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Bioinspired Collective Syntheses of Iboga-Type Indole Alkaloids

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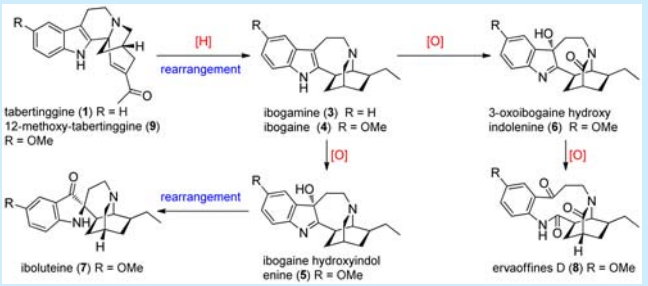
Supporting Information

ABSTRACT: We present the application of a bioinspired collective synthesis strategy in the total syntheses of seven iboga-type indole alkaloids: (±)-tabertinggine, (±)-ibogamine, (±)-ibogaine, (±)-ibogaine hydroxyindolenine, (±)-3-oxoibogaine hydroxyindolenine, (±)-iboluteine, and (±)-ervaoffines D. In particular, tabertinggine and its congeners serve as iboga precursors for the subsequent biomimetic transformations into other iboga-type alkaloids.



Iboga-type alkaloids are famous monoterpene indole alkaloids, mostly isolated from *Tabernanthe* or *Tabernaemontane* species of plants belonging to the Apocynaceae family.[1] Classic iboga-type alkaloids share a characteristic indole and isoquinuclidine unit fused with a seven-membered azepane ring (Figure 1, ibogamine (**3**)). Recently, a series of new iboga-type alkaloids with skeletal variations have also been isolated.[2] Iboga-type alkaloids show a wide range of pharmacological effects, such as antiaddiction,[3] antifungal or antilipase,[4] anti-HIV-1,[5] anticholinesterasic,[6] and leishmanicide activities.[7] Their medicinal evaluations and application potential have motivated synthetic chemists to execute concise and efficient syntheses as well as convenient late-stage derivatizations for building large collections of biologically relevant molecules. Great efforts have been made over the past years since the pioneering synthetic studies by Büchi and co-workers.[8] Moreover, most of synthetic routes have been targeting simple representatives in the iboga family. However, the reported approaches lack the synthetic flexibility in order to achieve other members of iboga-type alkaloids that are closely related to each other.[8a] Here, we demonstrate the application of a bioinspired collective synthesis strategy on the efficient and scalable preparation of several structurally diverse iboga-type alkaloids.

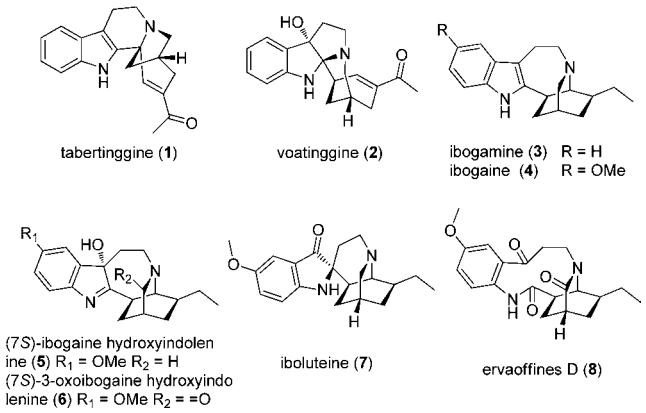


Figure 1. Representative members of iboga-type indole alkaloids.

A possible biotransformation pathway to these iboga-type alkaloids from an iboga precursor via related facile skeletal rearrangements and modifications is depicted in Scheme 1.[2] Oxidation of C19 and C16 of ibogamine (**3**) followed by vicinal migration of N4 from C21 to C16 readily generates tabertinggine (**1**). Similarly, oxidation of C19 and the indole olefin of C2/C7 of ibogamine (**3**) followed by the C21-to-C2 migration of N4 leads to voatinggine (**2**). Obviously, ibogaine (**4**) could be oxidized to produce (7*S*)-ibogaine hydroxyindolenine (**5**), which subsequently undergoes a pinacol rearrangement to yield iboluteine (**7**). Additionally, oxidation the C3 of (7*S*)-Ibogaine hydroxyindolenine (**5**) to lactam gives (7*S*)-3-oxoibogaine hydroxyindolenine (**6**), which undergo further oxidative cleavage of the indole moiety to afford ketoamide ervaoffines D (**8**).

Because tabertinggine (**1**) could be converted into ibogamine (**3**),[8c] we selected the concise and large-scale preparation of tabertinggine (**1**) and 12-methoxytabertinggine (**9**) as a starting point and the foundation of our overall synthetic plan. The retrosynthetic analysis is shown in Scheme 2. Compound **1** or **9** can be obtained from ketoaldehyde **10** via an intramolecular aldol condensation reaction. In turn, compound **10** could be derived from **11** through several functional group transformations, and the required compound **11** could be derived from **13**, which might be prepared from tryptamine or its methoxy-substituted derivative **14** and ketone **15** via a one-pot

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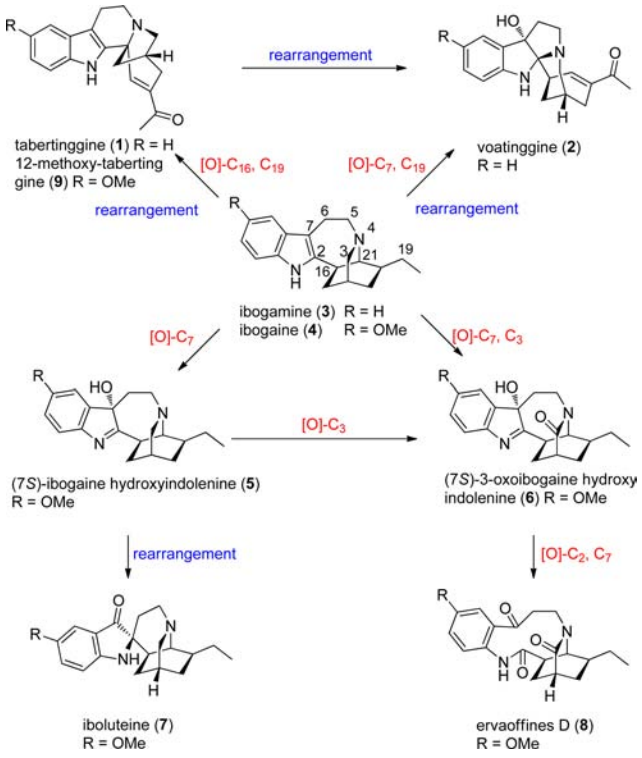
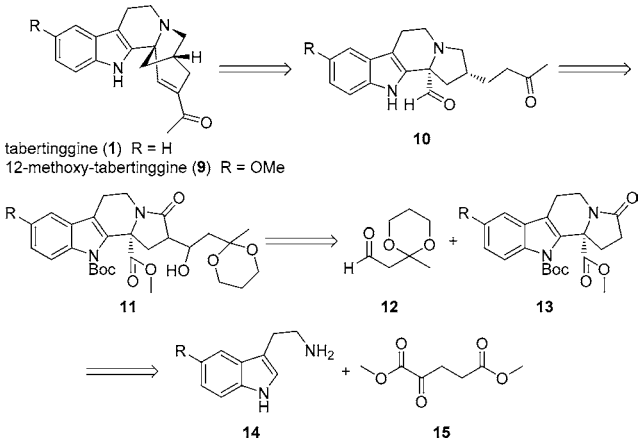
Scheme 1. Plausible Biosynthetic Pathways



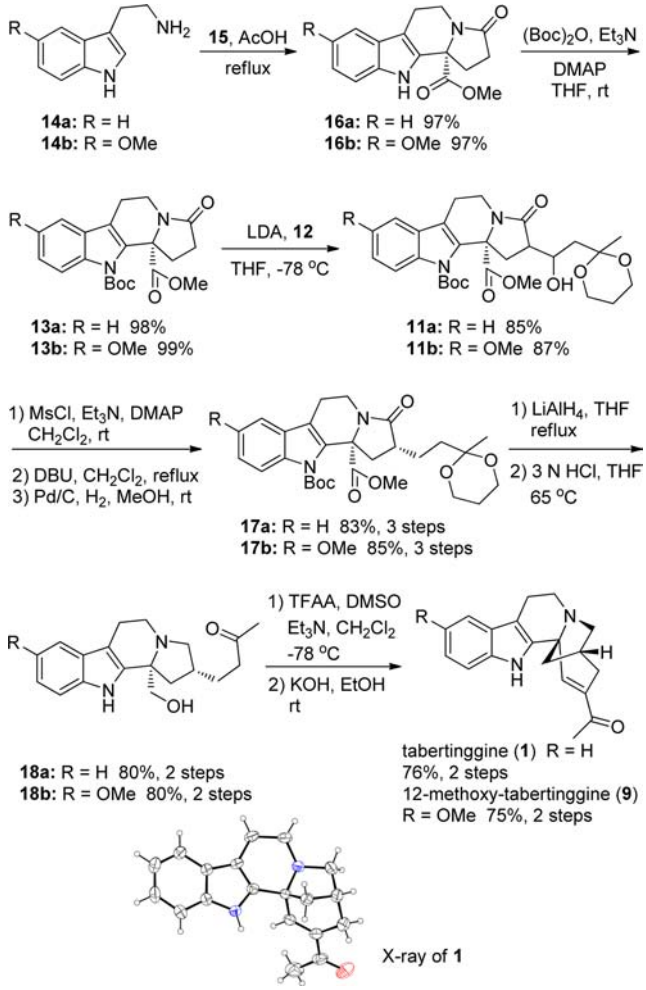
Scheme 2. Retrosynthetic Analysis of Tabertinggine (1) and 12-Methoxytabertinggine (9)



cascade Pictet−Spengler condensation/intramolecular ammonolysis reaction.[9]

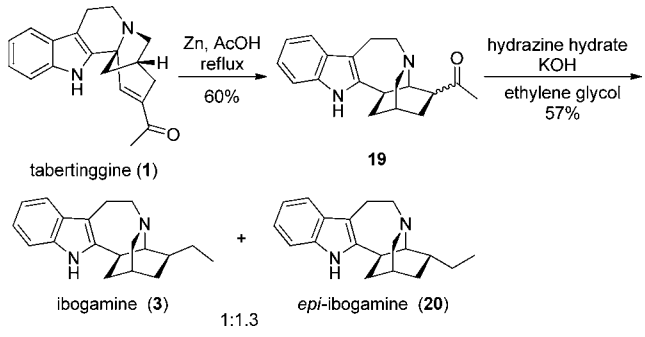
Our synthetic studies commenced with the preparation of amide **16** (Scheme 3). The one-pot Pictet−Spengler condensation/intramolecular ammonolysis reaction proceeded smoothly to give tetracyclic amide **16** in 97% yield. Then amide **16** was protected by *tert*-butoxycarbonyl to generate **13**, which was coupled with aldehyde **12** via an intermolecular aldol reaction to afford **11**. Mesylation of the resulting secondary hydroxyl group of **11** followed by elimination and hydrogenation gave a single isomer **17**. Reduction of **17** with excess $LiAlH_4$ also led to removal of the *tert*-butoxycarbonyl protecting group, and the newly generated product was subsequently treated with 3 N HCl (aq) to afford keto alcohol **18**. Swern oxidation of keto alcohol **18** produced the requisite ketoaldehyde **10**, which was efficiently converted to tabertinggine (**1**) and 12-methoxytabertinggine (**9**) by an intramolecular aldol condensation reaction. The structure of synthetic tabertinggine (**1**) was confirmed unambiguously by X-ray crystallographic analysis. It is worth mentioning that all of the above steps are easily performed and can be scaled up to gram-scale preparation.

Scheme 3. Synthesis of Tabertinggine (1) and 12-Methoxytabertinggine (9)



With sufficient tabertinggine (**1**) in hand, we then focused on its transformation to ibogamine (**3**) (Scheme 4). Accordingly, reduction of the α,β-unsaturated ketone **1** with zinc in acetic acid led to the cleavage of the carbon nitrogen bond and subsequent intramolecular Michael addition to afford a pair of

Scheme 4. Synthesis of Ibogamine



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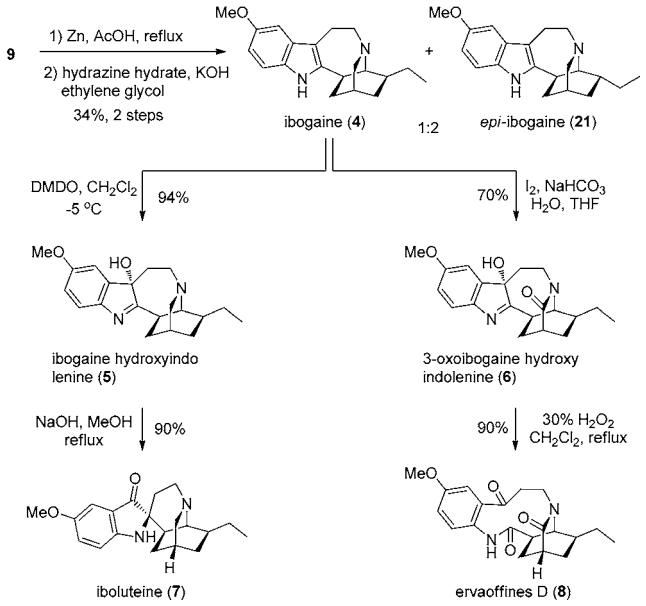
epimeric ketones **19**, which subsequently underwent Wolff–Kishner reduction to afford a mixture of ibogamine (**3**) and *epi*-ibogamine (**20**) in 34% overall yield (**3**:**20** = 1:1.2).[8c]

On the basis of the success of the above transformations, the exploration of collective syntheses of other iboga-type alkaloids was initiated. When the same procedure as for the synthesis of ibogamine was used, 12-methoxytabertinggine (**9**) was also successfully converted into ibogaine (**4**) (Scheme 5). The face-

Scheme 5. Biomimetic Transformations



selective oxidation of C2/C3-fused indoles is a well-established method for hydroxyindolenines, which serve as precursors to the corresponding pseudoindoxyls.[10] Therefore, ibogaine (**4**) was successfully oxidized to ibogaine hydroxyindolenine (**5**) by using DMDO as oxidant from the less hindered face.[11] NaOH in refluxing MeOH induced ring contraction of ibogaine hydroxyindolenine (**5**) to give iboluteine (**7**) with the desired spiro configuration.[12] In order to obtain 3-oxoibogaine hydroxyindolenine (**6**) and ervaoffines D (**8**), we turned our attention to the oxidation of ibogaine (**4**) to lactam. To our delight, after extensive investigation, 3-oxoibogaine hydroxyindolenine (**6**) was effectively generated by treating ibogaine (**4**) with I_2/Na_2CO_3.[13] Additionally, 3-oxoibogaine hydroxyindolenine (**6**) was further oxidized to cleavage of the indole moiety to afford ervaoffines D (**8**) by H_2O_2.

In summary, we have demonstrated the application of a bioinspired collective synthesis strategy in the syntheses of seven structurally diverse iboga alkaloids: (±)-tabertinggine, (±)-ibogamine, (±)-ibogaine, (±)-ibogaine hydroxyindolenine, (±)-3-oxoibogaine hydroxyindolenine, (±)-iboluteine, and (±)-ervaoffines D. Most importantly, tabertinggine can be prepared on gram scale in 10 steps with 40.8% overall yield. Ibogamine and ibogaine are accomplished in 12 steps with 6.1% and 4.8% overall yields, respectively. Ibogaine hydroxyindolenine, 3-oxoibogaine hydroxyindolenine, and ervaoffines D have been synthesized for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00989.

Detailed experimental procedures, ^{1}H NMR and ^{13}C NMR spectra, and X-ray data for compound **1** (PDF)
X-ray crystallographic data for **1** (CIF)

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Notes

The authors declare no competing financial interest.

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