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# Synthetic study of (−)-lasubine II via sequential cyclization process

Jaebum Lim and Guncheol Kim*

*Department of Chemistry, College of Natural Science, Chungnam National University, Taejon 305-764, Republic of Korea*

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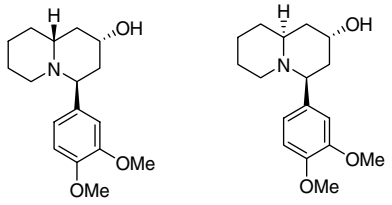
**Abstract**—A new synthetic pathway to lythraceae alkaloid lasubine II has been developed. In this approach, we designed a sequential cyclization pathway for the formation of quinolizidine ring. For the preparation of the requisite precursor, a known chiral β-amino ester has been used as a starting intermediate. Upon deprotection of Cbz group on nitrogen, *endo*-type Michael addition and the following $S_N2$ reaction were assumed to proceed to provide (−)-2-*epi* lasubine II.


Quinolizidine alkaloids lasubine I (**1**) and lasubine II (**2**), a class of lythraceae alkaloid, have been isolated from the leaves of *Lagerstroemia subcostata* Koehne by Fuji and co-worker (Fig. 1).[1] The broad biological activities and intriguing stereochemistry of the skeleton have attracted significant interest from organic chemists for suggesting new synthetic methodologies. Especially, a number of asymmetric syntheses of lasubine II (**2**) have been published until recently.[2–9]

As part of our study aimed at exploring successive ring formation of alkaloids,[10–12] herein we describe a sequential process for a stereoselective asymmetric synthesis of (−)-lasubine II skeleton.

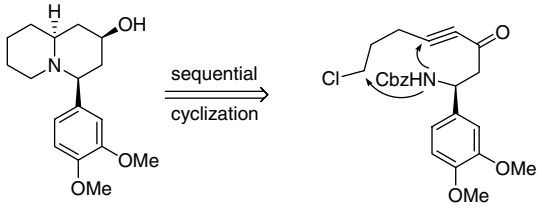
In the approach, we expected that the deprotection of Cbz group on nitrogen of **4** would induce an *endo*-Michael addition[13] and the $S_N2$ reaction before or after hydrogenation of the resulting double bond would afford the quinolizidine ring skeleton stereoselectively, affording (−)-2-*epi* lasubine II **3**, a known precursor[4] for (−)-lasubine II (Scheme 1).




**1**: (-)-lasubine I  **2**: (-)-lasubine II

**Figure 1.**

The requisite precursor **4** has been prepared from the known chiral amino ester **5**,[14] which was prepared by the addition of (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to methyl 3,4-dimethoxyphenylcinnamate followed by debenzylation using Pearlman's catalyst and $H_2$. The amino group of **5** was protected with Cbz-Cl to afford **6** in 88% yield. Ester **6** was reduced to **7** with DIBAL-H in toluene in 92% yield. Aldehyde **7** was reacted with the anion reagent prepared from 6-chloro-1-hexyne and *n*-BuLi, to provide **8** in 91% yield as a 6:4 diastereomeric mixture. In the reaction, $BF_3$·OEt addition to the alkyne lithium anion generated by the addition of *n*-BuLi was required to suppress cyclic carbamate by-product formation. Without separation of the diastereomers, $MnO_2$ oxidation converged **8** to the desired carbonyl compound **4**[15] in 84% yield (Scheme 2).




**3**  **4**

**Scheme 1.**

*Keywords*: Lasubine I; Lasubine II; Sequential cyclization; Michael addition.
* Corresponding author. Tel.: +42 821 5475; fax: +42 823 1360; e-mail: guncheol@cnu.ac.kr

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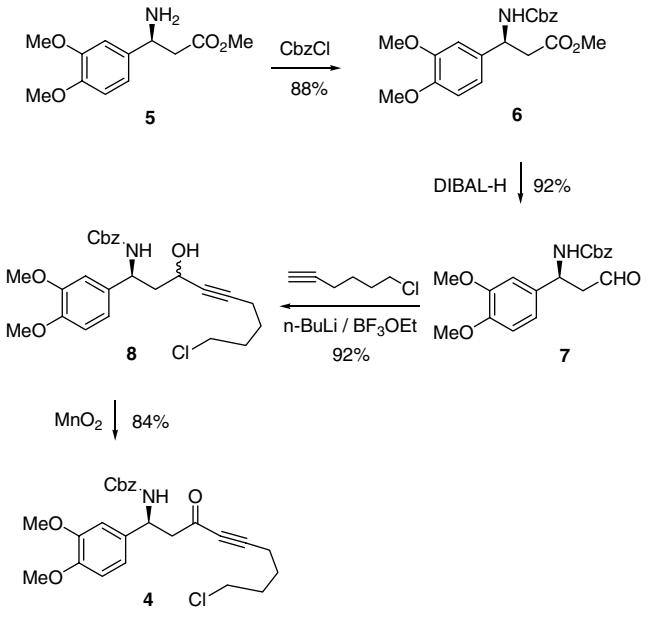
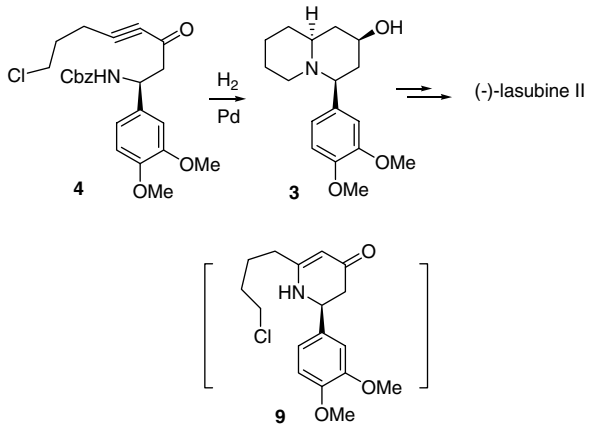



**Scheme 2.**




**Scheme 3.**

To find the proper condition for the sequential cyclization of compound **4**, we have tried a few reductive conditions, using catalysts such as Pd/C, $Pd(OH)_2$, and Lindlar catalyst in various solvents and temperatures under hydrogen atmosphere (Scheme 3).

Partly due to the presence of Cbz, alkyne, and carbonyl functional groups, normal reductive conditions provided a number of by-products, respectively, and most of which were hard to be characterized. However, we could separate intermediate **9** as well as the expected compound **3**, though very small amounts at first. We assumed that **9** should be formed through deprotection followed by intramolecular Michael addition as suggested in Scheme 1. Intermediate **9** would be converted to **3** through hydrogenation reaction of the double bond in vinylogous urethane and cyclization via $S_N2$ reaction between amine and chloride, virtually regardless of the order of the two reactions. And it has been shown that the process of reduction would arrange the quinolizidine ring and hydroxyl group in stereoselective manner.[4,16] Finally, we have searched the optimal reductive condition for the cyclization of **4** and found that refluxing the reaction mixture in MeOH under 1 atm of $H_2$ in balloon for 48 h in the presence of Pd/C afforded **3** most in 37% yield in agreement with the published data ($[\alpha]_D^{20}$ −40 (*c* 0.40, MeOH)); lit.[5] ($[\alpha]_D^{20}$ −53 (*c* 0.13, MeOH)). This epimer has been known to be readily converted to (−)-lasubine II (**2**) via epimerization of hydroxyl group by Ma and Zhu.[4]

In conclusion, we have suggested a new sequential process to a quinolizidine skeleton and achieved a formal synthesis of (−)-lasubine II in a concise manner.

## Acknowledgments

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15. $[\alpha]_D^{20}$ −16.1 (*c* 0.51, MeOH); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.63 (m, 2H), 1.76 (m, 2H), 2.30 (t, 2H, $J = 6.8$ Hz), 2.99 (m, 2H), 3.46 (t, 2H, $J = 6.4$ Hz), 3.76 (s, 3H), 3.77 (s, 3H), 5.00 (s, 2H), 5.12 (br, 1H), 5.42 (br, 1H), 6.73 (br, 3H), 7.20–7.26 (5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 18.2, 24.8, 31.3, 44.1, 50.9, 51.3, 55.8, 55.8, 66.8, 81.0, 94.7, 109.8, 111.1, 118.3, 128.0, 128.0, 128.4, 133.2, 136.2, 148.4, 149.0, 155.4, 184.8.
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