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Total Synthesis of (±)-Lundurine B

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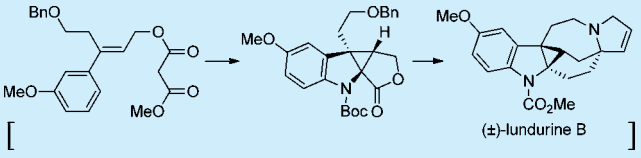
Supporting Information

ABSTRACT: A total synthesis of (±)-lundurine B was accomplished. A combination of stereoselective intramolecular cyclopropane formation and aryl amination furnished cyclopropane-fused indoline stereoselectively. Ring-closing metathesis (RCM) of siloxy diene and intramolecular aminoacetal formation followed by bridgehead vinylation of an anti-Bredt iminium cation led to the construction of six- and seven-membered rings with a quaternary carbon center. After the formation of dihydropyrrole by RCM, the Boc-protecting group of indoline was converted into the corresponding methyl carbamate via silyl carbamate to complete the total synthesis of (±)-lundurine B. The characteristic rearrangement of the cyclopropane-fused indoline skeleton is also described.



The genus *Kopsia* has been used in folk medicine and is a rich source of biologically active alkaloids.[1] These alkaloids have been reported to have unique polycyclic skeletons. Lundurines, which were first isolated from *Kopsia tenuis* by Kam and co-workers in 1995, are some of the most unique alkaloids in this category.[2] These compounds have an intriguing hexacyclic framework that includes an unprecedented cyclopropane-fused indoline skeleton. In addition to their interesting structures, lundurines have also been shown to have intriguing biological activities. Lundurines B (**1**) and D (**2**) (Figure 1) exhibit appreciable toxicity toward B16 melanoma

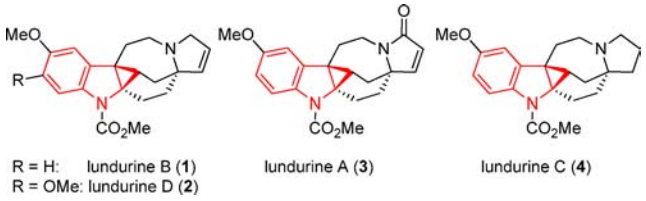
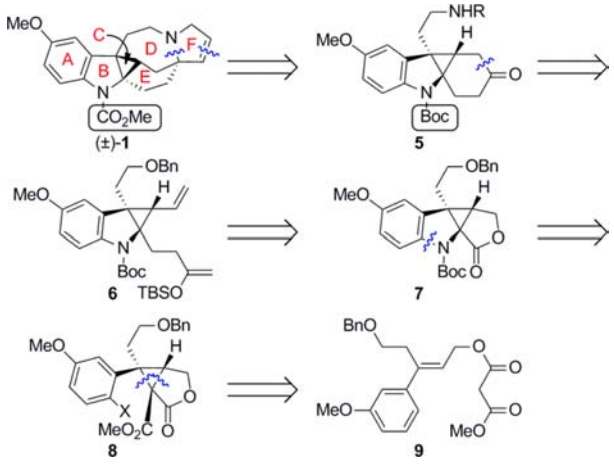


Figure 1. Structures of lundurine alkaloids.

cells and also reverse multidrug resistance in vincristine-resistant KB cells.[2b] These findings suggested that lundurines are promising leads for new antitumor drugs. However, no total synthesis of lundurines, or even a synthetic approach to their skeleton, has been reported to date.[3,4] Here we report a total synthesis of (±)-lundurine B (**1**).

A retrosynthetic analysis of **1** is outlined in Scheme 1. The dihydropyrrole and azacycloheptane rings (F and D rings) were prepared in a later stage of the synthesis from tetracyclic key intermediate **5**. The cyclohexanone ring of **5** (ring E) would be synthesized by the ring-closing metathesis (RCM) of siloxy diene **6**.[5] Intermediate **6** could be prepared from lactone **7** which contains a cyclopropane-fused indoline skeleton. For the construction of **7**, we envisioned the combination of intramolecular cyclopropanation and aryl amination. A key pentasubstituted cyclopropane intermediate should be derived

Scheme 1. Retrosynthesis



in a stereoselective manner from cinnamyl malonate **9** using a method developed by Töke and co-workers.[6]

The cyclopropanation precursor **9** was prepared from ethyl 5-(benzyloxy)pent-2-ynoate **10**[7] by palladium-catalyzed hydroarylation to give **11**,[8] followed by reduction with DIBALH and acylation (Scheme 2). According to the reported procedure,[6] **9** was subjected to iodine-mediated cyclopropanation to give **12a** and **12b** in high yield and selectivity. Saponification of both the lactone and ester of **12a** followed by acidification gave lactone-carboxylic acid, which was subjected to Curtius rearrangement to afford Boc-protected amine **13**. Site selective bromination of the aromatic ring proceeded to give **14**. Copper-mediated cyclization[9] occurred smoothly and gave the desired tetracyclic intermediate **7** in good yield.

We were interested in the characteristic reactivity of cyclopropane-fused indolines, including natural lundurines.

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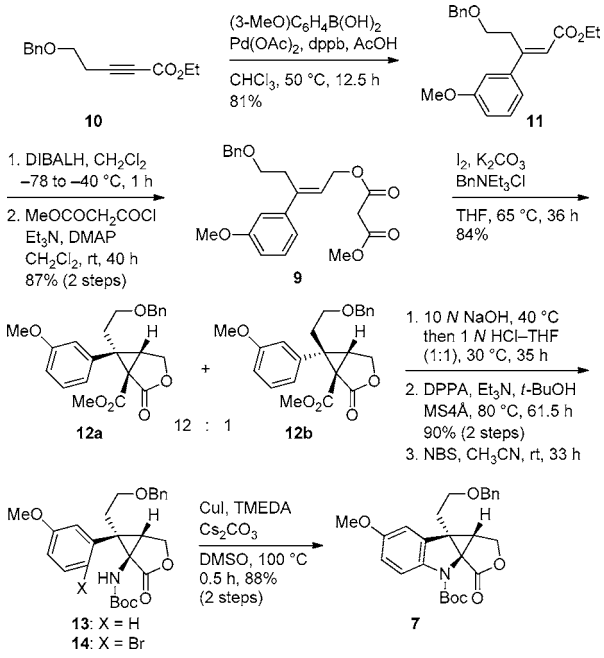
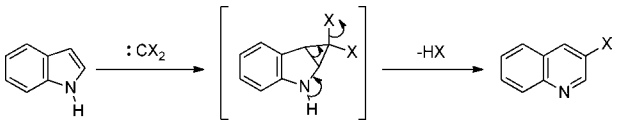
Scheme 2. Synthesis of Cyclopropane-Fused Indoline 7



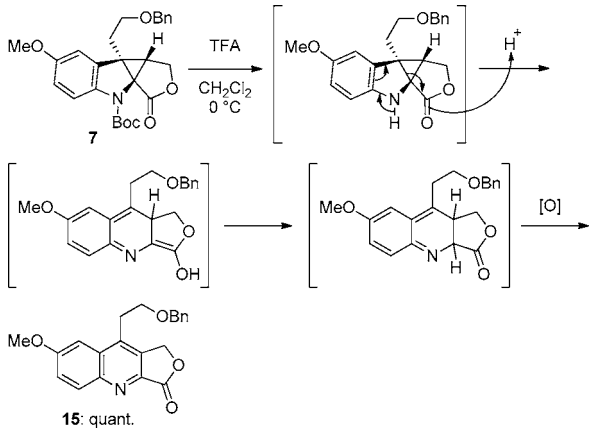
The old rearrangement of cyclopropane-fused indolines prepared by the reaction of indole and dihalocarbene gives a quinoline skeleton with a release of strain energy (Scheme 3).[10,11] This particular reactivity should be closely related to the stabilities of the intermediates and the success of the total synthesis.

Scheme 3. Rearrangement of Cyclopropane-Fused Indolines



With the cyclopropane-fused indoline in hand, we tested the stability of the skeleton under acidic conditions (Scheme 4).[12] When intermediate **7** was treated with TFA at 0 °C, deprotection of a Boc group and ring expansion occurred rapidly to give quinoline **15** in quantitative yield. This result

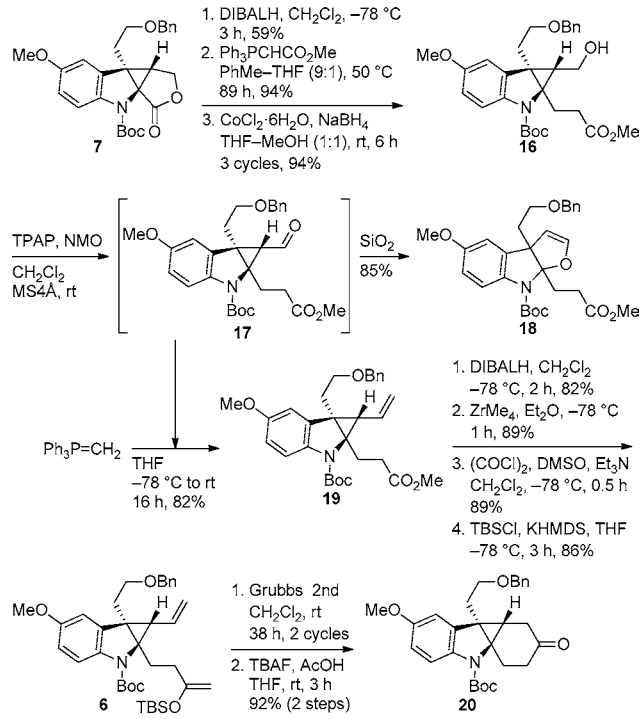
Scheme 4. Acid-Promoted Rearrangement of 7 to Quinoline 15



suggested that the methoxycarbonyl group of lundurines should be installed by transcarbamation[13] without deprotection of a Boc group.

Next, lactone **7** was reduced to the corresponding lactol, which was subjected to a Wittig reaction followed by the reduction of olefin to afford **16** (Scheme 5).[14] Next, the

Scheme 5. Synthesis of ABCE Core Skeleton



primary alcohol of **16** was oxidized to the corresponding aldehyde **17** and the reaction mixture was poured into a solution of Wittig reagent to introduce a vinyl group[15] because the instability of **17** gave rearranged **18** under silica gel column chromatography. To construct a fused cyclohexanone under mild conditions, the ring-closing metathesis of siloxy diene was an ideal transformation. For this purpose, an ester moiety of **19** was converted to the corresponding ketone by reduction, methylation,[16,17] and oxidation. The resulting ketone was silylated to give cyclization precursor **6**. Ring-closing metathesis of **6** proceeded under standard conditions using a second-generation Grubbs catalyst. Careful removal of the TBS group under slightly acidic conditions gave the desired ketone **20** in good yield.

We next focused on the formation of azacycloheptane by the intramolecular formation of a N,O-acetal on a cyclohexane carbonyl group.[18] A carbonyl group in **20** was converted to ketal,[19] and the benzyl ether was transformed to a 2-hydroxyethylamino group by deprotection, oxidation, and reductive amination to give **21** (Scheme 6). When the ketal group was removed, transacetalization occurred to give the desired cyclized product **22** in 81% yield.

The next task was vinylation of the acetal with cleavage of the C−O bond via a cyclic iminium cation intermediate.[20] A slight modification of the procedure developed by Kibayashi[18] worked nicely to give the desired vinylated product **23** as a sole product. The resulting hydroxyethyl group was converted to a propenyl group by oxidation followed by a Wittig reaction to give diene **24**. Ring-closing metathesis of **24** was again

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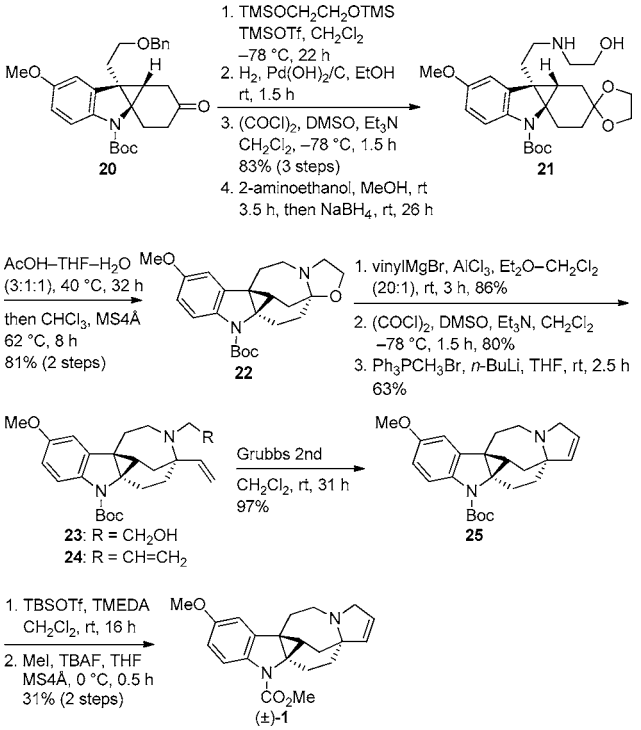
Scheme 6. Total Synthesis of (±)-Lundurine B (1)



adopted to afford **25**, which contains the entire carbon framework of lundurine B.

A key transcarbamation of Boc to methyl carbamate has been studied by Ohfune, and an efficient conversion via silyl carbamate has been reported.[13] The original conditions for the formation of silyl carbamate did not work at all because of the steric hindrance of the N-Boc group in **25**. The use of TMEDA instead of 2,6-lutidine or triethylamine was crucial for silyl carbamate formation. The crude silyl carbamate was converted to (±)-lundurine B (**1**) in 31% yield by methylation in the presence of MS4 Å. The spectral data of synthetic (±)-lundurine B were identical to those of natural lundurine B.[2]

In summary, a total synthesis of (±)-lundurine B was achieved from known **10** in 29 steps. This synthesis features a highly efficient and stereoselective synthesis of cyclopropane-fused indoline, siloxy-diene RCM for a fused cyclohexanone, bridgehead vinylation, and transcarbamation of a hindered N-Boc group. An asymmetric version of this total synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra. 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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