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Total Synthesis

Synthesis of (±)-Lasubine II Using *N*-Methoxyamines

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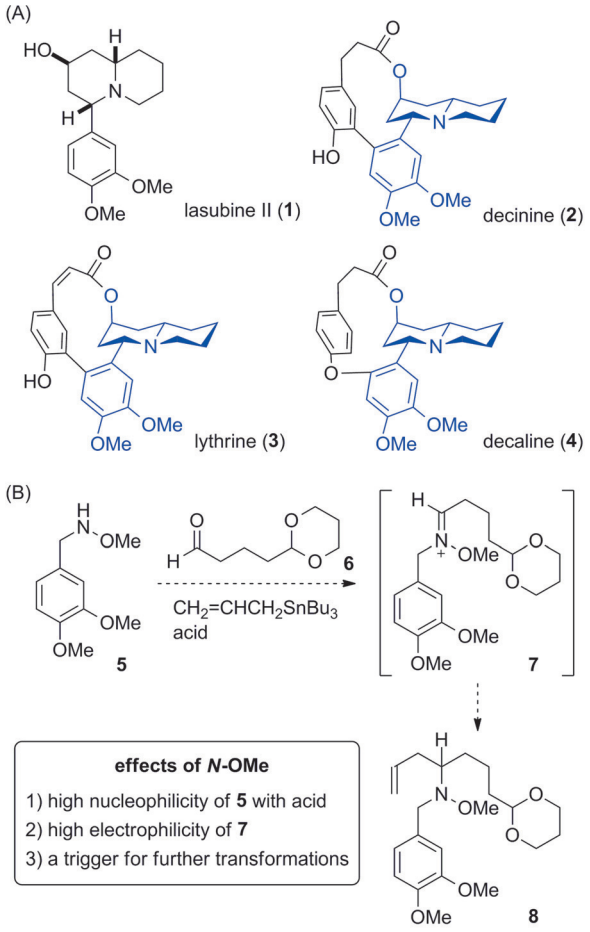
Abstract: The synthesis of (±)-lasubine II has been achieved through a three-component allylation capitalizing on the unique properties of *N*-methoxyamines. This reaction enabled the installation of all the carbon atoms of lasubine II in a single operation. The *N*-methoxy group was efficiently used for the subsequent nitrone formation. A single-step cyclization of isoxazolidines or *N*-methoxyamines to form functionalized piperidine rings was also developed.

Lasubine II (**1**) is the most well-known member of the Lythraceae alkaloids, isolated from the leaves of *Lagerstroemia subcostata* Koehne by Fuji and co-workers in 1978 (Scheme 1 A).[1] Although no biological activity of lasubine II (**1**) has been reported to date, the Lythraceae alkaloids have been shown to possess a range of biological activities.[2] Structurally, lasubine II (**1**) possesses an arylquinolizidine structure, which is embedded in a number of the Lythraceae alkaloids as a common scaffold. This widely distributed structure has received considerable attention from the synthetic chemists to demonstrate the utility of new methods.[3–5]

Our research group has been engaged in a program devoted to the efficient total synthesis of natural products by taking advantage of unique properties of hetero atom–hetero atom bonds.[6] In this context, we envisioned the synthetic approach to (±)-lasubine II (**1**), whose key step is the three-component allylation of *N*-methoxyamine **5**[7,8] (Scheme 1 B). Condensation of **5** with aldehyde **6**[9] in the presence of an acid would produce *N*-oxyiminium ion **7**,[10] which would subsequently undergo allylation to afford α-substituted *N*-methoxyamine **8**. This multi-component reaction could install all carbon atoms embedded in lasubine II (**1**) in a single operation. The key to success is based on the unique reactivities derived from the *N*-methoxy group.[6c,d,7] In the condensation step, *N*-methoxyamine **5** showed high nucleophilicity even in the presence of the acid without forming an unreactive salt. On the other hand, we previously reported that the resulting *N*-oxyiminium ion **7** had a higher electrophilicity than that of ordinary alkyl iminium ions. These two properties would promote the high-yielding three-component coupling reaction. Furthermore, the *N*-methoxy group in **8** could be used as a trigger for further transformations.



Scheme 1. (A) Representative Lythraceae alkaloids. (B) Synthetic plan for lasubine II (**1**) using a three-component allylation with *N*-methoxyamine **5**.

Our synthesis of lasubine II (**1**) commenced with condensation of 3,4-dimethoxybenzaldehyde with *N*-methoxyamine (Scheme 2). The resulting oxime ether was then reduced with $NaBH_3CN$ and HCl in a one-pot sequence to give *N*-methoxyamine **5** in 96% yield. The three-component reaction of **5** smoothly took place with known aldehyde **6** in the presence of $Gd(OTf)_3$ (30 mol%).[11] It is noteworthy that an undesired allylation of an aldehyde with allyltributylstannane prior to the

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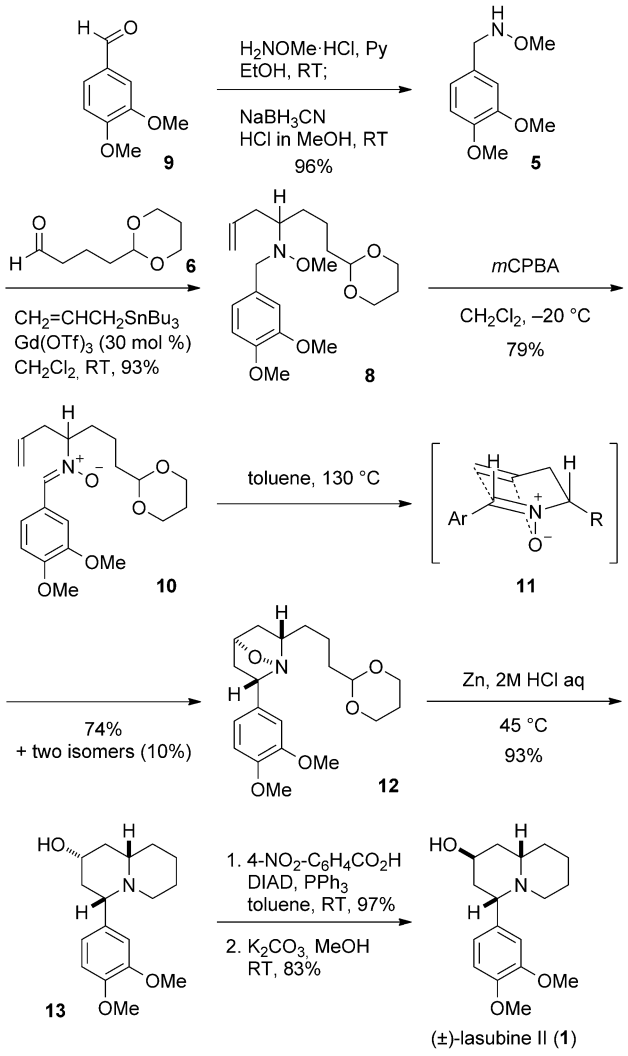
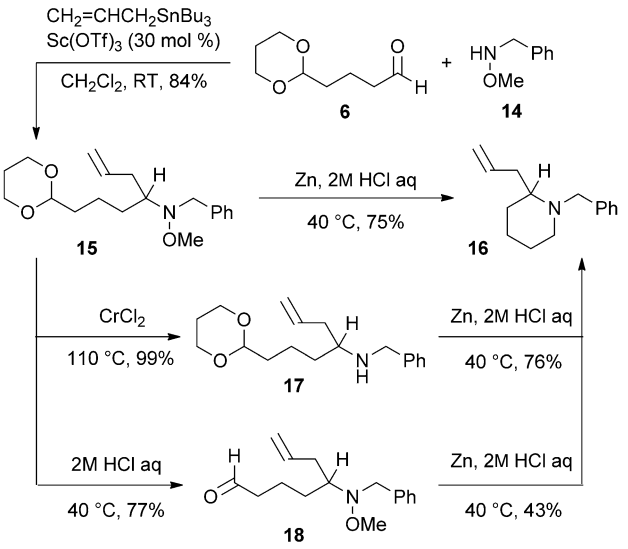


Scheme 2. Synthesis of (±)-lasubine II (**1**).

condensation with an amino group often becomes problematic in this type of three-component coupling. However, the reaction gave the α-substituted *N*-methoxyamine **8** in 93% yield without any detectable byproduct.

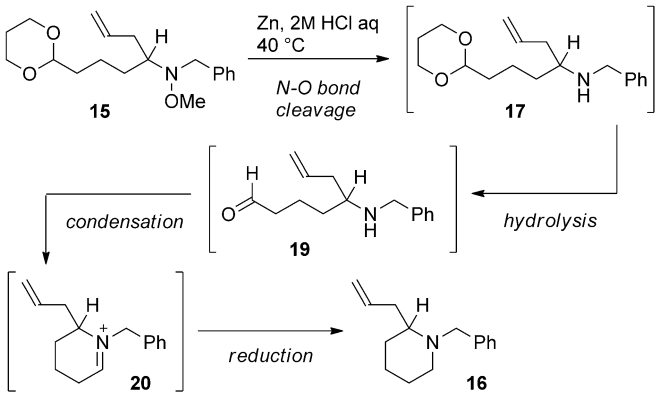
Having all carbon atoms needed for lasubine II (**1**) installed, we turned our attention to the construction of the quinolizidine framework (Scheme 2). The *N*-methoxyamino group in **8** was converted to the nitrone upon treatment with *meta*-chloroperoxybenzoic acid (*m*CPBA) at −20 °C, thus providing **10** in 79% yield with complete regioselectivity.[12] A solution of nitrone **10** and toluene was then heated to 130 °C in a sealed tube, resulting in stereoselective formation of isoxazolidine **12** in 74% yield through the transition state **11**, along with two other diastereomers in 10% yield.[13] Surprisingly, reduction of isoxazolidine **11** with activated zinc in aqueous HCl induced not only cleavage of the nitrogen–oxygen bond, but also the subsequent cyclization to provide known quinolizidine **13**[4d] in a single-step. The resulting hydroxy group was inverted under Mitsunobu conditions, followed by methanolysis to afford (±)-lasubine II (**1**). Our synthetic sample was found to be indistinguishable from reported spectral data including ^{1}H NMR, ^{13}C NMR, HRMS and IR.

During the course of our synthesis of lasubine II (**1**), we discovered the single-step formation of the quinolizidine from the isoxazolidine ring derived from the [3+2]cycloaddition (Scheme 2, **12**→**13**). We considered that this transformation could also be applied to *N*-methoxyamines instead of isoxazolidines, rendering our synthetic strategy based on the three-component reaction more useful (Scheme 3). Indeed, transformations of *N*-methoxyamines are much less explored than their construction. For example, cleavage of the methoxy group under reductive conditions is known to produce secondary amines. As we demonstrated in the synthesis, oxidation of *N*-methoxyamines to nitrones is another practical approach. However, there are few examples of direct formation of tertiary amines from *N*-methoxyamines. Our findings could be a solution to overcome this limitation. Therefore, the feasibility of the reaction was evaluated using model compound **15**, which was prepared by the three-component allylation of *N*-benzyl-*N*-methoxyamine **14**. As we expected, piperidine **16** was efficiently produced in 75% yield upon treatment of *N*-methoxyamine **15** with activated zinc in 2 M aqueous HCl at 40 °C. To elucidate the mechanistic pathway of this reaction, *N*-methoxyamine **15** was converted into two possible intermediates: secondary amine **17** and aldehyde **18**, which were exposed to the optimized conditions. While the reaction of aldehyde **18** gave piperidine **16** in only 43% yield, use of secondary amine **17** led to results similar to *N*-methoxyamine **15**. These control experiments indicated that cleavage of the methoxy group took place faster than hydrolysis of the acetal. Furthermore, prolonged exposure of the aldehyde to these reductive conditions led to decomposition.



Scheme 3. Control experiments in single-step cyclization of *N*-alkoxyamines.

A plausible reaction pathway in the cyclization of *N*-methoxyamines was proposed on the basis of the above control



Scheme 4. Plausible mechanism for single-step cyclization of *N*-alkoxyamines.

experiments (Scheme 4). The initial step is reductive cleavage of the nitrogen–oxygen bond through single electron transfer with activated zinc. The acetal group in **17** is then hydrolyzed under aqueous acidic conditions to generate aldehyde **19**, which readily forms iminium ion **20**. Finally, the resulting iminium ion **20** is efficiently reduced with activated zinc to produce piperidine **16**. These four processes are well orchestrated, and enable single-step access to piperidine rings from *N*-methoxyamines.

In conclusion, the synthesis of (±)-lasubine II (**1**) was achieved in 7 steps with an overall yield of 39%. The synthesis involved a three-component allylation of *N*-methoxyamines capitalizing on the *N*-methoxy group as a reactivity control element. In addition, a single-step cyclization of *N*-alkoxyamines (isoxazolidines and *N*-methoxyamines) broadened the utility of our synthetic strategy. The unified total synthesis of the Lythraceae alkaloids using the developed strategy is now in progress in our laboratory.

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Keywords: allylation · amines · lasubine · multicomponent reactions · total synthesis

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