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Total Synthesis **Hot Paper**

Concise Total Syntheses of Leuconoxine-Type Alkaloids Enabled by Palladium/Norbornene-Catalyzed Pyrrole Difunctionalization

Xin Liu, Yun Zhou, Yu Meng, Qi Zhu, Renhe Li, and Guangbin Dong**

Dedicated to Professor Jieping Zhu on the occasion of his 60th birthday

Abstract: Concise total syntheses of five leuconoxine-type alkaloids, i.e., chloromelodinine, leuconodine A, leuconodine F, melodinine E, and leuconoxine, are achieved through a pyrrole-centered strategy. The approach features a newly developed palladium/norbornene-catalyzed pyrrole double C─H functionalization reaction to generate the core skeleton and a divergent oxidative dearomatization to complete the end game. In addition, no protecting group was employed, and the strategic use of a chloro substituent offers a number of advantages in these syntheses, which could have implications beyond this work. The discovery of an unusual chloro 1,2-migration reaction enabled the first total synthesis of chloromelodinine E. This work represents the shortest syntheses of these natural products to date with 10–11 total steps.

Monoterpene indole alkaloids (MIAs), a large class of structurally complex natural products with diverse biological activities, have received enormous attention as synthetic targets and therapeutic candidates.[1] In particular, leuconoxine-type alkaloids (**1**–**9**, Figure 1), a subfamily of *Aspidosperma* alkaloids isolated from several *Apocynaceae* species,[2–6] exhibit a unique pentacyclic skeleton together with a spiroaminal motif and an adjacent all-carbon quaternary center. The recent discovery of new leuconoxine alkaloid chloromelodinine E (**1**) in 2024[6] and its selective cytotoxicity toward human ovarian cancer cells indicates continued interest in this class of natural products.

In nature, biosynthesis of MIAs generally involves tryptophan and secologanin as precursors.[7] Inspired by the biosynthetic pathways, a number of total syntheses of leuconoxine alkaloids have been achieved,[8,9] and the strategies are almost all centered on constructing the indoline core or using indole-derived starting materials (Scheme 1a). For example, in 2013, Zhu and coworkers reported their pioneer efforts on synthesizing different members of this family (**2**–**7**).[10,11] Their synthesis features early installation of the C18 quaternary center, followed by formation of the indole scaffold, and an end game with the pyrrolidone construction via an Aldol condensation. Subsequently, several other groups, including Tokuyama,[12] Dai,[13] Gaich,[14] Kawasaki,[15] Liang/Stoltz,[16] Wang,[17] Beaudry,[18] and Han[19] disclosed distinct and elegant approaches to furnish the total syntheses of natural products **4**–**9**. Their approaches are also based on the "indoline first and pyrrolidine later" logic. In addition, all these syntheses except Zhu's work,[10,11] only targeted leuconoxine alkaloids **4**–**9**, and strategies to efficiently construct the fully substituted pyrrolidone in natural products **1**–**3** remain limited. Moreover, total synthesis of **1** has not been reported yet. Therefore, a concise and unified approach to prepare various leuconoxine-type alkaloids, particularly those with a fully substituted pyrrolidinone ring, would be highly desirable. Here, we describe our strategy for divergent total syntheses of chloromelodinine (**1**), leuconodine A (**2**), leuconodine F

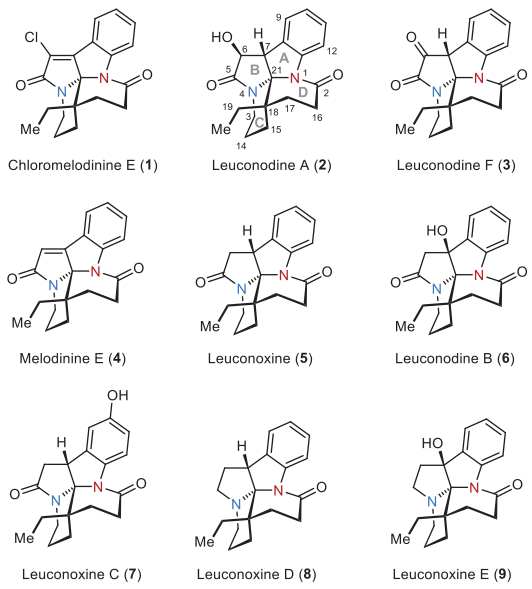

Figure 1. Selected leuconoxine-type alkaloids

[*] X. Liu, Y. Zhou, Y. Meng, Q. Zhu, R. Li, G. Dong
Department of Chemistry, University of Chicago, Chicago, Illinois 60637, USA
E-mail: rhlichem@gmail.com
gbdong@uchicago.edu

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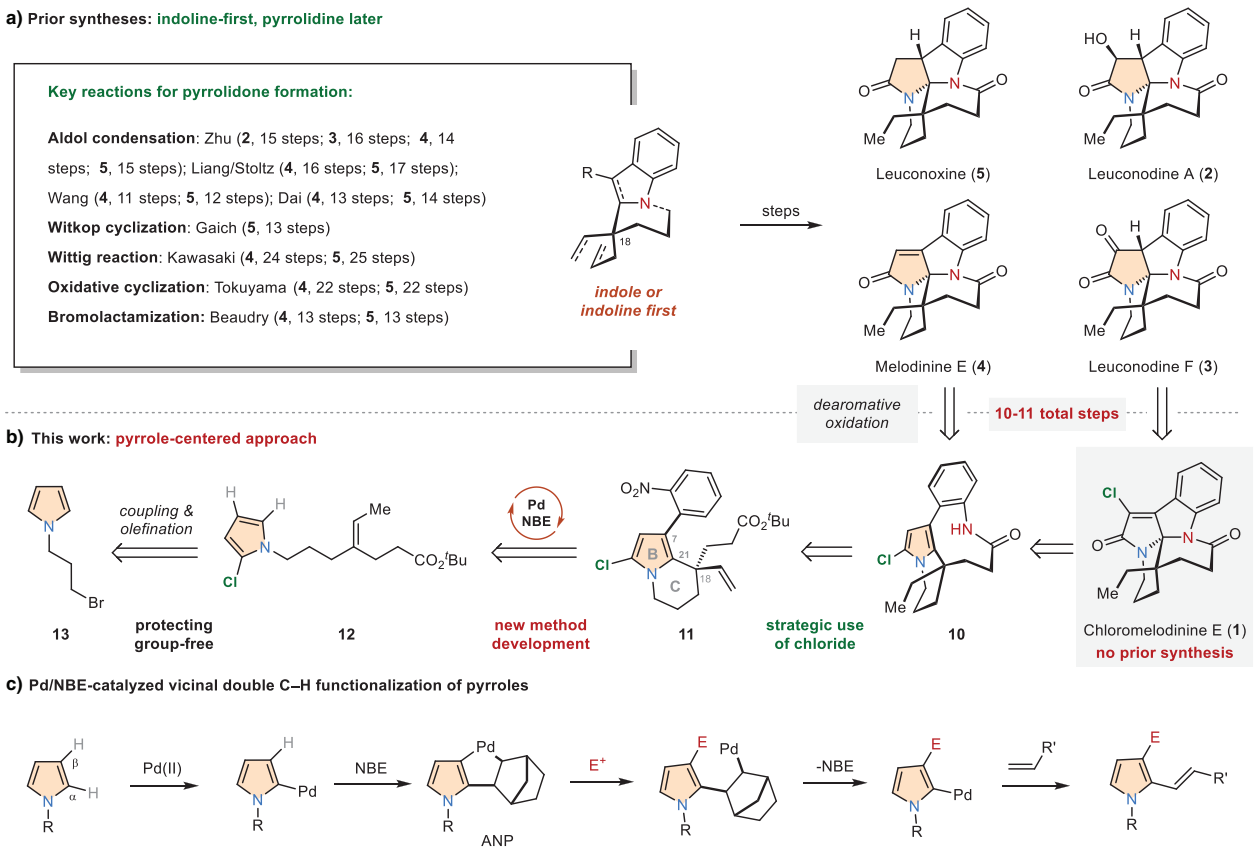


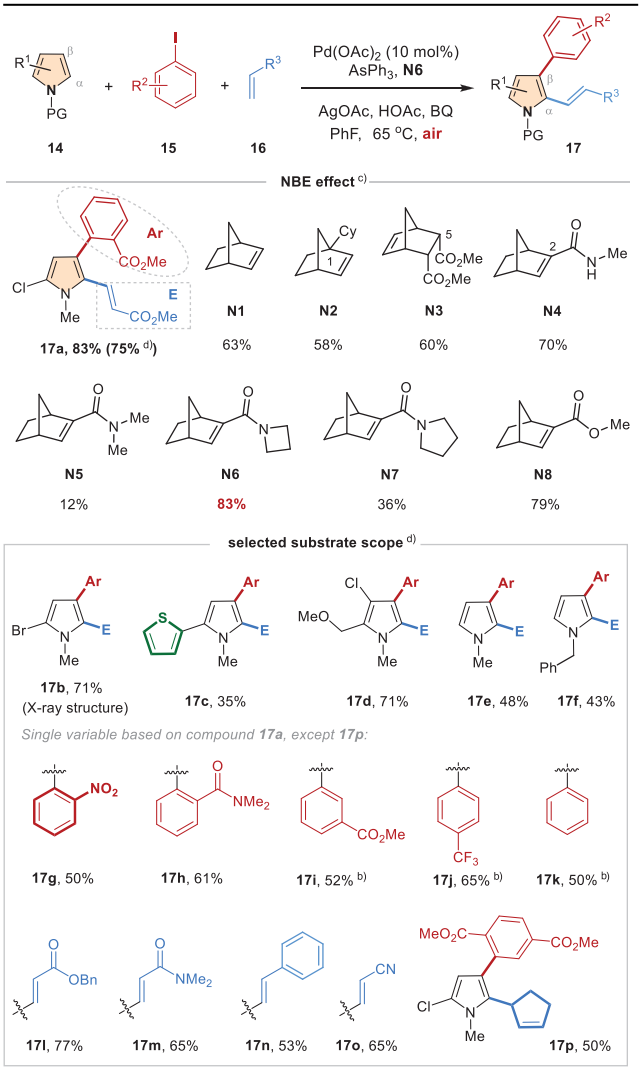
Scheme 1. Synthetic strategy for leuconoxine-type alkaloids. a) Prior synthetic strategies; b) This work is based on a pyrrole-centered approach; c) The proposed pathway for the Pd/NBE-catalyzed vicinal double C—H functionalization of pyrroles. E, electrophile.

(**3**), melodinine E (**4**), and leuconoxine (**5**), which is centered on efficient early construction of a poly-substituted pyrrole core structure using the palladium/norbornene (Pd/NBE) cooperative catalysis.[20–28]

Our proposed strategy is illustrated in Scheme 1b. We envisioned that dearomative transformations of a multi-substituted pyrrole could offer a rapid access to the complex pyrrolidinone B ring in leuconoxine alkaloids **1–3**. From the retrosynthetic viewpoint, leuconoxine alkaloids **1–5** can all be derived from common precursor **10**, which is a macrolactam that can be constructed from pyrrole-based B/C bicycle **11**. Although similar transannular cyclizations have been reported,[29,30] to the best of our knowledge, formation of the spiroaminal motif from a pyrrole precursor remains unexplored. The tetra-substituted pyrrole core in **11** could be rapidly accessed through developing a *new* double C—H functionalization method using the Pd/NBE cooperative catalysis. The precursor (**12**) could ultimately be synthesized from commercially available alkyl pyrrole **13**. Notably, the C5-chloro substituent in key intermediate **10** is strategically introduced for *multi-purposes*. First, the chloro substituent can enhance the efficiency in the Pd/NBE-catalyzed double C—H functionalization process (vide infra). Second, it can increase stability of the pyrrole intermediates throughout the syntheses. Third, it is expected to guide the site-selectivity during the late-stage oxidative dearomatization of the pyrrole, as there are two potential sites that can be oxidized. Fourth, the chlorine substitution can provide the desired oxidation state for the C5 carbon in the natural products, facilitating the generation of a carbonyl group. Lastly, the chloro group can be transferred to the C6 position as a chloride source in the total synthesis of chloromelodinine (**1**).

Clearly, the key to the proposed strategy is the efficient construction of the tetra-substituted pyrrole core using the Pd/NBE catalysis. To date, the Pd/NBE catalysis has become increasingly useful for site-selective difunctionalization of arenes and heteroarenes.[31–37] To achieve vicinal difunctionalization, typically substrates with an existing functional handle, such as halides, are needed, in which the *ipso* position couples with a nucleophile or an olefin and the *ortho* position couples with an electrophile. From the viewpoints of step economy and starting material availability, it would be more attractive to achieve vicinal double C—H functionalization from simpler substrates without halogen substituents. In 2019, we realized the first of such a transformation based on thiophenes,[38] and later extended to indoles.[39] Our proposed approach to leuconoxine alkaloids involves a Pd/NBE-catalyzed tandem β-C—H arylation/α-C—H Heck reaction of pyrroles to construct the B/C ring bicycle and the C18 all-carbon quaternary center, which represents a new variation of this type of transformations. Unlike indoles, it is expected that pyrroles should favor the initial C—H palladation at the α-position instead of the β-position (Scheme 1c). The subsequent migratory insertion into the NBE, followed by another C—H

Table 1: Reaction development and selected substrate scope.[a)]



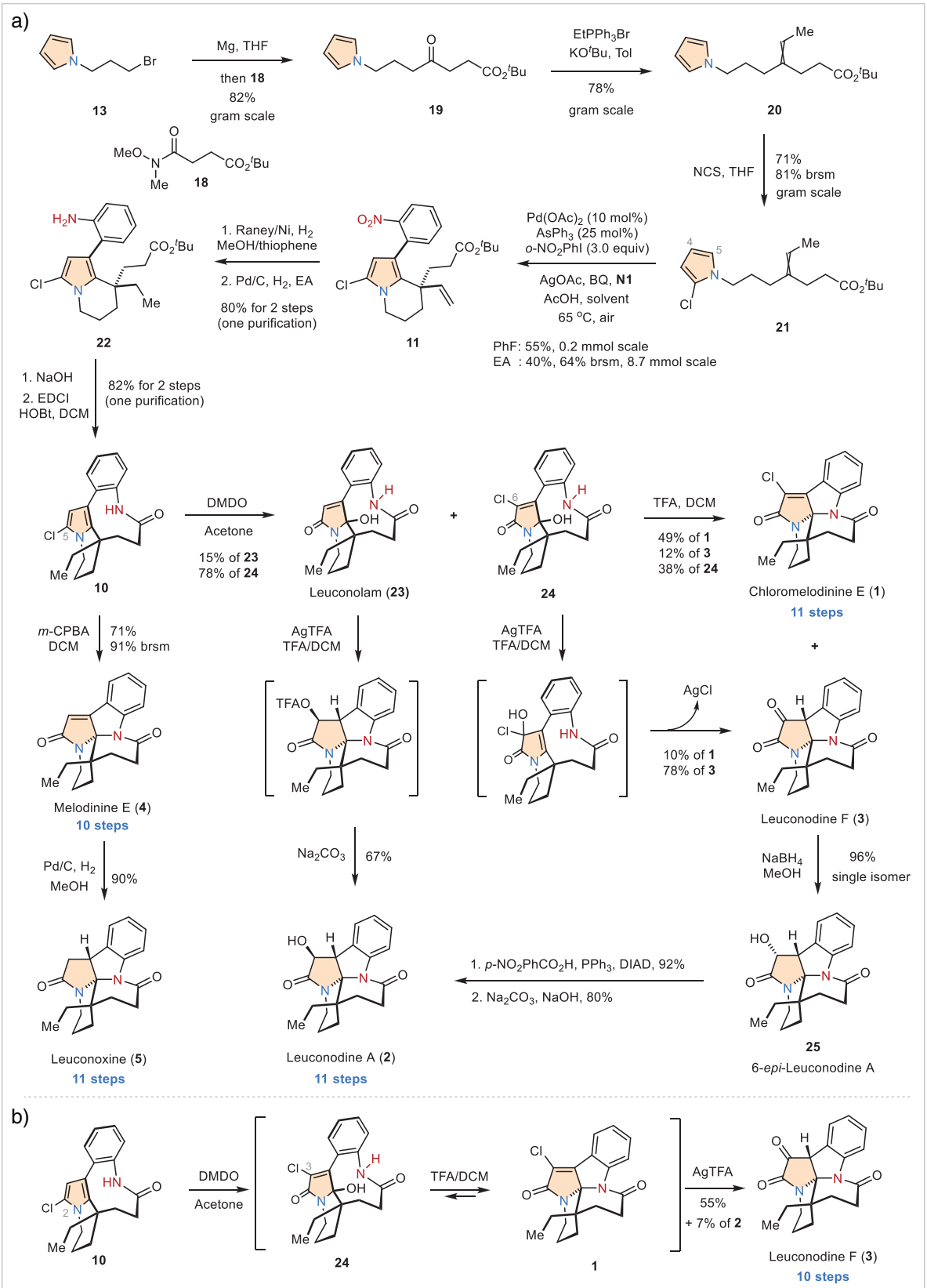
[a)] Reaction conditions: **14** (0.2 mmol), **15** (0.4 mmol), **16** (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), $AsPh_3$ (0.05 mmol), **N6** (0.3 mmol), BQ (0.2 mmol, 1.0 equiv), AgOAc (0.6 mmol, 3.0 equiv), and HOAc (1.0 mmol, 5.0 equiv), in PhF (1.0 mL), 65 °C, 72 h. [b)] **N3** (0.4 mmol, 2.0 equiv), AgOAc (0.8 mmol, 4.0 equiv), and TBME (*tert*-butyl methyl ether) were used. [c)] Yields were determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [d)] Isolated yield.

palladation at the β-position, should give an aryl-norbornyl-palladacycle (ANP), which is sufficiently electron-rich to react with an electrophile to furnish the functionalization at the β-position. Upon NBE extrusion, the resulting pyrrolyl-palladium species could then react with an alkene at the α-position, and the resulting Pd(0) can be re-activated by oxidants to form Pd(II) for the next catalytic cycle. Given that additional handles are not needed, this method is expected to offer a modular synthetic approach to access multi-substituted pyrroles from simple starting materials.

At the onset, our efforts focused on developing the Pd/NBE-catalyzed β-arylation, α-Heck reaction of simple *N*-alkylated pyrroles (Table 1). *N*-methyl-2-chloropyrrole (**14a**) was used as the model substrate, and the reaction conditions were systematically optimized (for details, see the Supporting Information). The desired tetra-substituted pyrrole product (**17a**) was obtained in 83% yield using 10 mol% $Pd(OAc)_2/AsPh_3$ as the catalyst, AgOAc/1,4-benzoquinone (BQ) as the oxidant, HOAc as the additive, and PhF as the solvent. Given the critical role of NBE in the catalytic cycle, various structurally modified NBEs (smNBEs) were surveyed,[40] among which C2-azetidine-amide-substituted NBE (**N6**) gave the best yield.[41] In contrast, structurally similar dimethylamide- (**N5**) and pyrrolidine amide-substituted (**N7**) NBEs were less effective, possibly due to the steric hindrance. Mono-methylamide- (**N4**) and ester-substituted (**N8**) NBEs gave slightly lower yields. Notably, simple NBE (**N1**) also gave a decent yield. The reaction is convenient to run with gentle heating (65 °C) in air.

The scope of this reaction was also investigated (Table 1; for additional examples, see Table S2 in Supporting Information). A series of C2- and C2/C3-substituted pyrroles underwent double C─H functionalization smoothly. Notably, the α-bromo group (**17b**), highly reactive with Pd(0) species, can be well tolerated under this Pd(II)-mediated catalysis. Interestingly, while thiophenes can undergo analogous vicinal difunctionalization,[38] a thiophene substituent can survive (**17c**) in this reaction, and there was only about 10% tetra-functionalized side-product, suggesting that the indole moiety is more reactive than thiophene. The use of a tri-substituted substrate can give fully substituted pyrrole **17d**, which is non-trivial to prepare otherwise. In addition, simple *N*-methylpyrrole **17e** and *N*-benzylpyrrole **17f** were compatible. Regarding the aryl iodide scope, those bearing *ortho* electron-withdrawing groups (EWGs), including ester (**17a**), nitro (**17g**), and amide (**17h**) groups, could all be coupled at the pyrrole *ortho* position in moderate to good yield. It is worth mentioning that, although *ortho* EWGs are often needed as an activating and directing group for aryl electrophiles in a number of Pd/NBE-catalyzed arylation reactions,[25,39] they are *not* necessary for this difunctionalization method. Aryl iodides only bearing *para* (**17j**) and *meta* (**17i**) substituents, and even simple phenyl iodide (**17k**), can be effectively coupled at the β-position, suggesting a broader scope than thiophene and indole-based reactions.[38,39] Moreover, diverse olefins, such as Michael acceptors (**17l**, **17m**, **17o**), styrene (**17n**), and cyclopentene (**17p**), are all excellent coupling partners for the pyrrole α-functionalization.

With this pyrrole difunctionalization method established, the total synthesis commenced with synthesis of ketone **19** from commercially available pyrrole **13**,[42] which involved in situ formation of the Grignard reagent from **13** followed by addition to known Weinreb amide **18**[43] (Scheme 2a). The reaction gave high yield on gram scale, and the *tert*-butyl ester group in **18** was intact. Next, Wittig olefination of the ketone moiety proceeded smoothly using potassium *tert*-butoxide as the base and toluene as the solvent. The resulting *E*/*Z* isomer mixture of olefin **20** could be converted into the same product in the later Pd/NBE catalysis. Treatment of olefin **20** with *N*-chlorosuccinimide (NCS) produced 2-chloro-substituted pyrrole **21** in 71% yield, along with 12% recovery of the starting material. The stage was set for the key vicinal double C─H functionalization of pyrrole to

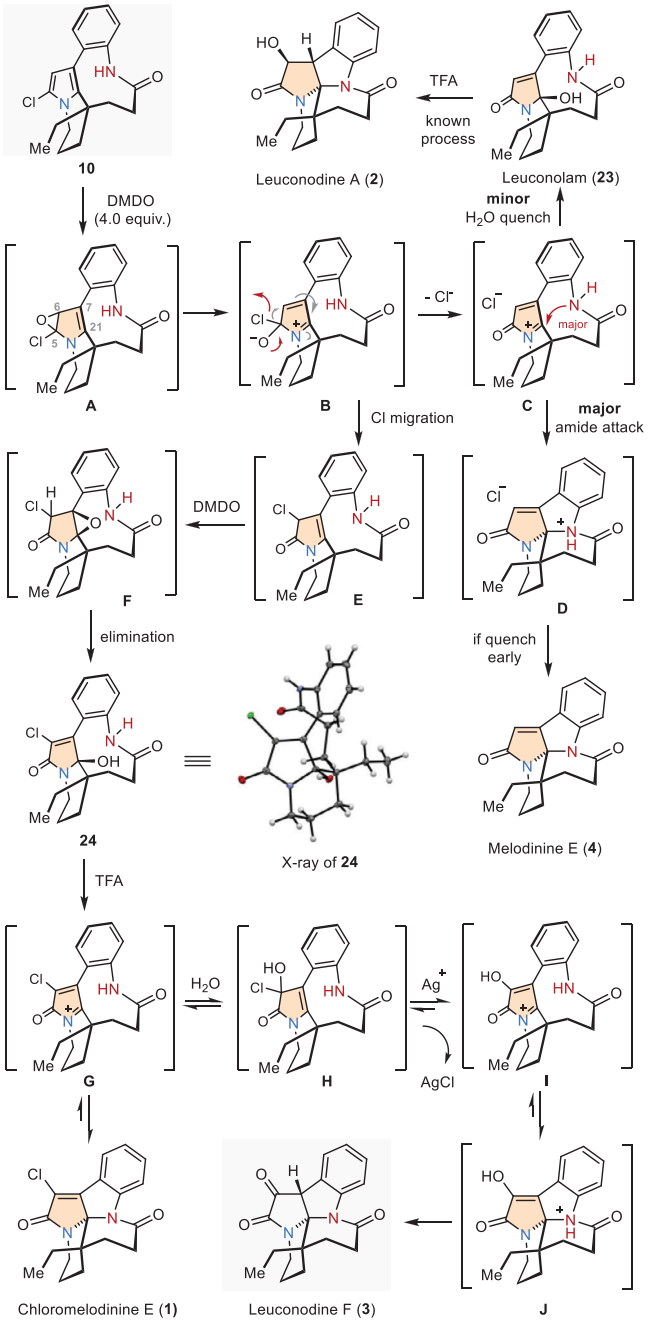


Scheme 2. a), Total syntheses of chloromelodinine E, leuconodine A, leuconodine F, melodinine E, and leuconoxine; b), Direct synthesis of leuconodine F from intermediate **10**. NCS, *N*-chlorosuccinimide. brsm, based on recovered starting material. EA, ethyl acetate. DIAD, diisopropyl azodicarboxylate. DMDO, dimethyldioxirane. AgTFA, silver trifluoroacetate. *m*-CPBA, 3-chloroperoxybenzoic acid. EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. HOBt, hydroxybenzotriazole.

construct B/C rings and the C18 quaternary center. After further optimization of the reaction conditions for better yield and scalability (see Supporting Information for details), the desired β-arylation/intramolecular α-Heck reaction was achieved with the chloropyrrole substrate (**21**) to afford bicycle **11** in decent yield.[44] *Ortho*-nitrophenyl iodide was used as the electrophile, and simple NBE (**N1**) worked better than **N6** in this case, likely because the less sterically hindered **N1** can coordinate with Pd more strongly so that the intramolecular Heck side-reaction can be minimized. Interestingly, the corresponding unsubstituted pyrrole substrate (**20**) showed much lower reactivity under these conditions.

With a sufficient quantity of bicycle **11** in hand, while simultaneous reduction of the nitro group and the double bond proved challenging due to the competing reactivity of the chloride moiety, a carefully optimized two-step sequence successfully afforded aniline **22**. Keeping the chloro group proved to be critical because the de-chlorinated product would become less stable and susceptible toward decomposition. Subsequently, hydrolysis of the ester yielded the corresponding carboxylic acid uneventfully, which then underwent macrolactamization under mild conditions to afford macrolactam **10** in 82% yield over two steps.[45–48]

Macrolactam **10** then served as the common intermediate to access several leuconoxine-type alkaloids in a divergent fashion. First, simply treatment of **10** with purified *m*-CPBA in anhydrous DCM afforded melodinine E (**4**) in 71% yield. The subsequent diastereoselective hydrogenation of the alkene moiety in **4**, following a reported condition,[11] completed the total synthesis of leuconoxine (**5**) in 90% yield. On the other hand, treating macrolactam **10** with excess freshly prepared dimethyldioxirane (DMDO) in acetone at low temperature yielded the chloro-1,2-migration (C5 to C6) compound **24**, along with some leuconolam (**23**). The structure of **24** was unambiguously characterized by X-ray crystallography.[49] Subsequently, allowing **24** to react in a TFA/DCM solution promoted the transannular cyclization to furnish chloromelodinine (**1**) in 49% yield and leuconodine F (**3**) in 12% yield. Generally speaking, the neutral DMDO condition promotes chloro-1,2-migration when operated carefully, whereas the acidic *m*-CPBA favours de-chlorination and the transannular cyclization (for detailed optimization, see Supporting Information, Scheme S3). Meanwhile, modifying the transannular cyclization condition by adding silver trifluoroacetate (AgTFA) led to isolation of leuconodine F (**3**) as the dominating product in 78% yield. Under similar conditions, leuconodine A (**2**) was obtained in 67% yield from leuconolam (**23**), based on a reported mechanism.[29] Furthermore, leuconodine F (**3**) could also be synthesized in a one-pot manner from macrolactam **10** in good yield through merging these processes (Scheme 2b). With sufficient **3** in hand, $NaBH_4$ reduction of the ketone moiety led to the formation of 6-*epi*-leuconodine A (**25**), which was then successfully converted to natural product **2** using the Mitsunobu/hydrolysis protocol. Altogether, we have demonstrated that leuconoxine-type alkaloids **1–5** can all be prepared through oxidative dearomatization from macrolactam **10** in 10–11 total steps.



Scheme 3. Proposed mechanism for the synthesis of natural products **1–3** from macrolactam **10**. Compounds **A–J** are proposed intermediates.

A plausible mechanism for the oxidative dearomatization of macrolactam **10** to access natural products **1–3** was proposed based on the intermediates detected during the syntheses (Scheme 3). It is anticipated that epoxidation likely takes place at the Cl side[50,51] to generate intermediate **A**,[52] which then undergoes epoxide ring opening via the electron pushing from the enamine nitrogen to give intermediate **B**. At this stage, chloride dissociation would form the cationic intermediate **C**, and the iminium can either undergo transannular attack by the amide (the major pathway), leading to melodinine E (**4**), or be quenched by water (the minor

pathway) to afford leuconolam (**23**) that can be further transformed into leuconodine A (**2**) via the known process.[29] On the other hand, the chloro group in intermediate **B** could also undergo 1,2-migration to form enamine **E**,[53] which can be rapidly oxidized by another equivalent of DMDO. The resulting transient epoxide **F** could then undergo β-elimination to form compound **24** containing the C6 chloro substituent. Under acidic conditions, hemiaminal **24** could be easily converted to iminium **G**, which then undergoes transannular cyclization to form chloromelodinine E (**1**). Alternatively, in the presence of AgTFA, the chloro group would be replaced with a hydroxy group, eventually resulting in formation of leuconodine F (**3**) via a similar pathway.

In conclusion, we have developed a concise approach to access leuconoxine-type alkaloids, specifically chloromelodinine E (**1**), leuconodine A (**2**), leuconodine F (**3**), melodinine E (**4**), and leuconoxine (**5**), in 10–11 total steps without the use of protecting groups.[54] This pyrrole-centered strategy is distinct from the previous efforts that are focused on constructing the indoline part first. The robust Pd/NBE-catalyzed pyrrole double C─H functionalization method, the strategic employment of the chloro substituent, and the unusual chloro-1,2-migration discovered here could have broad implications beyond these syntheses.

Supporting Information

The authors have cited additional references within the Supporting Information.[55–63]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Alkaloids · Dearomatization · Palladium/Norbornene catalysis · Pyrrole · Total synthesis

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