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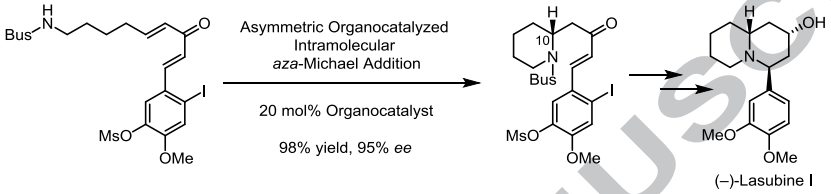

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ABSTRACT

A new procedure for the asymmetric total synthesis of lythraceous alkaloids with a 4-arylquinolizidine skeleton was developed, which involved an organocatalyzed asymmetric intramolecular *aza*-Michael addition.

Heimia salicifolia (Family Lythraceae) is the main ingredient of the law-evading drug "sinicuichi". When consumed, sinicuichi causes exhilarating feelings and alteration of awareness accompanied by bradycardia, hypomyotonia, and pleasant faintness.[1] To date, the active principles and the mechanism of action underlying the neurotropic effects of this drug have not been clarified. In the course of our investigation of bioactive alkaloids in medicinal plants,[2] we have isolated a number of biphenylquinolizidine alkaloids,[3] such as vertine (**1**),[4] lythrine (**2**),[5] and heimidine (**3**),[6] from *H. salicifolia* (Fig. 1). In order to evaluate their biological activities in detail, we have embarked on the development of an efficient method for the synthesis of biphenylquinolizidine alkaloids and their derivatives. In this letter, we report our efforts towards the asymmetric total synthesis of these alkaloids using the organocatalyzed asymmetric intramolecular *aza*-Michael addition to construct the phenylquinolizidine ring, and its application to the novel total synthesis of lasubine I (**22**).[7]

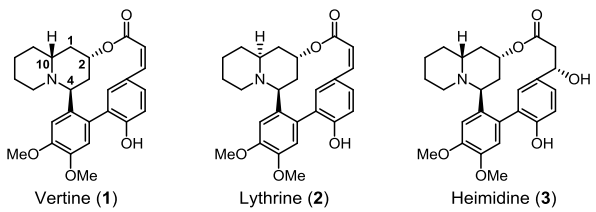
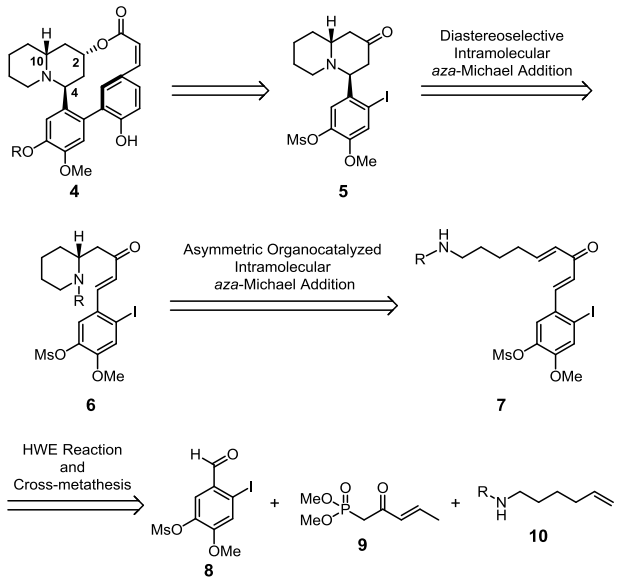


Figure 1. Biphenylquinolizidine alkaloids isolated from *Heimia salicifolia.*

The synthetic targets of biphenylquinolizidine alkaloids consist of a quinolizidine ring with three chiral centers at C2, C4, and C10 positions and a macrolactone with a 12-membered ring that includes a biphenyl moiety. Our retrosynthetic analysis of these alkaloids is shown in Scheme 1. Common skeleton **4** could be prepared from arylquinolizidinone **5** by installation of a



Scheme 1. Retrosynthetic analysis.

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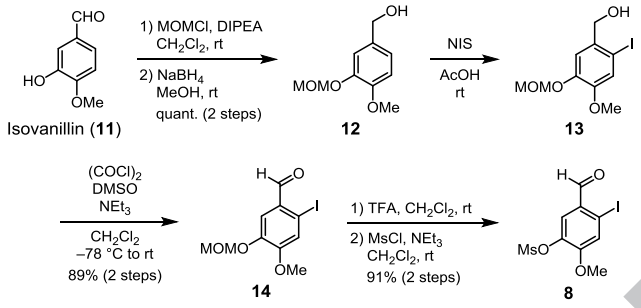
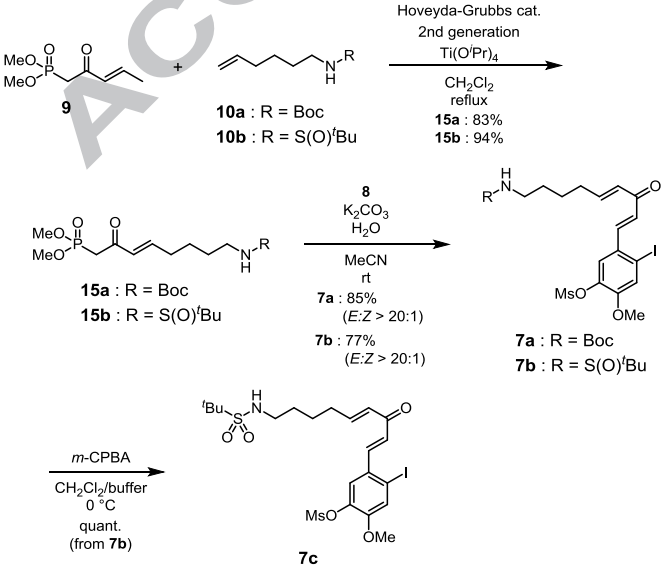
phenylpropanoid residue followed by macrolactonization. Arylquinolizidinone **5** could be constructed from linear dienone **7** *via* a double intramolecular *aza*-Michael addition. In this process, we have designed induction of chirality through the asymmetric cyclization of **7** using a chiral organocatalyst.[8] Substrate **7** could be prepared by the condensation of three units, i.e., aromatic aldehyde **8**, known phosphonate **9**,[9] and alkene **10**, *via* the Horner-Wadsworth-Emmons (HWE) reaction[10] and olefin cross-metathesis.

Initially, we prepared aromatic aldehyde **8** from isovanillin (**11**) (Scheme 2). Protection of the phenol in **11** with a methoxymethyl (MOM) group followed by reduction of the aldehyde with sodium borohydride gave alcohol **12**. Treatment of **12** with *N*-iodosuccinimide (NIS) afforded iodination product **13** regioselectively, which was then converted into aldehyde **14** by the Swern oxidation[11] (in 89% yield over 2 steps). Finally, replacement of the MOM group with a mesyl (Ms) group gave aromatic aldehyde **8** in 81% total yield over 6 steps from **11**.



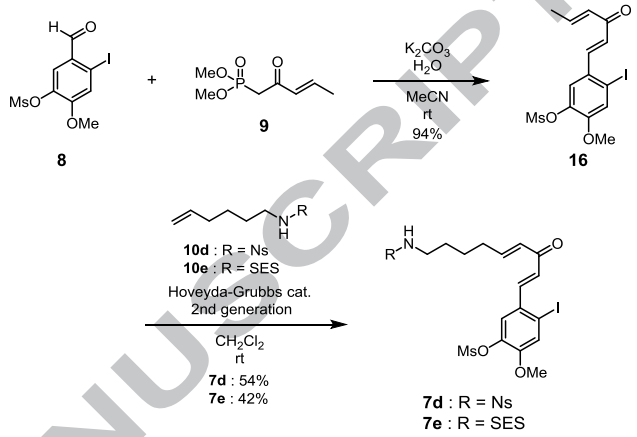
Scheme 2. Synthesis of aromatic unit **8**.

Next, we synthesized cyclization precursors **7a-e** (Scheme 3). Coupling of phosphonate **9** and alkene **10a** or **10b** with 2nd generation Hoveyda-Grubbs catalyst in the presence of $Ti(O^iPr)_4$[12] produced alkene **15a** or **15b** in good yield, respectively. Cyclization precursors **7a** and **7b** were obtained by the HWE reaction of aromatic aldehyde **8** with corresponding HWE reagents **15a** and **15b** in good yield with high *E/Z* selectivity. In this reaction, the electron-withdrawing Ms group was necessary to realize good *E/Z* selectivity of the product.[13] Next, oxidation of the sulfinamide group in **7b** with *m*-CPBA gave precursor **7c** having a *tert*-butylsulfonyl (Bus) group in a quantitative yield.



Scheme 3. Synthesis of cyclization precursors **7a-c**.

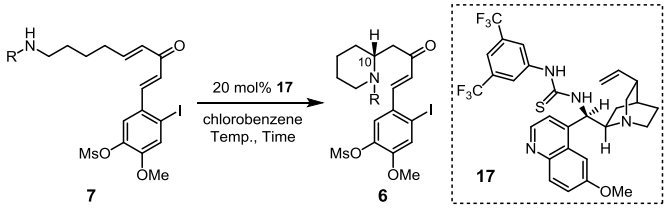
We prepared sulfonamides **7d** with a nosyl (Ns) group and **7e** with a 2-(trimethylsilyl)ethanesulfonyl (SES) group by applying another procedure (Scheme 4) to avoid the spontaneous *aza*-Michael addition of HWE products **7d** and **7e** under the basic condition. Thus, the HWE reaction between aromatic aldehyde **8** and phosphonate **9** was initially carried out to give dienone **16**, which was then treated with alkene **10d** or **10e** in the presence of 2nd generation Hoveyda-Grubbs catalyst to furnish corresponding dienone **7d** or **7e** in moderate yield, respectively.



Scheme 4. Synthesis of cyclization precursors **7d-e**.

With cyclization precursors **7a-7e** in hand, we next examined the asymmetric intramolecular *aza*-Michael addition using chiral organocatalyst **17**[14] (Table 1). In the case of *N*-Boc dienone **7a**, the reaction did not proceed and the starting material was recovered (entry 1). Although the cyclization using sulfoxide-protected substrate **7b** proceeded, the product was a racemate (entry 2). Based on these results, we considered that the acidity of the amide proton of **7a** or **7b** was so low that catalyst **17** did not participate in the cyclization. On the other hand, sulfonamide dienones **7c-e** gave desired products **6c-e** in good yields with high enantioselectivities (91% to 96% *ee*), respectively (entries 3-5). The absolute configuration of the newly formed chiral center at C10 in **6** was determined at a later stage as described below. This is the first report of the successful intramolecular asymmetric *aza*-Michael addition of the linear dienone compound catalyzed by a chiral organocatalyst.

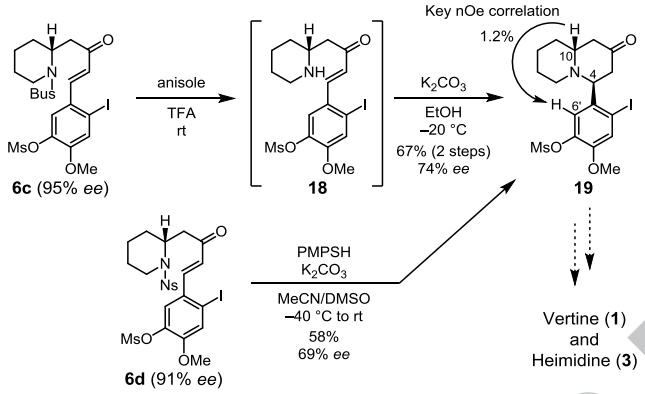
Table 1. Organocatalyzed asymmetric intramolecular *aza*-Michael addition.



Entry	Substrate	Temp. (°C)	Time (h)	Yield (%)	Ee (% *ee*)*
1	**7a** (R = Boc)	50	48	0	-
2	**7b** (R = S(O)^{t}Bu)	50	48	56	0
3	**7c** (R = Bus)	50	84	98	95
4	**7d** (R = Ns)	0	24	86	91
5	**7e** (R = SES)	40	22	97	96

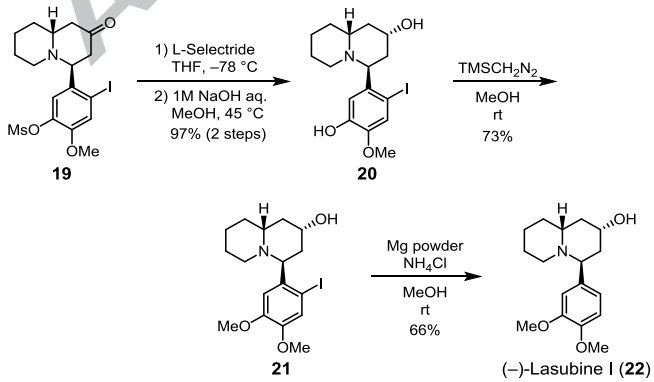
* Ee was determined by chiral HPLC analysis.

Next, the construction of the quinolizidinone ring from **6** was investigated (Scheme 5). *N*-Bus enone **6c** with 95% *ee* was treated with TFA in the presence of anisole[15] followed by cyclization under the basic condition to afford quinolizidinone **19** in 67% yield. The relative configuration at C4 and C10 in **19** was determined from the nOe correlation between H-10 and H-6'. Although the second *aza*-Michael addition proceeded in a highly diastereoselective manner to give **19**, the enantiomeric excess of the product was 74% *ee*. The decrease of the enantiomeric excess in the course of the reaction was probably caused by the partial racemization *via* the retro *aza*-Michael addition under the strong acidic condition to remove the Bus group or under the basic condition (K_2CO_3 in EtOH). Deprotection of the Ns group in **6d** under the basic condition gave desired quinolizidinone **19** in 58% yield, but the decrement of the enantiomeric excess was also observed (69% *ee*).[16] Nevertheless, thus-obtained compound **19** should play an important role as a synthetic intermediate of several biphenylquinolizidine alkaloids.



Scheme 5. Synthesis of chiral quinolizidinone **19** from **6c** or **6d**.

The absolute configuration of the major enantiomer in **19** (74% *ee*) was determined by conversion into known natural alkaloid lasubine I (Scheme 6). Diastereoselective reduction of the ketone in **19** with L-selectride followed by alkaline hydrolysis of the Ms group gave alcohol **20** in 97% yield (2 steps). Subsequently, methylation of phenol in **20** using trimethylsilyldiazomethane gave **21**.[17] Finally, deiodination of **21** with Mg metal afforded (–)-lasubine I (**22**). Synthetic **22** was identical in all respects with the natural product, including the optical property: synthetic, $[\alpha]_D^{26}$ –6.7 (*c* 0.20, MeOH) [18]; natural,[7a] $[\alpha]_D^{23}$ –8.8 (*c* 0.34, MeOH). Therefore, the stereochemistry including the absolute configuration of product **19** obtained by the organocatalyzed asymmetric *aza*-Michael addition/second *aza*-Michael addition was clarified.



Scheme 6. Determination of absolute configuration of key intermediate **19**.

In conclusion, we have developed a novel organocatalyzed asymmetric intramolecular *aza*-Michael addition of linear dienone and succeeded in the asymmetric synthesis of quinolizidinone **19**, which is a key intermediate in the synthesis of lythraceous biphenylquinolizidine alkaloids and the phenylquinolizidine alkaloid lasubine I (**22**). Further investigations of improvement of reaction conditions from enone **6** to **19** to avoid the partial racemization and the total syntheses of biphenylquinolizidine alkaloids using this strategy are ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (full experimental procedures and characterization data for new compounds) associated with this article can be found in the online version at ~.

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18. The Chiral HPLC analysis of benzoate derivative of synthetic **22** demonstrated 74% *ee*.

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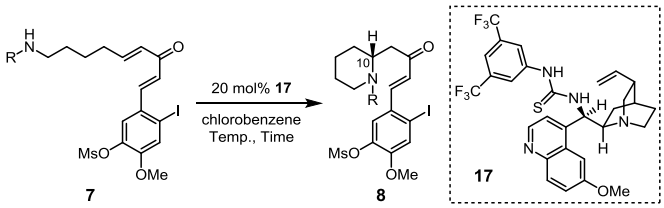

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* Ee was determined by chiral HPLC analysis

Research highlights

An organocatalyzed asymmetric intramolecular *aza*-Michael addition of linear dienone was developed.

A new synthetic method of chiral 4-arylquinolizidinone was developed.

A novel and efficient total synthesis of lythraceous alkaloid, lasubine I, was accomplished.