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A concise and enantioselective approach to the total synthesis of (−)-lasubine I

Shengyang Liu,[a] Yuping Fan,[b] Xinxiang Peng,[b] Wei Wang,[c,d,*] Weiyi Hua,[a] Haji Akber[b] and Lixin Liao[b,e,*]

[a]*Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, PR China*
[b]*Xinjiang Technical Institute of Physical and Chemistry, Chinese Academy of Sciences, Urumuqi 830011, PR China*
[c]*Department of Medicinal Chemistry, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, PR China*
[d]*Department of Chemistry, University of New Mexico, Albuquerque, NM 87131-0001, USA*
[e]*Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Graduate School of the Chinese Academy of Sciences, Shanghai 201203, PR China*

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Abstract—An efficient, enantioselective total synthesis of (−)-lasubine I (**1**) has been achieved in an overall 8.8% yield from readily available starting materials. The important features of this approach include the creation of stereogenic centers through two sequential highly stereoselective Roush allylborations and the use of S_N2 cyclization and ring-closing metathesis reactions for the construction of the quinolizidine skeleton.

The Lythraceae plant is a rich source of bioactive alkaloids and a number of them contain important quinolizidine skeletons.[1,2] For example, (−)-lasubine I (**1**) and (−)-lasubine II (**2**) possess the scaffold with cis- and trans-configurations, respectively (Fig. 1).[2] Their broad spectrum of biological activities associated with the 'privileged' quinolizidine scaffold has elicited considerable interest in their syntheses.[3–6] A survey of the literature reveals that intensive efforts have been directed toward their racemic syntheses.[3,5] However, the examples of their asymmetric synthetic versions have been limited.[4,6] To date, only four asymmetric syntheses of (−)-lasubine I (**1**) have been described.[4] More facile and practical methods are still needed in order to access the preparation of its analogs, used for exploring the structure–activity relationship and seeking more potent and selective lasubine derivatives. As part of our effort aimed at developing efficient, enantioselective syntheses of these quinolizidine alkaloids and exploring their pharmacology, we wish to illustrate a straightforward approach to the asymmetric preparation of (−)-lasubine I (**1**).

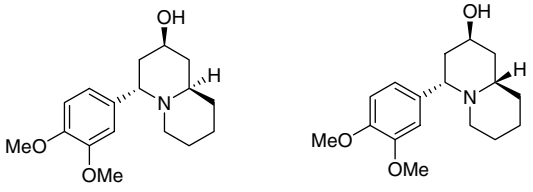

Figure 1. (−)-Lasubine I (**1**) and (−)-lasubine II (**2**).

Our synthetic strategy toward (−)-lasubine (**1**) is described in Scheme 1. We hypothesized that one of the rings in the quinolizidine could be constructed by a well established ring-closing metathesis (RCM),[7–9] thus suggesting the use of diene **3**, which contains two allylic groups as viable synthetic precursors. This disconnection raised a synthetic challenge related to the construction of the piperidine ring consisting of three chiral centers: the allyl group is trans to the phenyl

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* Corresponding authors. Tel.: +1 505 277 0756; fax: +1 505 277 2609 (W.W.); tel.: +86 21 5080 6600x3426 (L.L.); e-mail addresses: wwang@unm.edu; lixinliao@hotmail.edu

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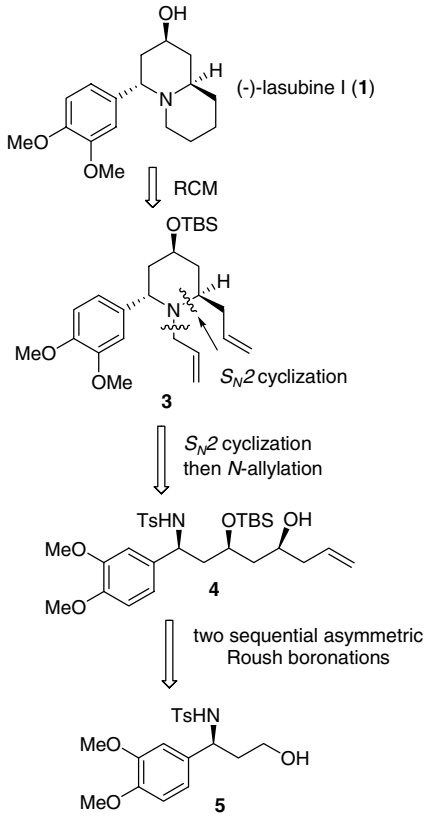
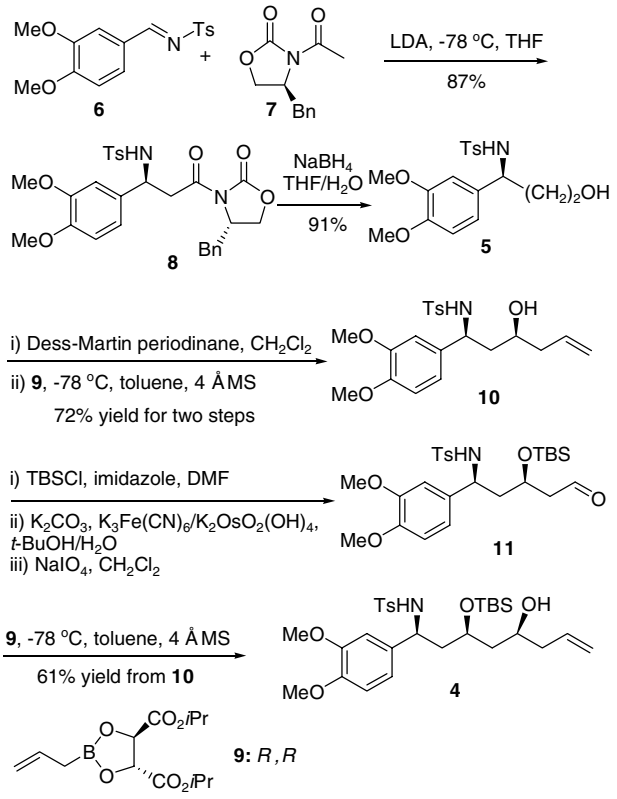


Scheme 1. Retrosynthetic analysis of (−)-lasubine (**1**).

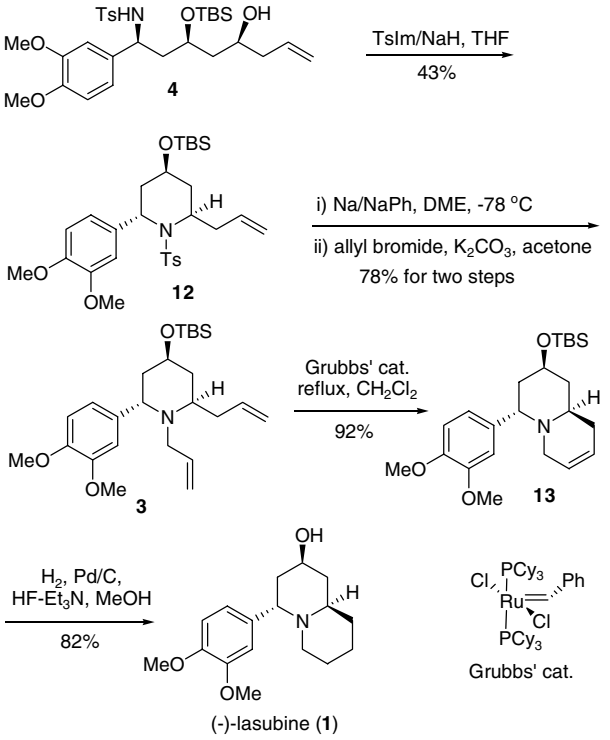


Scheme 2. Synthesis of intermediate **4**.

ring and cis to the hydroxyl group. We were intrigued by the possibility offered by the S_N2 type cyclization of linear amine alcohol **4**, which could be accessed by two sequential Roush asymmetric allylborations[10] from readily prepared chiral β-tosyl protected amino alcohol **5**. An advantage of this approach is that, generally, chiral (*R*,*R*) diisopropyl tartrate allyl boronate provides a product in a highly stereocontrolled manner with the formation of desired stereogenic centers.[10] Its readily available enantiomer (*S*,*S*) diisopropyl tartrate allyl boronate can allow for accessing other diastereomers. In addition, the first allylation product could be readily converted to an aldehyde, which served as a precursor for the second allylation reaction to produce a new allylic functionality for the RCM.

The synthesis started with a readily synthesized sulfinimine **6** and (*S*) 4-benzyl-2-oxazolidinone acetamide **7** (Scheme 2). The condensation of the commercially available compound *p*-toluenesulfinamide with 3,4-dimethoxybenzaldehyde in the presence of 4 Å MS and Dowex-50 afforded sulfinimine **6** in a 94% yield.[11] The deprotonation of Evans' chiral auxiliary acetamide **7** by treatment with LDA at −78 °C was followed by the addition of *N*-tosyl benzaldimine **6** to provide **8** with the desired *S* configuration in a 87% yield. The reduction of imide **8** by $NaBH_4$ furnished alcohol **5** in a 91% yield and 97% ee based on chiral HPLC analysis,[12] meanwhile the Evans' chiral auxiliary was recovered. Dess–Martin periodinane mediated oxidation of the hydroxyl group in **5** gave labile aldehyde, which was directly subjected to an enantioselective Roush allylboration by treatment with (*R*,*R*) diisopropyl tartrate allyl boronate **9** under standard reaction conditions, developed by Roush et al.,[10] to afford homoallylic alcohol **10** in favor of the generation of the desired *R* stereogenic center (>90%) in a 72% yield (two steps). The minor *S* diastereomer (<10%) of the Roush reaction was separated from **10** by column chromatography. The protection of the hydroxyl group in **10** as TBS ether was achieved by treatment with TBSCl in the presence of imidazole in DMF. The exposure of the protected homoallylic alcohol to $K_2OsO_2(OH)_4$ and $NaIO_4$ furnished aldehyde **11**.[13] The resulting aldehyde immediately underwent the second asymmetric Roush allylboration reaction to afford alcohol with the desired *R* configuration **4** as a major product. A high yield (61%) was obtained in the four transformations.

With the key intermediate **4** in hand, the stage was now set for the formation of the piperidine ring (Scheme 3). Toward this end, conversion of the hydroxyl group in **4** to tosylate by treatment with Ts-Im/NaH at 0 °C was followed by a spontaneous S_N2 intramolecular substitution to give cyclic product **12** in a 43% yield with the inversion of stereoconfiguration.[14] The exposure of **12** to a dark-green sodium naphthalenide solution at −78 °C resulted in the deprotection of Ts group.[15] N-Allylation of the resulting amino group by reacting with allyl bromide in the presence of K_2CO_3 in acetone afforded the precursor **3** in a 78% yield in two step conversion. Ring-closing metathesis (RCM) of **3** using the Grubbs'



Scheme 3. Synthesis of (−)-lasubine I (**1**).

catalyst (5 mol %) in CH_2Cl_2 under reflux gave rise to cyclic product **13** in a 92% yield.[7] Finally, Pd-catalyzed hydrogenation of **13** in HF/Et_3N and methanol resulted in the reduction of the double bond, and cleavage of the TBS group to furnish the target (−)-lasubine I (**1**) in a 82% yield. The spectroscopic and analytical data for synthetic **1** are in full agreement with those reported.[4]

In conclusion, a stereoselective total synthesis of (−)-lasubine (**1**) has been achieved. The strategy developed is distinguished by the construction of chiral quinolizidine skeleton using the two sequential highly stereoselective Roush allylboration, intramolecular S_N2 cyclization and RCM reactions. The general synthetic route described here paves the way for the preparation of (−)-lasubine (**2**) with cis configuration and other quinolizidine analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.137.

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