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# Alkaloid Synthesis Using Chiral δ-Amino β-Ketoesters: A Stereoselective Synthesis of (−)-Lasubine II

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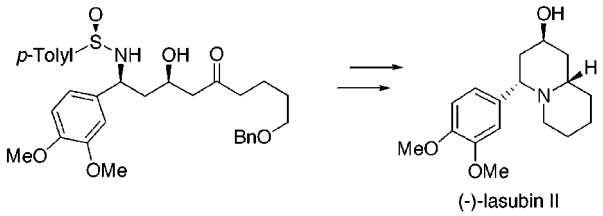
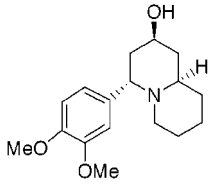
## ABSTRACT

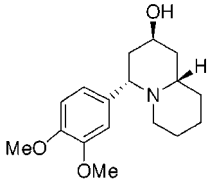



**A highly stereoselective asymmetric synthesis of the quinolizidine alkaloid (−)-lasubine II from a δ-amino β-hydroxy ketone, a new polyfunctionalized chiral building block, is described.**

The Lythraceaes are a large family of naturally occurring alkaloids, a number of which contain the 4-arylquinolizidine substructures.[1] Many biologically important and structurally interesting alkaloids have the quinolizidine skeleton.[2] For example, (−)-lasubine I (**1**) and (−)-lasubine II (**2**), which




(-)-lasubin I **1**




(-)-lasubin II **2**

have the cis- and trans-quinolizidine skeletons, respectively, were isolated by Fuji and co-workers from the leaves of *Lagerstroemia subcostata* Koehne.[3] While many racemic syntheses of **1** and **2** have been described, only four asymmetric syntheses have been reported.[4] The key step in Comins' synthesis of **1** was a diastereoselective (86% de) addition of a Grignard reagent to a chiral 1-acylpyridinium salt.[5] This alkaloid was also recently prepared via an aza-Diels−Alder reaction employing a resolved chiral arylaldehyde tricarbonylchromium complex.[6] A chiral 2-isoxazoline was employed in the synthesis of **2**,[7] and both **1** and **2** were prepared via the intramolecular cyclization of an *N*-acyliminium ion derived from a chiral amino ester.[4] However, in this synthesis the yield (16%) and diastereoselectivity in favor of **2** was poor.

As part of a program aimed at exploring the utility of δ-amino β-ketoester chiral building blocks for alkaloid synthesis, we describe a highly stereoselective asymmetric synthesis of (−)-lasubine II (**2**).[8]

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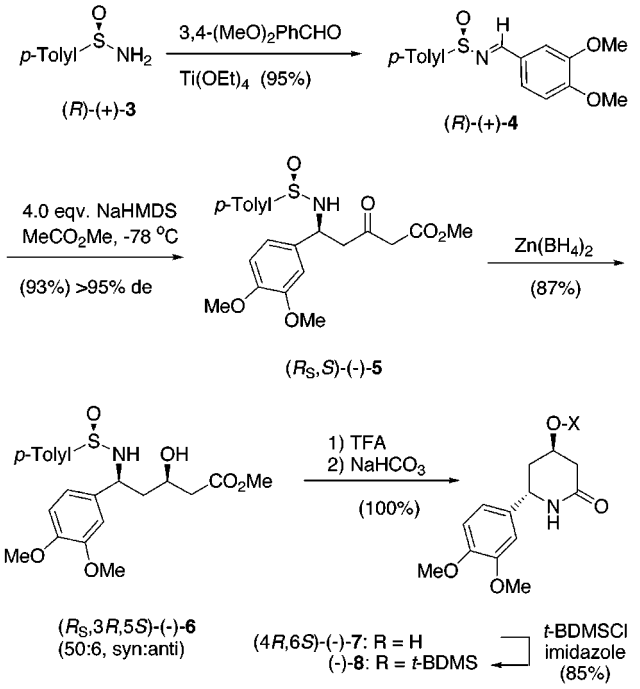
The requisite $\delta$-amino $\beta$-ketoester, ($R_S$,*S*)-(−)-methyl-3-oxo-*N*-(*p*-toluenesulfinyl)-5-amino-5-(3,4-dimethoxy-phenyl)pentanoate (**5**), was prepared in one pot by treating (*R*)-(+)-(3,4-dimethoxybenzylidene)-*p*-toluenesulfinamide (**4**) with 4.0 equiv of the sodium enolate of methyl acetate at −78 °C (Scheme 1). Flash chromatography gave (−)-**5** in 93%

**Scheme 1**

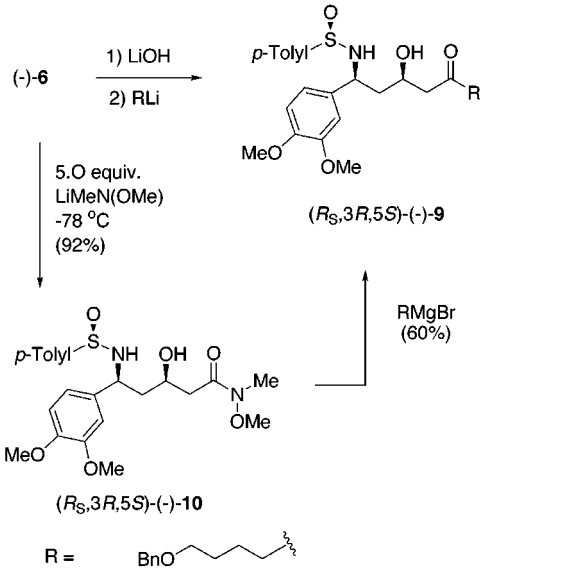



yield and >95% de. Condensation of commercially available (*R*)-(−)-*p*-toluenesulfinamide (**3**) with 3,4-dimethoxybenzaldehyde in the presence of $Ti(OEt)_4$ afforded sulfinimine (*R*)-(+)-**4** in 95% yield.[9] To produce the trans arrangement of the 1-aryl and 3-hydroxy groups in **2**, it was necessary to reduce the 3-oxo group in **5** with syn selectivity. This was readily accomplished using metal chelation control and Zn-$(BH_4)_2$.[10] Thus, treatment of (−)-**5** with 3.2 equiv of Zn-$(BH_4)_2$ at −78 °C for 1 h gave a 50:6 syn:anti ratio of $\beta$-amino alcohol (−)-**6** in 87% yield. In the syn isomer the C(2) protons appear at $\delta$ 2.38 ppm, whereas in the anti isomer one of these protons is shifted downfield to 2.49 ppm. These assignments were confirmed by cyclization of **6** to hydroxy piperidone **7** with TFA/$NaHCO_3$ in quantitative yield, which was converted into **2** (see below). In **7** the C(4) $J_{3,4}$ proton coupling constant is less than 2 Hz.

To proceed with our synthesis of (−)-**2**, it was necessary to replace the 2-oxo group in **7** with a substituent [$BnO(CH_2)_4^-$] that could be cyclized to give the quinolizidine skeleton. For efficiency it was important to accomplish this with a minimum of manipulation and/or protecting group chemistry. However, attempts failed to generate the *N*-trimethylsilyl lactam[11] or the imidoyl chloride[12] of **7**, for coupling with an appropriate organolithium reagent. The $^1$H NMR suggests that *O*-silylation occurred rather than *N*-silylation. Similarly, reaction of the *N*-Cbz derivative of **8** with LiHMDS followed by treatment of the resulting enolate with *N*-(5-chloro-2-pyridyl)triflimide resulted in decomposition. Comins has reported that enol triflates, prepared from *N*-acyllactams, readily react with organometallic reagents to give enecarbamates.[13] These failures may be a consequence of steric congestion at the amide nitrogen and/or instability of the intermediate enolate.

Since the synthesis of ketones from carboxylic acids and organolithium reagents is well-known,[14,15] we next explored the conversion of the carbomethoxy group in $\beta$-amino alcohol **6** to ketone **9** (Scheme 2). The amino alcohol **6** was treated

**Scheme 2**




with 1.0 equiv of LiOH, to hydrolyze the ester to the acid, and the solvent was removed to dryness. Azeotropic treatment with benzene was used to remove the last traces of water. When the lithium salt of **6** was reacted with 4 equiv of *n*-BuLi, ketone **9** (R = *n*-BuLi) was isolated in 60% yield. However, with lithium 4-benzyloxybutane, prepared from 4-benzyloxybutyl phenyl sulfide and lithium naphthalene,[16] ketone **9** was obtained in less than 20% yield.

*N*-Methoxy-*N*-methylamides, Weinreb amides, are important carbonyl equivalents and have been extensively explored

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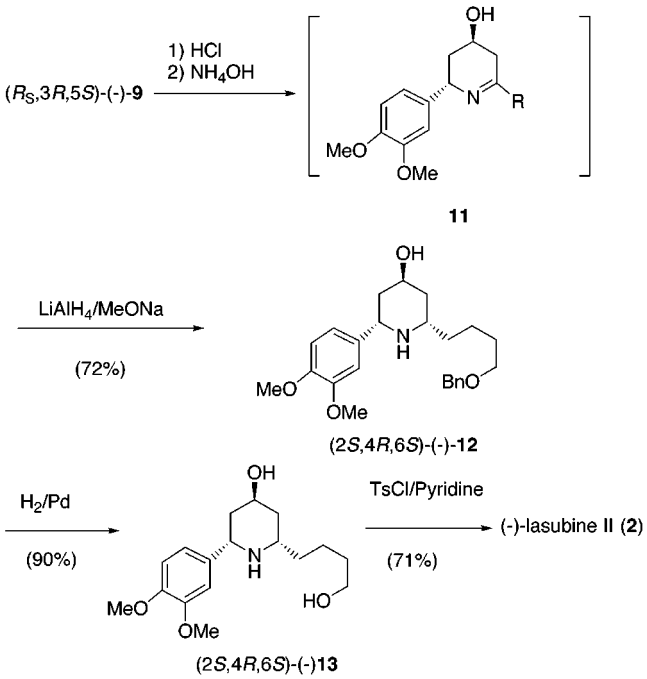
(16) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064.

for the synthesis of ketones.[17,18] Reaction of **6** with 5 equiv of lithium *N*,*O*-dimethylhydroxylamine gave amide **10** in 92% isolated yield (Scheme 2). Remarkably, the *N*-sulfinyl group remained intact and is a likely consequence of formation of the lithium *N*-sulfinyl amide which protects it from further reaction. With 10.0 equiv of 4-(benzyloxy)-1-butane magnesium bromide, **10** gave the desired ketone **9** in 60% yield. The sulfinyl group was removed with 4 N HCl, and neutralization with concentrated $NH_4OH$ gave the cyclic imine **11** (Scheme 3). The crude imine **11** was not isolated but was reduced with LAH/MeONa to give, exclusively, the cis hydroxy piperidine **12** in 72% overall yield for the conversion of **9** to **12**. Deprotection of the benzyl group with $H_2$/Pd gave a 90% yield of alcohol **13**. The quinolizidine ring was formed from **13** on reaction with pyridine and TsCl, affording (−)-lasubine II (**2**) in 71% yield with properties in agreement with literature values.

**Scheme 3**




In summary, a highly stereoselective asymmetric synthesis of (−)-lasubine II (**2**) from $\delta$-amino $\beta$-ketoester ($R_SS$)-(−)-**5** is presented. Noteworthy features of the synthesis include the preparation of $\delta$-amino $\beta$-hydroxy ketone (−)-**9** from Weinreb amide **10**, its ready conversion to the quinolizidine skeleton, and the absence of protecting group chemistry in these transformations. This new methodology further illustrates the utility of polyfunctionalized chiral building blocks such as **5** and **9** for alkaloid synthesis.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds **2**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0061438

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