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Unified Enantioselective Total Syntheses of (–)-Scholarisine G, (+)-Melodinine E, (–)-Leuconoxine and (–)-Mersicarpine

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ABSTRACT: A unified strategy enabled the enantioselective syntheses of (–)-scholarisine G, (+)-melodinine E, (–)-leuconoxine and (–)-mersicarpine from a common 2-alkylated indole intermediate bearing an all-carbon quaternary stereogenic center. The Smith-modified Madelung indole synthesis was used to couple simple *o*-toluidine with a chiral lactone (+)-8, incorporating the key elements for further cyclizations. The lactone (+)-8 was prepared via a palladium-catalyzed intermolecular asymmetric allylic alkylation. The unified and protecting-group-free reaction sequences allowed the synthesis of these alkaloids in a maximum of 10 steps and high efficiency.

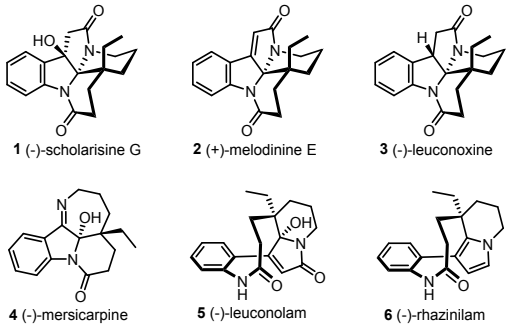

Fig. 1 The leuconolam-leuconoxine-mersicarpine group of alkaloids

The leuconolam-leuconoxine-mersicarpine triads are structurally complex and biologically interesting Aspido-sperma-derived monoterpene indole alkaloids (Fig 1).[1] Biosynthetically, these natural products share the same biogenetic origin from vincadifformine,[2] but feature intriguingly different ring connectivities. (–)-Scholarisine G (**1**),[3a,e] (+)-melodinine E (**2**)[3b] and (–)-leuconoxine (**3**)[3c-e] are pentacyclic alkaloids comprising an interesting [5.5.6.6]diazafenestrane core[4] with two or three contiguous quaternary stereogenic centers. (–)-Mersicarpine (4),[3f] however, have a fused tetracyclic 6/5/6/7 ring system characterized by an unusual tetrahydro-2*H*-azepine ring and a hemiaminal motif. The structural complexity, along with the intriguing bioactivities have rendered these alkaloids popular targets in total synthesis.[5-8] Specifically, the biosynthetic interrelationship of these compounds has inspired several unified synthetic strategies towards their synthesis.[6i,7f,8] Nevertheless, only a handful of enantioselective total synthesis has been reported.[7,8]

The intrinsic challenge to fulfil an enantioselective total synthesis lies on the construction of the all-carbon quaternary stereogenic carbon center.[6,9] In 2010, Fukuyama and co-workers reported the first total synthesis of (–)-mersicarpine (**4**).[7a] The key chiral intermediate ketoester (**B**) was prepared via an asymmetric Michael addition. Upon 7-step synthetic manipulations including the Eschenmoser-Tanabe fragmentation, Sonogashira cross-coupling reaction and gold-catalyzed cyclization, a 2-substituted indole (**C**) with a chiral quaternary carbon center was assembled, which was further elaborated to the final product. Intriguingly, in an effort to synthesize (–)-rhazinal, Luo observed an unexpected aziridination/rearrangement/oxidation tandem reaction leading to the total synthesis of (–)-mersicarpine (**4**) based on a similar alkenylated indole intermediate (**D**).[7d] Starting from the same chiral intermediate (**B**), Tokuyama and co-workers accomplished a concise total synthesis of (–)-mersicarpine via the key Fischer indole synthesis and DIBAL-H-mediated reductive ring-expansion reaction.[7b,7c] In 2013, Zhu and co-workers disclosed an enantioselective total synthesis of leuconolam-leuconoxine-mersicarpine group monoterpene indole alkaloids[8] based on an elegantly integrated oxidation/reduction/cyclization (*i*ORC) process.[10] The palladium-catalyzed enantioselective decarboxylative allylation was utilized to construct the chiral center. The same strategy was utilized by Liang and Stoltz by employing an optically active allylated lactone (**8**),[7f] prepared from an intramolecular

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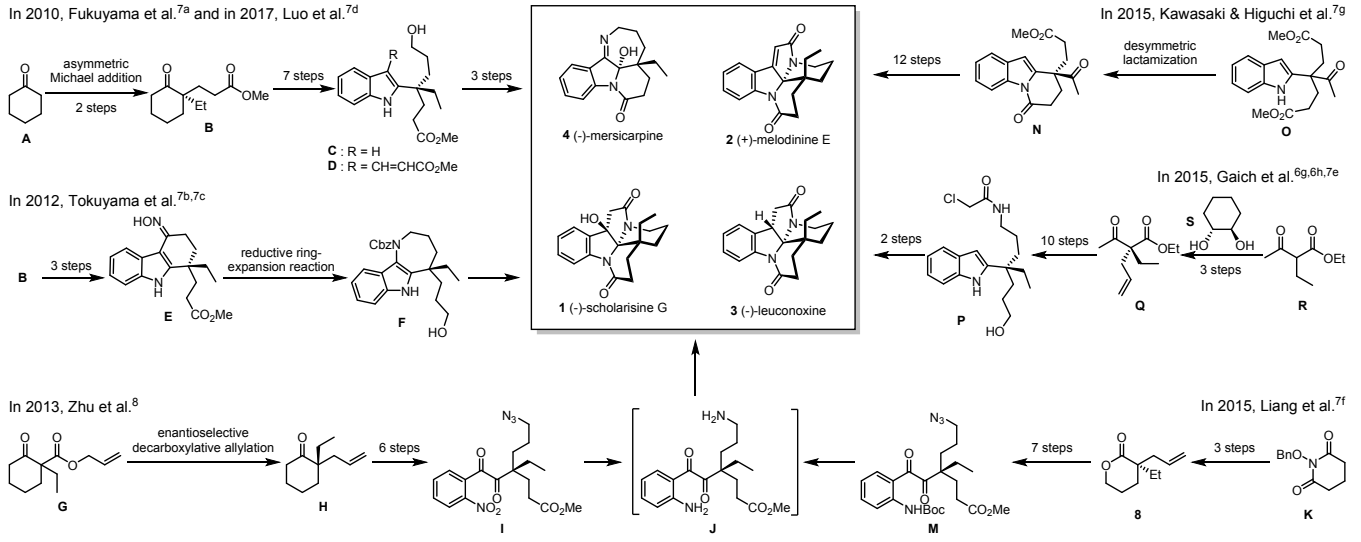
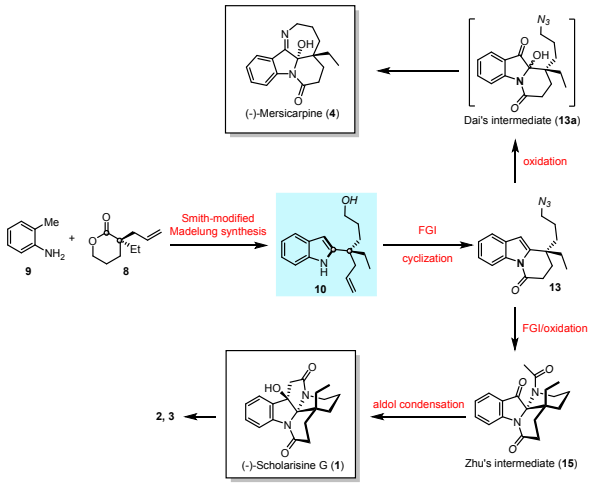
palladium-catalyzed asymmetric decarboxylative allylic alkylation of *N*-benzyloxy cyclic imide (**K**),[11] as key intermediate.



Scheme 1. Reported Enantioselective Total Syntheses of the Leuconolam-leuconoxine-mersicarpine Group Alkaloids

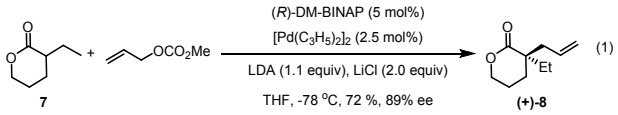
In another vein from Kawasakivia and Higuchi, the phosphoric acid-catalyzed desymmetric lactamization of a prochiral indole-substituted diester (**O**) provided the key enantio-merically enriched Kerr's intermediate with moderate ee 74%.[7g] In 2015, Gaich realized an enantioselective total synthesis of (–)-leuconoxine (**3**) by employing a photoinduced domino macrocyclization/transannular cyclization involving the Witkop cyclization.[6g,6h,7e] The optically active precursor (**P**) was obtained via the diastereoselective alkylation of ethyl 2-ethylacetoacetate (**R**) using chiral 1,2-diol (**S**) as an acetal chiral auxiliary.



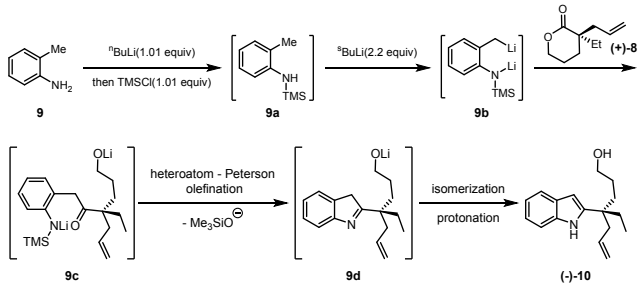
Scheme 2. Proposed Synthetic Strategy

The notable feature of Smith-modified Madelung indole synthesis[12] in the construction of 2-quantenary carbon sub-stituted indole inspired us to explore a novel enantioselective synthesis of leuconolam-leuconoxine-mersicarpine alkaloids starting from simple *o*-toluidine (**9**) and chiral lactone (**8**) (Scheme 2). The latter is commercially available and could be prepared via a palladium-catalyzed intermolecular asymmetric allylation developed by Hou.[13] The Smith-modified Madelung indole synthesis would provide a pivotal indole derivative with the chiral center being installed. The hydroxyl and vinyl functionality in **10** serve as valuable handles for further transformation. Therefore, upon proper functional group manipulation, lactam (**13**) is expected to be obtained. This species could be further elaborated to Zhu[8] and Dai's[6i] intermediates via oxidation of the indole motif,[6a,14] paving the way for (–)-scholarisine G (**1**) and (–)-mersicarpine (**4**) synthesis, respectively.

Our synthesis commenced with the preparation of the allylated lactone (+)-**8** starting from 3-ethyltetrahydro-2*H*-pyran-2-one and allyl methyl carbonate (**7**). In the presence of palladium catalyst and (*R*)-DM-BINAP ligand as developed by Hou,[13] (+)-(**8**) was obtained in 72% yield and 89% ee (Equation 1).



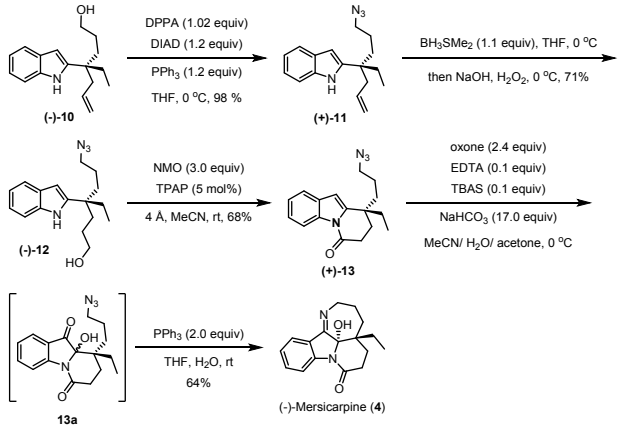
The key Smith-modified Madelung indole synthesis was started with the preparation of *N*-silylated *o*-toluidine (**9a**) by reacting *o*-toluidine (**9**) with stoichiometric amount of *n*-butyllithium and followed by quenching with chlorotrimethylsilane (Scheme 3). Without isolation, this intermediate was exposed to 2.2 equivalents of *sec*-butyllithium solution at low temperature to form a reactive lithium dianion (**9b**). Upon slow addition of lactone (+)-**8**, a cascade acylation/heteroatom Peterson olefination/isomerization proceeded smoothly to produce the 2-quantenary carbon substituted indole (–)-**10** in an overall 85% yield.



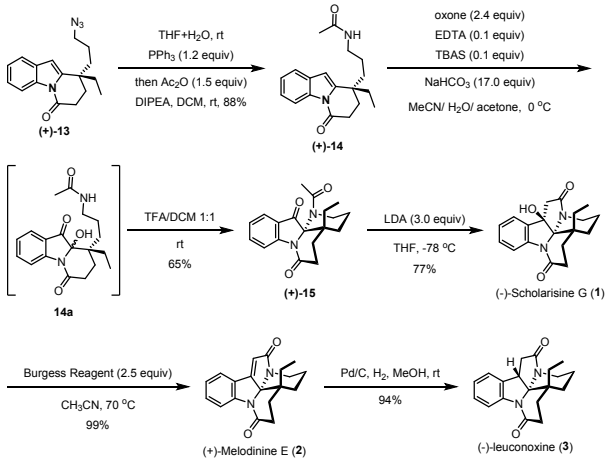
Scheme 3. Smith-modified Madelung Synthesis

The hydroxyl group in indole (–)-**10** was then replaced by azido in good yield via a Mitsunobu reaction in the presence of diisopropyl azodiformate (DIAD), triphenylphosphine and diphenylphosphonic azide (DPPA) (Scheme 4). The maintaining of low temperature (0 °C) is crucial for this step as a higher temperature (room temperature) led to significant amount of intramolecular nitrogen alkylation product. Following a hydroboration/oxidation of the C=C bond, the azidoindole (+)-**11** was converted to (–)-**12** in good efficiency (71% yield). Exposure of (–)-**12** to Ley oxidation[15] (TPAP and NMO, at rt) resulted in an intramolecular *N*-acylation reaction to afford *N*-acyl indole (+)-**13** in 68% yield. With (+)-**13** in hand, we next explored the synthesis of (**–**)-mersicarpine (**4**). Previous studies indicated that 2-substituted indole could be easily oxidized with various oxidants to form a keto hemiaminal structure.[14] Indeed, subjection of (+)-**13** to Kerr's conditions[6a] (oxone, acetone) afforded the desired keto hemiaminal (**13a**). Upon the in-situ treatment with PPh_3, **13a** underwent Staudinger-aza-Wittig cyclization to give (-)-Mersicarpine (**4**) in 64% yield over two steps. It should be noted the same intermediate **13a** has been obtained in Dai's (±)-mersicarpine synthesis via a Witkop-Winterfeldt oxidative cleavage of an advanced indole structure.

The azide intermediate (+)-**13** could also be converted to leuconoxine family alkaloids (Scheme 5). Thus, (+)-**13** was first reduced with triphenylphosphine and then acetylated by a follow-up treatment with acetic anhydride to give acetamide (+)-**14**. Under similar indole oxidation conditions with oxone as described above, the keto hemiaminal **14a** was produced. Without isolation, **14a** was converted under acidic conditions to Zhu's intermediate (+)-**15** for their leuconolam-leuconoxine indole alkaloid syntheses in 65% yield over two steps. An LDA-promoted intramolecular aldol cyclization provided leuconoxine in a good yield of 77%. Previously, mesylation of the tertiary hydroxyl group in (**—**)-scholarisine G (**1**) followed by base-promoted elimination was used to prepare (+)-melodinine E (**2**). We found that higher efficiency could be obtained when treating (**—**)-scholarisine G (**1**) with Burgess reagent (2.5 equiv) in acetonitrile at 70 °C. Finally, hydrogenation of (+)-melodinine E (**2**) delivered another member (**—**)-leuconoxine (**3**) in 94% yield. The spectroscopic data of (+)-melodinine E (**2**) and (**—**)-leuconoxine (**3**) (^{1}H and ^{13}C NMR) matched well those reported in the literature. Interestingly, the NMR spectra of our synthetic (**—**)-scholarisine G (1) matches with that of Zhu,[8a] but shows discrepancies with the isolated samples[3a,e] and some other synthetic samples.[6i,e,7f] We assumed the differences can be a result of different quality, therefore different acidity of $CDCl_3$ used for NMR studies.[16]



Scheme 4. Syntheses of (-)-Mersicarpine



Scheme 5. Synthesis of (–)-Scholarisine G, (+)-Melodinine E and (–)-Leuconoxine

In conclusion, we have accomplished divergent enantioselective syntheses of four monoterpene indole alkaloids: (**–**)-scholarisine G (**1**), (+)-melodinine E (**2**), (**–**)-leuconoxine (**3**) and (**–**)-mersicarpine (**4**). The syntheses feature a palladium-catalyzed intermolecular asymmetric allylation to construct a optically active lactone, a Smith-modified Madelung indole synthesis to quickly forge a quaternary carbon-substituted indole, and an oxone-mediated indole oxidation to form Dai' and Zhu's intermediates, respectively. Efforts were also attempted to improve the synthetic efficiency of transforming Zhu's intermediates (**15**) to the leuconoxine group alkaloid. No protecting group is needed for the whole processes, al-lowing concise syntheses of the title natural products in a maximum of 10 steps with high efficiency.

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Conflicts of interest

There are no conflicts to declare.

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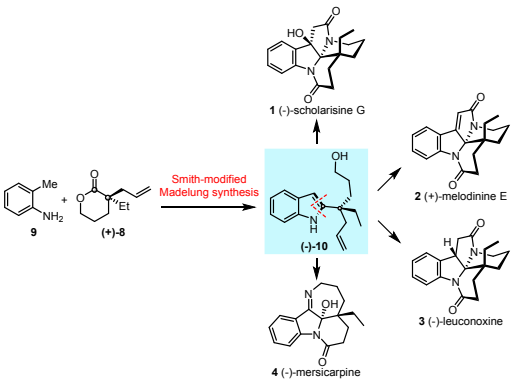

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