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Unified Total Synthesis of Pyrroloazocine Indole Alkaloids Sheds Light on Their Biosynthetic Relationship

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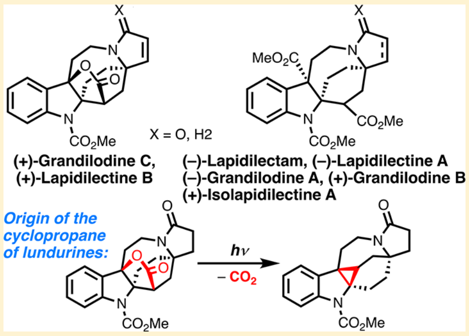
Supporting Information

ABSTRACT: The total synthesis of seven members of the lapidilectine and grandilodine family of alkaloids has been accomplished in racemic and enantiopure form without protection/deprotection of functional groups. The two key steps, an 8-*endo*-dig hydroarylation and a 6-*exo*-trig photoredox cyclization, were catalyzed using gold. A rationale for the formation of the cyclopropane ring of the lundurines is also provided.



INTRODUCTION

Lapidilectines and grandilodines are indole alkaloids, isolated from peninsular Malaysia species *Kopsia grandifolia* D. J. Middleton, that feature lactone (**1** and **2**) or diester (**3**−**7**) motifs (Figure 1).[1,2] Together with tenuisines and the cyclopropane-containing lundurines isolated from *Kopsia tenuis* species,[3] they represent a family of 16 indole alkaloids containing the common pyrroloazocine core. Preliminary studies on the biological activity of lapidilectines and grandilodines demonstrated their ability to reverse multidrug resistance in vincristine-resistant cancer cells.[2]

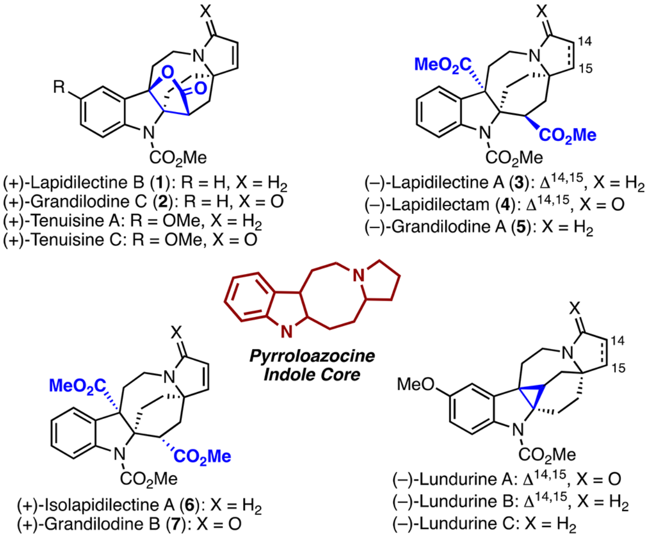


Figure 1. Pyrroloazocine indole alkaloids.

The first total synthesis of (±)-lapidilectine B (**1**) was achieved by Pearson et al. in 25 steps.[4] Only very recently, the total syntheses of (+)-lapidilectine B (**1**)/(+)-grandilodine C (**2**)[5] and racemic grandilodine B (**7**)[6] have been developed. However, a synthetic approach to lapidilectine A-type natural compounds **3**−**5** has not yet been disclosed. Our interest in *Kopsia* indole alkaloids launched with the discovery of a gold-catalyzed hydroarylation of alkynes that allows a fast access to the pyrroloazocine indole core of these natural compounds.[7] On the basis of this strategy, we developed a concise total synthesis of lundurines A−C.[8]

Besides the synthetic challenge the pyrroloazocine indole alkaloids pose,[9,10] we were intrigued by the biosynthetic relationships among the main classes of this family of alkaloids and, in particular, fascinated by the origin of the cyclopropane ring of the lundurines. Here we report a unified total synthesis of seven members **1**−**7** of the lapidilectine/grandilodine family streamlined by the use of two gold-catalyzed reactions for the key cyclization steps. With ready access to the main members of this natural product family, we have examined their chemical interconversions, uncovering that the cyclopropane ring can arise from the photochemical decarboxylation of a lactone. This photochemical origin differs from an early biosynthetic hypothesis[11] and is unprecedented among the many pathways that have been elucidated for the biosynthesis of cyclopropane-containing natural products.[12]

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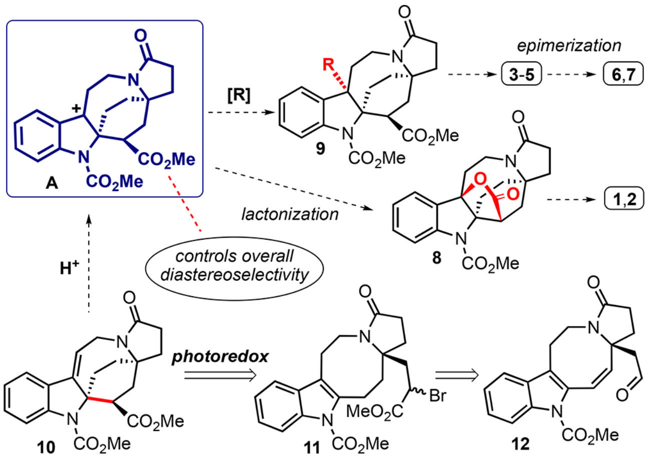
■ RESULTS AND DISCUSSION

We considered that compounds **1**/**2** and **3**/**4** might be biosynthetically connected through an oxidative decarboxylation[13] via carbocation **A**, which could become a key intermediate for the synthesis of lactone **8**, or be treated with a carbon nucleophile to construct the quaternary stereocenter in **9** en route to diesters **3**−**7** (Scheme 1). The diastereoselectivity of the latter transformation would be controlled by the CO_2Me moiety, which shields one face of carbocation **A** from nucleophilic attack. Intermediate **A** could be readily accessed from alkene **10**, whose synthesis was envisioned through a radical photoredox-catalyzed cyclization of **11.** This process was expected to favor the formation of the product with an *endo*-methoxycarbonyl group. Precursor **11** could ultimately be obtained from aldehyde **12**, whose 5-OMe-analogue was an intermediate in our synthesis of the lundurines.[8]

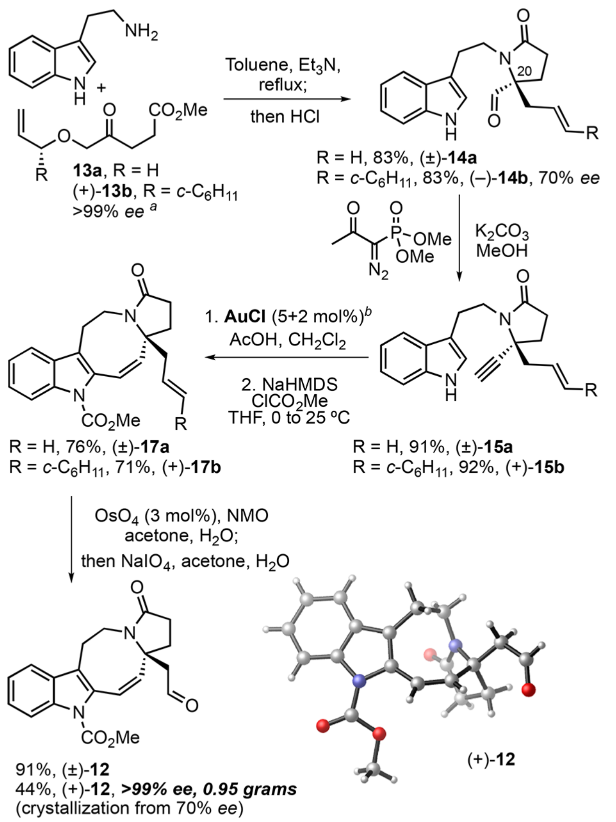
Scheme 1. Bioinspired Unified Retrosynthesis of Lapidilectine/Grandilodine Family of Alkaloids



Unified Total Synthesis. The synthesis of advanced pyrroloazocine compound **12** was realized in both enantiopure and racemic form in 5 steps, on gram scale, from commercially available tryptamine (Scheme 2). The first step in our synthetic sequence, a condensation/lactamization/Claisen rearrangement cascade of oxoesters **13a,b** with tryptamine occurred with high yield (83%) and for (+)-**13b** with a good level of chirality transfer from the allylic fragment to the C20 stereocenter (>99% *ee* for (+)-**13b** to 70% *ee* for (−)-**14b**).[8,14] Aldehydes **14a,b** underwent a Seyferth−Gilbert homologation to give alkynes **15a,b**.

The Au-catalyzed cyclization of **15** was found to be more challenging than that of its 5-OMe derivative.[8] In the presence of the standard AuCl-based catalytic system, the reaction stopped at an unsatisfactory ca. 60% conversion, due to catalyst decomposition. With ligand-stabilized cationic gold complex $[IPrAu(NCCH_3)]SbF_6$ (2 mol %), (±)-**15a** undergoes the gold-catalyzed cyclization with a satisfactory ca. 20:1 8-*endo*/7-*exo* selectivity. After subsequent reaction with methyl chloroformate and crystallization (removing traces of 7-*exo* product), (±)-**17a** was obtained in 65% yield over two steps.[14] Alternatively, in the presence of acetic acid, the AuCl catalyst was found to be more stable,[15] and full conversion could be achieved with 5 + 2 mol % catalyst loading (Scheme 2). The reaction proceeds with excellent 8-endo selectivity (>50:1 endo/exo) and with high yield (**16a,b**, 76−82%). After introducing the methylcarbamate, the exocyclic double bond of **17a,b** was cleaved by a one-pot $OsO_4/NaIO_4$ protocol to give aldehyde **12** in racemic and enantioenriched form. For the latter, the enantiomeric excess was enhanced from 70% to >99% by crystallization from acetone, and its absolute configuration was confirmed by high-resolution single-crystal X-ray diffraction.[16]

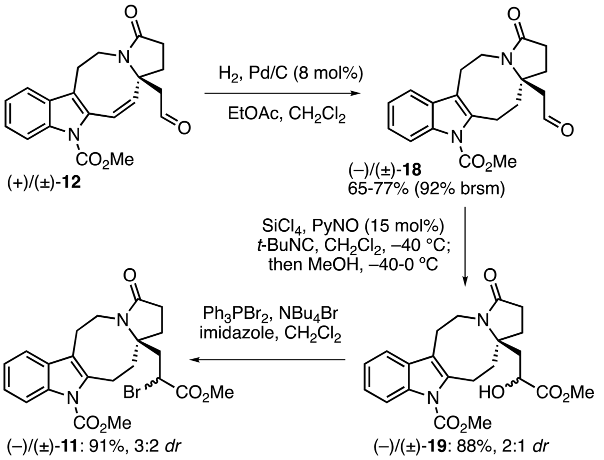
Scheme 2. Synthesis of Enantiopure Aldehyde Intermediate 12



[a] See Supporting Information for the synthesis of (+)-**13b**. [b] Initial 5 mol % of AuCl catalyst employed, then additional 2 mol % added after 0.5−1 h to reach full conversion.[14]

At this point the synthetic route diverges from the one previously developed for the lundurines.[8] Hydrogenation of the double bond in **12** required carefully controlled conditions[14] in order to prevent over-reduction of the indole into indoline. This was achieved with 10 wt % Pd/C catalyst in EtOAc/CH_2Cl_2 to give **18** in 65−77% and 92% brsm yields (Scheme 3). With aldehyde **18** in hand, we focused on the development of an approach to an ester-containing precursor for the radical cyclization. Current methods to access α-halo esters by aldehyde homologation are essentially limited to cyanohydrin synthesis, requiring several steps and harsh conditions. Thus, seeking an alternative, our attention turned to the work of Denmark et al., where α-hydroxy methyl esters were synthesized from aldehydes and *t*-BuNC, in a Passerini-type reaction, with an exceptional functional group tolerance.[17] To apply this transformation to compound **18**, we had to account for the presence of several Lewis-basic centers in the molecule, increasing the amount of $SiCl_4$ (4.35 equiv instead of 1.1 equiv) and raising the reaction temperature (from −74 to −40 °C).[14] The α-hydroxy ester **19** was obtained in an excellent 88% yield,

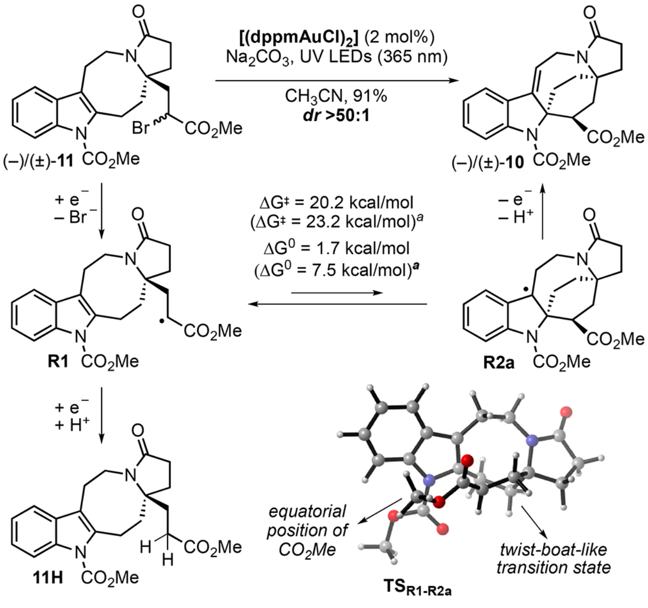
Scheme 3. Synthesis of α-Bromo Ester 11



while the relatively labile methylcarbamate remained intact (Scheme 3). Finally, bromide **11** was obtained in ca. 90% yield through an Appel-type reaction using a modified protocol.[14]

The photoredox process to build the rigid azabicyclic [4.2.2] skeleton was expected to be challenging, as it consists of a rare 6-*exo*-trig radical spirocyclization onto an indole through a transition state that cannot adopt a chairlike conformation.[18,19] Nevertheless, our initial study employing $[Ru(bpy)_3]Cl_2$[20] showed that **11** indeed underwent cyclization to the key synthetic intermediate **10** with excellent endo-diastereoselectivity, which most likely originates from the CO_2Me group adopting an equatorial position in a twist-boat-like transition state (Scheme 4). However, the reaction did not reach full conversion because of catalyst decomposition, and several other evaluated catalytic systems did not provide a significant improvement.[14] Remarkably, the digold photoredox catalyst $[(dppmAuCl)_2]$ introduced by Barriault and co-workers[21] showed an outstanding efficiency, leading to **10** in 91% yield (Scheme 4).

Scheme 4. Photoredox Cyclization of 11 into 10

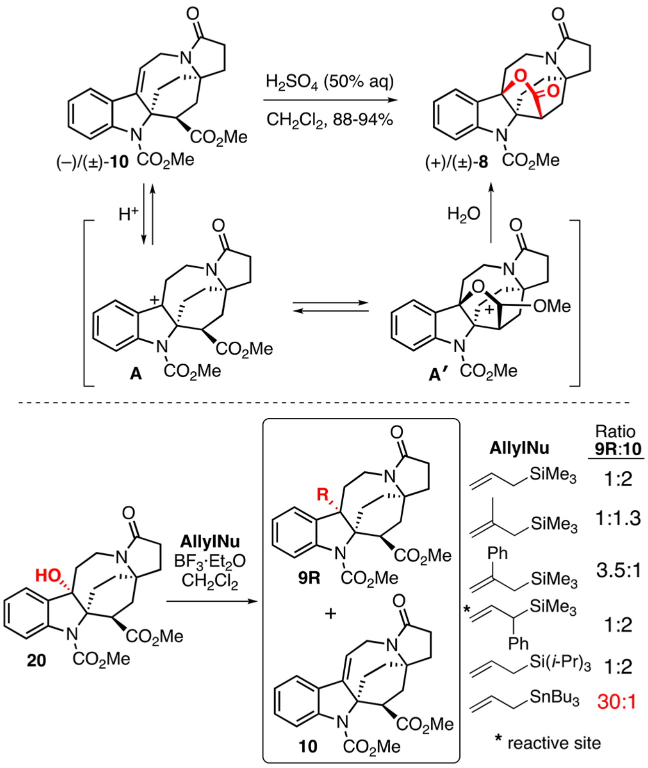


[a]Values for *exo*-CO_2Me isomer (**R2b**).

The main challenge of the photoredox transformation presumably arises from the lack of driving force for the cyclization of the relatively stable α-CO_2Me radical **R1** into strained benzyl radicals **R2a** (*endo*-CO_2Me) and **R2b** (*exo*-CO_2Me). Density functional theory (DFT) calculations[22] provided $\Delta G^{\ddagger}$ values of 20.2 and 23.2 kcal/mol for the cyclization of **R1** into **R2a** and **R2b**, respectively, which is in accord with the observed high endo-selectivity (Scheme 4). In addition, these barriers indicate that the radical cyclization is a relatively slow process, 4−6 orders of magnitude slower than a standard 6-*exo*-trig cyclization of 6-hepten-1-yl radical.[14] Furthermore, from a thermodynamic point of view, the open form of radical **R1** was found to be even more stable than the cyclized radical intermediates (ΔG^0 = 1.7 kcal/mol for **R2a** and 7.5 kcal/mol for **R2b**). This suggests that the oxidation of benzylic radicals **R2** is the main driving force of the transformation that shifts the equilibrium between **R1** and **R2**. Both kinetic and thermodynamic data of the radical cyclization imply that **R1** may accumulate in the reaction medium, causing side-reactions and catalyst decomposition. For example, the undesired reduction of **R1** leads to **11H**, which was isolated and identified as the main byproduct in both Au- and Ru-catalyzed photoredox processes.[14] This reduction into **11H** naturally results in the oxidation of the photoredox catalyst and ultimately leads to the deactivation of the catalytic system.[23] For $[Ru(bpy)_3]Cl_2$ catalyst, such a deactivation product, deep-purple *trans*-$[Ru(bpy)_2Br_2]Br$, was isolated and structurally characterized.[14]

Alkene **10** was used as a precursor of benzylic carbocation **A**, a common intermediate in the synthesis of both lactones **1** and **2** and diesters **3**−**7** (Schemes 1 and 5). Under strong acidic conditions (50% aqueous H_2SO_4), the styrene moiety underwent protonation. The subsequent hydrolysis of the ester,

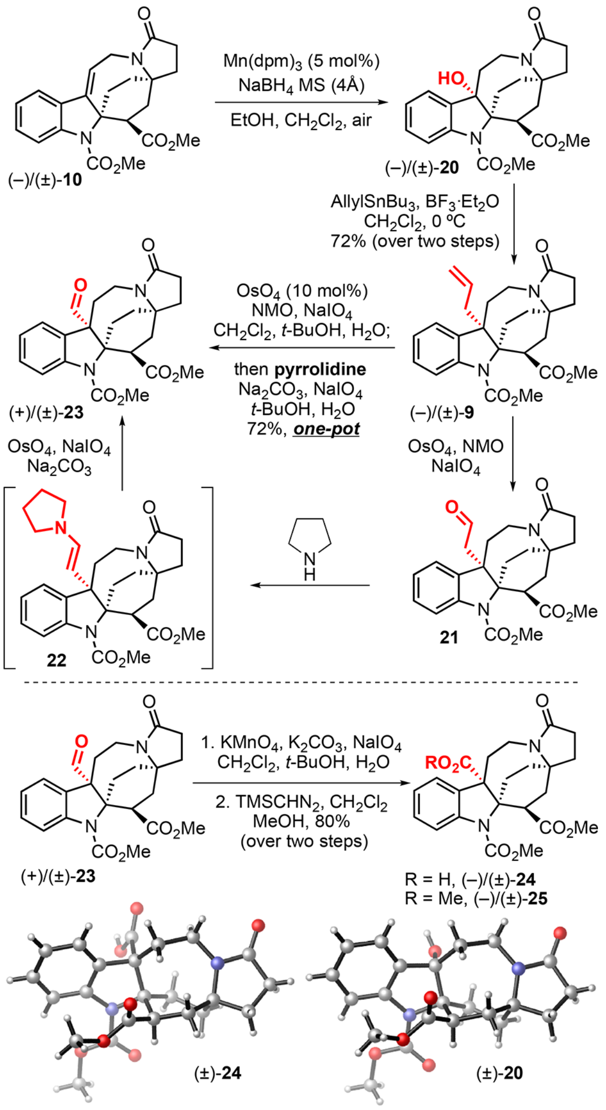
Scheme 5. Lactonization of 10 and Benzylic Allylation of 20



presumably involving cyclized cation **A′** (see below), led to the desired lactone **8** (Scheme 5). Forging the quaternary carbon center bearing the benzylic CO_2Me group proved to be challenging. Besides the obvious increase in molecular strain, this transformation goes in the opposite direction to that of the proposed natural biosynthetic scheme, in which the benzylic C−C bond is cleaved, not constructed. Our scouting experiments suggested that carbocation **A** undergoes proton elimination, providing alkene **10** or lactonization into **8** faster than it reacts with carbon nucleophiles (*t*-BuNC, trimethylsilyl cyanide (TMSCN), anisole, or 1,3-dimethoxybenzene).[14]

We found that benzylic alcohol **20**, accessible from **10** via Mukaiyama hydration,[24] can partake in a Hosomi−Sakurai-type allylation with allylTMS,[25] providing the desired product **9**. Although promising, this result was not suitable for application in the total synthesis because **9** was formed together with alkene **10** as an inseparable mixture in ca. 1:2 ratio. Other allylic nucleophiles were tested (Scheme 5), and allylSnBu_3[26] demonstrated outstanding efficiency (ca. 30:1 ratio of **9**/**10**). Allylated product **9** was obtained in 72% yield over two steps as a single diastereomer (Scheme 6), confirming that the ester moiety provides sufficient steric hindrance to favor the exclusive attack of the nucleophile on one face of carbocation **A**. Our attempts to perform a one-pot radical cyclization/benzylic C−C bond construction were unsuccessful.[14,27] The $[(dppmAuCl)_2]$-catalyzed photoredox cyclization of **11** in the presence of nucleophiles such as TMSCN and allylTMS led to elimination product **10**. Employing allylSnBu_3 (10 equiv) as nucleophile, this one-pot procedure provided a mixture of **9** and **10** in an unsatisfactory 1:2 ratio.[28]

Scheme 6. Introduction of Benzylic CO_2Me Group; X-ray Structures of (±)-20 and (±)-24

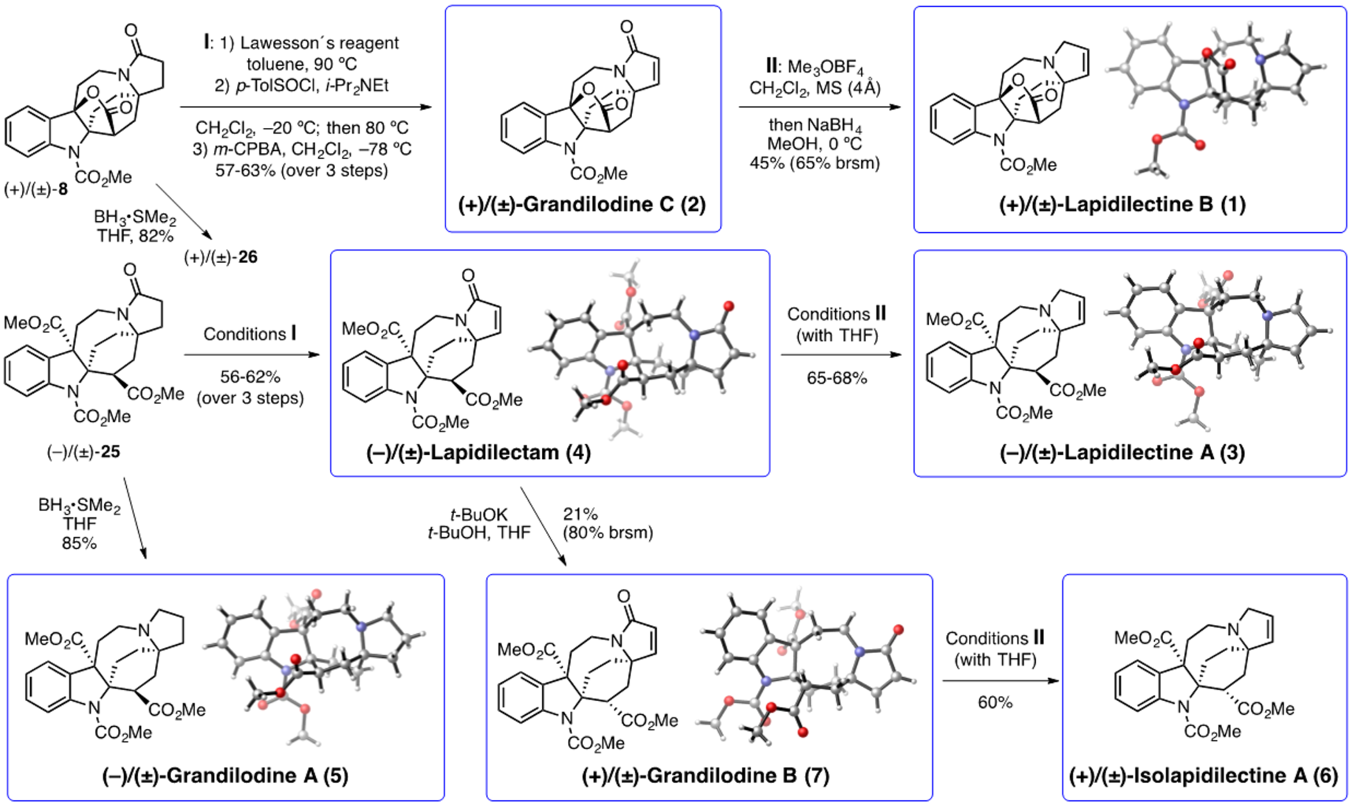


Two-carbon degradations of allyl moieties to aldehydes are typically performed through double-bond migration/ozonolysis sequence.[29] However, low conversion and difficult separation of isomeric alkenes made this strategy impractical in our case. To circumvent this issue, we envisioned to first cleave the double bond in **9** with $OsO_4/NaIO_4$ to aldehyde **21**, which could be further converted to an enamine that could undergo a second oxidative cleavage (Scheme 6).[30] Treating aldehyde **21** with pyrrolidine afforded enamine **22** quantitatively (^1H NMR), which was then fragmented to aldehyde **23**, under similar oxidative conditions. A base (Na_2CO_3) was utilized in the second C=C cleavage to efficiently generate the enamine intermediate and suppress the retro-Stork enamine alkylation reaction, which results in the formation of alkene **10** and/or alcohol **20** byproducts.[14] As both events involved $OsO_4/NaIO_4$, we combined them, thereby developing a novel one-pot degradation of an allyl group to the two-carbon lower aldehyde homologue. With this strategy, **9** was converted into **23** in 72% yield.[31] The oxidation of aldehyde **23** to carboxylic acid **24** was hampered by the steric hindrance of the substrate and the oxidative decarboxylation of the carboxylic acid product (see below). The oxidation under Pinnick conditions[32] was found to be less selective than that with $KMnO_4$. Excess of oxidants ($KMnO_4$ and $NaIO_4$) was employed to minimize the side decarboxylation, presumably mediated by reduced manganese species. Finally, carboxylic acid **24** was converted into methyl ester **25** by treatment with TMS-diazomethane (80% yield over two steps).

Seven pyrroloazocine indole alkaloids were accessed from lactone **8** and diester **25** utilizing a unified end-game strategy (Scheme 7). The introduction of a double bond in (+)-**8** and (−)-**25** following Magnus' thioamide sequence[8,33] provided (+)-grandilodine C (**2**) and (−)-lapidilectam (**4**), respectively. These results allowed us to revise the sign of the optical rotation for lapidilectam (**4**) from the previously reported[1b] (+) to (−).[14] Treatment of diester **4** under basic conditions led to a ca. 3.5:1 mixture of **4** and **7**, which could be separated, affording (+)-grandilodine B (**7**). The final reduction of amides **2**, **4**, and **7** with $Me_3OBF_4/NaBH_4$ led to (+)-lapidilectine B (**1**), (−)-lapidilectine A (**3**), and (+)-isolapidilectine A (**6**),[14] while (−)-grandilodine A (**5**) and unnatural (+)-dihydrolapidilectine B (**26**) were synthesized by direct reduction of (−)-**25** and (+)-**8** with borane.

On the Biosynthesis of Pyrroloazocine Indole Alkaloids. With the natural products and synthetic intermediates in hand, we studied the biosynthetic relationships of pyrroloazocine indole alkaloids. The initial proposal contains a rare oxidative decarboxylation of a methyl ester in lapidilectine A-type diesters, followed by a heterolytic decarboxylation of the lactone, furnishing the cyclopropane of the lundurines (Scheme 8).[11,14] However, to date, there is still no experimental support for this hypothesis. To probe the first decarboxylation event, we attempted to transform diester **25** into alcohol **20**, alkene **10**, or directly into lactone **8**. However, **25** was unreactive to SET

Scheme 7. Endgame: Diversification of Intermediates (+)-8 and (−)-25 into Seven Natural Products of the Lapidilectine/Grandilodine Family; X-ray Structures of (±)-1, (±)-3, (±)-4, (±)-5, and (±)-7



oxidation agents (ceric ammonium nitrate (CAN)), and no oxidation peak was observed (up to +2.0 V) by cyclic voltammetry. In contrast, the sodium salt of carboxylic acid **24** (oxidative potential peak of +0.9 V) underwent the desired oxidative decarboxylation with CAN in the presence of MeOH.[34] Under these conditions, a ca. 1:1 mixture of alkene **10** and the methyl ether of **20** (**20Me**) was formed. Treatment of this mixture with 50% aqueous sulfuric acid afforded lactone **8** in 62% NMR yield (Scheme 8).

Next, the hypothesis of heterolytic cleavage of lactones to cyclopropanes was tested. When lactone **8** was treated with KCl in wet dimethylsulfoxide (DMSO) at 85 °C for 17 h,[35] no cyclopropane product was observed. This led us to consider an alternative mechanism for the generation of the cyclopropane via homolytic photochemical decarboxylation of the γ-lactone.[36] To our delight, irradiation of lactone **8** with UVB light (300 nm) or UVC light (254 nm) gave the corresponding cyclopropane **27** in moderate NMR yield, with UVB wavelength being more selective and efficient (Scheme 8).

Finally, it was noticed that, despite their lower stability in comparison with the corresponding pyrrolones,[14] 3-pyrrolines (lundurine B, lapidilectines A and B, isolapidilectine A, and tenuisine A) were isolated in significantly greater amounts,[1a,2] suggesting that the pyrrolones (lundurine A, grandilodines B and C, lapidilectam, and tenuisine C) could arise from an autooxidation process. Indeed, synthetic lundurine B[8] spontaneously converted (>50%) into lundurine A upon storage under air for 16 months.

We suggest an alternative biosynthetic scheme that features carboxylic acids **28** as key intermediates and a homolytic mechanism for decarboxylation of lactone into cyclopropane. The new proposal is summarized in Scheme 8. It is in line with the experimentally observed reactivity and additional DFT studies (see below).

The new biosynthetic hypothesis starts with the hydrolysis of kopsijasminilam-type precursors to pyrroline-containing carboxylic acids **28** (Scheme 8). The close proximity between C20 and amide N atom in known kopsijasminilam-type structures[37] suggests that lactam hydrolysis might involve *N*-acyl ammonium cations **29** as key intermediates.[38,39] Indeed, the DFT optimization[22] of kopsijasminilam-type structures with planar amide and the carbocation at C20 led to more stable cations **29** that have short C20−N distances (ca. 1.62 Å), nonplanar nitrogen atoms, and elongated amide C21−N bonds (ca. 1.52 Å).[14] This geometry resembles the one previously reported for *N*-alkylated twisted amides, which are prone to hydrolysis of N−CO bond.[40]

Carboxylic acids **28** can be further converted into methyl esters lapidilectine A and isolapidilectine A. These compounds were previously proposed as precursors to lactones. Our experimental results suggest that this scenario is unlikely, but carboxylic acids **28** might undergo an oxidative decarboxylation/lactonization, leading to the formation of lactones lapidilectine B and tenuisine A. The proximity of the lactone carbonyl group and the pyrroline nitrogen atom in lapidilectine B (2.5 Å, X-ray structure, Scheme 7) suggests a possible intramolecular assistance of the latter in the lactonization process. While we were not able to obtain amino acid **28** or its 14,15-dihydro analogue to test this hypothesis experimentally, our DFT calculations[22] support this possibility. On one hand, open benzylic carbocation **A** is more stable than closed carbocation **A′** by 5.3 kcal/mol (Scheme 9). This suggests that the lactonization of lactam derivatives is hampered by this unfavorable equilibrium. Experimentally, we indeed observed

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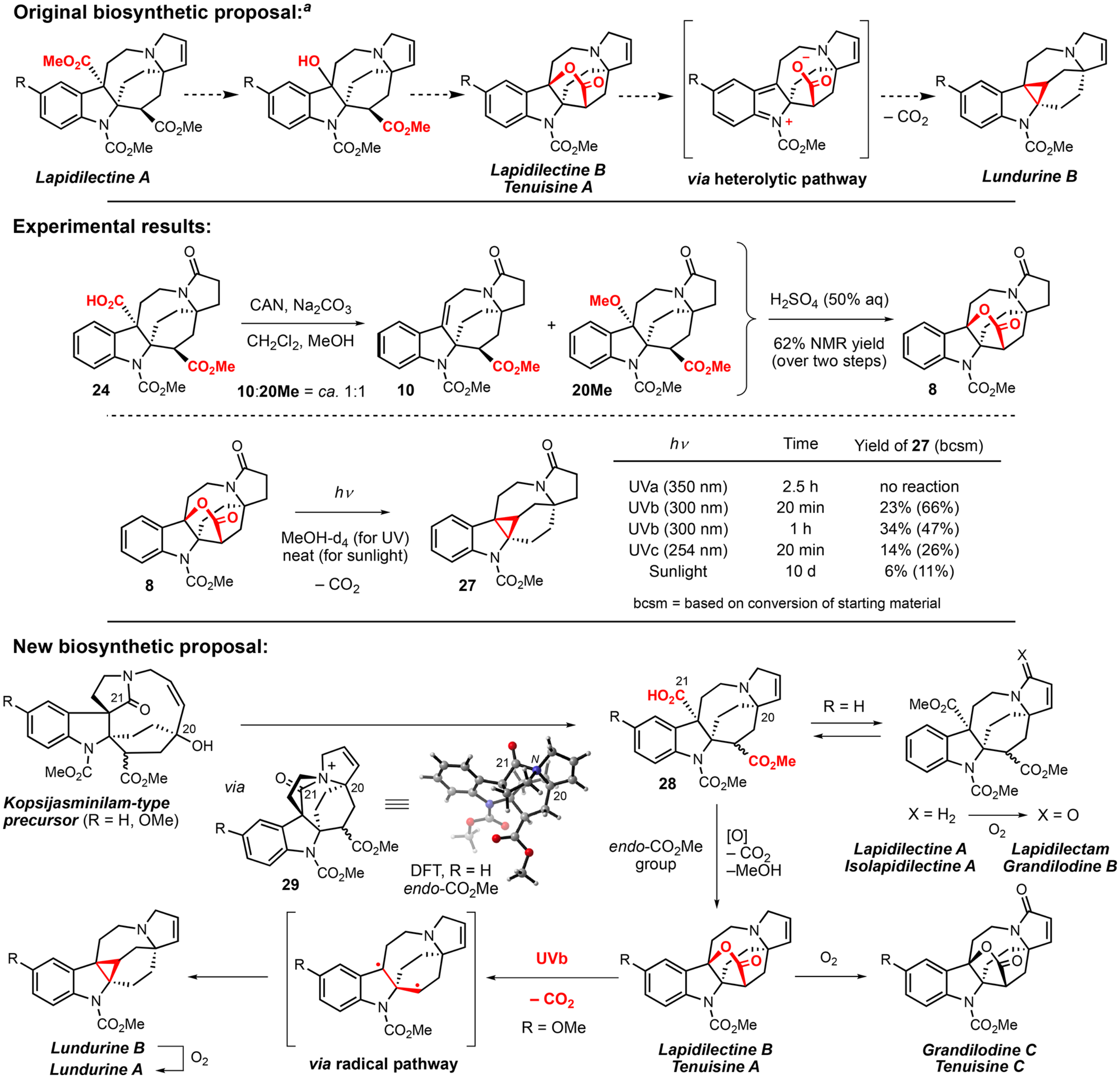
Scheme 8. Cyclopropane Formation by Stepwise Decarboxylation of Acid 24 and Lactone 8; Original and New Proposal for the Origin of the Cyclopropane of Lundurines



hν	Time	Yield of **27** (bcsm)
UVa (350 nm)	2.5 h	no reaction
UVb (300 nm)	20 min	23% (66%)
UVb (300 nm)	1 h	34% (47%)
UVc (254 nm)	20 min	14% (26%)
Sunlight	10 d	6% (11%)

bcsm = based on conversion of starting material

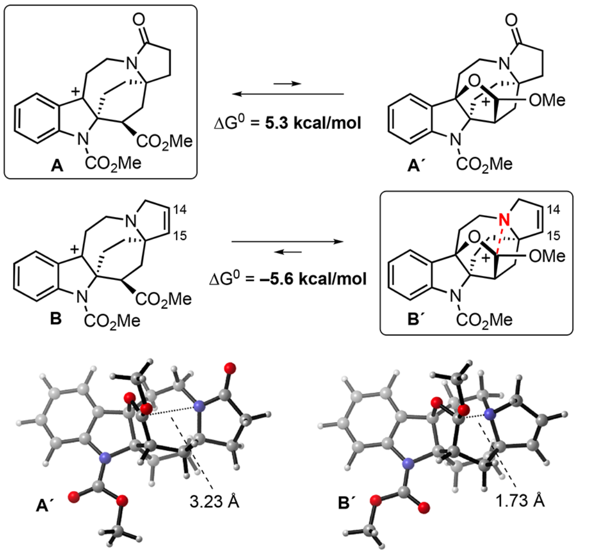
[a]Simplified version. For the full scheme, see Supporting Information and ref 11.

that this transformation only takes place efficiently in a strongly acidic medium, and that under milder conditions the major pathway observed is toward elimination product **10**. On the other hand, pyrroline-containing cation **B′** benefits from additional stabilization by the nitrogen and, in this scenario, is more stable than open benzylic cation **B** by 5.6 kcal/mol.[41] This, in turn, suggests that the lactonization of pyrroline derivatives should be a favorable natural process.

The subsequent decarboxylation into cyclopropane may be a light-induced process, as was demonstrated experimentally for **8**. Tenuisine A, after a photochemical decarboxylation, would give lundurine B, featuring a 3-pyrroline fragment. This transformation presumably proceeds with the initial excitation of the arene system (absorption band at 290 nm in **1**, **2**, and **8**), which results in the homolytic cleavage of the benzylic C–O bond, which is perpendicular to the aromatic system. Irradiation of a thin film of neat **8** between two quartz plates with sunlight over 10 days also showed formation of **27**, suggesting the relevance of the photochemical decarboxylation in the biosynthetic scheme and the sufficiency of UVb light to trigger this transformation.[42]

Finally, pyrrolines might undergo allylic oxidation, producing pyrrolones. As the decarboxylation of lactone and allylic oxidation do not require any specific enzyme, the corresponding compounds could have been formed after collection of the plant material and even can be artifacts of the isolation process.

Scheme 9. Relative Stability of Cation Intermediates A and A′, and B and B′



CONCLUSIONS

In summary, we have developed concise total syntheses (11−19 steps) of enantiomerically pure (+)-lapidilectine B (**1**), (+)-grandilodine C (**2**), (−)-lapidilectine A (**3**), (−)-lapidilectam (**4**), (−)-grandilodine A (**5**), (+)-isolapidilectine A (**6**), (+)-grandilodine B (**7**), and unnatural (+)-dihydrolapidilectine B (**26**) by means of two highly efficient gold-catalyzed cyclization processes. The skeleton of grandilodines/lapidilectines (**10**) was assembled in only 9 steps and 16% overall yield from tryptamine. We also propose a new hypothesis of biosynthetic relationship among *Kopsia* pyrroloazocine indole alkaloids by means of two decarboxylation events: the elimination of a carboxylic acid to form a lactone and a photoinduced conversion into the cyclopropane present in the lundurines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13484.

Additional details, theoretical calculations, experimental procedures, and characterization data (PDF)
Crystallographic data for $[Ru(bpy)_2Br_2]Br$ (CIF)
Crystallographic data for (±)-**1** (CIF)
Crystallographic data for (+)-**2** (CIF)
Crystallographic data for (±)-**2** (CIF)
Crystallographic data for (±)-**3** (CIF)
Crystallographic data for (±)-**4** (CIF)
Crystallographic data for (±)-**5** (CIF)
Crystallographic data for (±)-**7** (CIF)
Crystallographic data for (±)-**10** (CIF)
Crystallographic data for (+)-**12** (CIF)
Crystallographic data for (±)-**20** (CIF)
Crystallographic data for (±)-**23** (CIF)
Crystallographic data for (±)-**24** (CIF)
Crystallographic data for (−)-**25S2** (CIF)

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Notes

The authors declare no competing financial interest.

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