The Iboga Alkaloids

Catherine Lavaud and Georges Massiot

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Dedicated to the memory of Howard J Lotsof

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1 Introduction

There are four levels of definition for the term "Iboga Alkaloids". The most basic definition relates to the alkaloids isolated from a plant named "iboga", *Tabernanthe iboga* (Plate 1), in botanical words. The second level refers to those psychoactive alkaloids from plants used in ceremonies and cults in Central Africa, and which are the object of interesting pharmacological developments. The third definition belongs to chemists, who see behind the word "iboga" a specific arrangement of atoms containing an indole nucleus and an isoquinuclidine system. In turn, the fourth definition relies on biosynthesis, and characterizes those alkaloids in which two carbon atoms of the original secologanoside have departed from their original positions. In this series more than in others, nomenclatural problems are associated with the last-mentioned definition, so the present authors have decided to follow herein the so-called biogenetic nomenclature [1] and not that of IUPAC. For a complete overview of the monoterpene indole alkaloids classification, the reader is invited to read a survey by L. Szabó, in which these compounds are classified in three types and nine main skeletons [2]. Of

Plate 1 Iboga (*Tabernanthe iboga*) at the Centre National Floristique de l'Université Félix Houphouët-Boigny de Cocody (Abidjan); photograph courtesy of Philomène Akoua Kouassi, University of Cocody (Ivory Coast)

this nomenclature, the present chapter is concerned only with alkaloids based on the ibogan, isoplumeran, and isoeburnan skeletons.

Iboga alkaloids are produced by a small number of plants of the family Apocynaceae, inclusive of the genera *Catharanthus*, *Tabernaemontana*, *Corynanthe*, *Voacanga,* and *Aspidosperma*. There are about 100 alkaloids of this type, and among these, two have emerged for the chemistry or biology they have inspired. Included is catharanthine (**1**) (Fig. 1), one of the major alkaloids from *Catharanthus roseus* (Plate 2), the tropical periwinkle (also known as "Madagascar periwinkle"), and this is used in the partial synthesis of the anticancer drug Navelbine®. The second alkaloid is ibogaine (**2**), which has been a subject of intense attention for its putative anti-addiction properties and in general for its action on the central nervous system. It is worth noting at this point that these alkaloids belong to opposite optical series. Despite years of investigation, there still is fascinating chemistry being developed around this scaffold in order to provide a better access to these compounds and to better understand the coupling reactions used to make "dimers". The biology of ibogaine was the object of an entire volume in *The Alkaloids*: *Chemistry and Pharmacology* in 2001 [3]. The purpose of this contribution is to provide an update on these aspects in the hope of promoting innovative research in the field. The literature covered spans the years 2000–2016, and the interested reader is invited to consult references [3–5] for earlier contributions.

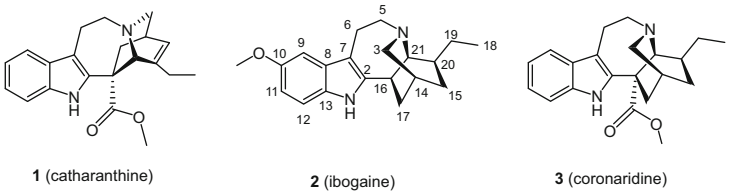


Fig. 1 Catharanthine (**1**), ibogaine (**2**), coronaridine (**3**)

Plate 2 Madagascar periwinkle (*Catharanthus roseus*); photograph courtesy of Bruno David, Pierre Fabre Laboratories, Toulouse (France)

2 Biosynthesis

Despite intensive work on *Catharanthus roseus*, which is a high-yield producer of the two iboga alkaloids catharanthine and coronaridine (**3**), there is no recent publication on the biosynthesis of these particular molecules [6–8]. There are no "omics" studies available on this part of the biosynthesis scheme and most details known date back to the 1970s with the incorporation of the strictosidine derivative preakuammicine (**8**) and more recently of stemmadenine (**5**) into catharanthine (**1**) [9]. The postulated intermediate dehydrosecodine (**6**), which ought to be highly unstable, remains undetected. While preakuammicine (**8**) is the well-accepted link in the sequence leading to the ibogans, there is no reason why its infamous and isomeric cousin precondylocarpine is not. The temptation is great to propose that **8** is the precursor of the coronaridine series while precondylocarpine (**9**) would lead to the catharanthine series (Figs. 2 and 3).

The formation of the azabicyclo ring system is thought to proceed via a Diels-Alder-like reaction and the question of its catalyst by means of an enzyme is of high relevance since examples of Diels-Alderases remain extremely rare. Only recently, one such enzyme has been isolated and its structure elucidated, but its genuine mechanism of action (catalyst or chiral template) is still an object of investigation [10,11]. It is to be noted that although dehydrosecodine (**6**) is achiral, coronaridine (**3**) and catharanthine (**1**) are chiral and belong to opposite series. While catharanthine (**1**) is predominant in *C. roseus*, the coronaridine series is generally prevalent in Nature, with ibogaine being the most representative alkaloid of the series. There is no reason, however, not to consider the two alternatives when working on the structural elucidation of an iboga-type alkaloid. The genus *Catharanthus* is of high relevance since it presents the unique feature of accumulating alkaloids in the two series, although at a different oxidation level. These are some of the reasons why the unraveling of the

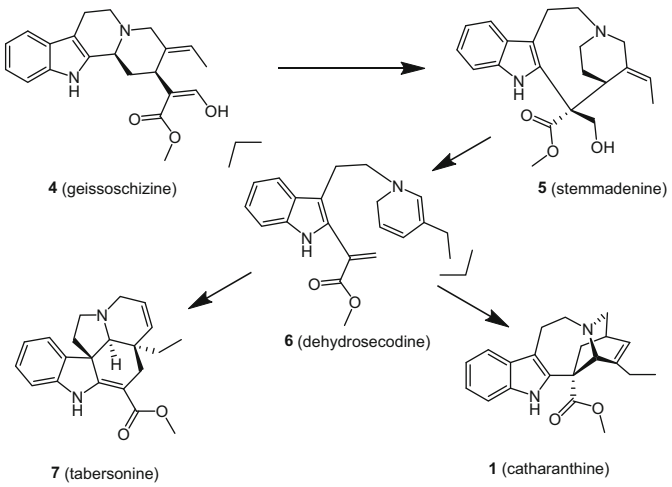


Fig. 2 Intermediates in the biosynthesis of catharanthine (**1**)

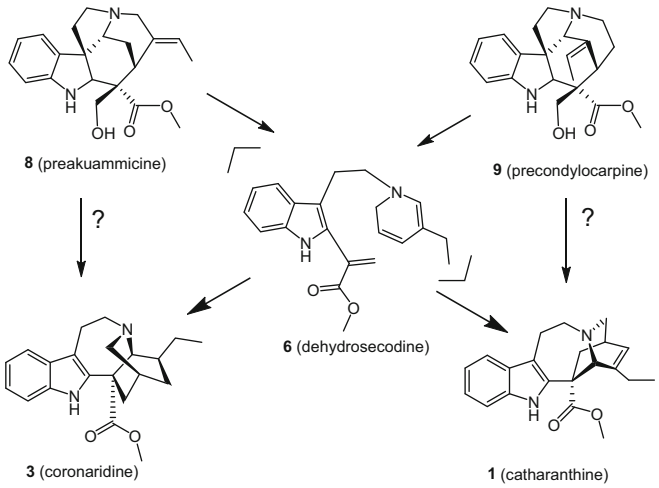


Fig. 3 The involvement of preakummicine (**8**) and of precondylocarpine (**9**) in the biosynthesis of iboga alkaloids

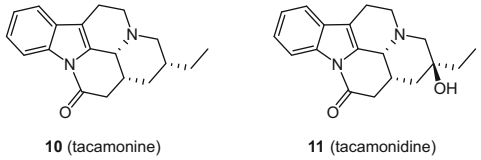


Fig. 4 Iboga alkaloids of the pseudo-vinca type

biosynthesis of the iboga alkaloids is important, not only for this particular field but for the whole of bio-organic chemistry.

Not all iboga alkaloids possess the isoquinuclidine skeleton, and there are a few examples of known alkaloids with the pseudo-aspidosperma (i.e. cleavamine) or pseudo vinca (i.e. tacamonine (**10**), Fig. 4) arrangement. For the moment, these alkaloids are but chemical curiosities and no experimental work has been performed to explain their biosynthesis. Soon after the isolation of tacamonine (**10**) from the well-known plant, *Tabernaemontana eglandulosa*, it has been suggested that its formation was due to an evolution of the plant when cultivated in greenhouses in The Netherlands [12]. This hypothesis was later seen not to be true since another of these alkaloids, tacamonidine (**11**) was isolated from wild *Tabernaemontana corymbosa* [13].

3 Structural Elucidation and Reactivity

The widespread availability of high-field NMR spectrometers and of sophisticated pulse sequences now enables chemists to determine structures of moderate complexity, such as the iboga alkaloids and even the "dimers", leading to full

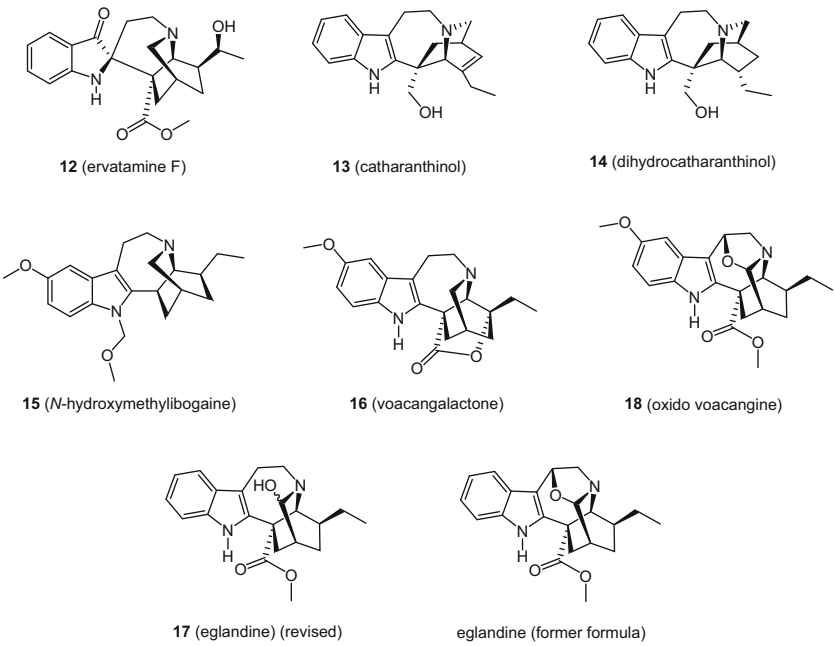


Fig. 5 Examples of structures of iboga alkaloids resolved by the Mosher method, X-ray crystallography, or total synthesis

unambiguous proton and carbon NMR assignments. Relative configurations in rings and ring junctions may be dealt with NOEs and coupling constant measurements. In these series, the only open chain fragment is the ethyl side chain, where chirality is present at C-19. The problem of its determination is best solved with one of the Mosher methods, an example of which is found in the structure elucidation of ervatamine F (**12**) (Fig. 5). In addition, X-ray crystallography allows the solving of structural problems whenever a single crystal is available and Sect. 4 lists several recent examples of such structural determinations. Catharanthinol (**13**), dihydrocatharanthinol (**14**), and *N*-hydroxymethylibogaine (**15**) have had their structure solved by X-ray crystallography, but unfortunately without absolute configuration determinations [14,15].

The problem of the absolute configuration of these alkaloids remains a difficulty and there are currently four methods available for this purpose. NMR spectroscopy is one of these, provided one stereogenic center is linked to the others and determined using Mosher derivatives. This procedure has often been used to determine the configuration of C-19, which unfortunately cannot be easily linked with the remaining stereogenic centers [16]. Circular dichroism is a general and sensitive method, which has been used to differentiate compounds in the (+)-catharanthine and (−)-ibogaine series [17]. It is now used to determine the absolute configurations of the linkages in dimers by application of the exciton chirality rule, which was first

proposed by Harada and Nakanishi [18], and then later used by others [19]. Ab initio calculation of electronic CD spectra and comparison with the experimentally obtained values also allows the determination of absolute configurations, but so far most examples have dealt with monomers [16]. X-ray crystallography using anomalous scattering is the most unambiguous method. It is more and more frequently used to solve structures. Finally, partial or total synthesis has often been used to link a new alkaloid to another of known absolute configuration.

Chemical reactivity, and partial and total synthesis, were until recently integral parts of the structural elucidation process. Simple reactions were used to determine functionalities or to prepare crystalline derivatives. As a bonus, it often happened that new and unexpected reactions were discovered during the process. With the advent of highly sensitive spectroscopic techniques, this approach is almost no longer utilized, and only one example could be found in the more recent literature of a total synthesis, aimed at establishing the structure of voacangalactone (**16**) [20].

The most intriguing aspects of the iboga alkaloids are their unusual oxidation reactions, which arise from the particular geometry of the isoquinuclidine ring system. The original experiments were described by Bartlett and Taylor, who transformed coronaridine (**3**) (Fig. 6) with iodine in aqueous methanol into the 3-hydroxy- and 3-oxo-coronaridine derivatives [21]. These reactions went unnoticed for a long time, even though their products were later shown to be naturally occurring substances. Eglandine (**17**) (3-OH coronaridine) is one example, but its structure was assigned initially as containing a tetrahydro-oxazole ring and later had to be corrected [22,23]. The present chapter authors long questioned the natural occurrence of these tetrahydro-oxazoles until definitive proof of their existence came from the X-ray structure of oxindole **57** (ervaoffine A) [24]. While working on this chapter, the authors corresponded with Professor Hiromitsu Takayama, whose group isolated the 3,6-oxido voacangine (**18**), and he provided good NMR spectroscopic evidence for the cyclic structure of oxidovoacangine [25]. However, the probability is high that derivatives with substitutions at C-3 (OMe, OEt, or acetonyl) originate from the intermediate carbinolamines. Interestingly, these do not lend themselves to reduction or Pictet-Spengler-like reactions although they can be considered as masked aldehydes. One of the reasons why these particular structures are not easily identified is that they "misbehave" in mass spectrometers and often show [M-2] fragments (a result of a dismutation). As a consequence, there is a considerable tendency to make an extra bond as in ervaoffine A (**57**) or as in ervataine (**19**) [26]. Ervataine (**19**) clearly violates Bredt's

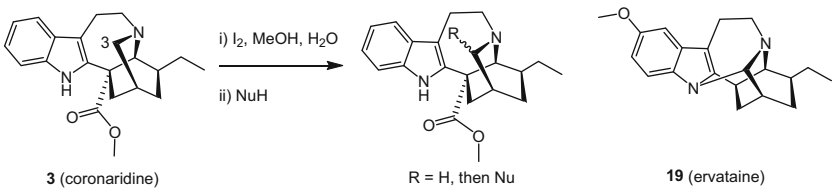


Fig. 6 Oxidation of coronaridine at position 3 and "structure" of ervataine (**19**)

rule [27] and its most probable structure is 3-OH ibogaine (C-3 showed a ^{13}C NMR resonance at 93.2 ppm).

More classical oxidations arise at C-7, yielding the pseudo-indoxyl chromophore after rearrangement or at C-2 as an intermediate to oxindole. The addition of dioxygen on the double bond of indole and fragmentation produces *N*-acyl derivatives as observed in the degradation of tryptophan into kynurenine. All these chromophores are detected in natural products (vide infra) and these products, if they are not extraction artefacts, may be considered as end products in biosynthesis processes (Fig. 7).

The most studied oxidation in the ibogan series is related to the *N*-oxides, which are easily prepared under acidic peroxide conditions. While in the ibogaine/coronaridine series the *N*-oxide is relatively stable, the *N*-oxide of catharanthine (**20**) (Fig. 8) lends itself to a Meisenheimer rearrangement, bringing about a N-4—C-3 bond cleavage. Such products have been observed but knowledge of their biosynthesis remains at the hypothetical stage. Fragmentation of the *N*-oxide of catharanthine is the key reaction in the synthesis of anhydrovinblastine and the related antitumor alkaloids vinblastine, vincristine, vinorelbine, and vinflunine. The subject has recently been reviewed and the interested reader will find an account of this chemistry involved in books by Langlois and Langlois [28] and by Guéritte and Le Roux [29].

The formal addition of HCN across the C-16—C-21 bond of catharanthine (**1**) provides an intermediate aminonitrile (**21**), which allowed Beatty and Stephenson to bridge the gap between this series and the pseudo-tabersonine and -vincadifformine alkaloids [30]. The initial reaction was brought about by visible light irradiation of **1** in the presence of the polyfluorinated catalyst $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ and with trimethylsilyl cyanide as reactant (Fig. 9). Remarkably, this reaction was run in a flow reactor in order to better control reaction parameters and confine the hazards linked to HCN generation. Although the conversion to pseudotabersonine (**24**) only required iminium generation and its "through nitrogen" isomerization, it took carefully controlled acidic conditions to achieve the transformation. One of the unexpected difficulties was a partial racemization linked

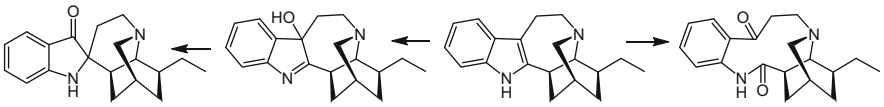


Fig. 7 Oxidation pathways for iboga alkaloids

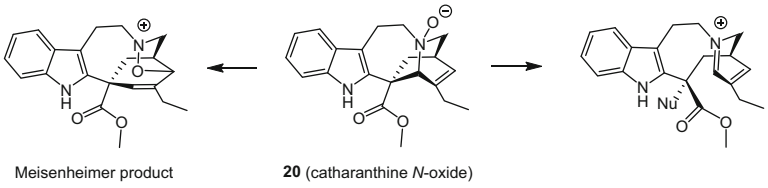


Fig. 8 The chemistry of catharanthine *N*-oxide (Meisenheimer product, left; reactivity under Polonovski conditions, right; Nu may be vindoline)

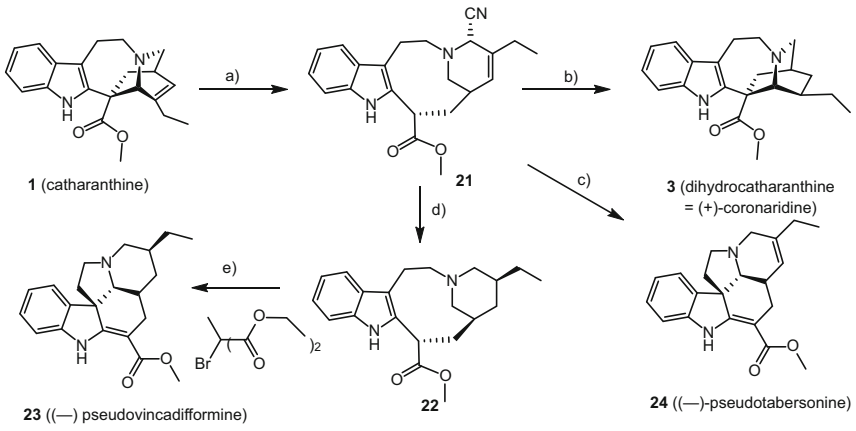


Fig. 9 Interconversion of catharanthine (**1**), pseudotabersonine (**22**), and pseudovincadifformine (**23**) via cyano compound **21**

to C-14 equilibration, and treatment of **21** with TFA led to an almost complete conversion into **24**. The optical rotation value and chiral HPLC parameters of the reaction product showed it to be a 2:1 mixture of enantiomers. While it was initially thought that these difficulties would be absent in the dihydro series, pseudovincadifformine (**23**) was not obtained but (+)-dihydrocatharanthine (**3**) occurred instead. Compound **23** was eventually reached in good yield through oxidative photoirradiation of **22**, the over reduction product of compound **21**. Among other things, this is to our knowledge, one of the rare articles daring to state that catharanthine (**1**) is a good starting material for partial synthesis due to its natural availability, a fact which is largely overlooked.

4 New Molecules

The list of compounds biogenetically linked to the iboga unit continues to be fed by new alkaloids but among the three skeletons of this group, the isoplumeran and isoeburnan variants remain scarce. This Section is divided into two parts: the monomers and the dimers, and, in each, molecules are grouped according to oxidation levels. The Apocynaceae family has continued to provide new occurrences, but at variance with other much more common indolomonoterpenes, the isolation of alkaloids of the iboga class is limited to only a few species in the genera *Ervatamia*, *Tabernaemontana*, *Voacanga*, and *Catharanthus*, with *Ervatamia* being considered as a synonym of *Tabernaemontana* by many authors (Tables 1 and 2). "The Plant List" [31] was chosen as the botanical reference. The total number of

Table 1 Sources of new monomeric iboga alkaloids

Plant name	Synonym	New monomeric alkaloids	Ref.
Catharanthus roseus (L.) G. Don		**63a** or **63b**	[45]
Ervatamia hainanensis Tsiang	*Tabernaemontana bufalina* Lour.	**39**, **41, 42**, **48, 49, 53, 54**	[39]
		12, **27**, **28**, **33**, **46**	[16]
Ervatamia officinalis Tsiang	*Tabernaemontana bovina* Lour.	**38**, **50**, **52, 56**, **57**, **59**, **60**	[24]
Tabernaemontana corymbosa Roxb. ex Wall.		**30**, **31**, **32**, **33**, **40**	[36]
		11, **34**, **55**, **59**	[13]
		61, **62**	[44]
		35	[37]
		36, **37**	[38]
		25, **26**, **29**, **44**, **45**	[32]
		65, **66**, **67**, **68**	[46]
Tabernaemontana divaricata (L). R.Br. ex Roem. & Schult.		**43**, **47**	[40]
Tabernaemontana hystrix Steud.		**51**	[42]
Voacanga africana Stapf ex Scott-Elliot		**16**	[20]

Table 2 Sources of new bisindole iboga alkaloids

Plant	Synonym	New bisindole alkaloids	Ref.
Tabernaemontana corymbosa Roxb. ex Wall.		**77**, **78**, **80**	[50]
		88, **89**, **92**, **95**, **96**, **97**, **98**, **99**, **100**, **101**	[51]
		102, **103**	[54]
		83, **86**	[13]
		94, **108**, **120**, **122**	[53]
		79, **80**	[36]
		76, **81**, **82**, **87**, **123**, **124**	[49]
		125, **126**	[46]
Tabernaemontana divaricata (L). R. Br. ex Roem. & Schult.		**90**	[52]
		104, **105**, **106**, **107**, **121**	[40]
Tabernaemontana sphaerocarpa Blume		**75**	[48]
Muntafara sessilifolia Baker	*Tabernaemontana sessifolia* Baker	**111**, **112**, **116**, **117**, **118**, **119**	[56]
		109, **110**, **111**, **113**, **114**	[55]
Ervatamia chinensis (Merr.) Tsiang	*Tabernaemontana corymbosa*	**83**, **84**, **85**, **93**	[19]

species mentioned below does not exceed ten for a total of a little more than a hundred compounds. This may be the tip of the iceberg since the number of *Tabernaemontana*, *Ervatamia*, and *Voacanga* species is close to 700. The limited presence of iboga alkaloids in these particular genera is probably a consequence of their elaborate biosynthesis, pertaining to well-evolved plants. Alkaloids are considered here as new when not mentioned in previous reviews.

4.1 Monomers

4.1.1 Ibogamine and Coronaridine Derivatives

Many of the newly isolated structures may be viewed as simple derivatives of ibogamine or coronaridine, with a limited range of oxidations. Typically, these variations concern oxidations at C-19 in the side chain, C-10 and C-11 of the indole nucleus, and more rarely C-15 and C-20 in the isoquinuclidine moiety. Molecules with substituents at C-11 remain scarce.

Four new 19-hydroxy derivatives have been reported: (19*S*)-hydroxyibogamine (**25**) (Fig. 10), 19-*epi*-isovoacristine (**26**) [32], and ervatamines A (**28**) and H (**27**) [16]. The relative configuration of C-19 was determined by comparison of the ^{13}C NMR chemical shifts of C-15 and C-21, as proposed by Wenkert in 1976 [33,34]. The problem of absolute configuration was ignored in Ref. [32], while ECD provided a solution with ab initio calculations for compound **28**, and a comparison with ECD of coronaridine for **27**. C-ring contraction is a very rare occurrence in the biosynthesis of indole alkaloids, for which the origin is a C-5—C-6 Polonosvski fragmentation. Ervatamine A (**28**) adds to this very short list and may be considered as a collateral pathway in the reaction of the corresponding ibogan *N*-oxide. This is the second ibogan-type alkaloid isolated where ring C is contracted to form an unusual six-membered ring as in flabelliformidine [35]. Ervatamine H (**27**)

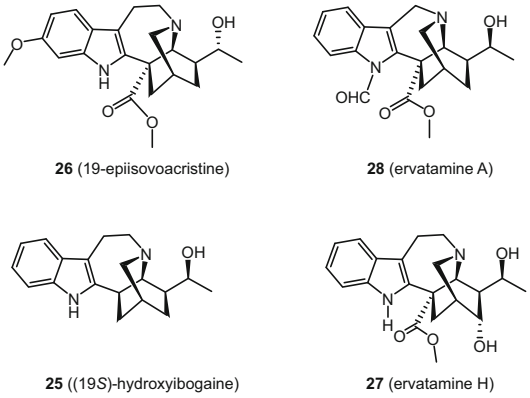


Fig. 10 The 19-hydroxy derivatives **25**–**28**

has a very unusual oxidation of C-15, which could also be envisioned as a hydration of a Δ^{14} double bond. Observation of a NOE correlation between H-18 and H-15, and ECD comparison with coronaridine allowed the (14*R*,15*R*,16*S*,20*S*,21*S*)-configuration to be proposed.

Five new alkaloids were found to contain an additional degree of oxidation and a ketone at C-19: isovoacryptine (**29**) [32], conodusines A-C (**30**–**32**) [36], and (−)-ervatamine I (**33**) [16], for which an isomer was named (+)-conodusine E (Fig. 11) [36]. The report on conodusine E was published subsequent to that on ervatamine I (**33**), and, given the similarities between the data for the two compounds, except for their optical rotations, great care was accorded to the determination of the relative and absolute configurations. First, a chemical correlation was carried out with (−)-heyneanine (Dess-Martin oxidation), then the ECD was measured and compared with the calculated ECD values for the two enantiomers, and finally an X-ray analysis was performed. All these experiments converged to the structure depicted as **33**. The Malaysian authors proposed that the so-called ervatamine I is an enantiomer of their own compound and therefore an alkaloid of the catharanthine series. However, the present authors feel that this hypothesis creates a precedent: the isolation of a catharanthine-like compound in a *Tabernaemontana* species. The sole rationale given for the absolute configuration of ervatamine I is the sign of the optical rotation (the same as coronaridine), which is an argument to be considered of little value at the present time. Conodusines A and B are isomeric at C-20, a position α to a carbonyl, and hence prone to isomerization. The possibility of conodusine B being an artefact was discussed but could not be established definitively. The same possibility holds for conodusine C (**32**), the *N*-oxide of conodusine B (**31**).

Voacanga africana is one of the most highly investigated West African medicinal plants. From this species, a Japanese group isolated a new bioactive alkaloid, voacangalactone (**16**) (Fig. 12), for which the structure was determined by spectroscopic means and by total synthesis [20]. All alkaloids with hydroxy groups at positions C-15, C-19, and C-20 may stem from precursors with a double bond between C-19 and C-20 or C-15 and C-20, isomeric with catharanthine (**1**), and until now never detected in this series.

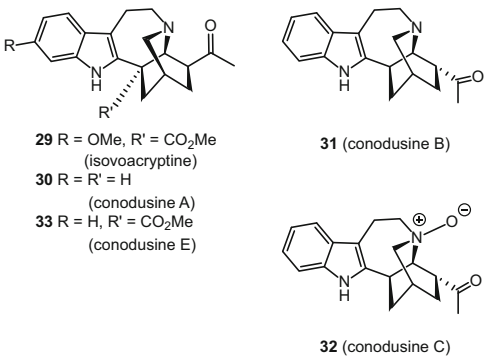
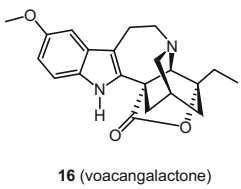


Fig. 11 The 19-keto derivatives **29**–**32**



16 (voacangalactone)

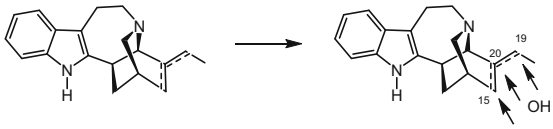
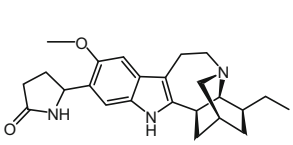
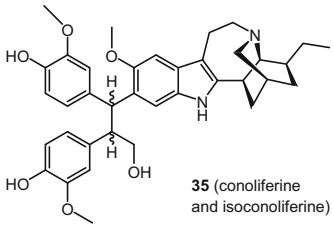


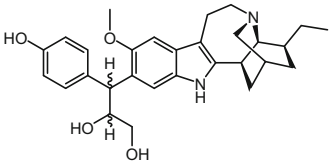
Fig. 12 Voacangalactone (**16**) and putative formation of derivatives with C-15, C-19, and C-20 OH



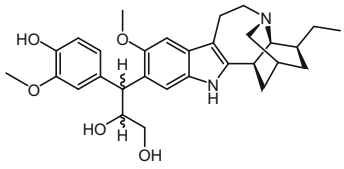
34 (cononusine)



35 (conoliferine and isoconoliferine)



36 (conomicidine A and isoconomicidine A)



37 (conomicidine B and isoconomicidine B)

Fig. 13 Pyrrolidone and lignan conjugates of ibogaine

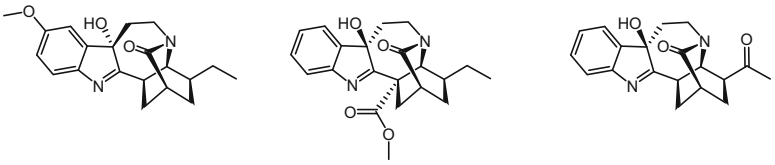
Nucleophilic attack on C-11 is favored when C-10 is substituted by a methoxy group, which is the situation for ibogaine, and leads to a group of iboga alkaloids diversely substituted at C-11, all found in *Tabernaemontana corymbosa* from Malaysia. These were: cononusine (**34**) with a pyrrolidone unit [13], and the lignan conjugates conoliferine and isoconoliferine (**35**) [37], conomicidines A and B (**36**), and isoconomicidines A and B (**37**) (Fig. 13) [38]. These included pairs of diastereomers that were not separated even though the authors discussed at length the relative configurations of the new chiral centers. The question of the absolute configuration of the iboga moiety was not a subject of debate, assuming that the configuration is prevalent in *Tabernaemontana*. In cononusine (**34**), the relative and absolute configurations of the chiral center in the pyrrolidone ring could not be

determined. The lignan conjugates were assumed to arise from a nucleophilic attack of ibogaine on a quinone methide derived from one or two coniferyl units.

4.1.2 3-Alkyl- or 3-Oxo-ibogamine/-coronaridine Derivatives

These alkaloids are, for most of them, oxidized forms of known compounds. Alkaloids **38**–**40** (Fig. 14) are all 7-hydroxylated indolenines, further oxidized as lactams at position C-3. They derive, respectively, from ibogaine, coronaridine, and conodusine A (20-oxo-ibogamine), although no chemical correlations were attempted as structural proof. The reactions leading to these compounds are well established in the literature on indolomonoterpenes and their biosynthesis follows the usual oxidation pathways. The most well-documented structure is 3-oxo-(7*R*)-coronaridinehydroxyindolenine (**39**), which was determined by X-ray diffraction, with Flack parameter calculations, thus making the absolute configuration definite [39]. The two other compounds have had their configuration determined by comparison of ECD spectra (**38**: λ_{max} ($\Delta\varepsilon$) 230 (−9.0), 258 (+18.6), 289 (−4.4) nm [24]; **39**: λ_{max} ($\Delta\varepsilon$) 221 (+26.3), 260 (−10.9), 294 (0) nm; **40**: λ_{max} ($\Delta\varepsilon$) 221 (+11.6), 257 (−5.7), 289 (+1.7) nm [36]). It would have been advisable to have the ECD also recorded for tabernaricatine F (**43**), for which the configuration of C-7 was proposed after observation of a NOE between OH and H-16.

Following the same biosynthesis, three other hydroxy indolenines (**41**–**43**) (Fig. 15) have been encountered in the coronaridine/ibogaine series, displaying

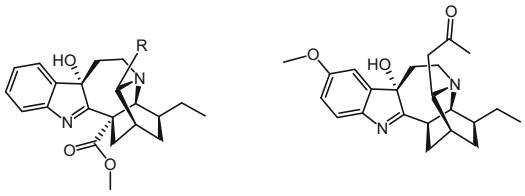


38 (3-oxo-(7*S*)-ibogaine hydroxyindolenine)

39 (3-oxo-(7*R*)-coronaridine hydroxyindolenine)

40 (conodusine D)

Fig. 14 The hydroxy indolenines (**38–40**)



41 R = OH ((3*R*)-hydroxy-(7*S*)-coronaridine hydroxyindolenine)
42 R = CN ((3*S*)-cyano-(7*S*)-coronaridine hydroxyindolenine)

43 (tabernaricatine F)

Fig. 15 Further hydroxy indolenines (**41**–**43**)

further oxidation at C-3. Compounds **41** and **42** share the same origin as **39**, from which the hydroxylated derivative **41** is an obvious precursor [39]. The cyano and acetonyl derivatives **42** and **43** arise from substitution of their respective 3-hydroxy precursors and while cyano derivatives are common in Nature, the origin of the acetone fragment is more dubious. It is not unreasonable to think that it comes from the solvent used for chromatography, with silica gel acting as an acid catalyst [40]. Observation of the suitable Cotton effects for **41** and **42** allowed their configuration to be established as (7*S*). The configuration at C-3 was deduced from NOE correlations observed between H-3↔H-6β↔H-17β, placing the H-3 to the "left", towards the respective indole ring.

Besides these cyano, hydroxy, and acetonyl derivatives, there are a large number of monomeric iboga alkaloids with miscellaneous alkyl or alkoxy substituents on C-3. The 3-alkoxy derivatives, (3*R*/*S*)-ethoxyheyneanine (**44**) and (3*R*/*S*)-ethoxy-19-*epi*-heyneanine (**45**) (Fig. 16), were isolated as mixtures of diastereomers, and could be artefacts formed by addition of ethanol on an iminium intermediate during the extraction steps [32]. Similar NOE effects were observed for four 3-alkyl derivatives: ervatamine G (**46**) [16], tabernaricatine G (**47**) [40], (3*S*,24*S*)- and (3*S*,24*R*)-hydroxyethyl-coronaridine (**48** and **49**) [39], suggesting a (3*S**) configuration. It is worth noting that these last two compounds were isolated from *Ervatamia hainanensis* roots in 1982 but their configuration could not be established at that time [41]. An X-ray structure determination for the (24*S*) compound **48** secured the relative and absolute configurations for the two isomers. Their ECD spectrum exhibited similar Cotton effects as observed for coronaridine, confirming their common (3*S*,14*R*,16*S*,20*S*,21*S*)-configuration. This was confirmed by preparing Mosher esters of the C-24 alcohols.

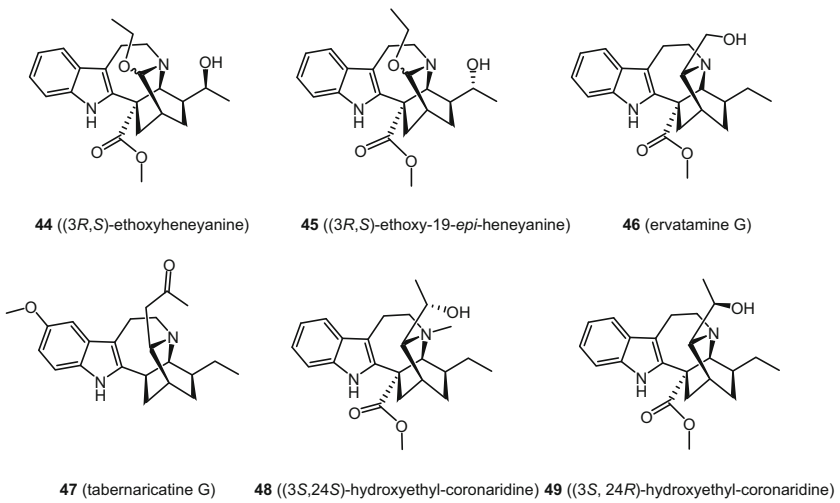


Fig. 16 The 3-substituted iboga alkaloids (**44**–**49**)

4.1.3 5- and/or 6-Oxo-ibogamine/-coronaridine Derivatives

Positions α to the basic nitrogen atom are prone to oxidation and in the iboga alkaloids, this most often occurs at C-3. 19-*epi*-5-Oxovoacristine (**50**) from *Ervatamia officinalis* is an exception, and the location of the amide carbonyl is based on HMBC correlations and on the presence of an isolated AB quartet for CH_2-6. The remainder of the asymmetric centers was determined by ^{13}C NMR chemical shifts (for C-19) and NOE correlations, and the absolute configuration was established by ECD (experimental vs. calculated). The location of the carbonyls in the 5,6-diones of ibogamine and ibogaine (**51**) [42] and (**52**) [40] was based on observation of HMBC correlations between H-3 and H-21 with O = C-5 (lactam near 169 ppm). The ion at *m*/*z* 170 (*m*/*z* 156 in ibogamine) in their mass spectra also suggested the presence of an oxygen atom at C-6. The ECD spectrum of **52** was measured and compared to the calculated value, which confirmed the (14*R*,16*R*,20*S*,21*S*)-configuration. 5-Oxo-(6*S*)-hydroxy- and 5-oxo-(6*S*)-methoxycoronaridine (**53** and **54**) are two other new products obtained from *Ervatamia hainanensis* [39]. An X-ray structure was obtained for the alcohol **53**, which allowed its full structural determination, and, as a consequence, establishment of the structure of **54**. The simplest compound **55** (6-oxo-ibogaine) is unique and unexpected. There are two arguments in favor of oxidation at C-6: a downfield shift of H-9 due to carbonyl anisotropy and HMBC correlations of H-5 (two d, $J = 18.1$ Hz) with C-3, C-7, and C-21. This compound has been an intermediate in a synthesis of ibogaine, but this is the first time that it was detected as a natural product [43] (Fig. 17).

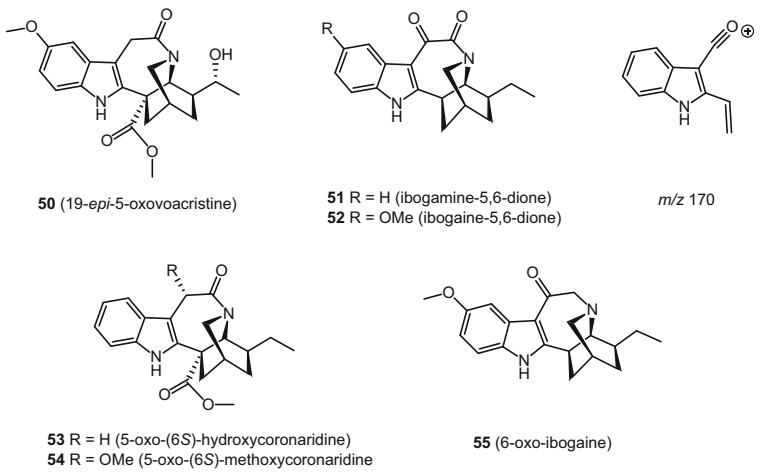


Fig. 17 Alkaloids oxidized at positions C-5 and C-6

4.1.4 Rearranged Ibogamine/Coronaridine Alkaloids

In this group of alkaloids, the present authors have chosen to place those in which one bond of the skeleton is cleaved, thus giving four rearranged types of structure: the 2,7-*seco*-, 6,7-*seco*-, 2,16-*seco*-, and the N(4),21-*seco*-iboga derivatives.

Ervaoffine D (**56**) (Fig. 18) is the only described iboga alkaloid with the 2,7-bond cleaved into a ketone and an amide [24]. Its structure was proved unequivocally by X-ray crystallography inclusive of the absolute configuration. Among the 6,7-*seco* derivatives, the structures of ervaoffine A (**57**) [24] and ervatamine F (**12**) [16] were confirmed by X-ray crystallography and the absolute configurations were found to be (2*S*,3*S*,6*S*,14*R*,16*R*,20*S*,21*S*) and (2*S*,14*R*,16*S*,19*S*,20*S*,21*S*) (ibogaine series). The priority order of C-3 and C-6 is modified by the introduction of the hydroxy group on position C-6 and these two same (2*S*)-configured compounds indeed have opposite spatial configurations at C-2. Iboluteine (**58**), also produced by the same plant, and the deoxy analog of ervaoffine A (**57**), have also been shown by X-ray crystallography to have the opposite configuration, and so **58** is not the precursor of **57**. In addition, measurements and calculations of ECD spectra for **57** were performed, allowing comparison to be made with alkaloids bearing the same chromophore. Mosher esters of **12** were prepared to confirm the C-19 stereochemistry. The third alkaloid, **59**, was isolated by two different groups in 2014 and 2015, and although published in the same journal, it was given different trivial names: ervaoffine B [24] and ervaluteine [36], when it could be simply have been named (6*R*)-hydroxy-(2*S*)-pseudo-indoxyl-ibogaine. It is interesting to note that the absolute configuration was given in the first paper, since the ECD spectrum was similar of that of ervaoffine A (**57**) [24] and a NOE was detected between OH-6 and H-3α and H-17β. In the second paper, the absolute configuration was deduced painfully from NOE correlations, comparison with (2*R*)-iboluteine (**58**), and examination of molecular models. Only one 2,16-*seco*-ibogamine, ervaoffine C (**60**), was characterized [24], and, as for the other ervaoffines, its absolute configuration (3*S*,6*R*,7*R*,14*R*,16*S*,20*S*,21*S*) was established

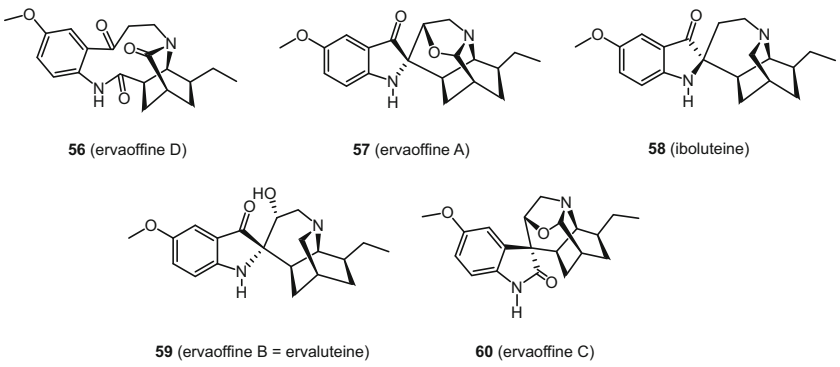


Fig. 18 *seco*-Iboga alkaloids **56–60**

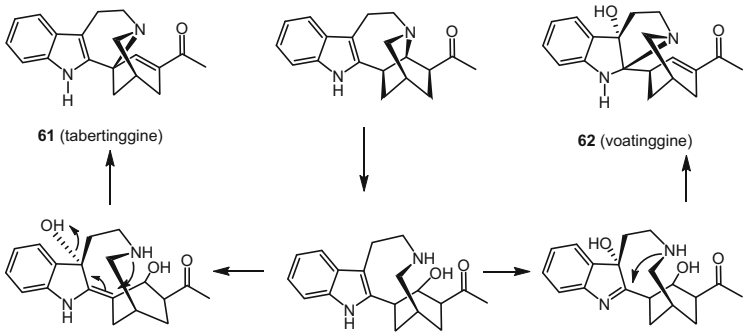


Fig. 19 Tabertinggine (**61**), voatinggine (**62**), and a proposal for their biosynthesis

from the similarity of Cotton effects with those obtained by calculated ECD for both enantiomers.

Tabertinggine (**61**) and voatinggine (**62**) (Fig. 19) are two exceptionally rearranged iboga alkaloids, for which their skeletons remain unique, and the X-ray crystallography used for both removed all doubt on their structures. A common biogenetic pathway was proposed for these compounds with initial cleavage of the C-21 to N-4 bond of conodusine A (**30**) and subsequent ring closure onto C-2 or C-3 [44].

4.1.5 Catharanthine and Pseudoeburnamonine Derivatives

All the monomers described until now in this Section are assumed to belong to the ibogaine/coronaridine series, whether demonstrated or not. There is but a single possible exception, alioline (**63**) (Fig. 20), isolated from *Catharanthus roseus* [45]. This is a strange and unique molecule possessing the features of catharanthine (**1**) to which is added a C_9 unit. However, if structure **63a** is proposed in the original article, the "Dictionary of Natural Products" changed it to structure **63b** under the same name and reference. Fragments I and II display the possibilities for the extra carbon atoms. The origin of the C_9 fragment is unclear: it could be a truncated terpene, although highly irregular, or an iridoid, but in this case, one of the methyl groups is missing.

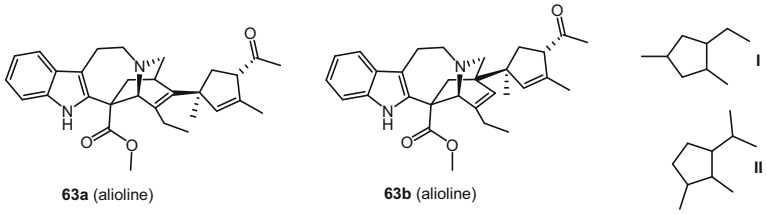
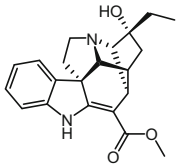


Fig. 20 Structural hypotheses for alioline (**63a** and **63b**). Comparison of the C_9 unit of alioline (**I**) and C_{10} of common iridoids (**II**)



64 (pandine)

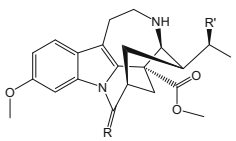
Fig. 21 Structure of pandine (**64**)

There is a single example of a new molecule with the isoeburnan skeleton, named tacamonidine (**11**), while just two reports of the isolation of pandine (**64**) (Fig. 21) are found in the isoplumeran categories [16]. Tacamonidine (**11**) belongs to the rare isoplumeran series and differs from tacamonine (**10**) by an OH group, for which the configuration was proposed by NMR spectroscopy [11].

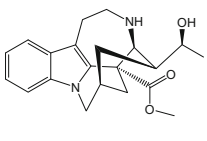
4.1.6 Miscellaneous Representatives and Another Enigma

Four new alkaloids were isolated from *Tabernaemontana corymbosa* and named tabercarpamines G–J (**65**–**68**) (Fig. 22). They belong to the small family of the chippiines and are characterized by an N-1 to C-3 bond instead of the N-4 to C-3 bond [46]. Their structures were established by NMR spectroscopy without any attempt at the determination of their absolute configurations. In tabercarpamine H, there is an OH at position C-19, the configuration of which was proposed on the basis of a ROE measurement. It would have been safer to make this determination on a partially synthetic derivative of **66**, in which, for example, the free OH and the secondary amine would be engaged in a six-membered ring.

The structures of the tabercarpamines are not exceptional but their mere existence is puzzling. It is not difficult to conceive a biosynthesis scheme starting from isovoacangine or coronaridine (**3**) and giving the tabercarpamine skeleton through the intermediate of a 3-hydroxy derivative and of an elusive aldehyde, **69** (Fig. 23). Whereas one would expect some stability of this aldehyde, it has never been identified and one hypothesis would be that it exists in such a high energy state that the seemingly more strained isoquinuclidine forms are predominant.



65 R = H_2, R' = H (tabercarpamine G)
66 R = H_2, R' = OH (tabercarpamine H)
67 R = O, R' = H (tabercarpamine I)



68 (tabercarpamine J)

Fig. 22 Structures of the tabercarpamines G–J (**65**–**68**)

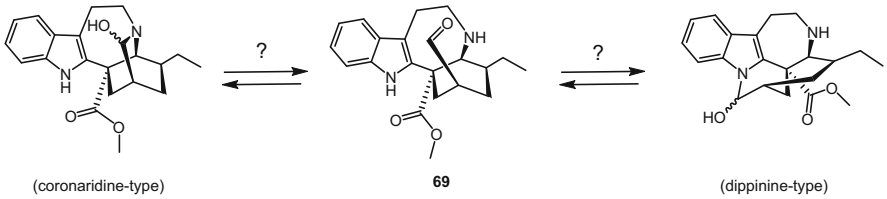


Fig. 23 A possible pathway between coronaridine-type and chippiine-type alkaloids

4.2 Dimers

The count of new dimeric alkaloids containing an iboga moiety amounts to 49 (Table 2), which adds to the previous 40 such compounds described in an earlier review [47]. This is therefore quite a well-represented class of alkaloids, and it appears that all but one contain the vobasinyl residue always substituted at position C-3′ (vobasine numbering). In all examples also, the ibogan moiety is linked on the α face, which is deduced from the multiplicity of H-3′ (dd, $J = 13$ and 3 Hz), and from its NOE with H-15′ and the indole NH. Nature utilizes a large variety of reactions to couple indole alkaloids, among which, coupling between an electron-rich indole nucleus and a carbenium ion is a privileged route. The reason why the vobasinyl cation is so common in couplings remains to be explained. It could be that, being stabilized by N-4, it is an especially long-lived species lending itself to slow kinetics reactions. Most of the newly isolated bisindoles are derived from five vobasan-type monomers (Fig. 24): vobasinol (**70**) (syn. perivine), dregamine (**71**), vincadiffine (**72**) (3-oxo tautomeric form), pagicerine (**73**), and difforlemenine (**74**). For the iboga moiety, the chemical diversity is more extensive but it is possible that chemical modifications in this moiety occur after coupling. The ibogan skeleton is equally represented by the voacangine or ibogaine series (with or without a carbomethoxy group at C-16) and substitution preferentially occurs *ortho* to the aromatic group if present. Compounds without an OH- or OMe-directing group on the aromatic part of the ibogan molecule are scarce but over the years several have been isolated.

Two alkaloids stand alone in the gallery of the iboga bisindoles (Fig. 25). One is biscarpamontine A (**75**), which is the result of a unique coupling between the iboga and aspidosperma units [48]. A further particularity is the presence of a methylene bridging the two moieties and assigned to the iboga moiety, according to a biogenetic hypothesis from the original authors. As far as we know, there are no natural iboga alkaloids possessing N-1-methyl or formyl groups and it is our belief that this supernumerary carbon atom belongs to the aspidosperma moiety (as the one found in the vobtusines is also present in the same plant). The overall structure of **75** was established by NMR spectroscopy and only relative configurations are given. Vobatensine E (**76**) is the only dimeric iboga alkaloid to have a linkage with the C-9 of ibogaine and this was deduced from analysis of the ^{1}H NMR spectroscopic features of the aromatic part of the molecule [49]. An attempt to prepare this

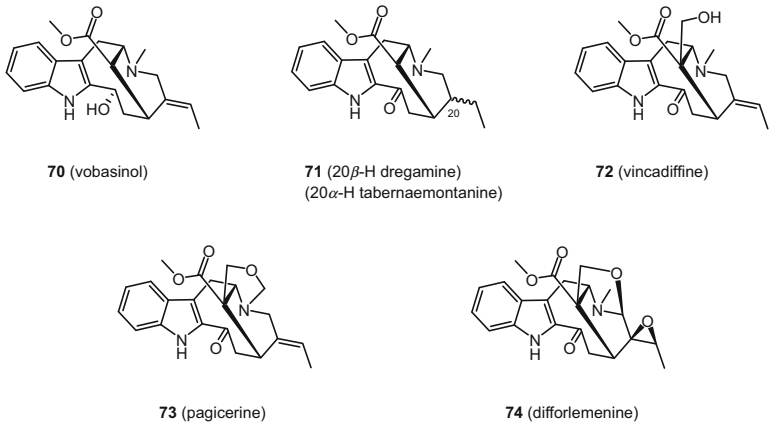


Fig. 24 Most usual vobasan-type monomers found in iboga dimers

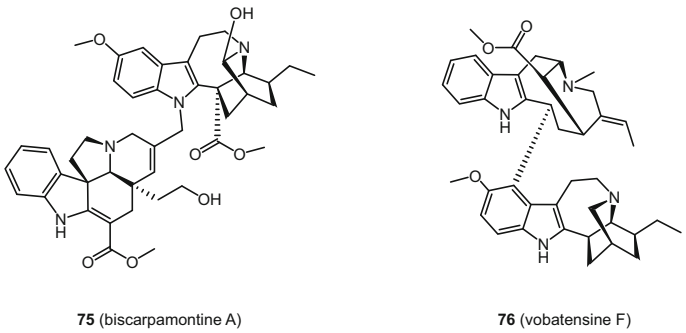


Fig. 25 Bisindoles **75** and **76**

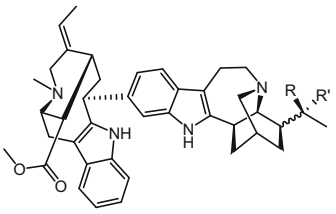
compound by condensing vobasinol and ibogaine under acidic conditions was unsuccessful. This substitution pattern is so far unique. In the C-11-OMe series, however, condensations occur on both sides of the ArOMe (C-10 and C-12).

Generally speaking, the structural elucidation strategy used for all bisindoles has been similar. The first step consists of recording high-resolution mass spectra (HR-ESI-TOF or HR-FAB-MS) and carbon NMR spectra to determine the nature of two moieties. Following this, a combination of COSY, HSQC, and HMBC NMR experiments allows the determination of the structures of the two monomers, which often are known, or by may be proposed by comparison with similar monomers and dimers. Finally, analysis of NOE and further HMBC correlations helps determine the linkage positions between the two monomeric moieties and the relative stereochemistry of some chiral centers. Very few bisindoles have had their absolute configuration determined (see below).

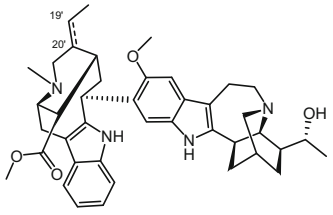
4.2.1 Bisindoles with an Ibogamine Moiety

There are only four bisindoles that lack an alkoxy substituent on the aromatic ring of ibogamine: (19*R*)- and (19*S*)-hydroxytabernamine (**77** and **78**), and tabernamidines A and B (**79** and **80**) (Fig. 26) [36,50]. Comparison of the NMR spectra of **77** and **78** with those of the heyneanines was key to the C-19 configuration determinations. A compound named originally oxotabernamine [50] and depicted as **79** was revised to **80** following a new isolation and comparison with the spectra of the corresponding monomers, conodusines A and B. Enolization of C-19 could explain the formation of the tabernamidines as seen in these last compounds. Vobatensine A (**81**) is the C-11-OMe analogue of (19*R*)-hydroxytabernamine and its structure was proven definitively by a partial synthesis from vobasinol and 19-*epi*-iboxygaine [49]. The same plant, *Tabernaemontana corymbosa*, yielded the dihydro derivative **82**, which was named vobatensine B, and was also prepared from tabernaemontaninol and 19-*epi*-iboxygaine. The configuration at C-20′ was deduced from the following NOE correlations: H-19′↔H-16′, H-18′↔H-21′, and H-20′↔H-14′.

Ervachinines B (**83**) and D (**84**) (Fig. 27) are two positional isomers, composed of vincadiffine (**72**) linked to 10-methoxy-ibogamine (ibogaine (**2**)) or to 11-methoxy-ibogamine (tabernanthine) [19]. Their absolute configurations were

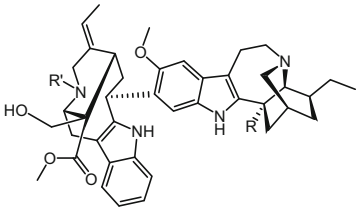


77 (R = H, R' = OH, 20α-H: (19*R*)-hydroxytabernamine)
78 (R = OH, R' = H, 20α-H: (19*S*)-hydroxytabernamine)
79 (R = R' = O, 20α-H: tabernamidine A)
80 (R = R' = O, 20β-H: tabernamidine B)

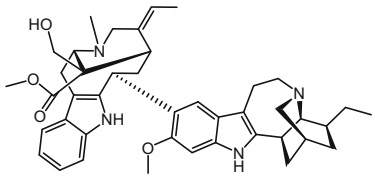


81 (Δ-19' : vobatensine A)
82 (20'α-H : vobatensine B)

Fig. 26 The hydroxytabernamines, tabernamidines A and B, and vobatensines A and B (**77–82**)



85 R = CO_2Me, R'= Me (ervachinine A)
83 R = H, R' = Me (ervachinine B = ervatensine A)



84 (ervachinine D)

Fig. 27 Ervachinines A, B, and D (**83–85**)

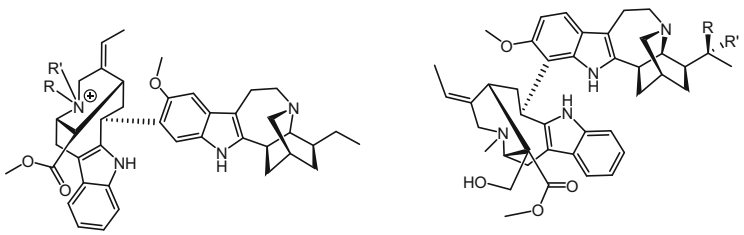


Fig. 28 Ervatensine B, vobatensine F, and condutarines A and B (**86**–**89**)

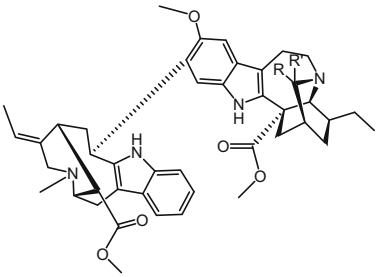
deduced from the similarity of their CD curves with that of ervachinine A (**85**) to which was applied, for the first time in bisindoles, the exciton chirality rule [19]. Its indole chromophores were found to be oriented in a clockwise manner with Cotton effects at 223 (−) and 243 (+) nm. Ervachinine B (**83**) had been previously isolated from the stem bark of *Tabernaemontana corymbosa* (syn. *Ervatamia chinensis*), and the name "ervatensine A" given in the 2008 Ph.D. thesis of K.-H. Lim was maintained, even though the work was not published until 2015 [13]. Discrepancies between the ^{13}C NMR spectra of ervatensine A and of ervachinine B led the Malaysian authors to perform an X-ray structure determination to ascertain the structure of ervatensine A and to establish once and for all the absolute configuration. The series was completed with ervatensine B (**86**) [13] and vobatensine F (**87**) [49], which are the *nor* analogue and the *N*-oxide of decarbomethoxyvoacamine, respectively. Two other similar compounds, conodutarines A and B (**88** and **89**) both have a less typical linkage involving C-12 instead of C-10 [51] (Fig. 28).

4.2.2 Bisindoles with a Voacangine (10-Methoxy-coronaridine) Moiety

Besides ervachinine A (**85**) (see above), there has been only one other bisindole reported with a voacangine unit, conodusarine (**90**), which is the 3-oxo derivative of voacamine (**91**) [52]. Its absolute configuration was not, strictly speaking, proven, but rather assumed, following the concomitant isolation of the parent compound (Fig. 29).

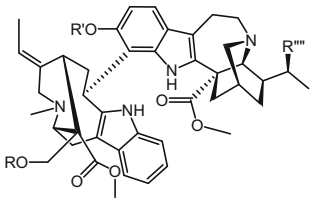
4.2.3 Bisindoles with an Isovoacangine (11-Methoxy-coronaridine) Moiety

There is a wealth of alkaloids of this type, with vincadiffine (**72**) and derivatives in the iboga category, or vobasinol (**70**) and derivatives in a non-iboga group. Variations of the iboga type are unsurprising and represent a similar diversity observed for the monomers. However, the authors of this chapter do have a concern in the

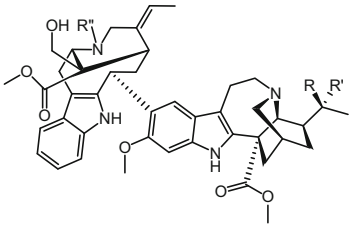


90 R = R' = O (conodusarine)
91 R = R' = H (voacamine)

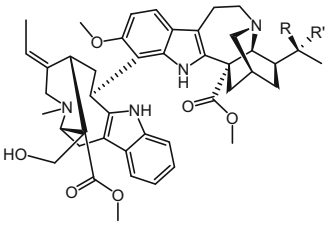
Fig. 29 Bisindoles with a voacangine moiety



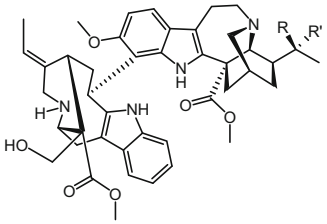
94 R = Ac R' = Me R" = H (17-acetyl-tabernaecorymbosine A)
92 R = R' = R" = H (cononitarine B)
97 R = R' = H R" = OH (cononitarine A)



93 R = R' = H, R" = Me (ervachinine C)
95 R = R' = O, R" = Me (conodiparine C)
98 R = OH, R' = H, R" = Me (conodiparine A)
99 R = OH, R' = R" = H (conodiparine E)



96 R = R' = O (conodiparine D)
100 R = OH, R' = H (conodiparine B)



101 R = OH, R' = H (conodiparine F)

Fig. 30 Bisindoles with a isovoacangine moiety (**92**–**101**)

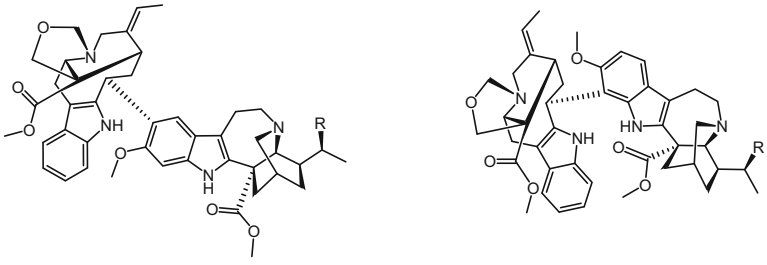
past lack of care in the choice of trivial names for new compounds, with little or no effort apparently having been made to correlate those names to literature references.

Cononitarine B (**92**) [51] and ervachinine C (**93**) (Fig. 30) [19] are two bisindoles composed of a 11-hydroxy- or a 11-methoxy-coronaridine moiety linked to a vincadiffine unit. As for other ervachinines, the absolute configuration of **93** was

deduced from the similarity of its CD spectrum to that of ervachinine A (**85**). In the same series, 17-acetyl-tabernaecorymbosine A (**94**) was isolated and its absolute configuration was confirmed by the CD exciton chirality method [53]. Conodiparine C (**95**) is the 19-oxo derivative of ervachinine C, and its isomer conodiparine D (**96**) simply differs in its location of attachment on the aromatic ring (C-12 instead of C-10) [51]. Cononitarine A (**97**) is (19*S*)-hydroxycononitarine B [51]. The other conodiparines (A (**98**), B (**100**), E (**99**), and F (**101**)) are pairs differing in the substitution pattern of N-4 in the affinisine moiety: NH vs. N-Me [51].

A peculiarity of the four alkaloids, conodirinines A and B (**102** and **103**) [54], and tabernaricatines C and D (**104** and **105**) (Fig. 31) [40], is the presence of an extra tetrahydro-1,3-oxazine ring bridging C-16 and N-4. The configuration assignment of the hydroxyethyl side chain was based on the ^{13}C NMR chemical shifts. As discussed by the authors, the signal for the N-Me group was conspicuously missing and it was the first reason to propose that it was embedded in a ring. The original paper [54] suggested that the methylene bridge is the result of a formaldehyde (or equivalent) condensation, but this also may be the result of the oxidation of the *N*-methyl into an iminium and subsequent trapping in a Polonovski fashion, as suggested by Zhang et al. [53].

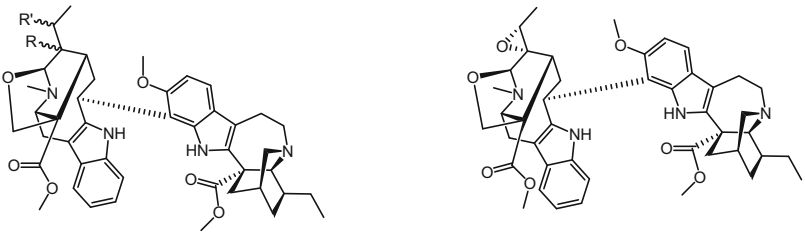
Like the set of preceding compounds, tabernaricatines A and B (**106**, **107**) [40], and tabercorine C (**108**) (Fig. 32) [53], also possess a tetrahydro-1,3-oxazine ring, this time incorporating C-21 rather than a N-Me functionality. The structures of **106** and **107** were proposed mainly after comparison of their NMR data and observed NOE correlations with those of conodiparine B (**100**). No chiroptical data were reported and the structures were considered as flat although configurations were drawn for all centers including the epoxy ring. The absolute configuration of **108** was discussed after its CD data were measured and differences between the spectra of **106** and **108** led to the conclusion that they had an opposite epoxide configuration, but unfortunately taking the configuration of **106** for granted (which is not the case). The biosynthesis scheme proposed for **108** [53] is more appealing and has the merit of explaining the origin of the other compounds as well.



102 R = OH (conodirinine A)
104 R = H (tabernaricatine C)

103 R = OH (conodirinine B)
105 R = H (tabernaricatine D)

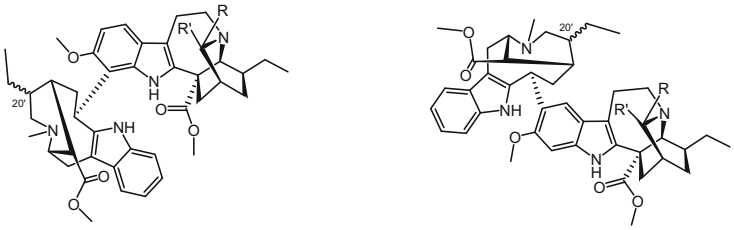
Fig. 31 The bridged compounds **102**–**105**



106 R, R' = oxido (tabernaricatine A)
107 R = R' = H (tabernaricatine B)

108 (tabercorine C)

Fig. 32 Tabernaricatines A and B, and tabercorine C (**106–108**)



109 R = R' = O, H-20'α (3-oxo-tabernaelegantine A)
111 R = OH, R' = H, H-20'α ((3*R*)-hydroxytabernaelegantine A)
112 R = OH, R' = H, H-20'β ((3*R*)-hydroxytabernaelegantine C)
113 R = H, R' = OH, H-20'α ((3*S*)-hydroxytabernaelegantine A)
114 R = H, R' = OH, H-20'β ((3*S*)-hydroxytabernaelegantine C)
115 R = CN, R' = H, H-20'β (tabernaelegantinine C)

110 R = R' = O, H-20'α (3-oxo-tabernaelegantine B)
116 R = OH, R' = H, H-20'β ((3*R*)-hydroxytabernaelegantine D)

Fig. 33 Oxo and hydroxy tabernaelegantines A, B, C, and D (**109–116**)

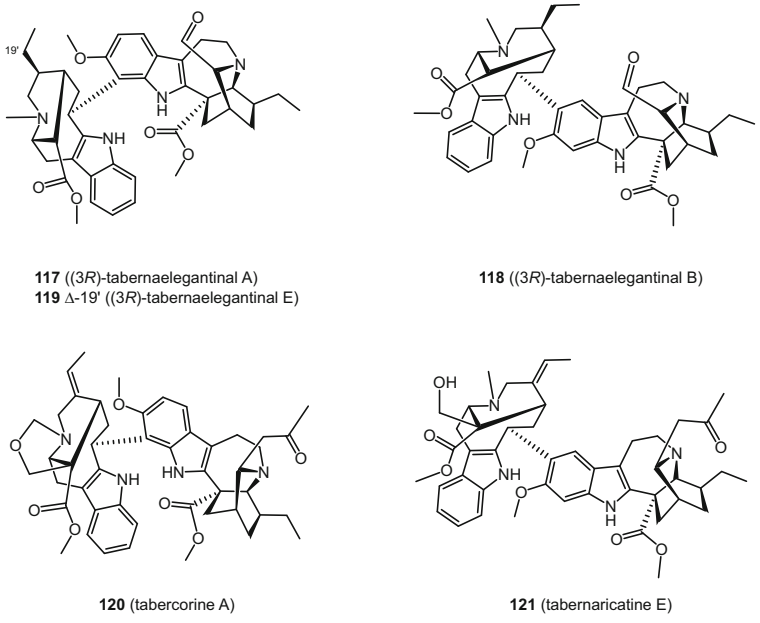
Muntafara sessifolia (syn. *T. sessifolia*) yielded 3′-oxo-tabernaelegantines A and B (**109** and **110**) (Fig. 33), which are regioisomers differing in the substitution pattern on the aromatic ring [55]. Their structures, including the relative configurations within the two moieties, were determined mainly by NMR spectroscopy. These are the oxidation products of the well-known tabernaelegantines, although this has not been proven. A particular feature of the NMR spectra was a line-broadening phenomenon, said by the authors to disappear upon cooling at 273 K. It was even stated that "lowering the temperature favored one conformer" [55], but this is not reasonable from a thermodynamic standpoint.

Four 3-hydroxy-tabernaelegantines were characterized, with three of these having a C-12—C-3′ bridge: (3*R*)-hydroxytabernaelegantine A (**111**), (3*R*)-hydroxytabernaelegantine C (**112**) [56], (3*S*)-hydroxytabernaelegantine A (**113**) [56], and (3*S*)-hydroxytabernaelegantine C (**114**) [56]. (3*R*)-Hydroxytabernaelegantine C (**112**) was known previously as a semisynthetic bisindole obtained by acidic hydrolysis of tabernaelegantinine C (**115**) [57]. The

configuration of C-3 was deduced from its ^{13}C NMR chemical shift value (i.e. near 86 ppm in the (*S*)-configuration and up to 93 ppm in the (*R*)-configuration). The interconversion of these carbinolamines under acidic conditions such as on the silica gel used for purification could explain the fact that hydroxytabernaelegantine A was isolated initially as a mixture of epimers, **111** and **113**. The configuration of the ethyl chains in the vobasinyl units was determined from the chemical shifts of C-14′, C-16′, C-18′, C-19′, and C-20′, and a NOE correlation observed between H-3′↔H-20′. (3*R*)-Hydroxytabernaelegantine D (**116**) was the sole carbinolamine bisindole containing a C-10—C-3′ bond [56].

The propensity of C-3 of the iboga alkaloids to capture nucleophiles was illustrated by the isolation of the three tabernaelegantinals A, B, and E (**117–119**) (Fig. 34) [56]. The (*R*)-configuration of C-3 was determined by the observation of a strong NOE interaction between the aldehyde proton and H-5b. It is assumed that the precursor, 3-formyl-isovoacangine, was formed by reduction of a 3-cyanoisovoacangine, itself produced from a 3-hydroxyisovoacangine via an iminium form in a Strecker-like reaction.

The same iminium intermediate could be scavenged by nucleophiles such as the acetylacetate anion to form 3-alkyl-isovoacangine. Examples among the bisindoles are tabercorine A (**120**) [54] and tabernaricatine E (**121**) [40], which is 3-oxopropyl-ervachinine C. A NOE or ROE correlation was observed between H-3↔H-17β, establishing that H-3 is β-("left")-oriented. The absolute



117 ((3*R*)-tabernaelegantinal A)
119 Δ-19' ((3*R*)-tabernaelegantinal E)

118 ((3*R*)-tabernaelegantinal B)

120 (tabercorine A)

121 (tabernaricatine E)

Fig. 34 C-3 substituted bisindoles (**117–121**)

configuration of tabercorine A was established by means of the CD exciton chirality method with the two indoles oriented in a clockwise manner.

4.2.4 Bisindoles with an Iboga-Indolenine or Rearranged Moiety

Dimers in the iboga series with an oxidized indole nucleus are rather rare compared to the situation observed in the monomers. Only two 7-hydroxy-indolenines, tabercorine B (**122**) [53] and vobatensine D (**123**) (Fig. 35) [49], corresponding to tabernaricatine D (**105**) and ervatensine B (**86**), have been isolated recently. The (7*R*)-configuration of 7-OH in **122** was deduced by comparison of the NMR data with those of the hydroxyindolenine of voacangine. No ROE correlation was observed for the OH, which is not surprising since the measurements were done in acetone-d_6, but the absolute configuration was established by the exciton chirality CD rule. Vobatensine D (**123**) was claimed to have the inverted (7*S*)-configuration (α-OH) on the basis of a dubious argument: the co-occurrence of the (7*S*)-hydroxyindolenine of ibogaine of known absolute configuration in the plant [58].

A bisindole has been reported with a pseudo-indoxyl chromophore, namely, (2*R*)-vobatensine C (**124**) [49]. The configuration of its spirocyclic C-2 was deduced from the chemical shifts of C-2, C-7, C-16, and C-21 as performed for iboluteine (**58**). A NOE correlation was observed between the indole NH and H-17β.

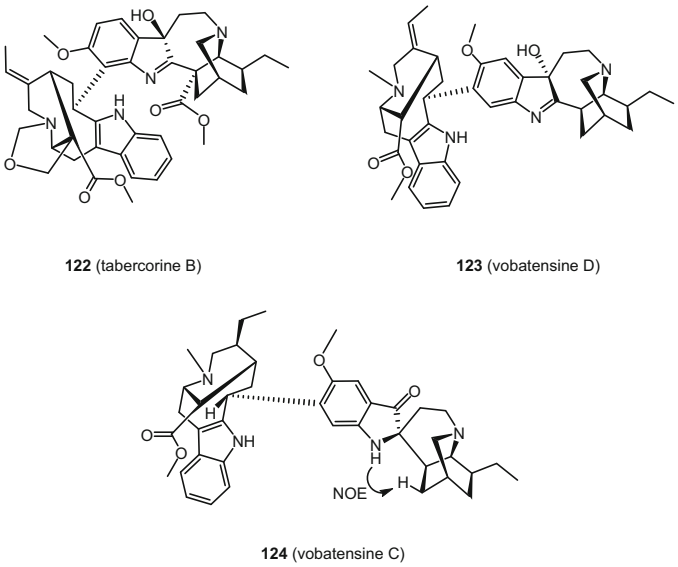


Fig. 35 Hydroxy indolenines and pseudo indoxyl bisindoles (**122–124**)

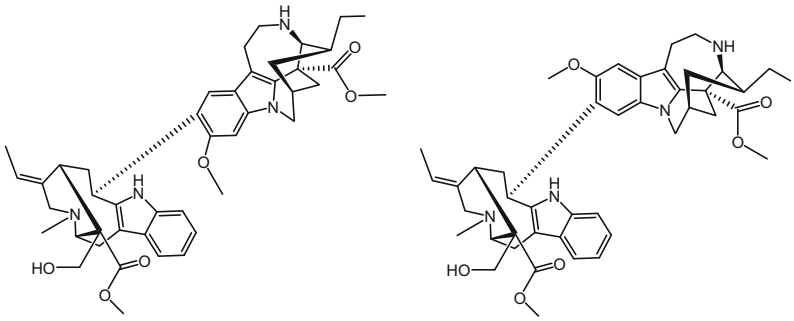


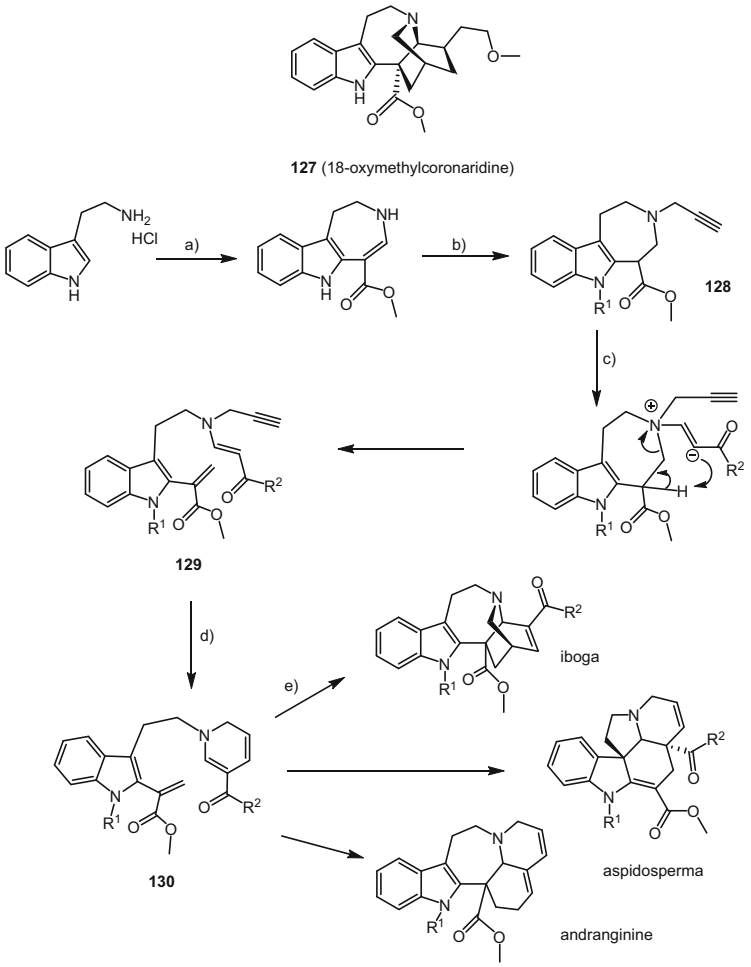
Fig. 36 Vobasinol-chippiine-type bisindoles (**125**–**126**)

4.2.5 Bisindoles with a Chippiine Moiety

Tabernaemontana corymbosa has yielded two dimeric alkaloids, tabercarpamines A (**125**) and B (**126**), possessing the usual vobasinol moiety and a chippiine portion [46] (Fig. 36). Their structures were established by NMR spectroscopy and mass spectrometry and a proposal was made for their absolute configurations based on the application of the exciton chirality rule. While it is perfectly acceptable to determine the helicity around the junction between moieties, this is based on an assumption that the configurations of the monomers have been determined already. In this example, as in others described previously, these are simply assumed based on biogenetic hypotheses rather than on any rigorous experiments.

5 Synthesis

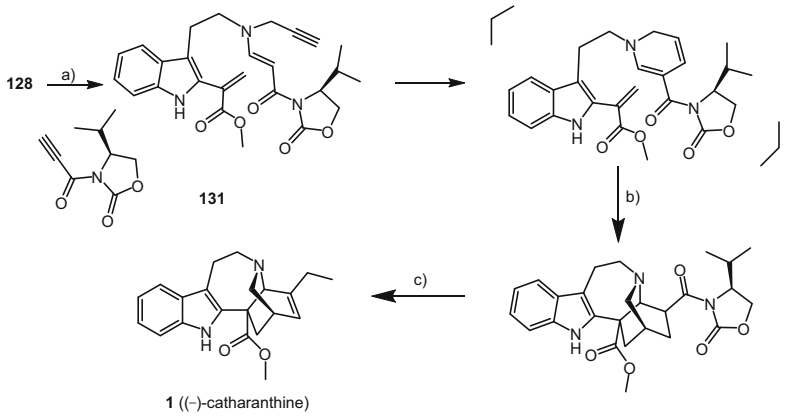
As mentioned earlier in this chapter, total synthesis is almost no longer in use in the structural elucidation domain. Unless major changes occur in the marketplace, most industrially or pharmacologically important alkaloids (e.g. catharanthine (**1**) and ibogaine (**2**)) will continue to be available competitively on a large scale starting from natural materials. An exception is the 18-OMe derivative of coronaridine (**127**) (Chart 1), which is in the pre-development phase and, in the absence of a reliable source of its precursor, albiflorine (18-OH coronaridine), will remain a fully synthetic compound. Total synthesis in the area is justified by the preparation of unnatural analogues or derivatives and by the development of methods of a more general application.



a) 1. methyl bromopyruvate, MeOH, reflux, 2. pyridine, reflux, b) 1. $NaBH_3CN$, AcOH, 2. Et_3N, propargyl bromide
c) $HCCCOR_2$, $ClCH_2CH_2Cl$, CF_3CH_2OH, d) Cu(dppf)(MeCN)PF_6, e) R^1= H, R^2 = OMe, $ClCH_2CH_2Cl$, 60°C, 48%

Chart 1 General principles of the unified synthesis for the preparation of the iboga, aspidosperma, and andranginine skeletons

Most of the first generation of iboga alkaloids syntheses were based on the assumed biosynthesis, and the main challenges were to build a molecule containing a reactive acrylate and an unstable dihydropyridine such as found in compound **130**. A quite innovative and general route to **130** inspired by biosynthesis was recently



a) AcOH, CH_2Cl_2, b) Cu(dppf)(MeCN)PF_6, c) 1.$CeCl_3$, MeOH, 2. DiBAL, 3. $(PhO)_2P(O)Cl$, Et_3N, 4. $Fe(acac)_3$, MeMgBr

Chart 2 Asymmetric total synthesis of (−)-catharanthine (**1**)

proposed by a group at Hokkaido University (Charts 1 and 2) [59]. The synthesis starts from azepinoindole **128**, prepared from tryptamine according to a process similar to the one used by Kuehne. It then takes advantage of a Kuehne-type fragmentation to generate the 2-indolyl acrylate **129** while the dihydropyridine is generated by a Cu-(I) catalyzed 6-*endo* cyclization of an ene-yne (step d, Chart 1). One of the characteristics of this very clever approach is the stabilization of the dihydropyridine in the presence of the acrylate function in **130** allowing all possible Diels-Alder adducts to be obtained, thus leading to the iboga, aspidosperma, or even andranginine skeletons. As a bonus, chirality was also obtained with the introduction of a chiral oxazolidinone in **131**, the precursor of the dihydropyridine (Chart 2). The synthesis follows a route similar to that used in the racemic synthesis and was illustrated by the preparation of (−)-catharanthine.

Another approach follows the historical route developed by Trost, in which a bond is formed between C-2 of indole and the isoquinuclidine bearing a suitably placed double bond [60]. The last cyclization stage (viz. **132** → **133** in Chart 3) requires a full equivalent of palladium and another full equivalent of silver, which makes the end product more valuable than these two metals together. This is clearly a disadvantage and attempts have been made to circumvent this difficulty and make this reaction catalytic. After using the Pd/Ag sequence to prepare analogues of ibogamine such as **134** (Chart 3) [61–63], Sinha introduced the Heck reaction to cyclize the azepinoindole system (Chart 4) [64,65]. Practically speaking, the precursor was a 2-iodinated indole either

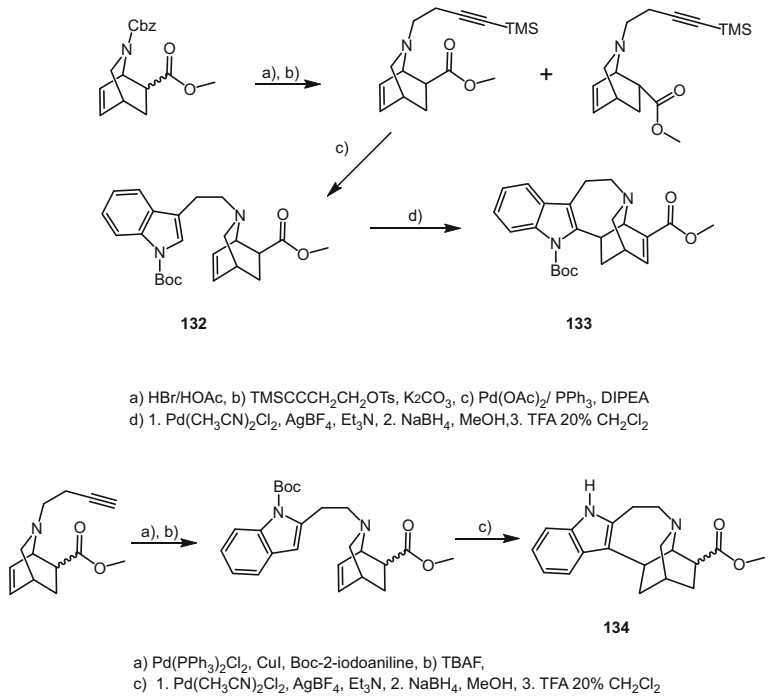
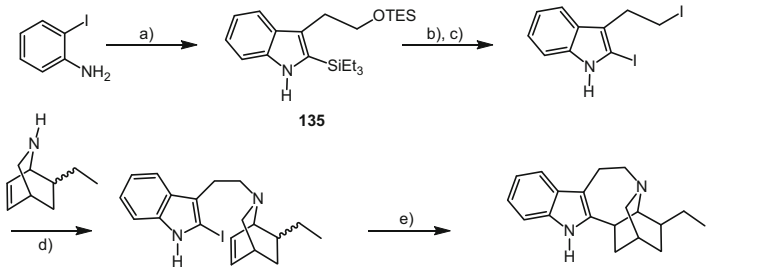


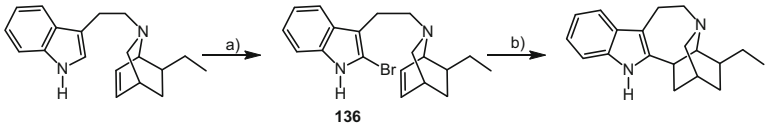
Chart 3 Syntheses of the iboga skeleton (top) and of iboga analogs (bottom) by the Sinha stoichiometric Pd/Ag route

prepared directly by iodination of the corresponding indole or in two steps via the triethylsilyl intermediate **135**. As an alternative, the same authors synthesized a 2-iodo tryptophyl iodide, which they condensed with the appropriate isoquinuclidine. Almost simultaneously, and as part of a program aiming at alleviating the metal stoichiometry problem, Sames at Columbia University also made use of a Heck cyclization, this time with the 2-bromo intermediate **136** (Chart 4) [66]. However, the most innovative part in this article is the search for a true catalytic reaction to perform the desired cyclization. It indeed worked with a Ni catalyst, but on a benzofuran analogue **137** (Chart 4). So far, the genuine nucleus of the iboga skeleton did not surrender to a fully catalytic CH insertion process.

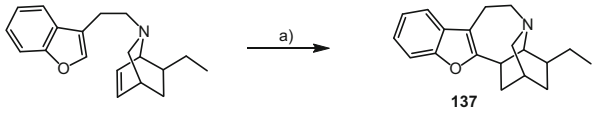
The question of the crucial C-2 to C-16 ring closure is more obviously solved when C-16 is at the ketone oxidation level. It is illustrated in the synthesis of (19*R*)-ibogaminol (**138**) by Höck and Borschberg, where a single acid treatment suffices to close the seven-membered ring (step g in Chart 5) [67]. The key step of



a) $Pd(OAc)_2$, Na_2CO_3, $Et_3SiCCCH_2CH_2OSiEt_3$, b) i) NIS, ii) TBAF,c) I_2, imidazole
d) isoquinuclidine, K_2CO_3, e) 1. separation, 2. $Pd(OAc)_2$, PPh_3, HCOONa



a) $PhMe_3NBr_3$, b) 10% $Pd(PPh_3)_4$, HCO_2Na

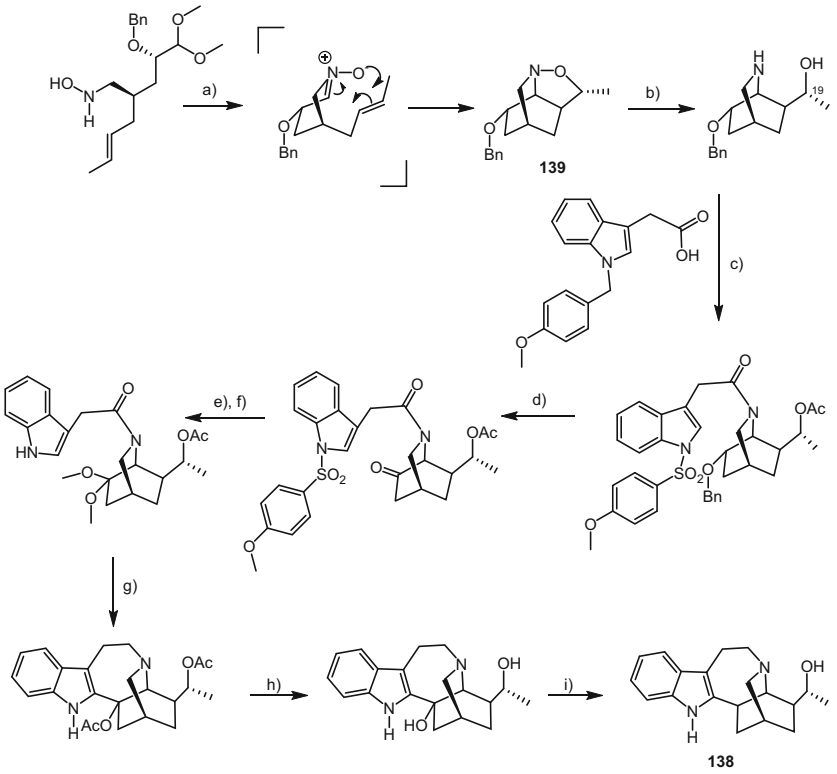


a) 20 mol% $Ni(COD)_2$, 24 mol% 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene

Chart 4 Sinha's (top) and Sames's (middle) routes to ibogamine via Heck cyclization. Sames's fully catalytic route to the iboga alkaloid analog **137** (bottom)

the procedure, however, was the diastereo- and enantio-selective synthesis of the isoquinuclidine **139** through a nitrone to olefin [3 + 2] cycloaddition, allowing the control of the C-19 configuration.

Asymmetric construction of the isoquinuclidine system was devised by Yang and Carter using organocatalysis based on the proline derivative **140** (Chart 6) [68]. The enantioselectivities obtained are excellent, but the presence of an aryl group and the location of the ketone on the isoquinuclidine will require several steps before reaching the natural products. There are not many articles associating medicinal chemistry and the iboga alkaloids. One of them by Sun et al. uses some of Kuehne's chemistry to build azepino-indoles like **141** adorned with functional groups, such as oxo-, thio-, and seleno-hydantoin units (Chart 6)



a) H_2SO_4, 47°C, b) Zn, AcOH, c) i) DCC, ii) Ac_2O, d) i) H_2, Pd/C, ii) DMSO, $(COCl)_2$, Et_3N, e) $HC(OMe)_3$, TsOH, f) Na/Hg, KH_2PO_4, THF/MeOH, g) AcCl, AcOH, cat MeOH, h) 1. $LiAlH_4$, 2. BF_3-Et_2O, i) $LiAlH_4$, $AlCl_3$, THF

Chart 5 The synthesis of (19*R*)-ibogaminol (**138**) by Höck and Borschberg

[69]. Unfortunately, no biological data were provided for the compounds synthesized.

The synthesis of voacangalactone (**16**) by Harada et al. qualifies as a high-yielding multiple-step total synthesis, for which the number of steps involved seems not to be an issue since every single step is high yielding (Chart 7) [20]. There are many innovations in this synthesis, and, for instance, the two-carbon atom chain of the tryptamine is installed in the last steps via an oxalyl chloride Friedel-Crafts reaction followed by a diborane reduction, a sequence used by Woodward to make methoxytryptamine in his approach to reserpine. To the best of our knowledge, this is the first time this reaction has been used to

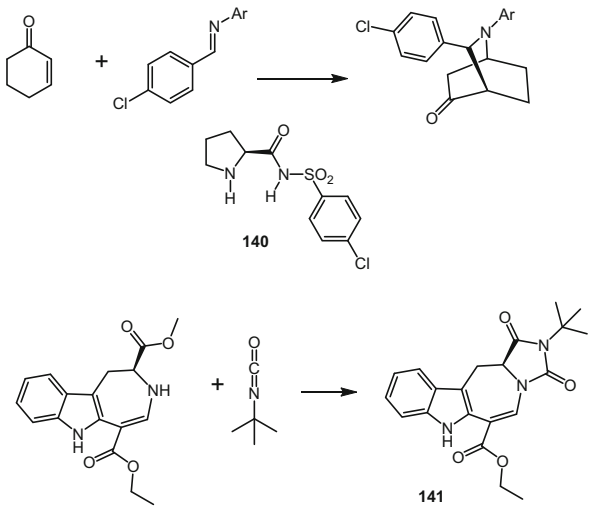
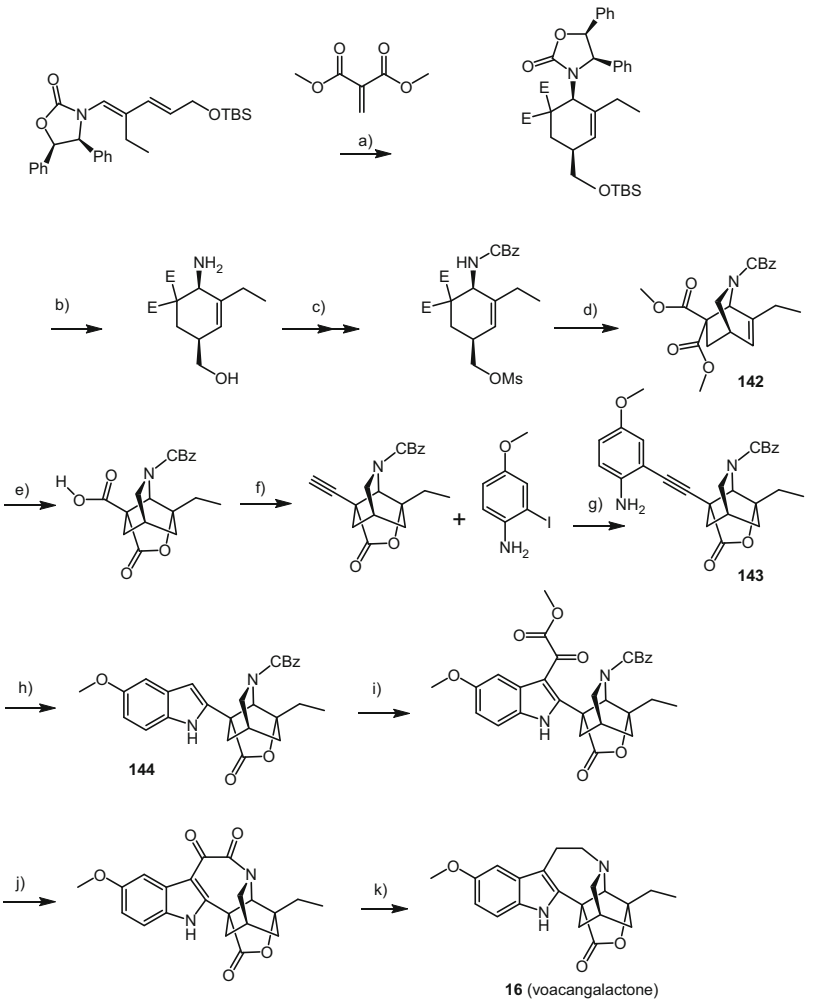


Chart 6 Asymmetric synthesis of the isoquinoline skeleton via organocatalysis (top) and synthesis of hydanthoin analogs of iboga alkaloids (bottom)

close the seven-membered ring of an azepino-indole, which is one of the difficulties in the synthesis of iboga alkaloids. Other salient features of this synthesis are the use of a Diels-Alder reaction to form the isoquinuclidine **142**, with a chiral induction and a gold-mediated indole synthesis (**143** → **144**). It took 14 steps for the synthesis of compound **142** and another 13 steps to make voacangalactone (**16**), for which 2 mg were added to the overall world resources of this compound!

Until now, 18-OMe-coronaridine (**127**) has not been obtained as a natural product, but from a pharmacological point of view it is a very promising candidate for pharmaceutical development (vide infra). Its synthesis is what may be considered as state of the art: short, convergent, enantioselective, and high yielding (see Chart 8 for an example of the synthesis of **127**). This starts with an azepino-indole, **145**, made in two steps from tryptamine, and which reacts with a wide variety of aldehydes to give intermediates of the secodine type, to then undergo Diels-Alder type cyclization. When a chiral auxiliary is placed on the nitrogen atom, chirality induction is obtained, with the efficiency of the process depending on the match between the chiral azepino-indole and the aldehyde. In the synthesis of 18-OMe-coronaridine (**127**), the aldehyde contains provisos for the methoxyethyl side chain, and, after the reaction, a masked aldehyde tetracycle (**146**) is obtained. The auxiliary group was then "exchanged" to a "handier" benzyl group and this was followed by reductive opening to a nine-membered ring to provide **147**. Upon debenzylation and removal of the aldehyde protection, a cyclization



a) CH_2Cl_2, rt, 60h, b) 1. H_2, Pd(OH), 2. CSA, 3. H_2, Pd, all in one pot, c) 1. CBzCl, $NaHCO_3$, 2. MsCl, Et_3N, d) $CsCO_3$, DMF, 100°, e) 1. KOH, 2. I_2, $NaHCO_3$, 3. $BH_3.Me_2S$, 4. I_2, $NaHCO_3$, 5. AIBN, Bu_3SnH, f) 1. DMP, 2. $MeCOCN_2PO(OMe)_2$, g) $Pd(PPh_3)_4$, $CuSO_4$, sodium ascorbate, h) $NaAuCl_4$, 2 H_2O, i) $(COCl)_2$, then MeOH, j) TMSCl, NaI, k) BH_3-THF

Chart 7 Harada's total synthesis of voacangalactone (**16**)

occurred uneventfully to produce the cleavamine derivative **148**. Simple heating of enamine **148** under reflux in toluene produced a "miracle", with an exquisite CH shift and ring closure to give the title compound in overall good yield and less than ten steps [70].

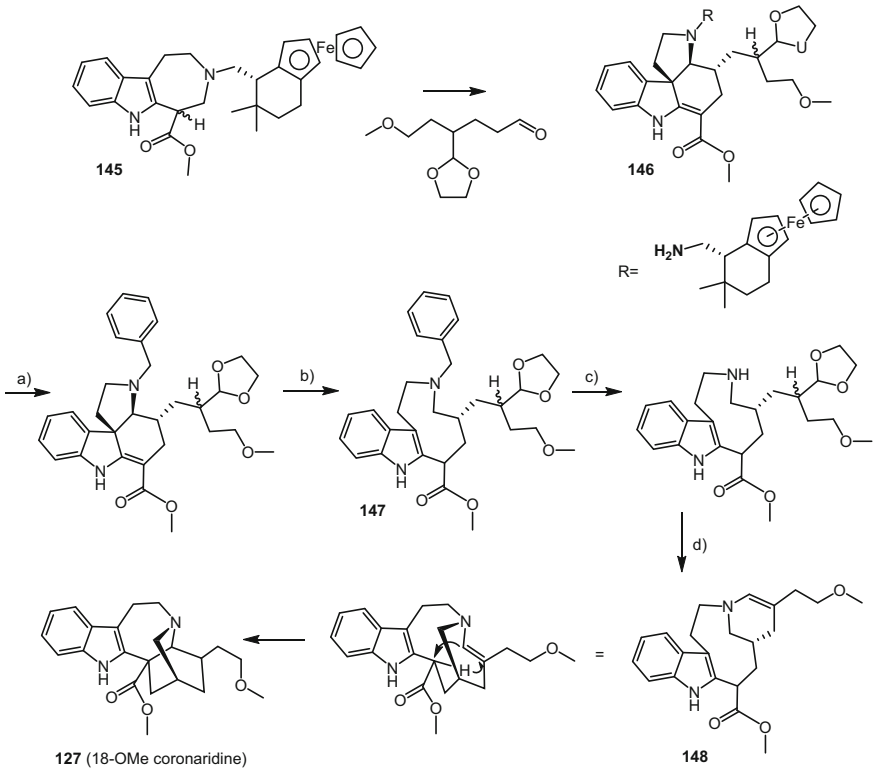


Chart 8 Kuehne's synthesis of 18-methoxy-coronaridine (**127**)

6 Biological Activities

6.1 Ibogaine and Noribogaine

6.1.1 Elements of Context

Ibogaine (**2**) is certainly included in any top list of alkaloids for its mystique and aura. It has its roots in the mythic Bwiti cult of Gabon and it has been for the past three decades the object of a fierce battle between its pros and cons when used as a drug abuse treatment. A full volume in the series "The Alkaloids" was dedicated to ibogaine, and, in the Introduction, G.A. Cordell wrote: "is ibogaine an alkaloid that can save the world from addiction? Probably not" [3]. That was in 2001, so why keep writing on this topic? Two of the reasons are that advances have been made in the understanding of the drug addiction phenomenon, and, also because, in the absence of an alternative treatment, **2** is still more or less openly in use.

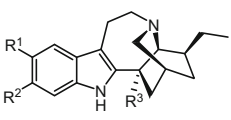
The story of ibogaine (**2**) has been written several times including its most recent developments as a treatment for drug abuse [71–74]. It is less well-known, however, that iboga root extracts were at one time available on the market as an anti-fatigue and stimulant agent. Formulated tablets were sold by the Laboratoires Houdé under the name of Lambarene®, after the city in Gabon where Albert Schweitzer had his dispensary. The drug was withdrawn from the market in 1970 but **2** reappeared on the scene when Howard Lotsof was granted a patent in 1985 for "a rapid method for interrupting the narcotic addiction syndrome". This was followed by a period of conflicts and experimental work that culminated in the first ibogaine conference held in New York in 1999 [75]. The story is still ongoing since a further ibogaine conference was convened in Mexico in 2016 [76].

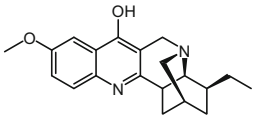
6.1.2 Security Problems and Fatalities

There is at least one major reason to explain the reluctance of health authorities to pursue ibogaine (**2**) as a potential therapeutic agent: security of use. Toxicity has always been a concern and it cannot be disclaimed that several "patients" have passed away some time after ingesting **2**. One can find in the forensic literature articles investigating the reasons for these fatalities [77–81]. However, there does not appear to be a general pattern linking such deaths to the intake of **2**. Neurotoxicity and cardiotoxicity are the most often suspected causes of death, and also activity on Purkinje cells has been observed in female rats under ibogaine treatment. Not all of these effects have been ascertained during patient autopsies, and the known tremorigenic effects of **2** seem to be unrelated to such fatalities.

6.1.3 Analytics

During forensic investigations, the levels of ibogaine (**2**) and related products in body fluids were determined. In the human body, the main metabolite of ibogaine (**2**) is noribogaine (12-hydroxy-ibogamine, **149**) produced by demethylation of **2** with cytochrome CYP2D6. It is also a constituent of the crude alkaloid mixture of the root bark of *Tabernanthe iboga*. The major alkaloids from the plant (also involved in poisoning cases) are ibogaine, noribogaine, voacangine (**150**), iboluteine (**58**), ibochine (**151**), ibogaline (**152**), and ibogamine (**153**) [82] (Fig. 37). In the same paper, the stability of the two main alkaloids ibogaine and noribogaine under daylight exposure was investigated and it was found that they rapidly transformed into iboluteine (**58**) and ibochine for **2**, and into their desmethoxy counterparts of **149**, with respective half-lives of 81.5 and 11 min. Liquid chromatography-MS with electrospray ionization is the method of choice to rapidly discriminate these alkaloids and many examples of the use of this technique are found in recent literature, as e.g., in Refs. [83] and [84].





149 R^1 = OH, R^2 = R^3 = H (noribogaine)
150 R^1 = OCH_3 , R^2 = H, R^3 = CO_2CH_3 (voacangine)
152 R^1 = R^2 = OCH_3 , R^3 = H (ibogaline)
153 R^1 = R^2 = R^3 = H (ibogamine)

151 (ibochine)

Fig. 37 Main alkaloids from the roots of *Tabernanthe iboga* (**149**–**153**)

6.1.4 Mechanism of Action

The mechanism of action of ibogaine (**2**) is very complex and a glimpse at this complexity is given in an article where the affinity of psychedelic drugs towards a large series of receptors and transporters is documented [85]. To make a long story short, ibogaine activates μ and κ opioid receptors as well as $\sigma 1$ and $\sigma 2$ receptors. Unsurprisingly, because of its structural similarities with serotonin, it also inhibits to a certain extent serotonin and dopamine receptors. The action of **2** on the μ opioid receptor (MOR) was investigated in detail by Alper et al. using hypothalamus cells overexpressing this receptor [86]. It was eventually found that **2** is a weak MOR antagonist without any agonist effect in rat thalamic membranes. The inhibition of acetylcholinesterase (AChE) by **2** was invoked at one time to explain some properties of the molecule and in particular the potentiation of morphine analgesia. This was reinvestigated and an IC_{50} of 520 ± 40 μM was found, a very high value suggesting that the physiological effect of **2** on AChE is negligible [87]. These findings led to the conclusion that the mechanism of action of ibogaine is different from that of other molecules with effects on opioid tolerance and withdrawal, indicating a novel mechanism with targets still to be discovered.

In a series of intriguing papers, Paškulin et al. raised the question of the duration of the effects of **2**, which is much longer than its pharmacokinetic parameters would allow. In particular, the mood-elevating effects appear generally a day after ingestion, a lapse of time where most of the drug and its metabolites are almost no longer observable. Two proteomic studies were performed on whole rat brain and on the yeast *Saccharomyces cerevisiae* subjected or not to **2**, and the overexpressed proteins were detected by 2D gel electrophoresis [88,89]. These were involved with cell metabolism: glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, enolase, and alcohol dehydrogenase, all related to compensation of the ATP pool decrease. Ibogaine (**2**) induces a new metabolic equilibrium aiming at saving energy [90] and at the same time increases the activity of antioxidative enzymes as an adaptation to oxidative stress [91].

The complex pharmacological profile of ibogaine was highlighted recently in a zebrafish study which, inter alia, allowed observation of its effects on social behavior (suggesting a wider use of this model for hallucinogenic and drug abuse research [92]). It must also be realized that due to the rapid transformation of **2** into

149, which possesses a different pharmacological profile, it is not easy to understand the origin of the effects (beneficial or deleterious) of the iboga alkaloids on human beings. This is probably the second major reason why it seems so difficult to bring one of these molecules to the market.

6.2 18-Methoxy-coronaridine (18-MC)

Faced with the difficulties associated with ibogaine (**2**), a search for an alternative molecule in the series was undertaken. Ibogamine (**143**) and coronaridine (**3**) were eventually considered as potential candidates since they retained the action on drug self-administration without any tremorigenic side effects. These properties were shared by many other similar compounds, among which 18-OMe-coronaridine (**127**) proved to be the most interesting [93,94]. Compound **127** was fully synthetic and therefore patentable, which has been an advantage over ibogaine and other natural products, and it has its own particular mechanism of action. It was thus found to have micromolar activity on κ, μ, and $\sigma 2$ opioid receptors and on 5-HT_3 receptor without affinity for the NMDA receptor and serotonin transporter. Particularly interesting was an affinity for the $\alpha 3\beta 4$ nicotinic receptor, which was the object of pharmacological experimentation by intracerebral administration in rats in a studies related to drug self-administration [95,96]. Compound **127** was also shown to act on the sucrose reward circuit and therefore may be considered as a possible antiobesity agent [97].

Also exciting is the observation that coronaridine (**3**) and particularly 18-MC (**127**) show promise against *Leishmania amazonensis*, a causative agent of leishmaniasis [98].

A small pharmaceutical company named Savant HWP (San Carlos, CA, USA) has commenced preclinical testing comprising IND-enabling studies and GMP scale-up work on 18-MC in the hope of gaining official approval as a drug cessation treatment. The company is also conducting human clinical safety studies on compound **127** in Brazil, so that it can be investigated further for the potential therapy of leishmaniasis.

6.3 Miscellaneous Biological Properties of Iboga Alkaloids

6.3.1 Cytotoxicity and Antiproliferative Activity

As often is the case currently, the isolation of new natural products may be accompanied by investigation of their biological properties, using in-house available assays. In this respect, cytotoxicity screens against one or several cancer cell lines is a common asset of many laboratories. Due to compound quantity

limitations, or the inavailability of follow-up in vivo assays, it may not always be possible to perform studies to determine antineoplastic activity using experimental tumor-bearing mouse models.

In a general screening procedure for inhibitors of the Wnt pathway, *T divaricata* gave a positive response that led subsequently lead to four bioactive iboga alkaloids: voacangine, isovoacangine, coronaridine (**3**), and coronaridine hydroxyindolenine (**41**), with IC_{50} values in the 10 μ*M* range [99]. The best compound was **3**, shown to down-regulate mRNA and therefore decrease the β-catenin protein level and inhibit the Wnt signaling pathway, which controls, among other factors, cell proliferation. Compound **3** has been known for a long time to be cytotoxic [100] and this may be a possible mechanism of action. 19-Oxocoronaridine, also named ervatamine I and conodusine E (**33**), was found to be ca. 40 times less potent [16]. A good level of activity was observed for tabercarpamine A (**125**) against the MCF-7, HepG2, and SMMC-7721 cancer cell lines [46]. Tabercarpamine A (**125**) was found to induce apoptosis, a biological activity shared with ervatensines A (**83**) and B (**86**) [13]. Vobatensines A–F (**81**, **82**, **124**, **123**, **76**, **87**) were assayed against a variety of cancer cell lines and showed cytotoxic effects in the 10 micromolar range [49]. No indication was given on their possible mechanism of action. Tabercorine A (**120**) and 17-acetyltabernaecorymbosine A (**94**) also displayed cytotoxic activities in the low micromolar range and were shown to be as potent in this regard as cisplatin, which was used as a positive control [53]. However, it is unlikely that they proceed through the same mechanism of action.

6.3.2 Central Nervous System Effects

Given the very potent and profound effects of ibogaine (**2**) on the central nervous system, it is not surprising to find reports of further new investigations of this type. One of the most promising arose from the total synthesis work of Sinha et al. and concerns a benzofuran analog of ibogaine, which possesses dual affinity for both the μ and κ opioid receptors (MOR and KOR). This compound was also nontremorigenic, and showed antinociception in mice in a standard hot-plate test of comparable potency to morphine. The identification of a new pharmacophore in this study may lead to the development of a new treatment for pain [101]. The roots of *Tabernaemontana divaricata* yielded two known alkaloids with a promising level of inhibition of acetylcholinesterase (a demonstrated target for Alzheimer's disease) [102]. These compounds were 19,20-dihydrotabernamine [103] and 19,20-dihydroervahanine A [104]. Voacamine, 3,6-oxidovoacangine, and 5-hydroxy-3,6-oxidovoacangine from *Voacanga africana* were found to be potent antagonists of the cannabinoid receptor CB1, with IC_{50} values in the submicromolar range [25]. This target is involved in memory, pain, and appetite and inhibitory compounds may show promise in the treatment of obesity, metabolic syndrome, and

related disorders inter alia. Coronaridine (**3**), alone among a series of 13 iboga alkaloids, was found to have protective effects in MPP+ (1-methyl-4-phenylpyridinium)-injured primary cortical neurons [39]. This may be of relevance in a treatment of Parkinson's disease but one should not underestimate the cytotoxicity of the molecule (ca. 2 μM).

6.3.3 Miscellaneous Biological Activities

The so-called ervatamines A-I, among which iboga alkaloids (**12**, **27**, **28**, **33**, **46**), as well as coronaridine (**3**), heyneanine, their 2′-oxo derivatives and pandine (**64**), were subjected to an anti-inflammatory in vitro test, and inhibition of lipopolysaccharide-induced NO production in RAW 264.7 macrophages was demonstrated for **3** and **64** [16]. The tabernaeelegantinals (**117–119**) from *Muntafara sessilifolia* were assayed against the chloroquine-resistant strain FcB1 of *Plasmodium falciparum* and showed moderate to good activity [55,56]. Selectivity indexes were determined after assessment of their cytotoxicity and it was concluded that their activity was the result of a general toxicity. However, when evaluated in vitro using the same strain of *P. falciparum*, 3′-oxo-tabernaelegantine A (**109**), also isolated from *M. sessiloflora*, was more promising, and showed antiplasmodial activity (IC_{50} 4.4 μM) with non-significant cytotoxicity for the L-6 rat skeletal muscle cell line [55].

7 Conclusion and Perspectives

Iboga-type alkaloids are one of the many types of indolomonoterpene alkaloids, but they are set apart owing to their unique biological properties. Notably, one of these is their possible use for drug cessation treatment. It must be kept in mind that cocaine addiction is so far without any reliable treatment and that the substitutes to opioids are not without any drawbacks, with one of them being their illicit diversion [105]. Could Howard Lotsof's dream come true and a true drug cessation treatment be introduced to the market in the future, hopefully inspired by *Tabernanthe iboga*?

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References

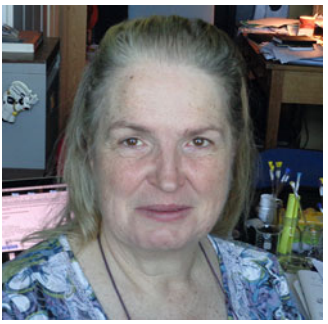
1. Le Men J, Taylor WI (1965) A uniform numbering system for indole alkaloids. Experientia 21:508
2. Szabó LF (2008) Rigorous biogenetic network for a group of indole alkaloids derived from strictosidine. Molecules 13:1875
3. Alper KR, Glick SD (2001). In: Cordell GA (ed) The alkaloids, vol 56. Academic Press, San Diego, San Francisco, New York, Boston, London, Sydney, Tokyo, p 1
4. Sundberg RJ, Smith SQ (2002) In: Cordell GA (ed) The alkaloids, vol 59. Elsevier, Amsterdam, p 281
5. Saxton JE (1994) The ibogamine-catharanthine group. In: Saxton JE (ed) The monoterpenoid indole alkaloids, supplement to part 4. The chemistry of heterocyclic compounds, Taylor EC (ed) vol 25. Wiley, Chichester, New York, Brisbane, Toronto, Singapore, p 487
6. O'Connor SE, Maresh JJ (2006) Chemistry and biology of monoterpene indole alkaloids biosynthesis. Nat Prod Rep 23:532
7. Miettinen K, Dong L, Navrot N, Schneider T, Burlat V, Pollier J, Woittiez L, van der Krol S, Lugan R, Ilc T, Verpoorte R, Oksman-Caldentey KM, Martinoia E, Bouwmeester H, Goossens A, Memelink J, Werck-Reichhart D (2014) The *seco*-iridoid pathway from *Catharanthus roseus*. Nat Commun 5:3606
8. Kries H, O'Connor SE (2016) Biocatalysts from alkaloid producing plants. Curr Opin Chem Biol 31:22
9. El-Sayed M, Choi YH, Frédérich M, Roytrakul S, Verpoorte R (2004) Alkaloid accumulation in *Catharanthus roseus* cell suspension culture fed with stemmadenine. Biotechnol Lett 26:79310
10. Townsend CA (2011) A "Diels-Alderase" at last. ChemBioChem 12:2267
11. Fage CD, Alsiorho E, Liu Y, Wagner DT, Liu HW, Keatinge-Clay AT (2011) The structure of SpnF, a standalone enzyme that catalyzes [4 + 2] cycloaddition. Nat Chem Biol 11:256
12. Saxton JE (1994) The ibogamine-catharanthine group. In: Saxton JE (ed) The monoterpenoid indole alkaloids, supplement to part 4. The chemistry of heterocyclic compounds, Taylor EC (ed) vol 25. Wiley, Chichester, New York, Brisbane, Toronto, Singapore, p 495
13. Lim K-H, Raja VJ, Bradshaw TD, Lim SH, Low Y-Y, Kam T-S (2015) Ibogan, tacaman, and cytotoxic bisindole alkaloids from *Tabernaemontana*. Cononusine, an iboga alkaloid with unusual incorporation of a pyrrolidinone moiety. J Nat Prod 78:1129
14. Moisan L, Doris E, Rousseau B, Thuéry P (2004) Catharanthinol and dihydrocatharanthinol: two iboga-class alkaloids. Acta Cryst C 60:792
15. Jarraya RM, Bouaziz A, Hamdi B, Ben Salah A, Damak M (2008) *N*-(Hydroxymethyl) ibogaine. Acta Cryst E 64:1739
16. Zhang D-B, Yu D-G, Sun M, Zhu X-X, Yao X-J, Zhou SY, Chen J-J, Gao K (2015) Ervatamines A–I, anti-inflammatory monoterpenoid indole alkaloids with diverse skeletons from *Ervatamia hainanensis*. J Nat Prod 78:1253
17. Blaha K, Koblicova Z, Trojanek J (1974) Chiroptical investigations on the iboga and voacanga alkaloids. Collect Czech Chem Commun 39:2258
18. Harada N, Nakanishi K (1983) Circular dichroism spectroscopy-exciton coupling in organic stereochemistry. University Sciences Books and Oxford University Press, Mill Valley, CA and Oxford, UK
19. Guo L-L, He H-P, Di Y-T, Li S-F, Cheng Y-Y, Yang W, Li Y, Yu J-P, Zhang Y, Hao J (2012) Indole alkaloids from *Ervatamia chinensis*. Phytochemistry 74:140
20. Harada M, Asaba KN, Iwai M, Kogure N, Kitajima M, Takayama H (2012) Asymmetric total synthesis of an iboga-type indole alkaloid, voacangalactone, newly isolated from *Voacanga africana*. Org Lett 14:5800
21. Bartlett MF, Dickel DF, Taylor WI (1958) The alkaloids of *Tabernanthe iboga*. Part IV.1 The structures of ibogamine, ibogaine, tabernanthine and voacangine. J Am Chem Soc 80:126

22. Le Men J, Potier P, Le Men-Olivier L, Panas, JM, Richard B, Potron C (1974) Alkaloids of *Gabonia eglandulosa*–eglandine and eglandulosine. Bull Soc Chim Fr:1369
23. Le Men-Olivier L, Le Men J, Massiot G, Richard B, Mulamba T, Potier P, Husson HP, Van Beek T, Verpoorte R (1984) Révision des structures de l'églandine et de l'églandulosine. Bull Soc Chim Fr:94
24. Tang B-Q, Wang W-J, Huang X-J, Li G-Q, Wang L, Jiang R-W, Yang T-T, Shi L, Zhang X-Q, Ye W-C (2014) Iboga-type alkaloids from *Ervatamia officinalis*. J Nat Prod 77:1839
25. Kitajima M, Iwai M, Kikura-Hanajiri R, Goda Y, Iida M, Yabushita H, Takayama H (2011) Discovery of indole alkaloids with cannabinoid CB1 receptor antagonistic activity. Bioorg Med Chem Lett 21:1962
26. Jin YS, Du Jing-Ling JL, Chen HS, Jin L, Liang S (2010) A new indole alkaloid from *Ervatamia yunnanensis*. Fitoterapia 81:63
27. Mak JYW, Pouwer RH, Williams CM (2014) Natural products with anti-Bredt and bridgehead double bonds. Angew Chem Int Ed 53:13664
28. Langlois N, Langlois Y (2015) La découverte de la navelbine: histoire vécue. Imprimerie de Bretagne, Morlaix, France
29. Guéritte F, Le Roux M (2016) La Navelbine et le Taxotere: histoires de sciences. Iste Wiley Elsevier, London
30. Beatty JW, Stephenson CRJ (2014) Synthesis of (−)-pseudotabersonine, (−)-pseudovincadifformine, and (+)-coronaridine enabled by photoredox catalysis in flow. J Am Chem Soc 136:10270
31. The Plant List (2015) A working list of all plant species. http://www.theplantlist.org/
32. Kam T-S, Sim K-M (2002) Five new indole alkaloids from *Tabernaemontana corymbosa*. J Nat Prod 65:669
33. Wenkert E, Cochran DW, Gottlieb HE, Hagaman EW, Braz Filho R, Matos FJA, Madruga MILM (1976) ^{13}C NMR spectroscopy of naturally occurring substances. 45: Iboga alkaloids. Helv Chim Acta 59:2437
34. Takayama H, Suda S, Chen IS, Kitajima M, Aimi N, Sakai S (1994) Two new dimeric indole alkaloids from *Tabernaemontana subglogosa* Merr. from Taiwan. Chem Pharm Bull 42:280
35. Chen HS, Huang M, Liang S, Zhang XD, Jin L, Chen MY, Zheng JM, Liu JG (2008) Indole alkaloids from *Ervatamia* and their use as detoxifying agents. Chin Pat 200610031038.0
36. Nge CE, Kam WC, Thomas NF, Lim S-H, Low Y-Y, Kam T-S (2016) Ibogan, aspidosperman, vincamine, and bisindole alkaloids from a Malayan *Tabernaemontana corymbosa*: iboga alkaloids with C-20α substitution. J Nat Prod 79:1388
37. Lim K-H, Goh T-S (2009) Conoliferine and isoconoliferine, structurally novel alkaloid-lignan conjugates from *Tabernaemontana corymbosa*. Tetrahedron Lett 50:3756
38. Lim K-H, Goh T-S (2009) Conomicidines A and B, unusual alkaloid—hydroxycinnamyl alcohol conjugates from *Tabernaemontana corymbosa*. Helv Chim Acta 92:1895
39. Liu Z-W, Huang X-J, Xiao H-L, Liu G, Zhang J, Shi L, Jiang R-W, Zhang X-Q, Ye W-C (2016) New iboga-type alkaloids from *Ervatamia hainanensis*. RSC Adv 6:30277
40. Bao M-F, Yan J-M, Cheng G-G, Li X-Y, Liu Y-P, Li Y, Cai X-H, Luo X-D (2013) Cytotoxic indole alkaloids from *Tabernaemontana divaricata*. J Nat Prod 76:1406
41. Feng XZ, Kan C, Potier P, Kan SK, Lounasmaa M (1982) Monomeric indole alkaloids from *Ervatamia hainanensis*. Planta Med 44:212
42. de Souza JJ, Mathias L, Braz-Filho R, Carcino Vieira IJ (2010) Two new indole alkaloids from *Tabernaemontana hustrix* Steud. (Apocynaceae). Helv Chim Acta 93:422
43. Rosenmund P, Haase WH, Bauer J, Frische R (1975) Contribution to chemistry of indole. 7. Syntheses in iboga series 3. Ibogamine, ibogaine and epiibogamine. Chem Ber 108:1871
44. Nge C-E, Gan C-Y, Low Y-Y, Thomas NF, Kam T-S (2013) Voatinggine and tabertinggine, pentacyclic indole alkaloids derived from an iboga precursor via a common cleavamine-type intermediate. Org Lett 15:4774
45. Habib-ur-Rehman, Atta-ur-Rahman (2005) NMR studies on alioline—a novel vinca alkaloid. Z Naturforsch 60b:870

46. Ma K, Wang J-S, Luo J, Yang M-H, Kong L (2014) Tabercarpamines A–J, apoptosis-inducing indole alkaloids from the leaves of *Tabernaemontana corymbosa*. J Nat Prod 77:1156
47. Sapi J, Massiot G (1994) Bisindole alkaloids. In: Saxton JE (ed) The monoterpenoid indole alkaloids, vol 4. Wiley, Chichester, New York, Brisbane, Toronto, Singapore, p 523
48. Zaima K, Hirata T, Hosoya T, Hirasawa Y, Koyama K, Rahman A, Kusumawati I, Zaini NC, Shiro M, Morita H (2009) Biscarpamontamines A and B, an aspidosperma-iboga bisindole alkaloid and an aspidosperma-aspidosperma bisindole alkaloid, from *Tabernaemontana sphaerocarpa*. J Nat Prod 72:1686
49. Sim DS-Y, Teoh W-Y, Sim K-S, Lim S-H, Thomas NF, Low Y-Y, Kam T-S (2016) Vobatensines A – F, cytotoxic iboga-vobasine bisindoles from *Tabernaemontana corymbosa*. J Nat Prod 79:1048
50. Kam T-S, Sim K-M (2002) New tabernamine derivatives from *Tabernaemontana*. Heterocycles 57:2137
51. Kam T-S, Sim K-M, Pang H-S (2003) New bisindole alkaloids from *Tabernaemontana corymbosa*. J Nat Prod 66:11
52. Kam T-S, Pang H-S (2004) Conodusarine, a new biologically active bisindole alkaloid from *Tabernaemontana divaricata*. Heterocycles 63:845
53. Zhang Y, Guo L, Yang G, Guo F, Di Y, Li S, Chen D, Hao X (2015) New vobasinyl-ibogan type bisindole alkaloids from *Tabernaemontana corymbosa*. Fitoterapia 100:150
54. Kam T-S, Sim K-M (2003) Conodirinines A and B, novel vobasine-iboga bisindoles incorporating an additional tetrahydro-1,3-oxazine unit on the vobasinyl moiety. Helv Chim Acta 86:122
55. Girardot M, Deregnaucourt C, Deville A, Dubost L, Joyeau R, Allorge L, Rasoanaivo P, Mambu L (2012) Indole alkaloids from *Muntafara sessilifolia* with antiplasmodial and cytotoxic activities. Phytochemistry 73:65
56. Girardot M, Gadea A, Deregnaucourt C, Deville A, Dubost L, Nay B, Maciuk A, Rasoanaivo P, Mambu L (2012) Tabernaelegantinals: unprecedented cytotoxic bisindole alkaloids from *Muntafara sessilifolia*. Eur J Org Chem:2816
57. Danieli B, Palmisano G, Gabetta B, Martinelli EM (1980) Tabernaelegantinines C and D, two new bisindole alkaloids containing a cyano group from *Tabernaemontana elegans* Stapf. J Chem Soc Perkin Trans 1:601
58. Madinaveitia A, de la Fuente G, González A (1998) The absolute configuration at C(7) of voacangine hydroxyindolenine. Helv Chim Acta 81:1645
59. Mizoguchi H, Oikawa H, Oguri H (2014) Biogenetically inspired synthesis and skeletal diversification of indole alkaloids. Nat Chem 6:57
60. Trost BM, Godleski SA, Genet JP (1978) Total synthesis of racemic and optically active ibogamine: utilization and mechanism of a new silver ion assisted palladium cyclization. J Am Chem Soc 100:3930
61. Jana GK, Sinha S (2010) Synthesis of iboga alkaloids by Pd-catalyzed heteroannulation of 2-iodoaniline with an internal alkyne as the key step. Tetrahedron Lett 51:1441
62. Jana GK, Sinha S (2010) A concise route to iboga-analogues via the formation of suitably substituted-2-indoles. Tetrahedron Lett 51:1994
63. Paul S, Pattanayak S, Sinha S (2011) Synthesis of a new series of iboga-analogues. Tetrahedron Lett 52:6166
64. Jana GK, Sinha S (2012) Reductive Heck coupling: an efficient approach toward the iboga alkaloids. Synthesis of ibogamine, epiibogamine and iboga analogs. Tetrahedron Lett 53:1671
65. Jana GK, Sinha S (2012) Total synthesis of ibogaine, epiibogaine and their analogues. Tetrahedron 68:7155
66. Kruegel AC, Rakshit S, Li X, Sames D (2015) Constructing iboga alkaloids via C–H bond functionalization: examination of the direct and catalytic union of heteroarenes and isoquinuclidine alkenes. J Org Chem 80:2062

67. Höck S, Borschberg H-J (2006) Enantioselective synthesis of (−)-(19*R*)-ibogamin-19-ol. Helv Chim Acta 89:542
68. Yang H, Carter RG (2009) Asymmetric construction of nitrogen-containing [2.2.2] bicyclic scaffolds using *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide. J Org Chem 75:5151
69. Barve IJ, Dalvi PB, Thikekar TU, Chanda K, Liu Y-L, Fang C-P, Liu C-C, Sun C-M (2015) Design, synthesis and diversification of natural product-inspired hydantoin-fused tetrahydroazepino indoles. RSC Adv 5:73169
70. Kuehne ME, Wilson TE, Bandarage UK, Dai W, Yu Q (2001) Enantioselective synthesis of coronaridine and 18-methoxycoronaridine. Tetrahedron 57:2085
71. Alper KR, Lotsof HS, Frenken GMN, Luciano DJ, Bastiaans J (1999) Treatment of acute opioid withdrawal with ibogaine. Am J Addict 8:234
72. Alper KR, Lotsof HS, Kaplan CD (2008) The ibogaine medical subculture. J Ethnopharmacol 115:9
73. Mačiulaitis R, Kontrimavičiūtė V, Bressolle FMM, Briedis V (2008) Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. Hum Exp Toxicol 27:181
74. Brown TK (2013) Ibogaine in the treatment of substance dependence. Curr Drug Abuse Rev 6:3
75. For a historical timeline see Alper KR, Glick SD (2001) In: Cordell GA (ed) The Alkaloids, vol 56. Academic Press, San Diego, San Francisco, New York, Boston, London, Sydney, Tokyo, p 4
76. http://www.ibogaineconference.org/
77. Alper KR, Stajić M, Gill JR (2012) Fatalities temporally associated with the ingestion of ibogaine. J Forensic Sci 57:398
78. Maas U, Strubelt S (2006) Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction. Med Hypotheses 67:960
79. Chèze M, Lenoan A, Deveaux M, Pépin G (2008) Determination of ibogaine and noribogaine in biological fluids and hair by LC–MS/MS after *Tabernanthe iboga* abuse. Iboga alkaloids distribution in a drowning death case. Forensic Sci Int 176:58
80. Papadodima SA, Dona A, Evaggelakos CI, Goutas N, Athanaselis SA (2013) Ibogaine related sudden death: a case report. J Forensic Leg Med 20:809
81. Mazoyer C, Carlier J, Boucher A, Peoc'h M, Lemeur C, Gaillard Y (2013) Fatal case of a 27-year-old male after taking iboga in withdrawal treatment: GC-MS/MS determination of ibogaine and ibogamine in iboga roots and postmortem biological material. J Forensic Sci 58:1666
82. Kontrimavičiūtė V, Mathieu O, Balas L, Escale R, Blayac JP, Bressolle FMM (2007) Ibogaine and noribogaine: structural analysis and stability studies. Use of LC-MS to determine alkaloid contents of the root bark of *Tabernanthe iboga*. J Liq Chromatogr Relat Technol 30:1077
83. Kontrimavičiūtė V, Breton H, Mathieu O, Mathieu-Daudé J-C, Bressolle FMM (2006) Liquid chromatography–electrospray mass spectrometry determination of ibogaine and noribogaine in human plasma and whole blood. Application to a poisoning involving *Tabernanthe iboga* root. J Chromatogr B 843:131
84. Kontrimavičiūtė V, Breton H, Barnay F, Mathieu-Daudé J-C, Bressolle FMM (2006) Liquid chromatography-electrospray mass spectrometry determination of ibogaine and 12-hydroxy-ibogamine in human urine. Chromatographia 63:533
85. Ray TS (2010) Psychedelics and the human receptorome. PLoS One 5, e9019
86. Antonio T, Childers SR, Rothman RB, Dersch CM, King C, Kuehne M, Bornmann WG, Eshleman AJ, Janowsky A, Simon ER, Reith MAE, Alper K (2013) Effect of iboga alkaloids on μ-opioid receptor-coupled G protein activation. PLoS One 8, e77262
87. Alper K, Reith MEA, Sershenc H (2012) Ibogaine and the inhibition of acetylcholinesterase. J Ethnopharmacol 139:879

88. Paškulin R, Jamnik P, Živin M, Raspor P, Štrukelj B (2006) Ibogaine affects brain energy metabolism. Eur J Pharmacol 552:11
89. Paškulin R, Jamnik P, Obermajer N, Slavić M, Štrukelj B (2010) Induction of energy metabolism related enzymes in yeast *Saccharomyces cerevisiae* exposed to ibogaine is adaptation to acute decrease in ATP energy pool. Eur J Pharmacol 627:131
90. Paškulin R, Jamnik P, Danevčič T, Koželj G, Krašovec R, Krstić-Milošević D, Blagojević D, Štrukelj B (2012) Metabolic plasticity and the energy economizing effect of ibogaine, the principal alkaloid of *Tabernanthe iboga*. J Ethnopharmacol 143:319
91. Nikolić-Kokić A, Oreščanin-Dušić Z, Spasojević I, Slavić M, Mijušković A, Paškulin R, Miljević Č, Spasić MB, Blagojević DP (2015) Ex vivo effects of ibogaine on the activity of antioxidative enzymes in human erythrocytes. J Ethnopharmacol 164:64
92. Cachat J, Kyzara EJ, Collins C, Gaikwada S, Green J, Roth A, El-Ounsia M, Davis A, Pham M, Landsman S, Stewart AM, Kalueff AV (2013) Unique and potent effects of acute ibogaine on zebrafish: the developing utility of novel aquatic models for hallucinogenic drug research. Behav Brain Res 236:258
93. Maisonneuve IM, Glick SD (2003) Anti-addictive actions of an iboga alkaloid congener: a novel mechanism for a novel treatment. Pharmacol Biochem Behav 75:607
94. Pace CJ, Glick SD, Maisonneuve IM, He L-W, Jokiel PA, Kuehne ME, Fleck MW (2004) Novel iboga alkaloid congeners block nicotinic receptors and reduce drug self-administration. Eur J Pharmacol 492:159
95. Panchal V, Taraschenko OD, Maisonneuve IM, Glick SD (2005) Attenuation of morphine withdrawal signs by intracerebral administration of 18-methoxycoronaridine. Eur J Pharmacol 525:98
96. Glick SD, Ramirez RL, Livi JM, Maisonneuve IM (2006) 18-Methoxycoronaridine acts in the medial habenula and/or interpeduncular nucleus to decrease morphine self-administration in rats. Eur J Pharmacol 537:94
97. Taraschenko OD, Maisonneuve IM, Glick SD (2010) 18-Methoxycoronaridine, a potential anti-obesity agent, does not produce a conditioned taste aversion in rats. Pharmacol Biochem Behav 96:247
98. Delorenzi JC, Freire-de-Lima L, Gattass CR, de Andrade CD, He L, Kuehne ME, Saraiva EMB (2002) In vitro activities of iboga alkaloid congeners coronaridine and 18-methoxycoronaridine against *Leishmania amazonensis*. Antimicrob Agents Chemother 46:2011
99. Ohishi K, Toume K, Arai MA, Sadhu SK, Ahmed F, Ishibashi M (2015) Coronaridine, an iboga type alkaloid from *Tabernaemontana divaricata*, inhibits the Wnt signaling pathway by decreasing β-catenin mRNA expression. Bioorg Med Chem Lett 25:3937
100. Gunasekera SP, Cordell GA, Farnsworth NR (1980) Anticancer indole alkaloids of *Ervatamia heyneana*. Phytochemistry 19:1213
101. Banerjee TS, Paul S, Sinha S, Das S (2014) Synthesis of iboga-like isoquinuclidines: dual opioid receptors agonists having antinociceptive properties. Bioorg Med Chem 22:6062
102. Ingkaninan K, Changwijit K, Suwanborirux K (2006) Vobasinyl-iboga bisindole alkaloids, potent acetylcholinesterase inhibitors from *Tabernaemontana divaricata* root. J Pharm Pharmacol 58:847
103. Henriques AT, Melo AA, Moreno PR, Ene LL, Henriques JA, Schapoval EE (1996) *Ervatamia coronaria*: chemical constituents and some pharmacological activities. J Ethnopharmacol 50:19
104. van Beek TA, Verpoorte R, Baerheim Svendsen A, Leeuwenberg AJM, Bisset NG (1984) *Tabernaemontana* L. (Apocynaceae): a review of its taxonomy, phytochemistry, ethnobotany and pharmacology. J Ethnophamacol 10:1
105. Bretteville-Jensen AL, Lillehagen M, Gjersing L, Burdzovic Andreas J (2015) Illicit use of opioid substitution drugs: prevalence, user characteristics, and the association with non-fatal overdoses. Drug Alcohol Depend 147:89



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