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Protecting Group-Free Total Synthesis of (−)-Lannotinidine B

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Supporting Information

ABSTRACT: The first total synthesis of (−)-lannotinidine B, a unique tetracyclic constitutent of *Lycopodium annotinum*, has been accomplished in 10 steps with 23% overall yield. The completed short and efficient synthesis is characterized with three highly chemo- and/or stereoselective reductive-amination steps to furnish the desired *trans*-fused 6/6 bicycle and the aza seven-membered ring system, and a direct intramolecular acyloin condensation to deliver the cyclopentanone moiety, as well as successful application of a protecting group-free strategy and an optimal redox order.

The *Lycopodium* alkaloids are a diverse group of structurally complex compounds with impressive biological activities,[1] and they have attracted significant synthetic interests for several decades.[2] Recently, the isolation and characterization of a group of closely related polycyclic alkaloids, lannnotinidine B,[3] lycovatine A,[4] and lycopladine D[3] (Figure 1), were reported

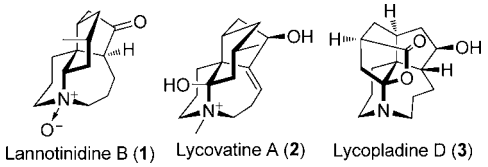

Figure 1. Three polycyclic C16N-type *Lycopodium* alkaloids.

by Kobayashi and co-workers. Among these, lannotinidine B (**1**) is a unique tetracyclic C16N-type alkaloid, whose structure consists of an exceptional tetracyclic carbon−nitrogen skeleton including five stereogenic centers and a rare *N*-oxide functionality. It was found to effectively improve mRNA expression of neurotrophic growth factor (NGF) in 1321N1 human astrocytoma cells. Owing to the intriguing structural features of fused/spiro multiring system and continuous stereogenic centers, synthesis of these compounds remains a formidable challenge. Herein, we report the first asymmetric total synthesis of (−)-lannotinidine B in a short and efficient route using a protecting group-free strategy.[5,6]

As outlined in Figure 2, we envisaged that the cyclopentanone moiety of lannotinidine B (**1**) could be assembled from an ester-ketone precursor **11** through an intramolecular reductive C4−C5 bond formation. To achieve quick and efficient formation of the tertiary amine functionality (C1,C9,C13/N) of **11**, successive order-controlled reductive aminations upon a multicarbonyl intermediate **8** were designed

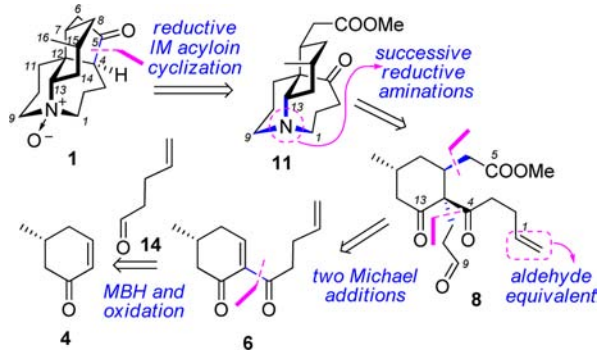

Figure 2. Retrosynthetic analysis of (−)-lannotinidine B (**1**).

as a key step-economic (protecting group-free) strategy in this synthesis. To achieve such a goal, establishment of the correct chemo- and stereoselectivities to form the *trans* 6/6 bicyclic core would be a major challenge in the synthesis. We believed that the C4 ketone of **8** was the most hindered and insufficiently reactive, and the C9 aldehyde should be a suitable position to accept the first reductive amination and introduce the nitrogen atom. To establish the correct stereochemistry of C13−N bond, two possible sequences (formation of C1−N and C13−N bonds in different orders) were theoretically compared, indicating that the C13−N cyclization would be more favorable as the second reductive amination with correct stereoselectivity. Formation of C1−N bond was thus arranged as the last one. A terminal olefin was accordingly devised in **8** as the equivalent of the C1 aldehyde, so that we could avoid insurmountable problem of chemoselectivity. With these considerations, the tricarbonyl compound **8** was then identified as the key intermediate for successive reductive aminations in a well-organized order. The chiral quaternary-carbon of **8** could be established by two Michael additions to the activated enone **6**, which could be further synthesized from the easily available chiral building block **4**[7] by a Morita−Baylis−Hillman reaction.

As depicted in Scheme 1, our synthesis commenced with chiral enone **4**. Treatment of the mixture of enone **4** and aldehyde **14** with *n*-Bu_3P and 1,1′-2-naphthol in THF under Ikegama conditions[8] afforded *β*-hydroxyl ketone **5** as an inseparable mixture of diastereomers in 83% yield. Dess-Martin oxidation of the newly born hydroxyl group gave **6** in almost quantitative yield. Subsequent Mukaiyama−Michael addition of *tert*-butyl(1-methoxyvinyloxy)dimethylsilane **15** to *α*,*β*-unsatu-

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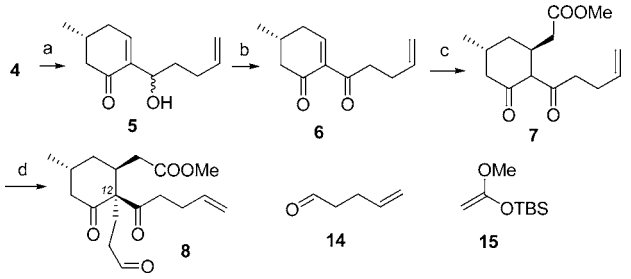
Scheme 1. Synthesis of Enantiopure Cyclohexanone Precursor 8[a]

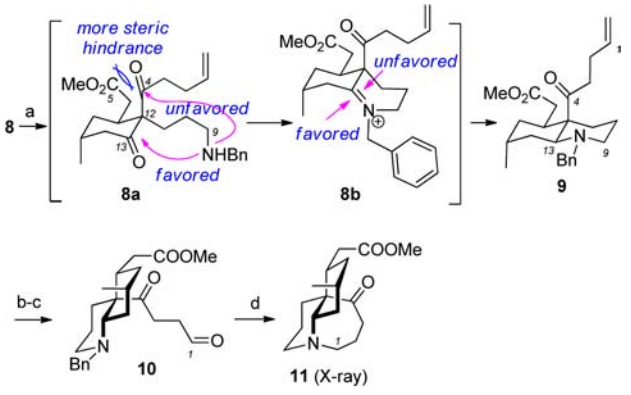


[a]Reagents and conditions: (a) *n*-Bu_3P, 1,1′-2-naphthol, **14**, THF, rt, 96 h, 83%; (b) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C → rt, 2 h, 100%; (c) **15**, $LiClO_4$, DCM, 0 °C → rt; then 2 N HCl, THF, 90%; (d) acrolein, DMF, Et_3N, rt, 12 h, 81%.

rated diketone **6**, followed by treatment with 2 N HCl, furnished **7** as an inseparable tautomer mixture of 1,3-diketone and enone (~3/7 ratio judged by ^1H NMR) in 90% yield. The all functionality-equipped cyclohexanone **8** with C12 quaternary carbon was finally established by the second Michael addition of **7** to acrolein in the presence of Et_3N.

With the tricarbonyl compound **8** in hand, cascade reductive aminations were conducted as shown in Scheme 2. As

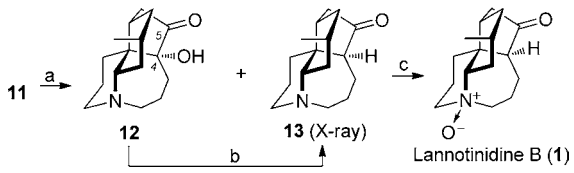
Scheme 2. Chemo- and Stereoselective Sequential Reductive Aminations[a]



[a]Reagents and conditions: (a) Benzylamine, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, −30 °C → rt, 48 h, 87%; (b) $K_2OsO_2(OH)_4$, NMO, acetone/H_2O, 12 h; (c) $NaIO_4$, THF/H_2O, 3 h, 87% (2 steps); (d) H_2 (3.5 atm), 10% Pd/C, MeOH, 110 °C, 5 h, 73%. NMO = *N*-methylmorpholine-*N*-oxide.

mentioned above, we hypothesized that the C13 ketone could be predominantly attacked by the newly introduced secondary amine at C9 intramolecularly with assistance of the steric hindrance between the C5 ester and the C4 ketone.[2h] Further inspection of the transition state models suggested that hydride approach to **8b** might be less hindered from the α-face. Such hypothesis was proven to accord with the facts because the bicycle **9** was obtained as the sole product (87% yield, >99% ee by chiral HPLC analysis). The relative stereochemistry of **9** was subsequently confirmed by the NOE experiment and X-ray analysis of *rac*-**11** (see Supporting Information for the details).[9] Exposure of olefin **9** to $K_2OsO_2(OH)_4$/NMO followed by oxidative cleavage with $NaIO_4$ gave aldehyde **10**, which was perfectly applied to the third reductive amination to construct the seven-membered ring intramolecularly (Scheme 3).[10] Hydrogenolysis of the *N*-benzyl group of **10** followed by reductive amination with C1

Scheme 3. Completion of the Total Synthesis[a]



[a]Reagents and conditions: (a) Lithium naphthalide, THF, −78 °C, 15 min, **12** (63%) + **13** (17%); (b) SmI_2, THF/*t*-BuOH, rt, 10 min, 94%; (c) *m*CPBA, DCM, 0 °C → rt, 1 h, 91%. *m*CPBA = *meta*-chloroperbenzoic acid.

aldehyde was completed in one pot in an optimized high temperature (110 °C) and high pressure (3.5 atm), delivering the tricycle **11** in good yield (73%).

Conversion of ester **11** into the corresponding hydroxylketone **12** usually needs four sluggish redox steps (reduction of the ester group to primary alcohol, then oxidation to aldehyde, reductive pinacol coupling to form a new C−C bond, and oxidation of the newly born secondary alcohol to ketone).[2g,h] To achieve a step-economic transformation, we decided to explore a direct reductive ketyl radical anion coupling[11,12] between C4-ketone and C5-ester. After many experimental trials, our attempt was fortunately achieved with lithium naphthalide in THF for 15 min at −78 °C under Gössinger conditions[13] to provide α-hydroxyketone **12** (63% yield) and cyclopentanone **13** (17% yield).[14] Further treatment of **12** with SmI_2 smoothly gave **13**, whose structure was confirmed by the X-ray analysis of a single crystal of its HCl salt (see Supporting Information for the details). Finally, the bridged tertiary amine **13** was smoothly transformed to the natural *N*-oxide **1** (91% yield) upon exposure to *m*CPBA in dichloromethane at room temperature. The NMR spectroscopic data of the synthetic lannotinide B (**1**) well agree with those reported for the natural product.[3] The optical rotation {$[\alpha]_D$ −54 (*c* 0.8 MeOH)} was also consistent with the literature value {$[\alpha]_D$ −62 (*c* 1.0 MeOH)},[3] thereby providing further confirmation of the absolute configuration.

In summary, we have accomplished the first total synthesis of (−)-lannotinidine B in 10 steps and 23% yield with excellent chemo- and stereoselectivities. The short and efficient synthesis features a successful protecting group-free strategy and careful considerations on step- and redox-economy, and therefore demonstrated the pursuing values of modern organic synthesis. The strategy and methodologies applied in this synthesis are also flexible and capable to expand to the synthesis of other *Lycopodium* alkaloids.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterizations of new compounds, and NMR spectra of new compounds (PDF); X-ray single crystal data for *rac*-**11** and (−)-**13** (CIF). 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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(9) A sample of *rac*-**11** was obtained from our initial methodology study using *rac*-**4** as the starting material.

(10) When repeating the procedures, we found only one silica-gel column chromatography was needed from **5** to **10** with 62% isolated yield.

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(14) With ∼3.0 equiv of lithium naphthalide in THF at −78 °C, the starting material **11** can be consumed completely. However, ketone **13** was isolated as a minor product, which was thought as a further reduced product by deoxygenation of the α-hydroxylketone **12**. Use of largely excess amount of lithium naphthalide (up to 10.0 equiv) could not completely convert **12** into **13**. Instead, several unidentified byproducts were given.