# Asymmetric Sequential Allylic Transfer Strategy for the Synthesis of (–)-Adaline and (–)-Euphococcinine

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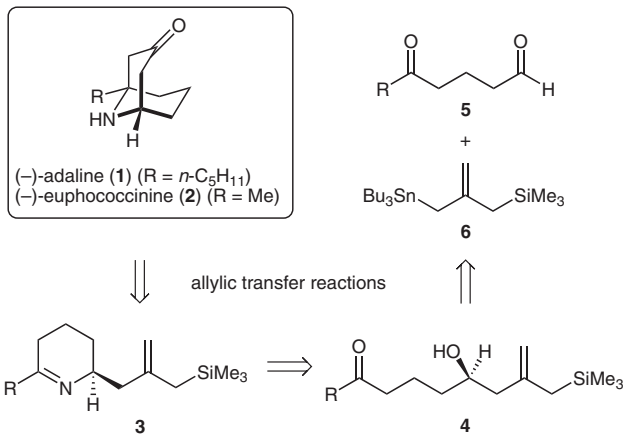
**Abstract:** Enantioselective synthesis of the piperidine alkaloids, (–)-adaline (**1**) and (–)-euphococcinine (**2**), were achieved from **7** in a six-step sequence through stepwise allylic transfer reactions. Dramatic additive effect of $Bu_3SnF$ for the conversion of **3** into **9** was observed to expedite the process to afford the cyclized products in good yields.

**Key words:** alkaloid, allylation, chiral, cyclization, stereoselectivity

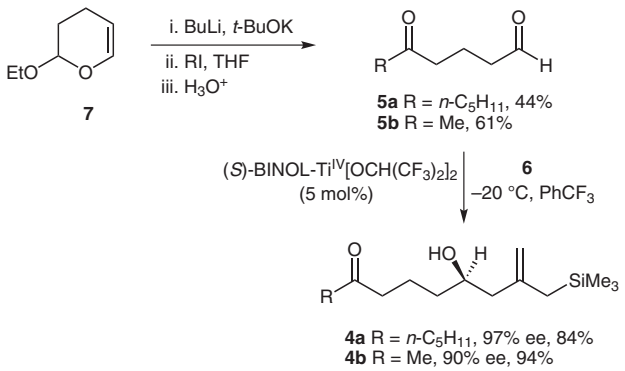
Development of stereocontrolled sequential processes can offer advantages over the stepwise transformations by increasing chemical efficacy due to a simple operation.[1] In the course of our research program aimed at finding new synthetic methods in the stereoselective construction of cyclic system via stepwise allylic transfer reactions,[2] we disclosed our investigations on the transition-metal-catalyzed intramolecular allylation mainly between allene and carbonyl functionality to afford cyclic compounds in high levels of stereoselectivity.[3] With these observations in hand, we became quite interested in designing an enantioselective synthetic route for naturally occurring the piperidine alkaloids (–)-adaline (**1**) and (–)-euphococcinine (**2**) possessing bridged cyclic system as shown in Scheme 1.




**Scheme 1**

(–)-Adaline (**1**) was isolated from secretion of the ladybugs *Cryptolaenus mintrouzieri* and *Adalia bipunctata*.[4] A methyl analogue, (+)-euphococconine (ent-**2**), has been found from the plant and animal kingdoms. It was first isolated from *Euphorbia acto* and has also been found in the defense secretion of ladybugs *Cryptolaenus mintrouzieri* and *Epilachna varivestis*.[5] These bridged piperidine alkaloids[6] were found to exhibit repulsive activity against different insect. The biological behaviors coupled with their interesting structural features have stimulated considerable synthetic efforts to construct bicyclic piperidine systems.[7] It was envisaged that the asymmetric sequential allylic transfer reactions starting from **5** and **6**[8] leading to the synthesis of **1** and **2** could be realized by the four-step sequence as described in Scheme 1.

With this issue in mind, the 5-oxoaldehydes **5** were prepared according to the modification of known procedure.[9] Treatment of **7** with a mixture of *n*-BuLi and KO*t*-Bu in the presence of TMEDA in pentane at –78 °C to –20 °C for 1 hour, followed by reaction with corresponding alkyl iodides in THF at –20 °C for 4 hours, and then acidic cleavage of acetal afforded **5** as described in Scheme 2. The stage was thus set for the allylic transfer reaction of **5** with **6** catalyzed by a chiral Lewis acid catalyst.[2a] The allylic transfer reactions were conducted by the dropwise addition of **6** in $PhCF_3$ at –20 °C to a mixture of (*S*)-BINOL-Ti(IV)$[OCH(CF_3)_2]_2$ (5 mol%) and **5** in $PhCF_3$. After 12 hours at –20 °C, the mixture was quenched by addition of a saturated aqueous $NaHCO_3$. Workup and chromatography on triethylamine-treated silica gel gave **4** in good yields with high levels of enantioselectivity as shown in Scheme 2.




**Scheme 2**

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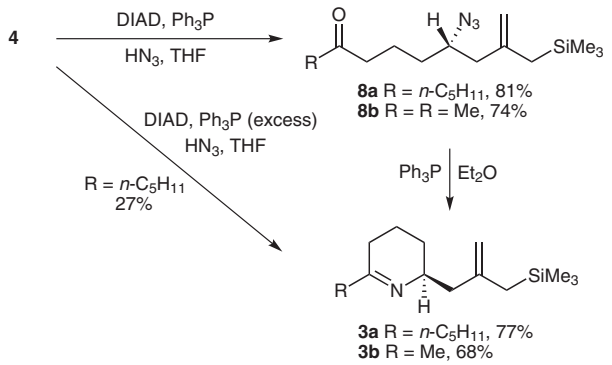
The next stage was the synthesis of a cyclic imine **3** as a precursor for an intramolecular allylic transfer reaction to establish a bridged piperidine system. Compound **4** was converted into the azido-ketone **8** using Mitsunobu conditions in good yields.[10] Treatment of **4a** with DIAD and $HN_3$ (benzene solution) in THF at 20 °C for 2 hours gave **8a** in 81% purified yield. With the azido-ketone **8**, we tried to cyclize **8** to a tetrahydropyridine **3** via an aza-Wittig reaction.[11] In the event, the azido-ketones **8** were converted into the corresponding tetrahydropyridines **3** by treating with $Ph_3P$ at 20 °C for 4 hours in diethyl ether in good yields. However, attempts to a direct conversion of **4a** into **3a** under same conditions except the use of excess $Ph_3P$ (4 equiv) gave only marginal due to low chemical yield (Scheme 3).

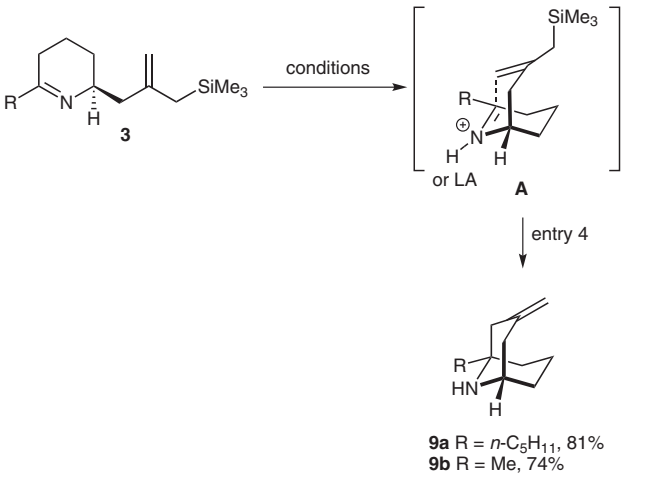



**Scheme 3**

With the tetrahydropyridines **3** in hand, we had reached a suitable intermediate for the construction of the required piperidine **9** through an intramolecular allylic transfer reaction under proper reaction conditions. Several attempts to cyclization of **3a** (R = *n*-pentyl) with Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ indicated that the conversion into the corresponding **9a** could not be realized under various conditions. The use of TMSOTf turned out to be a limited outcome. We observed the formation of only trace of product (ca 10%) except the decomposition of the intermediate. We then turned to other reagents especially Brønsted acids that could promote this conversion. A series of such reagents was tested without success. Finally, we were delighted to find that $CF_3SO_3H$ could be a proper reagent for this purpose. After surveying numerous conditions as summarized in Table 1, several key findings emerged: i) the use of $CF_3SO_3H$ turned out to be marginal but encouraging; ii) the introduction of $Bu_3SnOMe$ as an additive increased chemical yield; iii) a dramatic additive effect was observed by introducing $Bu_3SnF$ in terms of reactivity and chemical yield presumably due to an exchange of silane to stannane; iv) the use of toluene proved to be most suitable solvent compared to others such as $CH_2Cl_2$ and MeCN.

Under optimal conditions, the reaction was conducted by an addition of $CF_3SO_3H$ (1.1 equiv) in toluene at 0 °C to a solution of **3a** (1 equiv) in toluene. After 5 minutes, $Bu_3SnF$ (1.2 equiv) was slowly added to the resulting reaction mixture. After stirring at 0 °C for 1 hour, the reaction mixture was warmed to 20 °C. Reaction was then allowed to proceed for additional 12 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether. After removal volatile materials under reduced pressure, final purification was effected by column chromatography to yield **9a** in 81% yield.

**Table 1** Synthesis of Compounds **9** under Various Conditions

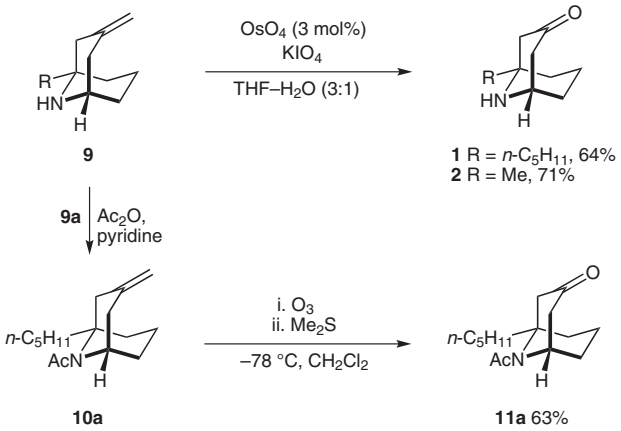



| Entry | Additive[a] | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | none | toluene | 21 |
| 2 | $Bu_3SnOMe$ | toluene | 38 |
| 3 | $Bu_3SnF$ | $CH_2Cl_2$ | 66 |
| 4 | $Bu_3SnF$ | toluene | 81 |

[a] 1.2 equiv.
[b] Refer to purified yields.

The final transformation was an oxidative cleavage of an olefin to a ketone. We were surprised that the ozonolysis of **9a** followed by treating with $Me_2S$ did not afford the corresponding **1** except the decomposition of starting material to a mixture of unidentified compounds. Acetylation of **9a** gave the amide **10a**, which was converted into the corresponding ketone **11a** by the same ozonolysis process. After examined with several reagents, the final step for the synthesis of **1** {64%, $[\alpha]_D^{20}$ –12.2 ($CHCl_3$, *c* 1.1)} and **2** {71%, $[\alpha]_D^{20}$ –6.1 (*c* 1.3, MeOH)} was achieved by the reaction of **9** with $KIO_4$ in the presence of $OsO_4$ catalyst (3 mol%) in a mixture of THF and $H_2O$ at 20 °C as shown in Scheme 4.[12]

In summary, this paper describes the enantioselective synthesis of the piperidine alkaloids (–)-adaline (**1**) and (–)-euphococcinine (**2**) starting from the commercially available **7** in a six-step sequence through the stepwise sequential asymmetric allylic transfer reactions as key transformations.




**Scheme 4**

## Acknowledgment

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