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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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 tuning 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. Among them, the terpene indole alkaloids (TIAs) are one of the most important families, from which drug molecules such as vincristine, vincristine, yohimbine, ajmalicine, ajmaline, quinine, and camptothecin have been identified.2 Biosynthetically, the TIAs are produced from the combination of tryptamine and secologandin.3 Following structural rearrangement of the resulting strictosidine, several major TIA subfamilies are produced including the aspidosperma, iboga, corynanthe, ajmaline, and quinoline subfamily. Monoterpene indole alkaloids with novel structural skeletons were isolated as well such as mersicarpine (2, Scheme 1A),4,15 leuconodines (3−6),5,15 leuconoxine (7),6,5c,15 melodinine E (8),7,5c,15 leuconolam (9),8 rhazinilam (10),9,8b rhazinal (11),10,8b,9k,1 meloscine (12),11,9s,12 and meloscline (13).12 Biologically, leuconodine E showed moderate activity in reversing multidrug resistance in vincristine-resistant KB cells, and rhazinilam was identified to interfere with tubulin polymerization.13 Biosynthetically (Scheme 1B), these TIA members are proposed to be derived from the aspidosperma subfamily such as aspidospermidine (1).14 Cleavage of the C3−C7 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 N1 and C21 would provide skeleton C, which is the core structure of 3−8. Additional N-migration from C21 to C5 followed by fragmentation would produce skeleton E (cf. C → D → E), the carbon skeleton of mersicarpine (2). On the other hand, C2−C16 bond formation from B would give the meloscin skeleton F. C7 migration from C2 to C16 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.4−12 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 9.15

Our interest16 in developing functional group pairing strategies17 for divergent synthesis18 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 C4−C7 bond of compound 14 would give nine-membered lactam 15.19 Transannular cyclization of N1 and C21 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,20 a Bestmann ketene lactonization,21 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), melodidine E (8), leuconolam (9), and rhazinilam (10), an unnatural analogue with an unprecedented
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.\textsuperscript{22} Compound 19 was advanced to allyl ketocarboxylate 20 via a Boc-protection, α-carboxylation, and ethylation in excellent yield. Pd\textsubscript{2}(dba)\textsubscript{3}, catalyzed decarboxylative allylation\textsuperscript{23} in the presence of the DPPE ligand followed by Boc-removal converted latter was transformed to azidoketone 14. 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 mCPBA under anhydrous conditions successfully cleaved the indole ring.\textsuperscript{24} 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\textsubscript{3}, 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\textsubscript{21} 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\textsubscript{3}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.\textsuperscript{15} but match those reported by Tokuyama et al. (see the Supporting Information for details).\textsuperscript{25} 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.\textsuperscript{26} 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 reduce the six-membered lactam presum-ably 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\textsubscript{3}Al), to probably form a methylated amidinium intermediate that was then reduced by sodium cyano-borohydride in one pot to complete the first total synthesis of leuconodine D (5).\textsuperscript{27} The success of this chemo-selective 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 structural skeleton (24), and the first total synthesis of leuconodine D (5).

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\textsubscript{3}, 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.
moiety, a chemoselective reduction of the 5-hydroxy-pyrrolone of 9 was needed. After extensive investigation, we developed the first direct conversion of leuconolam (9) to rhazinilam (10) in 74% yield in an atropselective manner by DIBAL-H reduction. Notably, Gaunt recently developed an elegant three-step procedure to convert rhazinilam (10) to aspidospermidine (1). In summary, we have developed efficient and divergent total syntheses of seven monoterpene indole alkaloids. The syntheses feature a Witkop–Winterfeldt oxidative indole cleavage followed by a transannular cyclization to provide pivotal intermediate 16, which was then advanced to three key skeletons 2, 23, and 18 by tuning the functional groups of 16 into a Staudinger–aza-Wittig reaction, a Bestmann ketene lactonization, and an amide synthesis followed by aminal formation, respectively. Compound 18 served as a platform for the total synthesis of leuconodine B (4), melodinine E (8), leuconoxine (7), leuconolam (9), and rhazinilam (10) and the first total synthesis of leuconodine D (5). Closely related unnatural analog 24 with a novel structural skeleton was synthesized as well. This concise and flexible synthetic route provides new insights in the potential biosynthesis of these terpene indole alkaloids and offers opportunities to create analogues and focused libraries based on them for anticancer drug discovery.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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