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Collective Total Synthesis of (−)-Lundurines A−C

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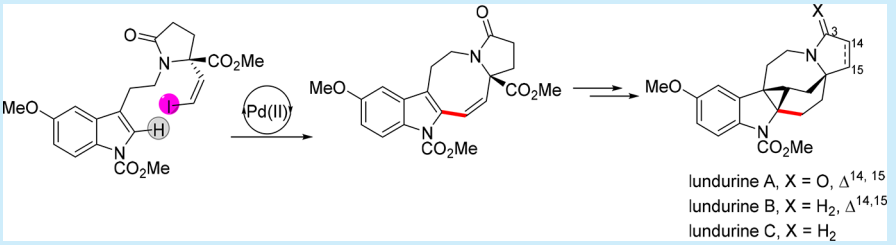
Supporting Information



ABSTRACT: A collective asymmetric total synthesis of lundurines A−C using L-pyroglutamic acid derived from the chiral pool is described. The key steps include a tandem reductive amination/lactamization sequence to introduce the pyrrolidinone ring, a palladium-catalyzed intramolecular direct C−H *vinylation* of indole to construct the crucial polyhydroazocine ring, and a Lewis acid promoted formal [3 + 2] cycloaddition/N_2 extrusion process to install the polysubstituted cyclopropyl ring.

Occurring with molecular complexity and diversity, natural products serve as an important basis for drug development, which has been playing a crucial role in life science.[1] Chemical total synthesis of natural products is the most effective way to obtain these compounds because of their pervasive scarcity in nature. The development of novel strategies to collectively synthesize natural products with similar scaffolds has resulted in greatly improved synthetic efficiency.[2] Over the past century, hundreds of *Kopsia* alkaloids with complex structures have been isolated.[3] Among them, (−)-lundurines A−D (**1**−**4**), isolated from *Kopsia* tenuis by Kam and co-workers in 1995−2004,[4] share a unique hexacyclic skeleton with a pentasubstituted cyclopropane being fused to the indoline moiety, an aza cyclooctane, and a pyrrolidine ring. In addition, several structurally and biogenetically related *Kopsia* indole alkaloids,[4b,5] such as lapidilectine B (**5**),[5a] grandilodines (**6**, **10**, and **11**),[5e] tenuisines (**7**−**9**),[4b,5c,d] lapidilectinol (**12**), and *epi*-lapidilectinol (**13**),[5b] were isolated from the plants of the same genus (Figure 1). Most of these structurally fascinating molecules possess important bioactivities. For example, lundurines B (**2**) and D (**4**) were found to be cytotoxic against B16 melanoma cells in vitro and also showed potential activity to reverse multidrug resistance in vincristine-resistant KB cells.[4b]

Due to their intriguing structure and promising bioactivities, lundurines have attracted considerable attention from synthetic chemists after their isolation, and numerous synthetic explorations have been implemented.[6] A remarkable breakthrough was made by Nishida and co-workers in 2014, as they accomplished the first total synthesis of lundurines A (**1**) and B

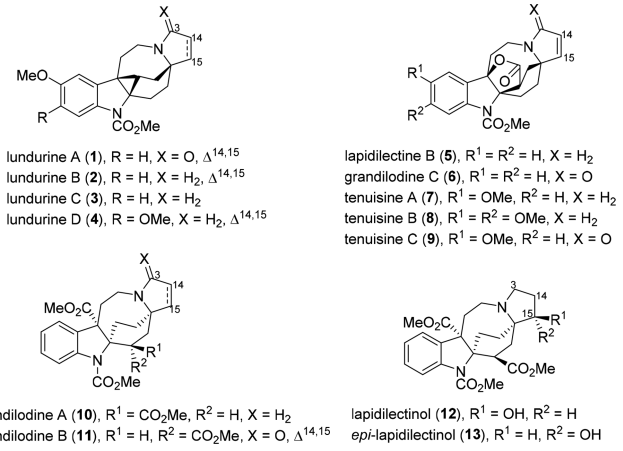


Figure 1. Lundurines (**1**−**4**) and related alkaloids.

(**2**) in racemic form.[6c,d] In the same year, Qin's group achieved the first asymmetric synthesis of (−)-lundurine A (**1**) using an intramolecular Simmons−Smith reaction to establish the cyclopropyl ring and confirmed its absolute configuration.[6f] In 2016, Echavarren and co-workers achieved an elegant and collective asymmetric synthesis of (−)-lundurines A−C (**1**−**3**),[6h] utilizing a gold(I)-catalyzed alkyne hydroarylation to build the crucial eight-membered ring.[6a] Having been continuously interested in the synthesis of indole alkaloids[7] and enamored by

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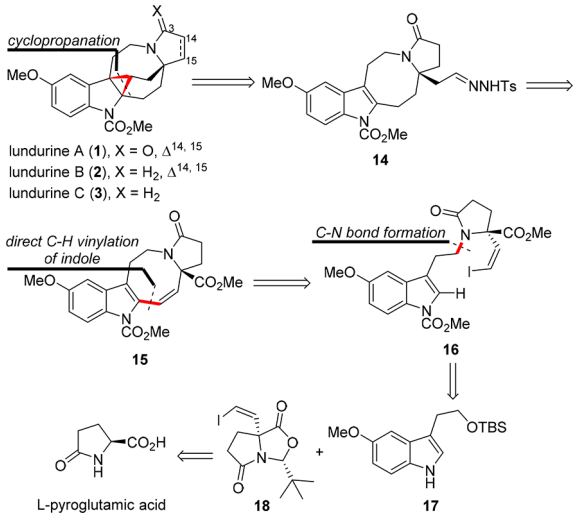
these structurally unique compounds, we initiated a research program to explore the synthesis of lundurine alkaloids. A novel strategy, featuring a tandem reductive amination/lactamization sequence and a palladium-catalyzed direct intramolecular C−H vinylation[8] of indole, was developed, leading to a collective total synthesis of (−)-lundurines A−C.

Our synthetic strategy for the synthesis of lundurines A−C (**1**−**3**) is outlined in Scheme 1. A cyclopropanation[9] could be

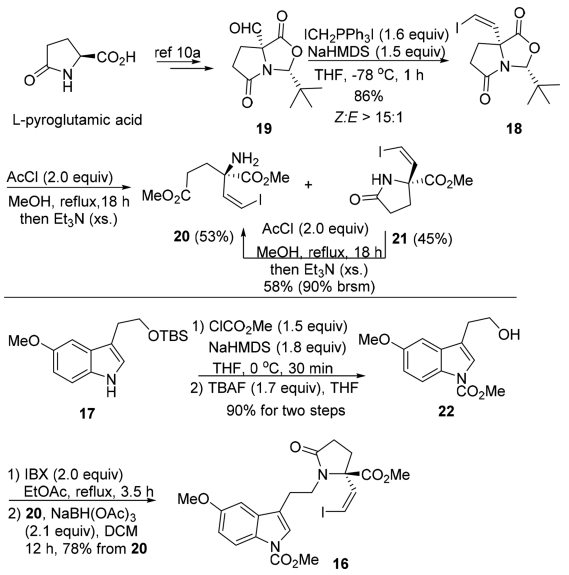
Scheme 1. Retrosynthetic Analysis of Lundurines A−C



achieved through a Lewis acid promoted formal [3 + 2] cycloaddition of sulfonyl hydrazone **14**, followed by extrusion of nitrogen, a novel protocol developed by Echavarren.[6h] Sulfonyl hydrazone **14**, in turn, could be accessed from tetrahydroazocine **15** via a series of functional group transformations. We envisaged that the key tetracyclic intermediate **15** could be obtained from vinyl iodide **16** through a direct ring-closing C−H bond *vinylation* of indole,[8a−j] which has rarely been utilized in natural product synthesis. Disconnection of the C−N bond led to two fragments, i.e., tryptophol derivative **17** and bicyclic compound **18**. The latter could be prepared from commercially available L-pyroglutamic acid in several steps, from which the first chiral quaternary carbon center is established.[10]

Our synthesis commenced with the preparation of vinyl iodide **16**, the key precursor to perform the direct vinylation (Scheme 2). Stork−Zhao−Wittig olefination[11] of known aldehyde **19**, prepared from L-pyroglutamic acid according to the procedure reported previously,[10a] led to the (*Z*)- iodide **18** as the major product (>15:1, *Z*/*E*) in 86% yield after isolation, which underwent a ring-opening alcoholysis in acidic methanol to give two thermodynamically equilibrative compounds, the unstable linear amine **20** (53%), and the lactam **21**(45%). The latter could be partially converted into **20** in 58% yield (90% brsm) under the same conditions. Methoxycarbonylation of the nitrogen atom in 5-methoxyl tryptophol TBS ether **17**, followed by desilylation, afforded alcohol **22** in 90% yield over two steps. Next, we turned our attention to the linkage of C−N bond to obtain vinylation precursor **16**. Extensive attempts toward direct *N*-alkylation of pyrrolidone **21** proved to be problematic. We then tried to explore a reductive amination[12]/lactamization sequence with **20**, a protocol previously used by Echavarren and co-workers.[6a] Oxidation of alcohol **22** with IBX led to the corresponding aldehyde, which

Scheme 2. Synthesis of Vinyl Iodide 16



was very unstable and used for the next step without further purification. Gratifyingly, when a mixture of the aldehyde and amine **20** was treated with $NaBH(OAc)_3$[12a,c] and then reacted for a prolonged period, the reductive amination and the subsequent lactamization proceeded smoothly to give desired iodide **16** in 78% yield from **20**.

With the precursor **16** in hand, the crucial indole C−H vinylation was then evaluated. As summarized in Table 1, the

Table 1. Optimization of the Reaction Conditions[a]

entry	Pd(II)	temp (°C)	time (min)	yield (%)[b]
1	$Pd(OAc)_2$	40	240	22
2	$Pd(OAc)_2$	50	150	31
3	$Pd(OAc)_2$	65	45	35
4	$Pd(OAc)_2$	80	25	38
5	$Pd(OAc)_2$	90	15	45
6	$Pd(OAc)_2$	100	10	40
7	$Pd(TFA)_2$	90	15	58
8	$Pd(MeCN)_2Cl_2$	90	15	56
9	$Pd(dppf)Cl_2$	90	15	38
10	$PdCl_2$	90	15	42

[a]Reaction conditions: **16** (0.23 mmol), Pd(II) (0.1 equiv), AcOK (3.0 equiv), DMF (8 mL). [b]Isolated yields.

reaction was initially carried out with 0.1 equiv of $Pd(OAc)_2$ as the catalyst and AcOK as the base in DMF at 65 °C (entry 3), and the C−H vinylation proceeded smoothly to provide the desired tetrahydroazocine **15**, albeit in poor yield (35%). Encouraged by the success, we then optimized the reaction conditions. Entries 1 and 2 show that only lower yields were obtained, even with a prolonged reaction time when the temperature was lowered. We then elevated the reaction temperature and observed an increase in yields (entries 4 and 5). Surprisingly, a slightly higher temperature (100 °C) led to a

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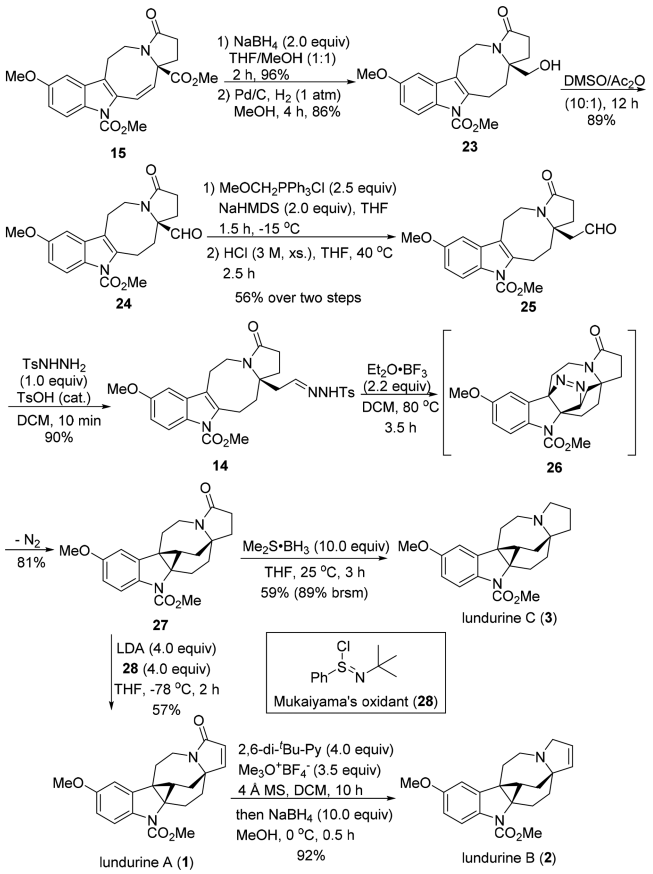
decreased yield (entry 6). Consequently, the optimal temperature turned out to be 90 °C. Furthermore, in order to confirm the effect of catalyst, we substituted $Pd(OAc)_2$ with $Pd(TFA)_2$, $Pd(MeCN)_2Cl_2$, $Pd(dppf)Cl_2$, and $PdCl_2$ (entries 7−10), to perform the reaction, and we found that $Pd(TFA)_2$ gave the highest yield (58%), which was slightly superior to $Pd(MeCN)_2Cl_2$. Several ligands and bases were also employed for further screening; however, we failed to gain a higher yield. Unexpectedly, we found that **16** remained unreacted in the presence of catalytic phosphine ligands (such as PPh_3), or tertiary amines (such as Et_3N) as bases.

Having rapidly constructed the eight-membered ring, our attention was shifted to the challenging cyclopropanation and the completion of the total synthesis of lundurines A−C (**1**−**3**). Thus, reduction of the α-amino carboxylic ester **15** with $NaBH_4$ provided the corresponding alcohol in 96% yield, and hydrogenolysis of the double bond delivered **23**. Upon exposure to a mixture of 10:1 (v/v) DMSO and Ac_2O,[13] compound **23** was oxidized to aldehyde **24** in 89% yield. Aldehyde **25** was obtained in 56% overall yield via a two-step homologation sequence. Condensation of compound **25** with tosyl hydrazine in the presence of catalytic tosylic acid afforded hydrazone **14**, a scaffold poised for cyclopropanation (Scheme 3).

According to Echavarren's protocol,[6h] exposure of hydrazone **14** to $Et_2O{\cdot}BF_3$ at 80 °C yielded cyclopropane **27** via N_2 extrusion of pyrazoline intermediate **26**, which was not isolated due to its instability (Scheme 3). At this point, further elaboration of the lactam ring was required to complete the synthesis. Reduction of **27** with $Me_2S{\cdot}BH_3$ proceeded smoothly

Scheme 3. Total Synthesis of (−)-Lundurines A−C



to furnish (−)-lundurine C (**3**) in 89% (brsm) yield with a small amount of lactam remaining. However, the optical rotation ($[\alpha_D^{598}$ = −2.0°, CH_2Cl_2, *c* 1.0, 294 K]) of the synthetic lundurine C (**3**) is close to Echavarren's value ($[\alpha_D^{598}$ = −6.2 ± 0.8°, CH_2Cl_2, *c* 0.3, 301 K]) but significantly different from the one reported by Kam ($[\alpha_D^{598}$ = −25°, $CHCl_3$, *c* 0.067]).[4] On the other hand, lithium enolate generated from **27** in the presence of LDA at −78 °C was oxidized with Mukaiyama's oxidant **28** (*N*-*tert*-butylbenzenesulfinimidoyl chloride)[14] to furnish (−)-lundurine A (**1**) in a single step. Lundurine A (**1**) showed an optical rotation ($[\alpha_D^{598}$ = −114.0°, $CHCl_3$, *c* 1.0, 297 K]) similar to the value of the natural product ($[\alpha_D^{598}$ = −90°, $CHCl_3$, *c* 0.09]). Finally, *O*-methylation of the unsaturated lactam with Meerwein's salt ($Me_3O^+BF_4^-$) and subsequent $NaBH_4$ reduction of the resulting iminium ion yielded (−)-lundurine B (**2**), with an optical rotation ($[\alpha_D^{598}$ = −27.9°, $CHCl_3$, *c* 0.43, 296 K]) similar to that of the natural product ($[\alpha_D^{598}$ = −34°, $CHCl_3$, *c* 0.16]). The spectral data of synthetic lundurines A−C are identical to those reported for natural products[4] and previous syntheses.[6]

In conclusion, we have accomplished a collective asymmetric total synthesis of lunduines A−C (**1**−**3**) in 15, 16, and 15 steps, respectively, from tryptophol derivative **17** and bicyclic compound **18**. Optically pure and readily available L-pyroglutamic acid was employed as the chiral pool to establish the first chiral quaternary carbon center. The pyrrolidone ring was forged through a tandem reductive amination/lactamization sequence. A palladium(II)-catalyzed direct C−H *vinylation* of indole allowed us to rapidly construct the central eight-memberd ring. Finally, the pentasubstituted cyclopropanyl ring was installed by a late-stage Lewis acid promoted formal [3 + 2] cycloaddition/N_2 extrusion process.[6h] Further synthetic exploration of related indole alkaloids is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00210.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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