

Total Synthesis

Total Synthesis of (–)-Lundurine A and Determination of its Absolute Configuration**

Shuaijiang Jin, Jing Gong, and Yong Qin*

Abstract: A 15-step total synthesis of (–)-lundurine A (**1**) from easily accessible (*S*)-pyrrolidinone **18** is reported. A Simmons–Smith reaction allows the efficient, simultaneous assembly of the cyclopropyl C ring, the six-membered D ring, the seven-membered E ring, and the quaternary carbon stereocenters at C2 and C7. The absolute configuration of natural (–)-lundurine A was deduced to be 2*R*,7*R*,20*R* based on the stepwise construction of the stereocenters during the total synthesis.

Lundurines A–D (**1–4**, Figure 1) are *Kopsia* alkaloids isolated from Malaysian *Kopsia tenuis*,^[1] and effective at bypassing multidrug resistance in vincristine-resistant KB cells (IC₅₀ 4.6–14.2 μg mL^{−1}). Lundurines B and D also show promising in vitro cytotoxic activity against B16 melanoma cells (IC₅₀ 2.8–7.2 μg mL^{−1}).^[1b] Lundurines A–D are biosynthetically related to several indoline alkaloids isolated from the same genus of plants,^[2] including (iso)lapidilectines (**5**, **7**, and **8**), grandilodines (**6** and **10**), lapidilectam (**9**), and pauciflorines (**11** and **12**). Lundurines are attractive targets to synthetic chemists not only because of their promising biological activities, but also because of their unusual

skeleton. These alkaloids consist of a hexacyclic ring system that includes a unique cyclopropyl ring fused to an indoline ring, as well as three quaternary carbon stereocenters. The major challenge in the synthesis of lundurines is the stereoselective formation of the cyclopropyl ring. Intensive efforts toward the synthesis of lundurines^[3] and biosynthetically related alkaloids^[4,5] have led to two long total syntheses of racemic lundurines A and B from Nishida and co-workers.^[6] However, they did not address the absolute configuration of the naturally occurring compounds in their racemic synthesis. Here we report a concise asymmetric total synthesis of (–)-lundurine A (**1**), and deduce its absolute configuration.

The retrosynthetic analysis of lundurine A is shown in Scheme 1. We envisioned a Simmons–Smith reaction (**11** to **1**) to simultaneously assemble the C, D, and E rings and create

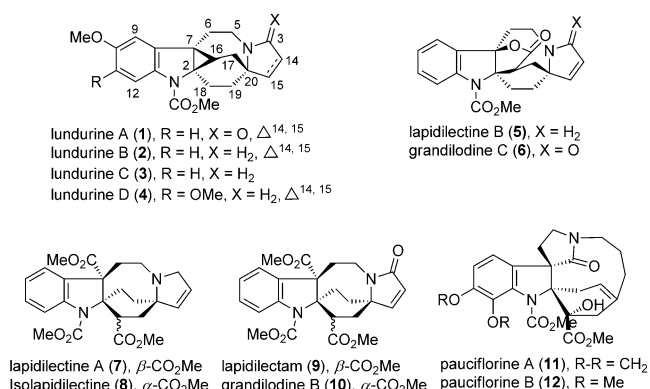
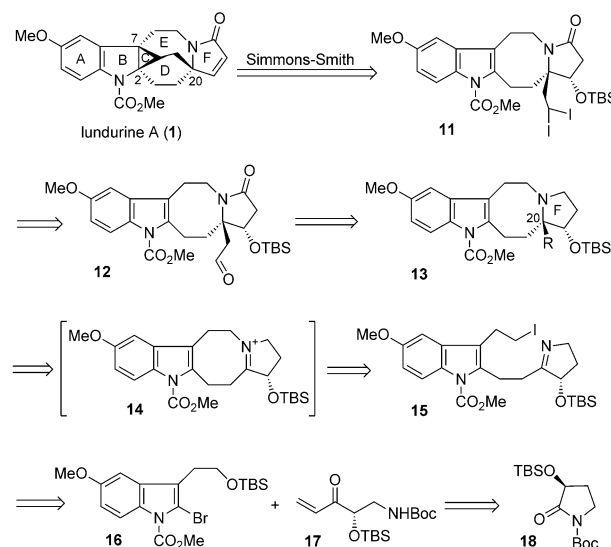


Figure 1. Structure of lundurines and biosynthetically related alkaloids.



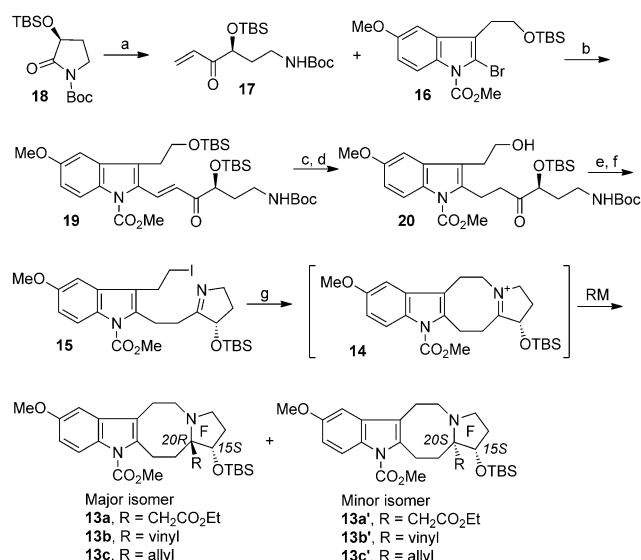
Scheme 1. Retrosynthetic analysis of lundurine A (**1**).

two quaternary carbon centers at C2 and C7. Diiodide **11** can be readily prepared from aldehyde **12** using Barton's protocol. Aldehyde **12** can be generated by regioselective oxidation of the tertiary amine, followed by modification of the R functional group in **13**. Stereoselective organometallic addition to the iminium cation in **14**, which can be generated in situ from imine **15**, allows construction of the quaternary carbon center at C20 and the F ring in **13**. Imine **15** can be prepared from bromo indole **16** and enone **17** through a Heck reaction. Enone **17** can be generated from easily accessible (*S*)-pyrrolidinone **18**.

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Scheme 2. Preparation of the F ring intermediate **13**. Reagents and conditions: a) VinylMgBr (1.5 equiv), THF, 0 °C, 2 h, 72 %; b) Pd(Ph₂PCH₂CH₂PPh₂)₂ (0.2 equiv), K₂CO₃ (3 equiv), toluene, reflux, 4 h, 81 %; c) H₂ (balloon), Pd/C (10 %), EtOAc, 25 °C, 5 h, 88 %; d) HOAc:THF:H₂O 1:2:1, 25 °C, 24 h, 94 %; e) I₂ (2 equiv), imidazole (3 equiv), PPh₃ (3 equiv), CH₂Cl₂, 25 °C, 30 min, 84 %; f) TMSOTf (5 equiv), 2,6-lutidine (8 equiv), CH₂Cl₂, 25 °C, 1 h, 82 %; g) MeCN, reflux, 1 h. TMSOTf = trimethylsilyl triflate.

Based on this retrosynthetic analysis, we commenced our total synthesis by preparing the F-ring compound **13** (Scheme 2). Vinylmagnesium bromide addition to (*S*)-pyrrolidinone **18**^[7] provided enone **17** in 72 % yield. Heck coupling of **17** with bromoindole **16**^[8] gave **19** in 81 % yield. Hydrogenation of the double bond in **19**, followed by selective removal of the TBS protecting group afforded **20** in high yield. Iodinating the hydroxy group of **20** and removing the Boc protecting group generated the five-membered imine intermediate **15**. Heating a solution of this imine intermediate **15** in acetonitrile generated the iminium intermediate **14**. This intermediate was then reacted, without purification, with organometallic reagents in THF at −78 °C to form the quaternary carbon center at C20. The results are summarized in Table 1.

Table 1: Two-step addition of organometallic reagents to **14**.

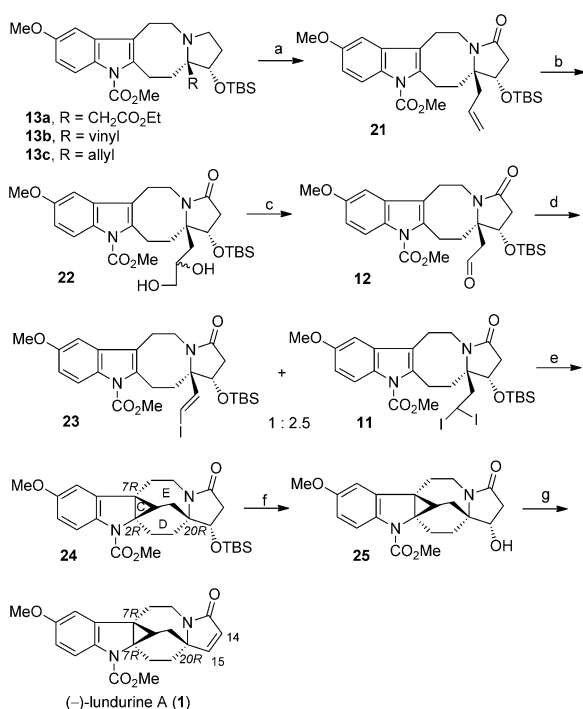
Entry	Reagents	Yield of 13 [%] ^[a]	Ratio (major:minor) ^[b]
1	EtOAc/LDA	41 (13a + 13a')	1:1
2	EtOAc/LiHMDS	46 (13a + 13a')	2:1
3	EtOAc/NaHMDS	27 (13a + 13a')	6:1
4	vinylMgBr	62 (13b + 13b')	> 30:1
5	allylMgBr	65 (13c + 13c')	5:1

[a] Yield of isolated product. [b] Ratio was determined by ¹H NMR analysis of the crude product.

We anticipated that organometallic addition to the iminium cation **14** should occur preferentially at the upper face and thereby provide the desired *R* stereoisomer as the major product, because the lower face of **14** is shielded by the bulky TBS protecting group. Unfortunately, initial experiments using the lithium enolate of ethyl acetate (LDA as a base) gave a 1:1 mixture of **13a** and **13a'** in 41 % yield (2 steps from **15**, Table 1, entry 1). Repeating this addition with bulky LiHMDS instead of LDA gave a slightly better 2:1 ratio of **13a** and **13a'** (Table 1, entry 2). We suspect that the poor selectivity of lithium enolate addition to **14** is caused by a coordination effect between lithium enolate and the siloxy group adjacent to the iminium cation.^[9] This interaction favors enolate addition from the lower face. Consistent with this interpretation, replacing lithium enolate with sodium enolate gave a much better 6:1 ratio of **13a** and **13a'**, though the yield was only 27 % (Table 1, entries 1–3). Adding vinylmagnesium bromide to **14** provided **13b** as the sole stereoisomer in 62 % yield (Table 1, entry 4). Similarly, the reaction of allylmagnesium bromide with **14** provided **13c** and **13c'** in an acceptable ratio of 5:1 and 65 % yield (Table 1, entry 5). NOE experiments showed NOE correlation between the proton at C15 and the protons in the R group of major isomers **13a–c**, confirming an (*R*)-configuration at C20 for the major stereoisomers. No such NOE correlation was found between the proton at C15 and the protons in the R group in the minor isomers **13a'** and **13c'**.

Having established the quaternary carbon stereocenter at C20 with an *R* configuration, we continued the synthesis of (–)-lundurine A from **13a–c** (Scheme 3). Initial attempts using DIBAL-H or LiAlH₄ to selectively reduce the ester group in **13a** to an aldehyde or hydroxy group failed because of a lack of selectivity between the ester and the carbamate groups. Trying to convert the sterically hindered double bond in **13b** to a hydroxy group through hydroboration using 9-BBN or BH₃ was unsuccessful under various conditions. Ozonolysis of the double bond in **13c** in CH₂Cl₂ at −78 °C also failed to give the desired product. This reaction not only converted the double bond in **13c** to an aldehyde functional group, but also led to the decomposition of the electron-rich indole substructure. In the end, after oxidizing the tertiary amine to an amide (from **13c** to **21**) with RuCl₃ and NaIO₄,^[10] we were able to cleave the double bond in **21** to an aldehyde group by a two-step procedure: dihydroxylation of **21** with AD-mix-α in aqueous *t*BuOH to give diol **22** in 62 % yield, followed by quantitative oxidative cleavage of the diol in **22** with NaIO₄. We used AD-mix-α instead of OsO₄ as a catalyst in the dihydroxylation step because when we used OsO₄ and NMO under the same conditions, the yield of **22** was less than 10 %, and several unidentified by-products were obtained.

We envisioned that a Simmons–Smith reaction^[11] would allow us to simultaneously and efficiently assemble the cyclopropyl C ring, the six-membered D ring, the seven-membered E ring, and the quaternary carbon stereocenters at C2 and C7 (Scheme 3). The success of this approach would depend on whether the diiodo compound **11** would react in the Simmons–Smith procedure. Based on this plan, we reacted **12** with hydrazine in CH₂Cl₂ and then added I₂ in a mixture of Et₂O and Et₃N (2:1) in order to transfer the



Scheme 3. Synthesis of (–)-lundurine A (**1**). Reagents and conditions: a) RuCl₃ (0.05 equiv), NaIO₄ (2.5 equiv), EtOAc:H₂O 1:1, 25 °C, 3 h, 45 %; b) AD-mix- α : **21** = 5:1, tBuOH:H₂O = 1:1, 2 days, 62 % yield based on 55 % recovered **21**; c) NaIO₄ (10 equiv), CH₂Cl₂:H₂O = 1:1, 2 h, 98 %; d) N₂H₄·H₂O, then Et₂O:Et₃N = 2:1, I₂, 0 °C, 5 min, **23**:**11** = 1:2.5; e) Et₂Zn (40 equiv), CH₂Cl₂, 25 °C, 20 h, 63 % of **24**, 27 % of **23** over 2 steps; f) TBAF (2.5 equiv), THF, 30 min, 98 %; g) Martin sulfurane (5 equiv), CH₂Cl₂, 92 %. AD mix- α = mixture of K₂OsO₄, K₃[Fe(CN)₆], K₂CO₃, and (DHQD)₂PHAL in a 1:712:712:2.3 molar ratio. MsCl = methanesulfonyl chloride; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; NMO = 4-methylmorpholine N-oxide; Martin sulfurane = bis-[α,α -bis(trifluoromethyl)benzenemethanolato]diphenylsulfur.

aldehyde functional group in **12** to a diiodo functional group using Barton's protocol.^[12] This functional-group transformation resulted in an inseparable mixture of **23** and **11** in quantitative yield and in a 1:2.5 ratio. To our delight, treating the mixture of **23** and **11** with a large excess of Et₂Zn in CH₂Cl₂ at room temperature for 20 h generated compound **24**, possessing a hexacyclic ring system, in 63 % yield (two steps from **12**), leaving the unreacted compound **23** in 27 % yield. The absolute configuration of the newly constructed quaternary carbon centers at C2 and C7 in **24** was inferred to be 2*R*,7*R* because the Simmons–Smith reaction of **11** can proceed only from the upper face of the indole double bond. After the TBS protecting group in **24** was removed using Bu₄NF, the resulting alcohol **25** was reacted with Martin sulfurane reagent^[13] to form directly the double bond at positions C14 and C15, thus completing the total synthesis of (–)-lundurine A (**1**). The synthesized lundurine A (**1**) showed NMR spectra identical to those of natural lundurine A and previously synthesized lundurine A.^[1b,6] Our synthesized lundurine A had a negative specific rotation value ($[\alpha]_D = -83$ (CHCl₃, $c = 0.08$)), consistent with the rotation reported for natural lundurine A ($[\alpha]_D = -90$ (CHCl₃, $c = 0.09$)).^[1b]

These results indicate that the natural (–)-lundurines possess a 2*R*,7*R*,20*R* configuration.

In summary, we have developed a concise asymmetric total synthesis of (–)-lundurine A (**1**) in 15 steps with approximately 2 % overall yield, starting from the easily accessible (*S*)-pyrrolidinone **18**. Stereoselective organometallic addition to the in situ generated iminium cation **14** allowed us to construct the quaternary carbon center at C20, and the Fring. A Simmons–Smith reaction then allowed us to simultaneously and efficiently construct the cyclopropyl C ring, the six-membered D ring, and the seven-membered E ring, together with the quaternary carbon stereocenters at C2 and C7. The absolute configuration of (–)-lundurine A (**1**) was determined to be 2*R*,7*R*,20*R* based on the stepwise construction of stereocenters during the total synthesis.

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- [1] a) T.-S. Kam, K. Yoganathan, C.-H. Chuah, *Tetrahedron Lett.* **1995**, 36, 759–762; b) T.-S. Kam, K.-H. Lim, K. Yoganathan, M. Hayashi, K. Komiyama, *Tetrahedron* **2004**, 60, 10739–10745; c) T.-S. Kam, K. H. Lim, *The Alkaloids*, Vol. 66 (Ed.: G. A. Cordell), Elsevier, Amsterdam, **2008**, chap. 1, pp. 1–105.
- [2] a) K. Awang, T. Sévenet, A. H. A. Hadi, B. David, M. Païs, *Tetrahedron Lett.* **1992**, 33, 2493–2496; b) K. Awang, T. Sévenet, M. Païs, A. H. A. Hadi, *J. Nat. Prod.* **1993**, 56, 1134–1139; c) W.-S. Yap, C.-Y. Gan, Y.-Y. Low, Y.-M. Choo, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* **2011**, 74, 1309–1312; d) T.-S. Kam, K. Yoganathan, T. Koyano, K. Komiyama, *Tetrahedron Lett.* **1996**, 37, 5765–5768.
- [3] For synthetic studies of lundurines, see: a) E. E. Schultz, B. G. Pujanauski, R. Sarpong, *Org. Lett.* **2012**, 14, 648–651; b) C. Ferrer, A. Escribano-Cuesta, A. M. Echavarren, *Tetrahedron* **2009**, 65, 9015–9020.
- [4] For synthetic studies of (iso)lapidilectines and grandilodines, see: a) W. H. Pearson, I.-Y. Lee, Y. Mi, P. Stoy, *J. Org. Chem.* **2004**, 69, 9109–9122; b) T. Wanatabe, S. Arai, A. Nishida, *Synlett* **2004**, 5, 907–909; For the total synthesis of racemic lapidilectine B, see: W. H. Pearson, Y. Mi, I.-Y. Lee, P. Stoy, *J. Am. Chem. Soc.* **2001**, 123, 6724–6725.
- [5] For the biogenetic syntheses of pauciflorine analogues, see: a) M. K. Kuehne, Y.-L. Li, *Org. Lett.* **1999**, 1, 1749–1750; b) M. K. Kuehne, Y.-L. Li, C.-Q. Wei, *J. Org. Chem.* **2000**, 65, 6434–6440; c) P. Magnus, L. Gazzard, L. Hobson, A. H. Payne, T. J. Rainey, N. Westlund, V. Lynch, *Tetrahedron* **2002**, 58, 3423–3443; d) P. Magnus, L. Hobson, N. Westlund, V. Lynch, *Tetrahedron Lett.* **2001**, 42, 993–997; e) P. Magnus, L. Hobson, A. H. Payne, *Tetrahedron Lett.* **2000**, 41, 2077–2081.
- [6] a) M. Hoshi, O. Kaneko, M. Nakajima, S. Arai, A. Nishida, *Org. Lett.* **2014**, 16, 768–771; b) S. Arai, M. Nakajima, A. Nishida, *Angew. Chem. Int. Ed.* **2014**, 53, 5569–5572; *Angew. Chem.* **2014**, 126, 5675–5678.
- [7] X. Zheng, Ch.-G. Feng, J.-L. Ye, P.-Q. Huang, *Org. Lett.* **2005**, 7, 553–556.
- [8] S. Luo, C. A. Zifcsak, R. P. Hsung, *Org. Lett.* **2003**, 5, 4709–4712.
- [9] a) M. Yoshida, Y. Nagasawa, A. Kubara, S. Hara, M. Yamanaka, *Tetrahedron* **2013**, 69, 10003–10008; b) X. Zhou, T. Xiao, Y.

- Iwama, Y. Qin, *Angew. Chem. Int. Ed.* **2012**, *51*, 4909–4912; *Angew. Chem.* **2012**, *124*, 4993–4996; c) C. Palomo, M. Oiarbide, E. Gómez-Bengoa, A. Mielgo, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, P. Bañuelos, A. Linden, *ARKIVOC* **2005**, (VI), 377–392.
- [10] J. C. Sheehan, R. W. Tulis, *J. Org. Chem.* **1974**, *39*, 2264–2267.
- [11] a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256–4264; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324; for applications of the Simmons–Smith reaction to natural product synthesis, see: c) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589–8627; d) P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773; e) T. Onoda, R. Shirai, Y. Koiso, S. Iwasaki, *Tetrahedron Lett.* **1996**, *37*, 4397–4400; f) L. A. Paquette, T. Z. Wang, E. Pinard, *J. Am. Chem. Soc.* **1995**, *117*, 1455–1456.
- [12] a) D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc.* **1962**, 470–476; b) A. Pross, S. Sternhell, *Aust. J. Chem.* **1970**, *23*, 989–1003.
- [13] a) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010; b) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329.
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