

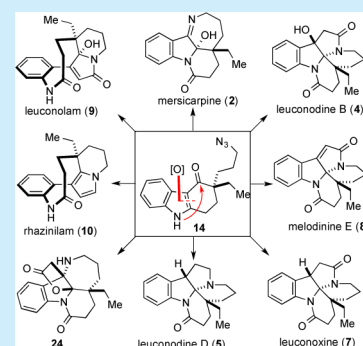
# Biosynthetically Inspired Divergent Approach to Monoterpene Indole Alkaloids: Total Synthesis of Mersicarpine, Leuconodines B and D, Leuconoxine, Melodinine E, Leuconolam, and Rhazinilam

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## S Supporting Information

**ABSTRACT:** Inspired by their potential biosynthesis, we have developed divergent total syntheses of seven monoterpene indole alkaloids including mersicarpine, leuconodines B and D, leuconoxine, melodinine E, leuconolam, and rhazinilam, and one unnatural analogue with an unprecedented structural skeleton. The key steps involve a Witkop–Winterfeldt oxidative indole cleavage followed by transannular cyclization. The transannular cyclization product was then converted to the corresponding structural skeletons by pairing its functional groups into different reaction modes.



Nature has endowed us with many small-molecule natural products with important functions and diverse structural skeletons. These molecules are indispensable to the discovery of life-saving drug molecules for various human diseases.<sup>1</sup> Among them, the terpene indole alkaloids (TIAs) are one of the most important families, from which drug molecules such as vinblastine, vincristine, yohimbine, ajmalicine, ajmaline, quinine, and camptothecin have been identified.<sup>2</sup> Biosynthetically, the TIAs are produced from the combination of tryptamine and secologanin.<sup>3</sup> Following structural rearrangement of the resulting strictosidine, several major TIA subfamilies are produced including the *aspidosperma*, *iboga*, *corynanthe*, *ajmalan*, and *quinoline* subfamily. Monoterpene indole alkaloids with novel structural skeletons were isolated as well such as mersicarpine (**2**, Scheme 1A),<sup>4,15</sup> leuconodines (**3–6**),<sup>5,15</sup> leuconoxine (**7**),<sup>6,5c,15</sup> melodinine E (**8**),<sup>7,5c,15</sup> leuconolam (**9**),<sup>8</sup> rhazinilam (**10**),<sup>9,8b</sup> rhazinal (**11**),<sup>10,8b,9k,l</sup> rhazincine (**12**),<sup>11,9j,m</sup> and meloscine (**13**).<sup>12</sup> Biologically, leuconodine E showed moderate activity in reversing multidrug resistance in vincristine-resistant KB cells, and rhazinilam was identified to interfere with tubulin polymerization.<sup>13</sup> Biosynthetically (Scheme 1B), these TIA members are proposed to be derived from the *aspidosperma* subfamily such as aspidospermidine (**1**).<sup>14</sup> Cleavage of the C<sub>2</sub>–C<sub>7</sub> bond of **A** (the original indole ring of tryptamine) would give rise to skeleton **B** resembling the core structure of **9–12**. Bond formation between N<sub>1</sub> and C<sub>21</sub> would provide skeleton **C**, which is the core structure of **3–8**. Additional N-migration from C<sub>21</sub> to C<sub>7</sub> followed by fragmentation would produce skeleton **E** (cf. **C** → **D** → **E**), the carbon skeleton of mersicarpine (**2**). On the other hand, C<sub>7</sub>–C<sub>16</sub> bond formation from **B** would give the meloscine skeleton **F**. C<sub>7</sub> migration from C<sub>2</sub> to C<sub>16</sub> of **A** would give the same product. Due

to their intriguing structures and important biological activity, a significant amount of synthetic efforts have been directed toward their de novo chemical synthesis and elegant total syntheses of several of them have been developed.<sup>4–12</sup> Notably, while we were working toward the total synthesis of these molecules, Zhu et al. recently reported an efficient and unified synthesis of **2**, **4**, **7**, **8**, and **9**.<sup>15</sup>

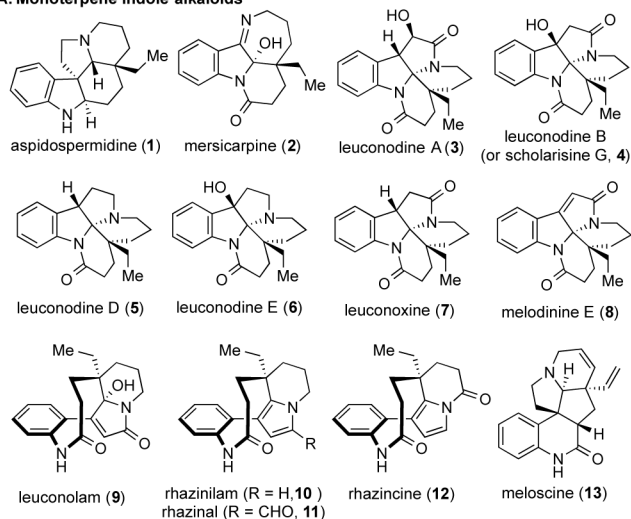
Our interest<sup>16</sup> in developing functional group pairing strategies<sup>17</sup> for divergent synthesis<sup>18</sup> of complex bioactive natural products prompted us to synthesize these intriguing rearranged TIAs and their analogues. Inspired by their potential biosynthesis, we wondered about the possibility of synthesizing them from intermediate **14**. As shown in our synthetic plan (Scheme 1C), we envisioned a Witkop–Winterfeldt oxidative indole cleavage of the C<sub>2</sub>–C<sub>7</sub> bond of compound **14** would give nine-membered lactam **15**.<sup>19</sup> Transannular cyclization of N<sub>1</sub> and C<sub>21</sub> of compound **15** would provide pivotal intermediate **16**. By tuning the functional groups of this reactive intermediate into different reaction modes, we were hoping to obtain three structural skeletons: mersicarpine (**2**), **17**, and **18**, via a Staudinger–aza-Wittig reaction,<sup>20</sup> a Bestmann ketene lactonization,<sup>21</sup> and an azide reduction followed by cyclization, respectively. The latter two intermediates would then be converted to several monoterpene indole natural products and unnatural analogues. Herein, we report efficient and divergent total syntheses of mersicarpine (**2**), leuconodine B (**4**), leuconoxine (**7**), melodinine E (**8**), leuconolam (**9**), and rhazinilam (**10**), an unnatural analogue with an unprecedented

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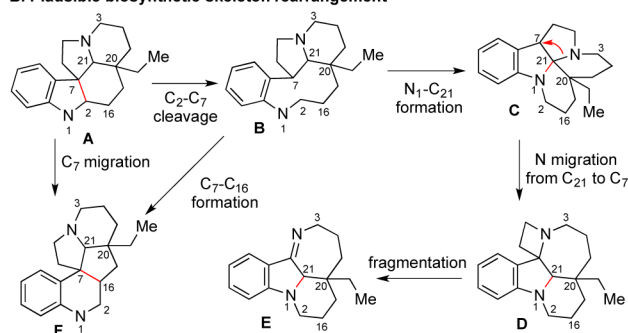
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# Scheme 1. Structures of Representative Monoterpene Indole Alkaloids, Their Potential Biosynthesis, and Our Proposed Divergent Synthesis

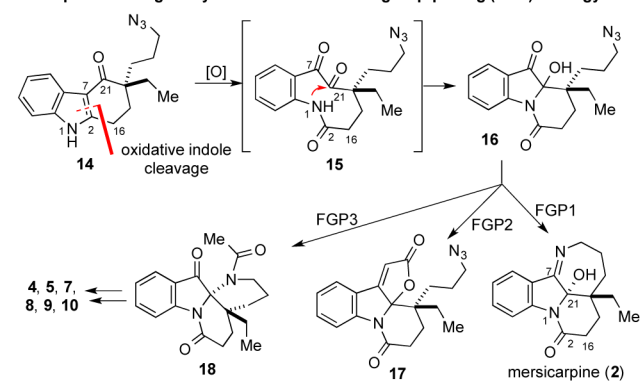
## A. Monoterpene indole alkaloids



## B. Plausible biosynthetic skeleton rearrangement



## C. Proposed divergent synthesis via functional-group-pairing (FGP) strategy



structural skeleton (**24**), and the first total synthesis of leuconodine D (**5**).

Our synthesis commenced with commercially available starting material **19** (Scheme 2), which can be readily synthesized in one step from Fischer indole synthesis as well.<sup>22</sup> Compound **19** was advanced to allyl ketocarboxylate **20** via a Boc-protection,  $\alpha$ -carboxylation, and ethylation in excellent yield. Pd<sub>2</sub>(dba)<sub>3</sub>-catalyzed decarboxylative allylation<sup>23</sup> in the presence of the DPPE ligand followed by Boc-removal converted **20** to **21**.<sup>24</sup> The latter was transformed to azidoketone **14** smoothly via hydroboration/oxidation, mesylation, and S<sub>N</sub>2 azide replacement. With intermediate **14** in hand, we started to explore the proposed Witkop–Winterfeldt oxidative indole cleavage. After extensive investigations of various commonly used oxidative

conditions, we found that freshly purified *m*CPBA under anhydrous conditions successfully cleaved the indole ring.<sup>25</sup> The primary 9-membered lactam **15** underwent spontaneous transannular cyclization to provide tricyclic hemiaminal **16** as a 2/1 mixture of diastereomers. Compound **16** was not stable on silica gel, and the crude product after base wash was either used directly in the next step or purified quickly with flash chromatography. Upon treatment of crude **16** with PPh<sub>3</sub>, a Staudinger–aza-Wittig process proceeded smoothly to produce mersicarpine (**2**) as a single diastereomer in 43% yield from **14**. Presumably, the hemiaminal center epimerized under the reaction conditions to give the desired stereoisomer.

We then advanced compound **16** to lactone **23** by employing a Bestmann ketene lactonization in 83% yield. The primary cycloadducts were produced as ~2/1 diastereomers at C<sub>21</sub> and converged to **23** after purification on a silica gel flash column. Our original plan was to divergently convert **23** to melodinine E (**8**) and rhazinilam (**10**). We were hoping that, after reduction of the azide group of **23** to a primary amine, an intramolecular aminolysis of the lactone would take place to provide melodinine E (**8**) in one step. Upon selective reduction of the lactone group of **23** to a lactol, we were also hoping to develop a one-pot simultaneous double bond and azide reduction followed by Paal–Knorr pyrrole synthesis to synthesize rhazinilam (**10**) from **23** in two steps. In short, all of our attempts toward these two goals were not successful. Notably, when the azide group of **23** was reduced by Ph<sub>3</sub>P, compound **24** with an unprecedented structural skeleton was produced in good yield.

We then converted azide **16** to acetamide **25** via catalytic hydrogenation and in situ amide formation. The latter upon acid treatment cyclized to give compound **18**, Zhu's intermediate for their leuconolam-leuconoxine terpene indole alkaloid syntheses, in 30% yield over three steps from **14**. Interestingly, when we followed Zhu's procedure to synthesize leuconodine B (cf. **18** → **4**), the NMR spectra of our synthetic leuconodine B (**4**) do not match completely with those reported by Zhu et al.,<sup>15</sup> but match those reported by Tokuyama et al. (see the Supporting Information for details).<sup>5c</sup> Zhu et al. obtained a crystal structure of **4** to support their structure. We were able to obtain a crystal structure of **4** to unambiguously confirm our structure assignment as well.<sup>26</sup> We then converted leuconodine B (**4**) to melodinine E (**8**) via a formal dehydration process, then to leuconoxine (**7**) via catalytic hydrogenation. In order to convert the latter to leuconodine D (**5**), a chemoselective reduction of the five-membered tertiary lactam in the presence of the six-membered tertiary lactam was needed. Reducing reagents such as DIBAL-H selectively reduced the six-membered lactam presumably due to the electron-withdrawing and conjugative effect of the aromatic ring on the six-membered lactam as well as the stereoelectronic effect, which makes it more susceptible to hydride reduction. After extensive investigation, we were able to effectively reduce the five-membered lactam by treating **7** with Meerwein's salt (Me<sub>3</sub>OPBF<sub>4</sub>) to probably form a methylated amidinium intermediate that was then reduced by sodium cyanoborohydride in one pot to complete the first total synthesis of leuconodine D (**5**).<sup>27</sup> The success of this chemoselective process presumably relies on the relatively more nucleophilic nature of the five-membered lactam vs the six-membered lactam of **7** in the presence of Meerwein's methylating reagent. Additionally, we were able to rearrange melodinine E (**8**) to leuconolam (**9**) following Zhu's acid treatment procedure. To convert leuconolam (**9**) to rhazinilam (**10**), which contains a strained nine-membered lactam ring incorporating a biaryl





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