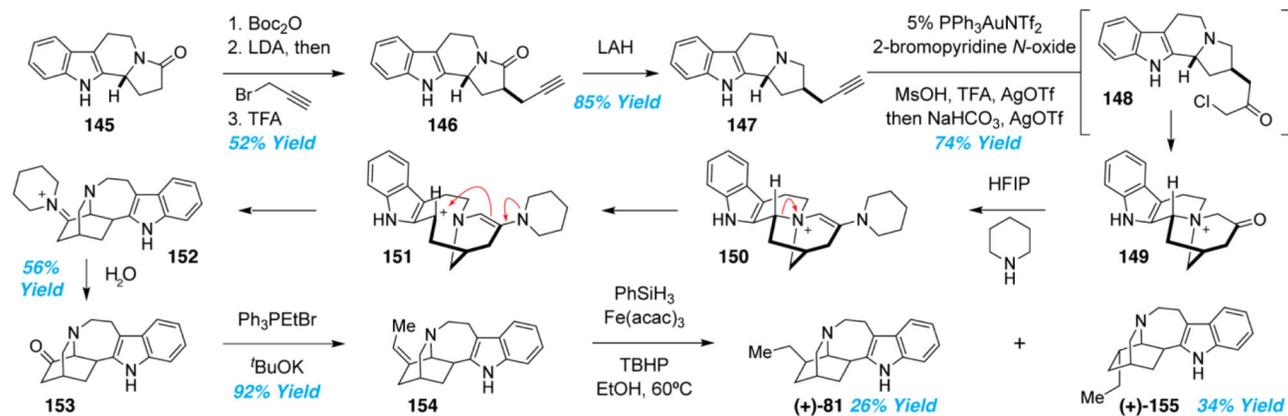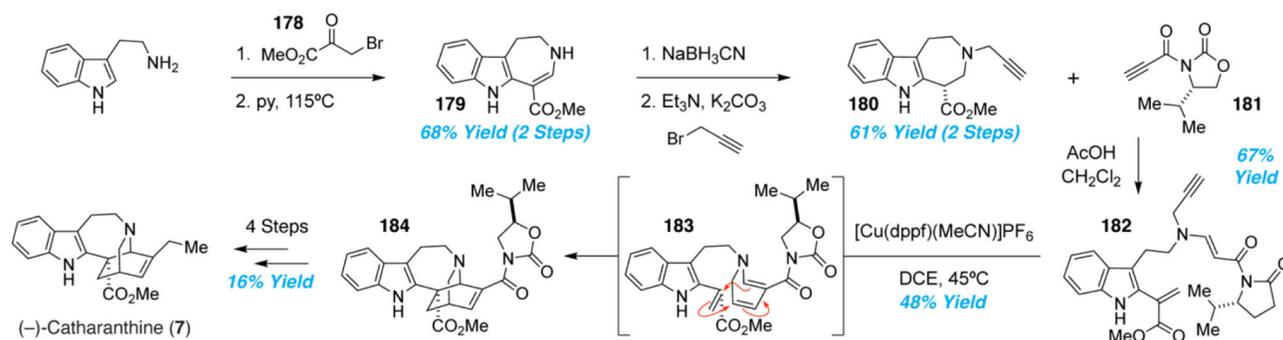
Scheme 6.
Luo's 2016 asymmetric synthesis of (+)-ibogamine
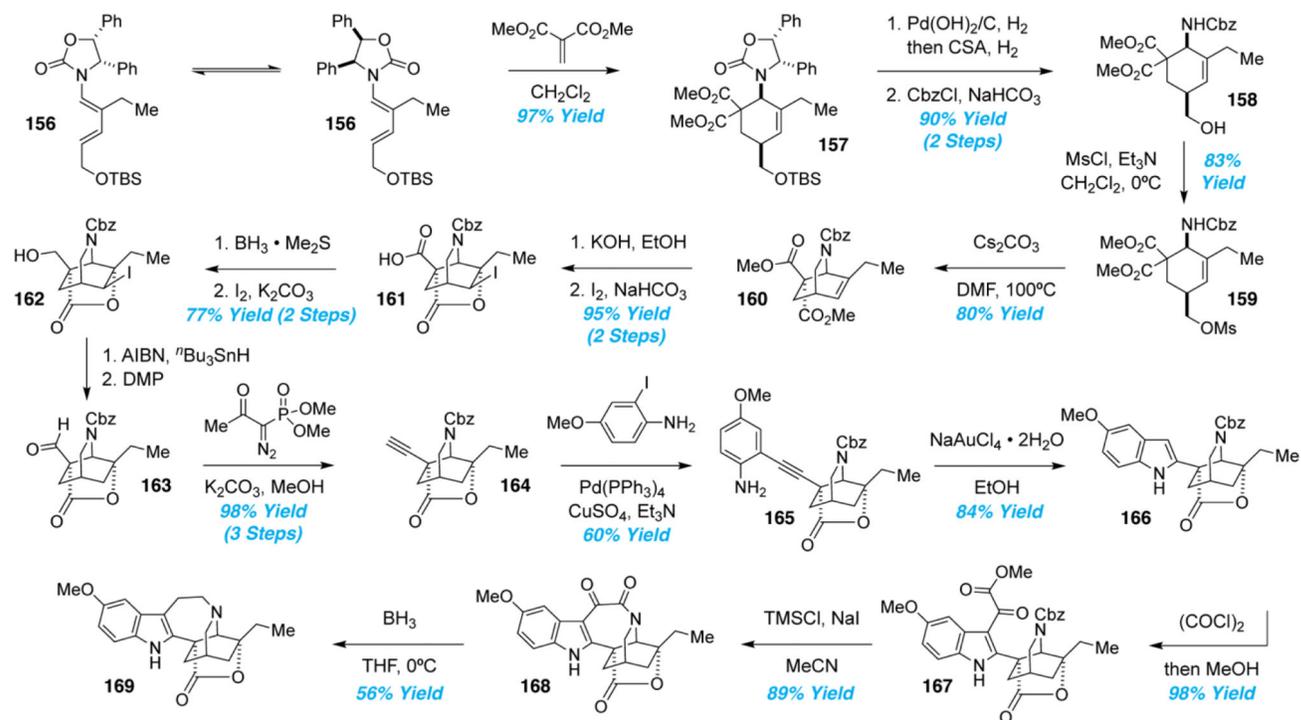
Scheme 7.
Takayama's 2012 asymmetric synthesis of (–)-voacangalactone
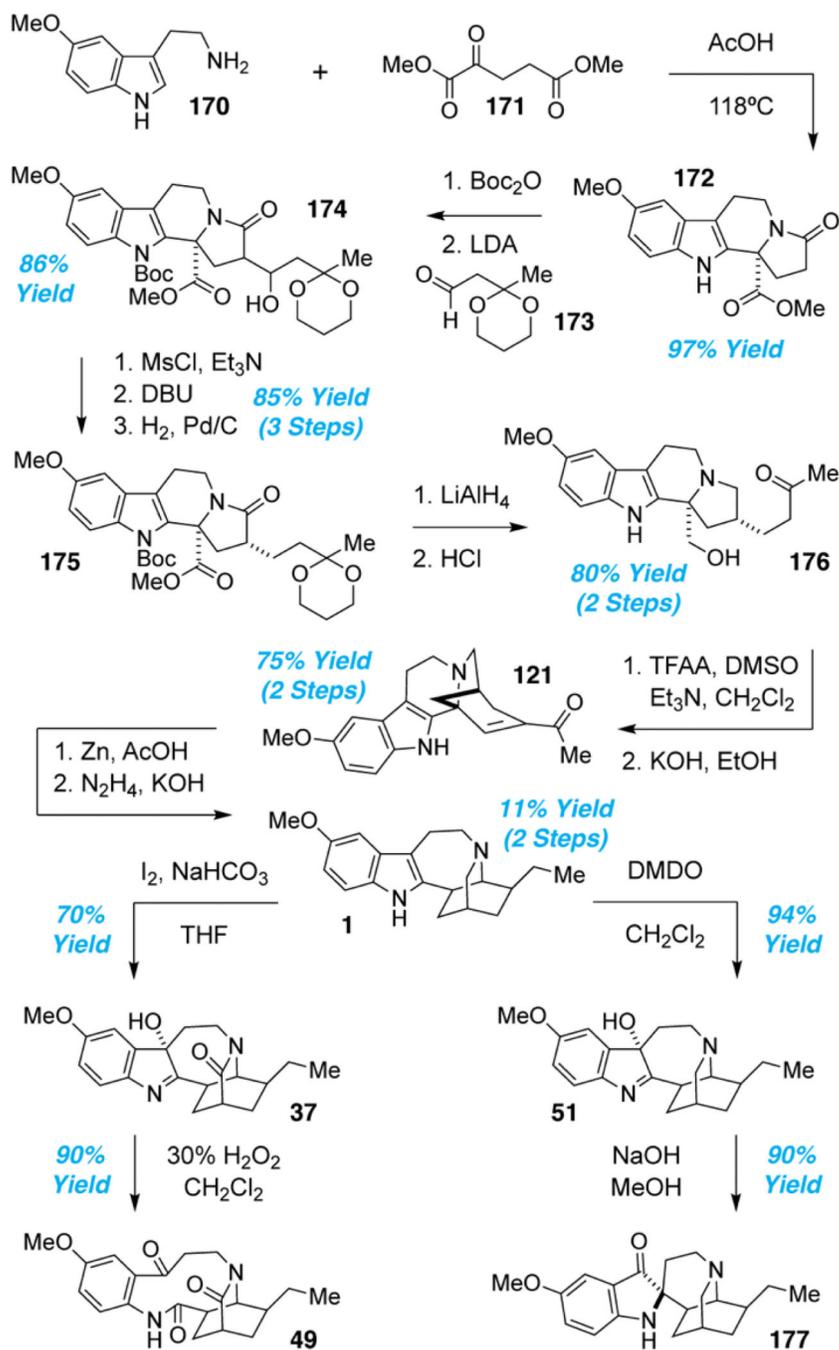
Scheme 8.
She's 2016 racemic syntheses of (±)-**1**, (±)-**37**, (±)-**49**, (±)-**51**, and (±)-**177**

Scheme 9.
Oguri's 2014 biomimetic synthesis of (–)-catharanthine

Table 1.

Approximate yields of iboga alkaloids isolated from the whole root bark of various sources. Percentages indicate the weight of the alkaloid free base relative to the weight of the plant source. TR = trace (< 0.01%). NR = Not Reported.

Plant Species	Ibogaine	Ibogamine	Voacangine	Coronaridine	Catharanthine
T. iboga[9,10,11,12]	0.27–0.32	0.097–0.40	0.043–0.28	NR	NR
V. africana[13]	0.25	TR	1.67	TR	NR
T. arborea[13,12]	0.27	0.036	0.96	0.073	NR
C. roseus[14]	NR	NR	NR	NR	0.003–0.099
T. alba[12]	0.046–0.22	0.042–0.30	0.033–0.96	0.075–0.52	NR
T. donnell-smithii[12]	0.069–0.74	0.028–0.032	0.21–0.44	0.046–0.23	NR
T. amygdalifolia[12]	0.047	0.76–0.96	0.19–0.22	1.092–1.38	NR

Table 2.

Total syntheses of iboga alkaloids. The order in which the indole (I), isoquinuclidine (Q), and tetrahydroazepine (A) rings were formed is indicated. A " / " indicates that two ring systems were formed in the same step. NR = not reported (i.e., not enough information was provided to calculate an overall yield or determine step count).

Year	Group	Alkaloid(s)	Formation Sequence	Step Count	Overall Yield (%)
1965	Buchi	(±)-Ibogamine (**81**)	Q → I → A	14	1.3
1966	Buchi	(±)-Ibogaine (**1**)	Q → I → A	15	0.2
1967	Sallay	(±)-Ibogamine (**81**)	A → Q → I	14	NR
1968	Nagata	(±)-Ibogamine (**81**)	Q → I → A	16	0.8
1978	Trost	(+)-Ibogamine (**81**)	I → Q → A	NR[*]	NR[*]
1981	Hanaoka	(±)-Ibogamine (**81**)	Q → I → A	17	3.9
1985	Kuehne	(±)-Ibogamine (**81**)	I/Q → A	10	2.6
1985	Raucher	(±)-Catharanthine (**7**)	Q → I → A	11	9.0
1991	Herdeis	(±)-Ibogamine (**81**)	Q → I → A	8	14
1996	Grieco	(±)-Ibogamine (**81**)	I → Q → A	9	7.0
1999	Fukuyama	(±)-Catharanthine (**7**)	Q → I → A	17	6.0
2000	White	(−)-Ibogamine (**81**)	A → Q → I	15	4.6
2001	Kuehne	(−)-Coronaridine (**4**)	I → Q/A	10	NR
2005	Hodgson	(+)-Ibogamine (**81**)	Q → I → A	11	2.0
2006	Borschberg	(−)-19-hydroxyibogamine	Q → I → A	20	1.9
2012	Sinha	(±)-Ibogaine (**1**) (±)-Ibogamine (**81**)	Q → I → A	9 9	9.4 5.6
2012	Takayama	(−)-Voacangalactone (**169**)	Q → I → A	25	3.2
2014	Oguri	(−)-Catharanthine (**7**)	I → Q/A	10	2.8
2015	Sames	(±)-Ibogamine (**81**)	Q → I → A	9	7.3
2016	Luo	(+)-Ibogamine (**81**)	I → Q/A	12	4.2
2016	She	(±)-Ibogaine (**1**) (±)-Ibogamine (**81**) (±)-Tabertinggine (**25**) (±)-**37** (±)-**51** (±)-Iboluteine (**177**) (±)-Ervaoffines D (**49**)	I → Q/A	12 12 10 13 13 14 14	4.6 6.0 41 3.2 4.3 3.9 2.9

[*] Trost synthesized (+)-ibogamine from an intermediate in 4 steps (17% yield). However, the synthesis of this intermediate from simpler precursors was not detailed, and thus, we cannot provide an overall step count and yield for the Trost synthesis.