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Enantioselective Total Syntheses of Leuconolam–Leuconoxine–Mersicarpine Group Monoterpene Indole Alkaloids

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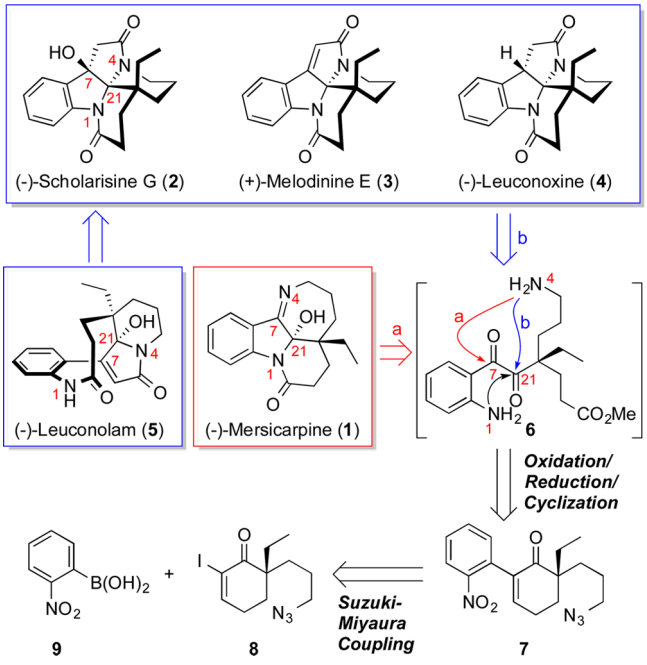
Supporting Information

ABSTRACT: A unified strategy allowing enantioselective total syntheses of (−)-mersicarpine, (−)-scholarisine G, (+)-melodinine E, (−)-leuconoxine, and (−)-leuconolam from a common cyclohexenone derivative was reported. The Suzuki–Miyaura reaction was used to couple two simple fragments incorporating the key elements for total synthesis, and unprecedented oxidation/reduction/cyclization processes were developed that converted the substituted cyclohexenone to either a mersicarpine or leuconoxine skeleton. In a reverse biomimetic synthesis fashion, (+)-melodinine E was converted to (−)-leuconolam under acidic conditions.

The class of monoterpene indole alkaloids, comprising currently over 2000 members with broad skeleton diversity and important bioactivities, has attracted the attention of synthetic chemists for over a century.[1] Specifically, the leuconolam–leuconoxine–mersicarpine triad is a subfamily of *Aspidosperma* alkaloids. Although sharing the same biogenetic origin from vincadifformine, these polycyclic alkaloids have completely different ring connectivities.[1a] (−)-Mersicarpine (**1**), having a fused 6/5/6/7 ring system centered around a hemiaminal carbon, was isolated from the *Kopsia* genus in 2004 by Kam.[2] It is characterized by an unprecedented tetrahydro-2*H*-azepine ring system, together with a contiguously arranged imine, hemiaminal, and a quaternary carbon motif. Three total syntheses were achieved in the groups of Kerr,[3a] Fukuyama,[3b] and Tokuyama,[3c,d] and two formal syntheses were reported from the groups of Zard[4a] and Han.[4b] (−)-Scholarisine G (also named as leuconodine B) (**2**),[5a,b] recently isolated from the bark of *Alstonia scholaris* by Luo, has a pentacyclic structure with three contiguous quaternary stereogenic centers and a labile aminal function. Related natural products included (+)-melodinine E (**3**)[5c] and (−)-leuconoxine (**4**), the latter being isolated by Abe and Yamauchi in 1994 from *Leuconotis eugenifolius*.[5d] It is interesting to note that similar structures were obtained before the isolation of this class of natural products, either by oxidative rearrangement of vincadifformine (e.g., oxymetavincadifformine)[6a,b] or by acid treatment of leuconolam (e.g., 6-chlorodiazaspiroleuconolam).[6c-6d] However, no total synthesis of these natural products has been reported until now. Isolated by Goh from *Leuconotis* plants *L. griffithii*, (−)-leuconolam (**5**)[7] is a tetracyclic alkaloid containing an unusual nine-membered lactam and a 1,5-dihydro-2*H*-pyrrol-2-one unit. Two total syntheses were reported from the groups of Banwell[8a] and Hoye,[8b] respectively.

In the context of our continuous interest in the construction of indole rings at the late stage of total synthesis,[9] we devised a unified strategy to reach different skeletons of aforementioned alkaloids from the same intermediate. As shown in Scheme 1, both leuconoxine and mersicarpine skeletons were thought to be elaborated from the same functionalized amino diketone **6** by controlling the chemoselectivity of the cyclization mode. Bis-imine formation by selective condensation of N1 to C21 and N4 to C7 would lead to the mersicarpine skeleton, while addition of both N1 and N4 onto C21 would afford the spiroaminal motif found in the leuconoxine skeleton.[10] Amino diketone **6**, unstable due to its multiple reactivity-matched functional groups, could be generated in situ from substituted cyclohexenone **7**, which could in turn be prepared by the

Scheme 1. Unified Strategy for the Total Syntheses of Leuconolam–Leuconoxine–Mersicarpine Group Monoterpene Indole Alkaloids



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Suzuki–Miyaura coupling reaction between enantiomerically enriched vinyl iodide **8** and 2-nitrophenyl boronic acid (**9**). By utilizing the acid lability of the aminal function, we planned to prepare leuconolam (**5**) by acid-promoted fragmentation of melodinine E (**3**), a reverse process of the biosynthesis pathway.[11]

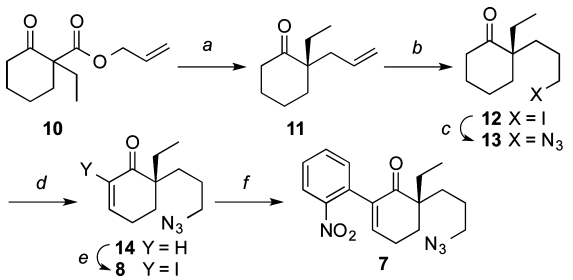
Our total synthesis commenced with palladium-catalyzed enantioselective decarboxylative allylation of β-ketoester **10** (Scheme 2). Using conditions developed by Stoltz and co-workers,[12] **10** was converted to the known (*S*)-2-allyl-2-ethyl cyclohexanone (**11**) in 90% yield with 92% *ee*. A hydroboration–iodination sequence[13] converted **11** to alkyl iodide **12** that was subsequently transformed to alkyl azide **13** under standard conditions. Enone **14** could be obtained in 70% yield by treatment of **13** with an excess of IBX (6.0 equiv) in DMSO.[3b,14] Iodination of **14** afforded cleanly the vinyl iodide **8** in 95% yield, which underwent the Suzuki–Miyaura coupling with 2-nitrophenyl boronic acid (**9**) to give the functionalized cyclohexenone **7** in 75% yield.[15]

With key intermediate **7** in hand, the stage was set for the construction of natural products by a planned skeleton rearrangement process. The total synthesis of (−)-mersicarpine is shown in Scheme 3. Ozonolysis of the enone **7** in CH_2Cl_2/MeOH buffered with $NaHCO_3$ at −78 °C, followed by addition of Ac_2O and Et_3N, afforded the diketone ester **15** in 92% overall yield.[16] After having surveyed different reducing agents, we found that hydrogenation of diketone **15** in the presence of Pd/C (3 mol % based on Pd) directly provided (−)-mersicarpine (**1**), albeit in only 23% yield. The major product was the unstable hexahydroazepino[3,2-*b*]indole **16** (50% yield). Being aware of the easy oxidation of the 3-aminoindoles,[3b−d,17] a one-pot protocol allowing the direct conversion of **15** to (−)-mersicarpine (**1**) was developed. Hydrogenation of diketone ester **15** in the presence of Pd/C (10 mol % based on Pd) gave **16**, which underwent lactamization to tetracycle **17** upon addition of potassium hydroxide. Purging the reaction mixture with argon followed by oxygen afforded presumably peroxide **18** which, upon addition of dimethyl sulfide, was reduced to (−)-mersicarpine (**1**) in 75% overall yield. We stress that workup was not needed in the conversion of **15** to (−)-mersicarpine (**1**) and the entire transformation was realized in EtOH by sequential addition of reagents (KOH, oxygen, and then Me_2S).

The high synthetic efficiency observed in the conversion of **15** to (−)-mersicarpine (**1**) under such simple reaction conditions indicated that compound **15**, after release of two latent amino groups, was instructed to undergo the highly chemo- and regioselective cyclization. It is reasonable to assume that the C21 carbonyl is more reactive than the C7 carbonyl, the latter being a vinylogous amide.[18] Intramolecular nucleophilic attack of aniline onto C21 would lead to 3*H*-indol-3-one **19**, which could evolve in two directions. Condensation of primary amine to the C7 carbonyl group would produce bisimine **20** corresponding to the mersicarpine skeleton (*path a*, Scheme 4), while intramolecular nucleophilic addition of the primary amine (N4) to the imine would furnish spiroindolin-3-one **21** (*path b*, Scheme 4). Due to the reversibility of both steps, the reaction was presumably under thermodynamic control leading to a more stable compound **20** (*path a*), which was in situ reduced to indole **16**.

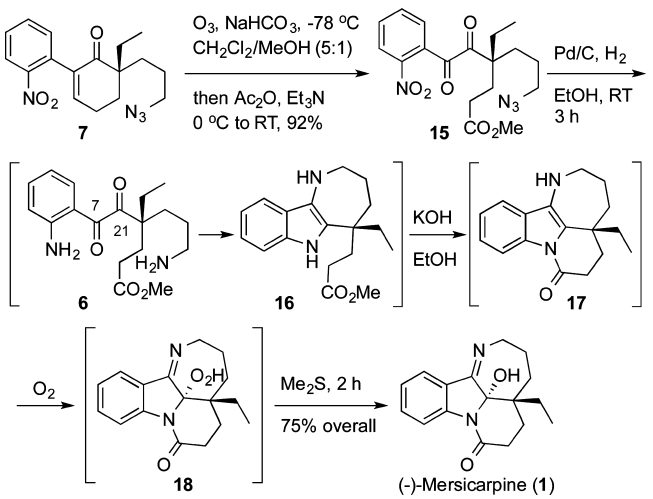
For the total synthesis of the leuconoxine skeleton from the same diamino diketone **6**, we need to orient the nucleophilic addition of N4 to the iminyl carbon C21 instead of the

Scheme 2. Synthesis of Substituted Cyclohexenone 7[a]

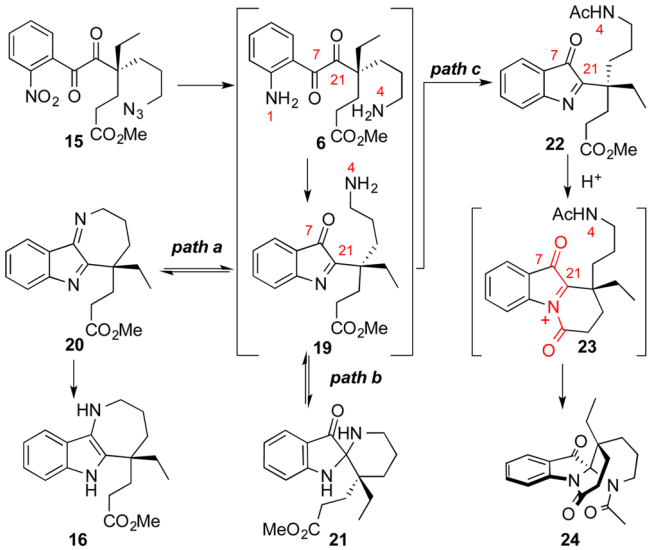


[a]Reagents and conditions: (a) $Pd_2(dba)_3$, (*S*)-*t*-BuPhox, THF, 25 °C, 90% yield, 92% ee; (b) disiamyl borane, THF, 0 °C to rt, then NaI, NaOAc, Chloramine-T, MeOH, H_2O, 80%; (c) NaN_3, DMF, rt, overnight, 92%; (d) IBX, DMSO, 80 °C, 12 h, 70%; (e) I_2, DMAP, CCl_4/Py (1:1), 95%; (f) 2-$NO_2C_6H_4B(OH)_2$ (**9**), $Pd_2(dba)_3$, JohnPhos, $Ba(OH)_2{\cdot}8H_2O$, THF, H_2O, 75%.

Scheme 3. Total Synthesis of (−)-Mersicarpine (1)



Scheme 4. Tuning the Cyclization Mode of Diamino Diketone Ester 6



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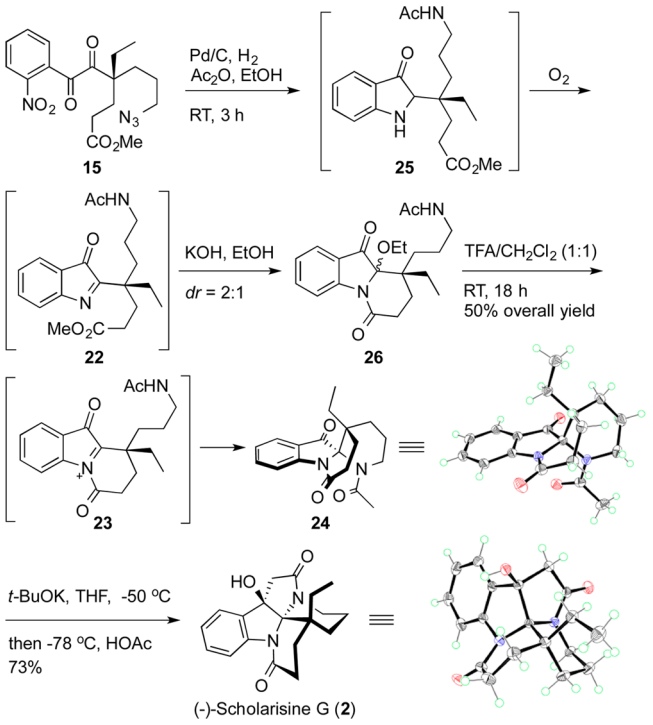
carbonyl carbon C7. Noting the higher nuclophilicity of the aliphatic primary amine (N4), we assumed that a chemoselective N4-acetylation under the hydrogenation conditions should be possible. In addition, it was envisioned that formation of a highly reactive, cyclic *N*-acyl iminium ion **23** could then undergo intramolecular attack by the acetamide to give aminal **24**, a compound presumed to be more thermodynamically stable than **21**.

Putting principle into practice, the total synthesis of (−)-scholarisine G (**2**) is accomplished as detailed in Scheme 5. Hydrogenation of diketone **15** in the presence of Pd/C and

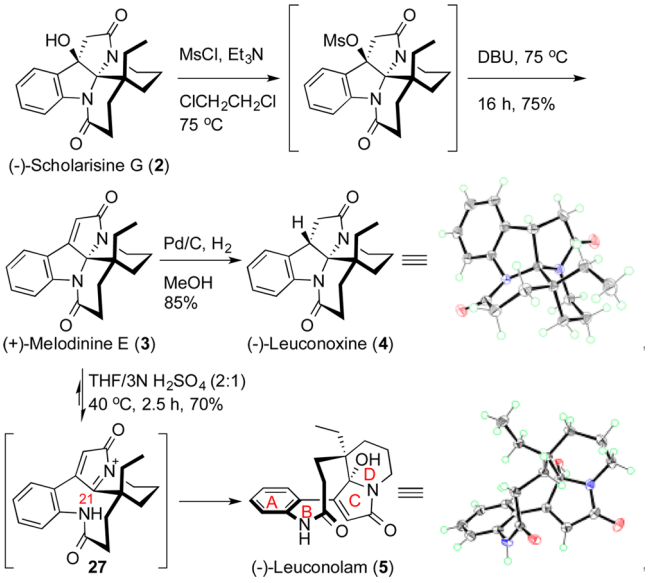
Scheme 5. Total Synthesis of (−)-Scholarisine G (2)



acetic anhydride (5.0 equiv) afforded indolin-3-one **25**. Under these conditions, the N4 was selectively acetylated and its condensation with C7 carbonyl was effectively inhibited. Without isolation, compound **25** was directly oxidized to the unstable indol-3-one **22** upon purging the reaction mixture with argon followed by oxygen. Addition of potassium hydroxide into the above reaction mixture afforded 2-ethoxyindoline-3-one **26** as a mixture of two diastereomers (dr = 2:1). The lack of diastereoselectivity in the hemiaminal formation is of no consequence since it will be converted to the *N*-acyliminium ion in the next step. To our delight, treatment of the crude mixture of **26** with TFA in CH_2Cl_2 afforded the desired tetracycle **24** as the only diastereomer whose structure was fully determined by X-ray analysis. The intramolecular nucleophilic addition of amide NH to the in situ generated *N*-acyliminium ion took place therefore from the side opposite to the neighboring ethyl group. It is interesting to note that both piperidine rings in **24** adopted the boat conformation in its solid state. An intramolecular aldolization of **24** will complete the synthesis of (−)-scholarisine G (**2**). This reaction was found to be quite sensitive to the choice of base, solvent, and quenching process. For example, using potassium ethoxide in ethanol resulted in the ring opening of the aminal to afford 2-ethoxyindoline-3-one **26**. After many trials, the optimum conditions found consisted of performing the reaction in THF at −50 °C in the presence of an excess amount of *t*-BuOK followed by quenching the reaction mixture with acetic acid at −78 °C. Under these conditions, (−)-scholarisine G (**2**) was isolated in 73% yield. It is worth noting that using an excess amount of *t*-BuOK (8.0 equiv) was crucial, as the desired product appeared only after addition of around 6 equiv of *t*-BuOK. Quenching the reaction with acetic acid at low temperature is also important, as significant degradation was observed when the reaction was quenched with H_2O, MeOH, or saturated aqueous NH_4Cl. There are small discrepancies in the ^1H NMR spectrum between our synthetic sample and natural (−)-scholarisine G (**2**),[5a,b] due probably to the presence of varying amounts of water. However, its structure was unequivocally confirmed by single crystal X-ray analysis of our synthetic sample. As a result, our synthesis also confirmed the absolute configuration of (−)-scholarisine G (**2**), previously assigned based on the biosynthetic hypothesis.

Conversion of (−)-scholarisine G (**2**) to other members of the leuconoxine group was straightforward (Scheme 6). *O*-

Scheme 6. Further Structure Diversification: From (−)-Scholarisine G (2) to (+)-Melodinine E (3), (−)-Leuconoxine (4), and (−)-Leuconolam (5)



Mesylation of the tertiary hydroxy group in (−)-scholarisine G (**2**) followed by DBU-promoted elimination afforded (+)-melodinine E (**3**) in 75% yield. Reduction of the double bond in (+)-melodinine E (**3**) by hydrogenation is highly diastereoselective furnishing (−)-leuconoxine (**4**) in 85% yield. The spectroscopic data of synthetic (+)-melodinine E (**3**)[5c] and (−)-leuconoxine (**4**)[5d,19] were identical to those reported in the literature. Furthermore, the structure of leuconoxine was confirmed by X-ray analysis.

(−)-Leuconolam (**5**) was proposed to be a biogenetic precursor of leuconoxine type alkaloids,[2] and the chemical conversion of **5** to melodinine derivatives in the presence of *conc* HCl has been reported.[6c,d] Reasoning that this conversion might be an equilibrium process going through an *N*-acyliminium ion intermediate **27**, we thought that it should be possible to drive the equilibrium toward the formation of leuconolam (**5**) by intermolecular addition of water to **27**.

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Experimentally, it was found that dissolving (+)-melodinine E (**3**) in acidic THF solution (THF−3N H_2SO_4 (v/v = 2/1)) at room temperature led to the rapid disappearance of **3** affording presumably the *N*-acyliminum ion **27**. However, only starting material was recovered upon workup indicating that the intermolecular addition of water to **27** might be a kinetically slow process at this temperature. Gratefully, by simply heating a solution of **3** in THF−3N H_2SO_4 (v/v = 2/1) at 40 °C for 2.5 h, the (−)-leuconolam (**5**) was produced cleanly in 70% isolated yield. The structure of our synthetic sample was confirmed by X-ray crystal analysis, confirming therefore the absolute configuration of this natural product. It is worth noting that the addition of water to C21 of the *N*-acyliminium took place from the same face occupied by the neighboring ethyl substituent placing therefore both the hydroxy and the ethyl groups in the convex face defined by the B−C−D ring. Additionally, only one atropisomer corresponding to the natural product was produced.

In conclusion, we developed a convergent and divergent approach to reach the structurally distinct leuconolam−leuconoxine−mersicarpine subfamily of *Aspidosperma* alkaloids. The Suzuki−Miyaura coupling of vinyl iodide **8** with 2-nitrophenyl boronic acid (**9**) afforded a functionalized cyclohexenone derivative **7** that was subsequently diversified into different natural products by controlled oxidation/reduction/polycyclization sequences. Key to the success of the structure diversification is the fine-tuning of the nucleophilicity of the primary amine (N4) and the electrophilicity of the C7 carbonyl vs C21 iminyl groups in the putative 3*H*-indol-3-one intermediate. This deceptively simple synthetic strategy allowed us to develop a protecting-group-free synthesis[20] of structurally complex and diverse alkaloids under operationally simple conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experiment procedures, spectroscopic data, copies of the ^1H and ^{13}C NMR spectra, and X-ray structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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