Natural Products

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A Concise and Versatile Synthesis of Alkaloids from *Kopsia tenuis*: Total Synthesis of (±)-Lundurine A and B**

*Shigeru Arai, Masaya Nakajima, and Atsushi Nishida**

Abstract: *A total synthesis of (±)-lundurines A and B is described. These natural products have a unique hexacyclic skeleton which includes a cyclopropane-fused indoline. A stereospecific construction of the pentasubstituted cyclopropane core was achieved, by radical cyclization using SmI_2, with perfect stereoselectivity. Cyclizations to give seven- and five-membered heterocycles, under palladium and ruthenium catalysis, respectively, accomplished the total syntheses. The late-stage construction of the F ring by ring-closing metathesis enabled access to the title compounds from a spiroindoline intermediate which is a common structure of other kopsia alkaloids.*

Kopsia alkaloids are interesting molecules because of their biological activities and their unique polycyclic skeletons (Figure 1). For their synthesis or scalable preparation, facile access to the spiroindoline core, shown in red, should lead to a unified total synthesis of all of the related alkaloids shown.

The *kopsia* alkaloids called lundurines have been particularly attractive compounds for synthetic chemists because they are the only natural products which have an indoline cyclopropane structure and most of the stereogenic centers, including two quaternary carbon atoms, which are part of the cyclopropane ring. However, while their biological effects, such as the high toxicities of lundurines B and D toward B16 melanoma cells and reverse multidrug resistance in vincristine-resistant KB cells, are also interesting, their limited availability and scalable preparation has constrained their application as a biological tool.[1a,b] Since their discovery by Kam and co-workers in 1995,[1] the total synthesis of these natural products has been a challenging issue. However, only two synthetic approaches have been reported to date.[2a,b]

Very recently, we developed a stereoselective method for the synthesis of cyclopropane-fused indolines and applied it to the total synthesis of (±)-lundurine B (**1b**).[2c] Boc protection on the nitrogen atom of the indoline was a key point in this synthesis because its removal from **1e** (for structure see Scheme 1) caused the cleavage of the cyclopropane into a quinoline and the transcarbamation of **1e** into **1b** was quite unsatisfactory (32% yield). These results prompted us to introduce methyl carbamate to the indoline nitrogen atom at an earlier stage of the total synthesis, and a revised synthetic strategy was investigated. Herein we describe the effective conversion of the spiroskeleton into the cyclopropane-fused indoline and confirm the structure of **1a** through its first total synthesis.

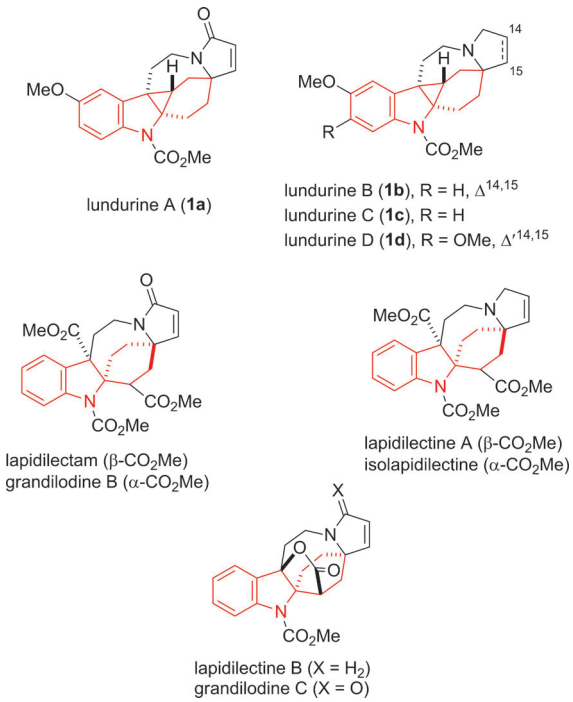

Figure 1. Structure of lundurines and related alkaloids.

Our focus was the facile preparation of **5**, and the retrosynthesis of **1a** is outlined in Scheme 1. Since this synthetic strategy includes the late-stage construction of the F ring by ring-closing metathesis (RCM), a general and facile access to all lundurines could be achieved unlike our previous synthesis of lundurine B.[2c] The precursor of the F ring was designed to be the diene **2** and formation of the D ring could be achieved by a palladium-catalyzed intramolecular amination of **3**. The key step for the preparation of the cyclopropane core is a radical coupling reaction between electron-deficient olefins. Once radical species are generated at each of the β-positions to the carbonyls in **5**, these carbon radicals could be connected stereoselectively because of the rigid structure of **4**. The ester and ketone carbonyls in **4** can be independently transformed into the corresponding primary amine and allyl

[*] Prof. S. Arai, M. Nakajima, Prof. A. Nishida
Graduate School of Pharmaceutical Sciences, Chiba University
1-8-1 Inohana, Chuo-ku, Chiba 2608675 (Japan)
E-mail: anishida@faculty.chiba-u.ac.jp

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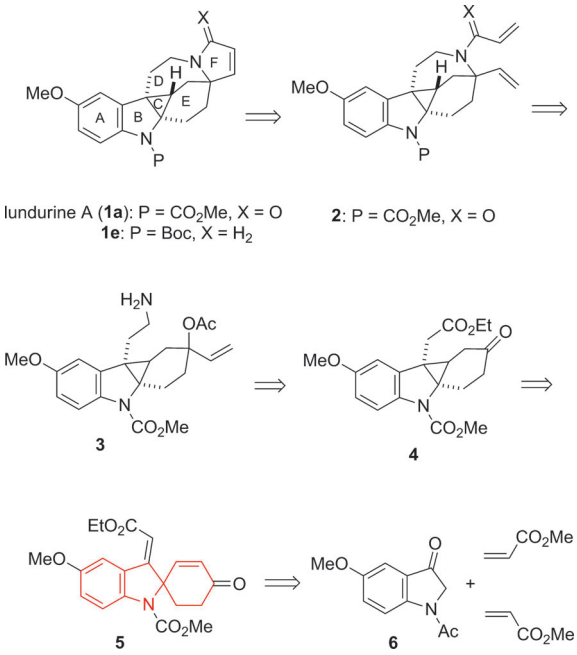


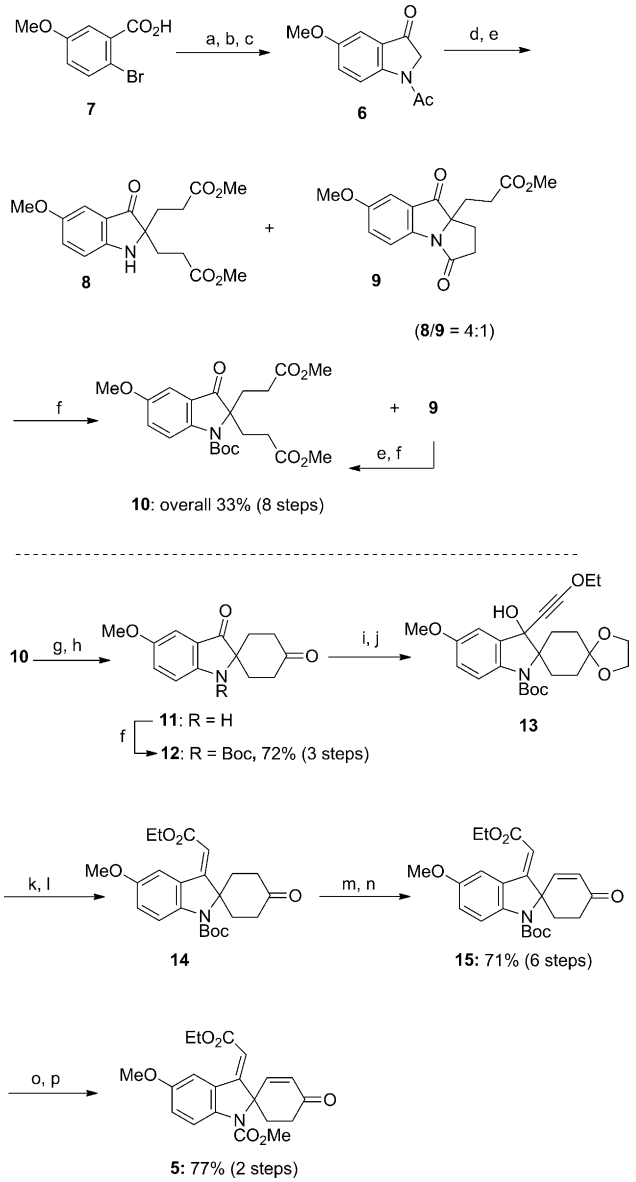
Scheme 1. Retrosynthesis of **1a**.

acetate in **3**. The key spiro-intermediate **5** can be constructed by double Michael addition with subsequent Dieckmann condensation, decarboxylation, and oxidation from the known compound **6**.

5-Methoxy-3-oxoindoline (**6**) was prepared from **7** as reported in the literature (Scheme 2).[3] Michael addition and deacetylation with base gave an inseparable mixture of **8** and **9** (4:1 ratio). The resulting mixture was subjected to N-Boc protection to give **10** along with unreacted **9**, which was easily converted into **10** by ring-opening followed by N-Boc protection. The overall yield of **10** was 33% from **7** with a single purification by chromatography (87%, average yield).

The treatment of **10** with LHMDS for the Dieckmann condensation with subsequent decarboxylation gave **11**, which was readily protected with a Boc group (72% yield in 3 steps; (Scheme 2). After acetalization[4]of the less-hindered carbonyl, nucleophilic addition of lithium acetylide gave the tertiary alcohol **13**, which was smoothly converted into the corresponding unsaturated *E*-ester **14** by copper(II)-catalyzed Meyer–Schuster rearrangement[5] followed by deacetalization. A subsequent Saegusa–Ito reaction,[6] proceeding via the TMS enol ether after the removal of aceta,l gave **15** in 71% yield from **12** (6 steps). To avoid the cleavage of the cyclopropane to give the quinoline,[2c,7] a methyl carbamate was readily introduced at this stage. Treatment with TFA and subsequent acylation gave **5** in 77% yield.

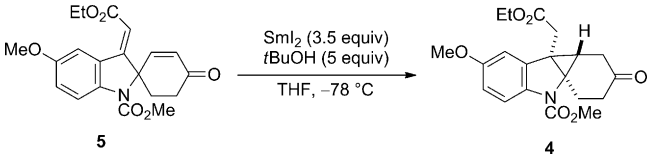
With a key precursor for cyclization in hand, we next investigated SmI_2-mediated intramolecular radical cyclization (Table 1).[8a–d] When the spiroenone **5** was treated with 3.5 equivalents of SmI_2 at −78 °C in the presence of *t*BuOH in THF, the desired cyclopropane **4** was obtained in 34% yield (entry 1). This product was assigned to be the desired cyclopropane, and two newly generated stereogenic centers



Scheme 2. Preparation of **5**. Reagents and conditions: a) KOH (2.3 equiv), glycine (1.5 equiv), K_2CO_3 (1.0 equiv), Cu powder (0.7 mol%), H_2O, reflux, 20 h; b) NaOAc (1.2 equiv), Ac_2O, reflux, 3 h; c) Na_2SO_3 (1.5 equiv), H_2O/EtOH (1:2), reflux, 3 h; d) Methyl acrylate (3 equiv), DBU (3 equiv), THF, RT, 24 h; e) K_2CO_3 (3 equiv), MeOH, RT, 3 h; f) Boc_2O (2 equiv), NEt_3, (3 equiv), DMAP (0.5 equiv), THF, reflux, 10 h; g) LHMDS (3 equiv), THF, −40 °C, 14 h; h) wet DMSO, NaCl (1 equiv), 160 °C, 4 h; i) $(TMSOCH_2)_2$ (2 equiv), TMSOTf (0.33 equiv), CH_2Cl_2, −78 °C, 2 h; j) ethoxyacetylene (2 equiv), *n*BuLi (2 equiv), THF, −78 °C to RT, 3 h; k) $Cu(OTf)_2$ (5 mol%), CH_2Cl_2/EtOH (4:1), RT, 2 h; l) TsOH (0.3 equiv), acetone, 40 °C, 14 h; m) LHMDS (2 equiv), TMSCl (3 equiv), THF, −78 °C, 1 h; n) $Pd(OAc)_2$ (0.25 equiv), DMSO, O_2, RT, 15 h; o) trifluoroacetic acid (2 equiv), TMSOTf (1 equiv), CH_2Cl_2, 0 °C, 15 min; p) K_2CO_3 (3 equiv), $ClCO_2Me$, reflux, 13 h. Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-(N,N-dimethylamino)pyridine, DMSO = dimethylsulfoxide, LHDMS = lithium hexamethyldisilazide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

were successfully controlled through this cyclization. The addition of HMPA to enhance reactivity resulted in lower

Table 1: SmI_2-mediated cyclopropanation of **5**.



5 **4**

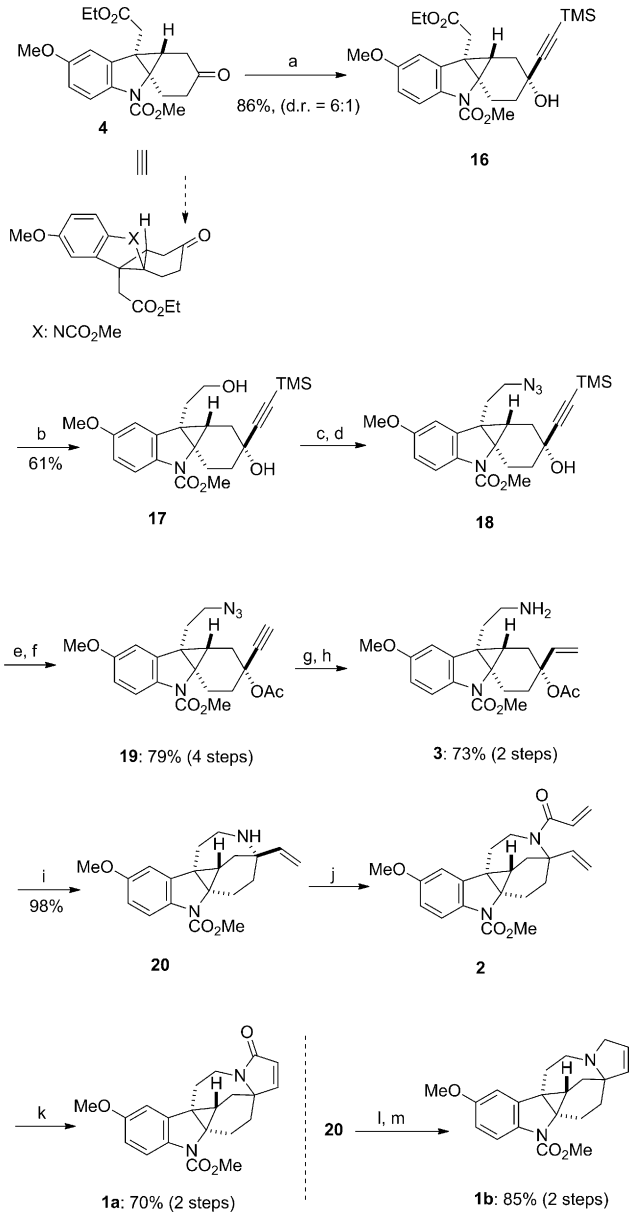
Entry	Additive (equiv)	*t*	Yield [%][a]
1	none	3 h	34
2	HMPA (12)	5 min	23
3	LiBr (20)	1 min	42
4	LiCl (20)	1 min	52

[a] Yield of isolated product, except entry 2 in which yield was estimated by ^1H NMR spectroscopy.

conversion into give **4** along with the recovery of **5** and unidentified products (entry 2). In contrast, the addition of LiCl or LiBr[9] promoted the cyclization of **5** and gave **4** in 52 or 42% yields, respectively (entries 3 and 4). These salts were effective for smooth conversion and gave a single isolable product (**4**) without the recovery of **5**. While the reaction details are still unclear, the side reaction might be the polymerization of **4** or **5**.

To construct the D ring, a lithium trimethylsilylacetylide was initially introduced to the ketone carbonyl in **4** to give **16** as a mixture of diastereomers in a ratio of 6:1 (Scheme 3). The stereochemistry of the major isomer could be predicted by a result similar to that reported in Pearson's total synthesis of lapidilectine B.[2d,e] A bulky ester moiety could prevent attack from the α site, and thus the axial attack of a small and linear nucleophile, such as acetylide, occurred from the β site, selectively.

Further transformation for formation of the D ring was as follows: reduction of **16** by $LiBH_4$ gave the primary alcohol **17** in 61% yield. The primary hydroxy group in **17** was then converted into the azide **18** via the tosylate, and subsequent protodesilylation and O-acetylation gave **19** in 79% yield (4 steps).[10] Sequential reduction of the azide by SmI_2[11] and hydrogenation of the triple bond successfully proceeded to give the cyclization precursor **3** (73% in 2 steps). The compound **3** was smoothly transformed into **20**, which involves an aza-cycloheptane ring, under palladium catalysis in 98% yield.[12] Finally, we focused on completing the total synthesis. For construction of the F ring, we chose a metathesis strategy and the precursor **2a** was prepared by the acylation of **20**. Subsequent RCM using Grubbs second-generation catalyst proceeded smoothly, even at 50°C in DCE, to accomplish the total synthesis of **1a** in 70% yield (2 steps). A similar strategy of N-allylation and subsequent RCM using **20** completed the total synthesis of **1b** in 85% yield (2 steps). The spectroscopic data for both synthetic and natural lundurine A and B were in excellent agreement with published values.



Scheme 3. Total synthesis of **1a** and **1b**. Reagents and conditions: a) *n*BuLi (1.1 equiv), TMSC≡CH (1.1 equiv), Et_2O, −78°C, 5 h, (d.r. = 6:1); b) $LiBH_4$ (5 equiv), EtOH (5 equiv), THF, RT, 20 h; c) TsCl (2 equiv), NEt_3 (5 equiv), DMAP (0.5 equiv), CH_2Cl_2, RT, 2 h; d) NaN_3 (3 equiv), DMF, 80°C, 2 h; e) K_2CO_3 (5 equiv), MeOH, RT, 1.5 h; f) Ac_2O (5 equiv), DMAP (1 equiv), pyridine, 65°C, 17 h; g) SmI_2 (3 equiv), THF, 0°C, 10 min; h) Lindlar cat, quinoline (2 equiv), AcOEt, RT, 3 h, 73% (2 steps); i) $[Pd(PPh_3)_4]$ (20 mol%), NEt_3 (3 equiv), MeCN, 65°C, 13 h; j) CH_2=CHCOCl (4 equiv), NEt_3 (6 equiv), DMAP (cat.), CH_2Cl_2, 0°C, 2 h; k) Grubbs second-generation (20 mol%), $(CH_2Cl)_2$, 50°C, 12 h; l) allyl bromide (10 equiv), K_2CO_3 (20 equiv), MeCN, 50°C, 2 h; m) Grubbs second-generation (20 mol%), CH_2Cl_2, RT, 12 h. DMF = *N*,*N*-dimethylformamide.

In summary, we have succeeded in the total synthesis of (±)-lundurine A and B by using a new radical cyclization protocol to join the unsaturated ester and ketone. A key cyclopropanation mediated by SmI_2 is quite suitable for the synthesis of a highly functionalized cyclopropane core because of 1) perfect stereoselectivity and 2) efficacy of transformation of both oxygen functionalities to achieve elegant construction of the C, D, and F rings at a late stage in the synthesis. The spiroindoline intermediate **5** is expected to be a versatile intermediate for the unified total synthesis of

the *Kopsia* alkaloid family and further studies are currently underway.

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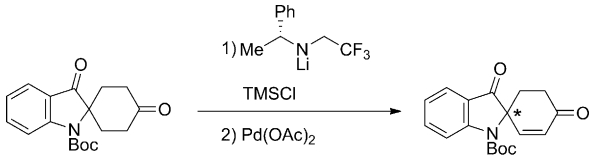

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