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Unified enantioselective total syntheses of (−)-scholarisine G, (+)-melodinine E, (−)-leuconoxine and (−)-mersicarpine†

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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 chiral lactone (+)-8, incorporating the key elements for further cyclizations. 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 with high efficiency.

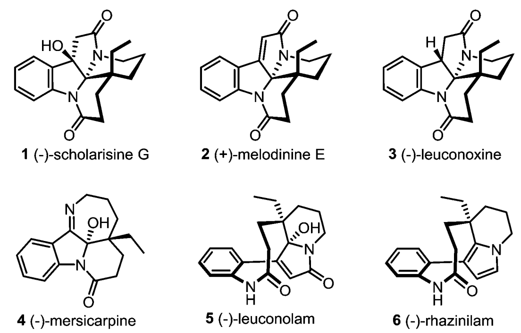

Fig. 1 The leuconolam–leuconoxine–mersicarpine group of alkaloids.

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, has 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 has 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.[6j,7f,8] Nevertheless, only a handful of enantioselective total syntheses have been reported.[7,8]

The intrinsic challenge to fulfil an enantioselective total synthesis lies in 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) (Scheme 1).[7a] The key chiral intermediate ketoester (**B**) was prepared *via* asymmetric Michael addition. Upon 7-step synthetic manipulations including 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,c] 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 (iORC) 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 intramolecular palladium-catalyzed asymmetric decarboxylative allylic alkylation of *N*-benzyloxy cyclic imide (**K**),[11] as a key intermediate.

In another vein from Kawasaki and Higuchi, the phosphoric acid-catalyzed desymmetric lactamization of a prochiral indole-substituted diester (**O**) provided the key enantiomerically

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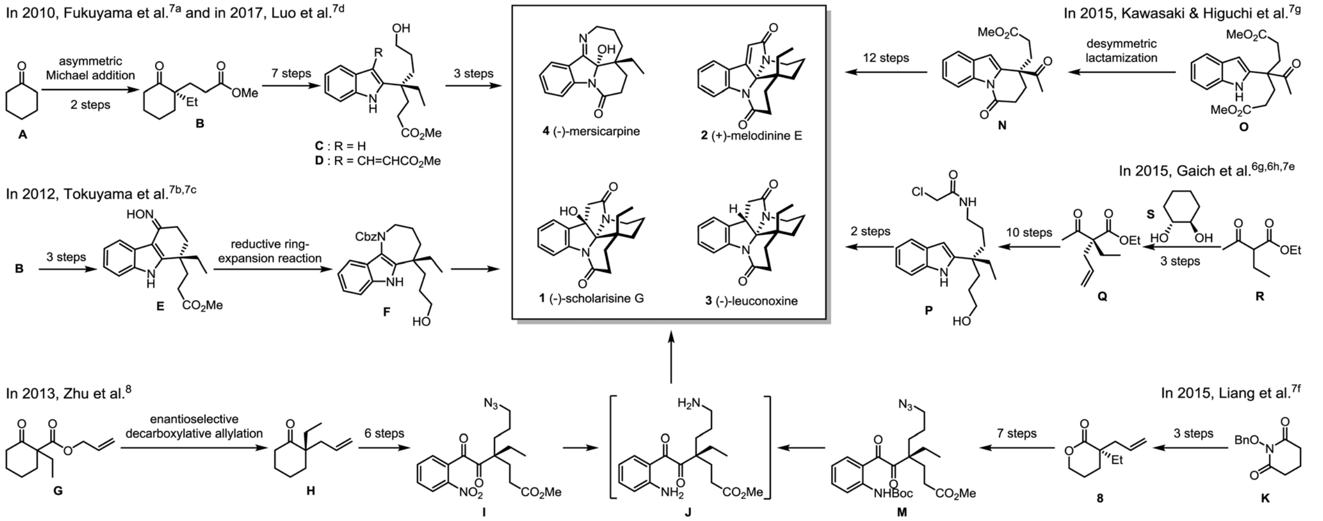
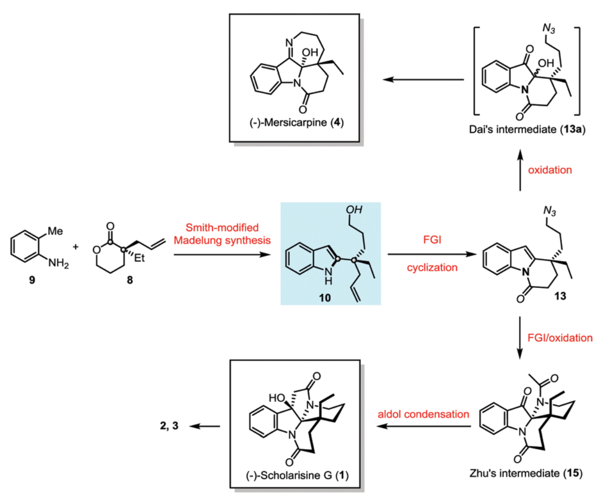


Scheme 1 Reported enantioselective total syntheses of the leuconolam–leuconoxine–mersicarpine group alkaloids.

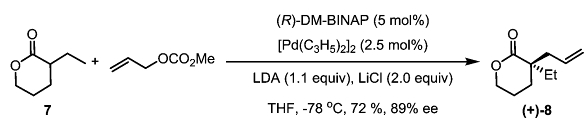
enriched Kerr's intermediate with moderate ee of 74%.[7g] In 2015, Gaich realized enantioselective total synthesis of (−)-leuconoxine (**3**) by employing photoinduced domino macrocyclization/transannular cyclization involving Witkop cyclization.[6g,h,7e] The optically active precursor (**P**) was obtained *via* the diastereoselective alkylation of ethyl 2-ethylacetoacetate (**R**) using chiral 1,2-diol (**S**) as an acetal chiral auxiliary.

The notable feature of Smith-modified Madelung indole synthesis[12] in the construction of 2-quaternary carbon substituted indole inspired us to explore 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* 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[6j] intermediates *via* oxidation of the indole motif,[6a,14] paving the way for (−)-scholarisine G (**1**) and (−)-mersicarpine (**4**) synthesis, respectively.



Scheme 2 Proposed synthetic strategy.

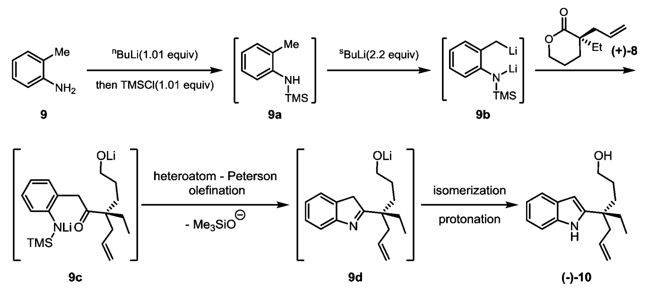
Our synthesis commenced with the preparation of the allylated lactone (+)-**8** starting from 3-ethyltetrahydro-2*H*-pyran-2-one and allyl methyl carbonate (**7**). In the presence of the palladium catalyst and (*R*)-DM-BINAP ligand as developed by Hou,[13] (+)-(**8**) was obtained in 72% yield and 89%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



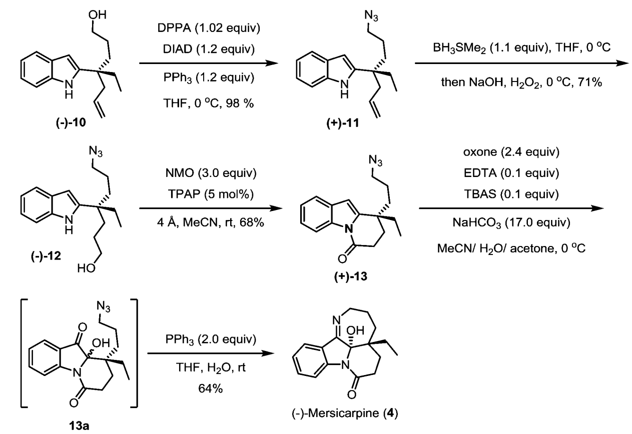
(1)

The key Smith-modified Madelung indole synthesis was started with the preparation of *N*-silylated *o*-toluidine (**9a**) *via* the reaction of *o*-toluidine (**9**) with a 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**, cascade acylation/heteroatom Peterson olefination/isomerization proceeded smoothly to produce 2-quaternary carbon substituted indole (−)-**10** in an overall 85% yield.

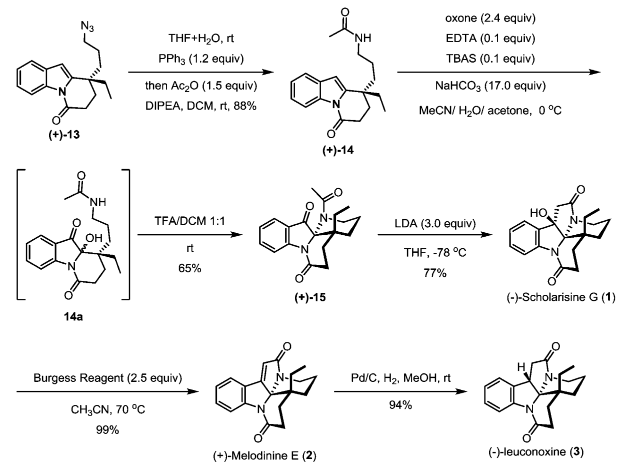
The hydroxyl group in indole (−)-**10** was then replaced by azido in a good yield *via* a Mitsunobu reaction in the presence of diisopropyl azodiformate (DIAD), triphenylphosphine and diphenylphosphonic azide (DPPA) (Scheme 4). The maintenance of low temperature (0 °C) is crucial for this step as a higher temperature (room temperature) led to a significant amount of the intramolecular nitrogen alkylation product. Following hydroboration/oxidation of the C=C bond, azidoindole (+)-**11** was converted to (−)-**12** in good efficiency (a 71% yield). Exposure of



Scheme 3 Smith-modified Madelung synthesis.



Scheme 4 Syntheses of (−)-mersicarpine.



Scheme 5 Synthesis of (−)-scholarisine G, (+)-melodinine E and (−)-leuconoxine.

(−)-**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 easily be 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 *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 that 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 using 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, 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% yields over two steps. 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 a 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 with those reported in the literature. Interestingly, the NMR spectra of our synthetic (−)-scholarisine G (**1**) match with that of Zhu,[8a] but show discrepancies with the isolated samples[3a,e] and some other synthetic samples.[6e,j,7f] We assume that the differences are a result of different quality, and therefore different acidity, of $CDCl_3$ used for the NMR studies.[16]

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 an optically active lactone, 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 process, allowing 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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