

HETEROCYCLES, Vol. 79, 2009, pp. 433 - 439. © The Japan Institute of Heterocyclic Chemistry
Received, 30th October, 2008, Accepted, 25th December, 2008, Published online, 26th December, 2008.
DOI: 10.3987/COM-08-S(D)75

NEW ENTRY TO THE ASYMMETRIC SYNTHESIS OF (–)-LASUBINE I AND (+)-SUBCOSINE I¹

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Abstract – A new synthetic entry to (–)-lasubine I and (+)-subcosine I has been established by employing the (*S*)-allylalkoxy benzylamine as a chiral synthon. The synthesis involves the formation of an α,β -unsaturated lactone by RCM reaction followed by an intramolecular Michael-type addition reaction as a key step, which enables the stereoselective construction of the *cis*-quinolizidine skeleton of lasubine I and subcosine I.

INTRODUCTION

Lasubine I (**1**) and lasubine II (**2**),² and their ferulates subcosine I (**3**) and subcosine II (**4**)² are members of the arylquinolizidine class of lythraceae alkaloids.³ The structural difference between lasubines I (**1**) and II (**2**) is the stereochemistry at C-10 of the quinolizidine ring, which generates the difference in the *cis*- and *trans*-relationship between C-10 and N-5 on the quinolizidine ring system (Figure 1).³ To date, many examples of the synthesis of lasubines in racemic and chiral forms have been reported.^{4,5} On the other hand, reports of synthetic examples of subcosines in both racemic and chiral forms have been very few.^{6,7} During the course of our investigations on the diastereoselective addition of alkylolithiums to chiral oxime ethers,⁸ we found that the allylation proceeded in a moderate selectivity (5-4:1) by employing a η^3 -allyllithium complex with (*R*)-2'-(2-naphthyl)-bearing hydroxyoxime ethers **6** to give (*S*)-1-(aryl)homoallylic amino derivatives **7** (Scheme 1), one of which was successfully transformed into the *trans*-quinolizidine alkaloid, (+)-abresoline (**5**).⁹ In this paper we present a new synthetic entry to

cis-quinolizidine alkaloids, (–)-lasubine I (**1**) and (+)-subcosine I (**3**), utilizing this (*S*)-1-(aryl)homoallylic amino derivative.

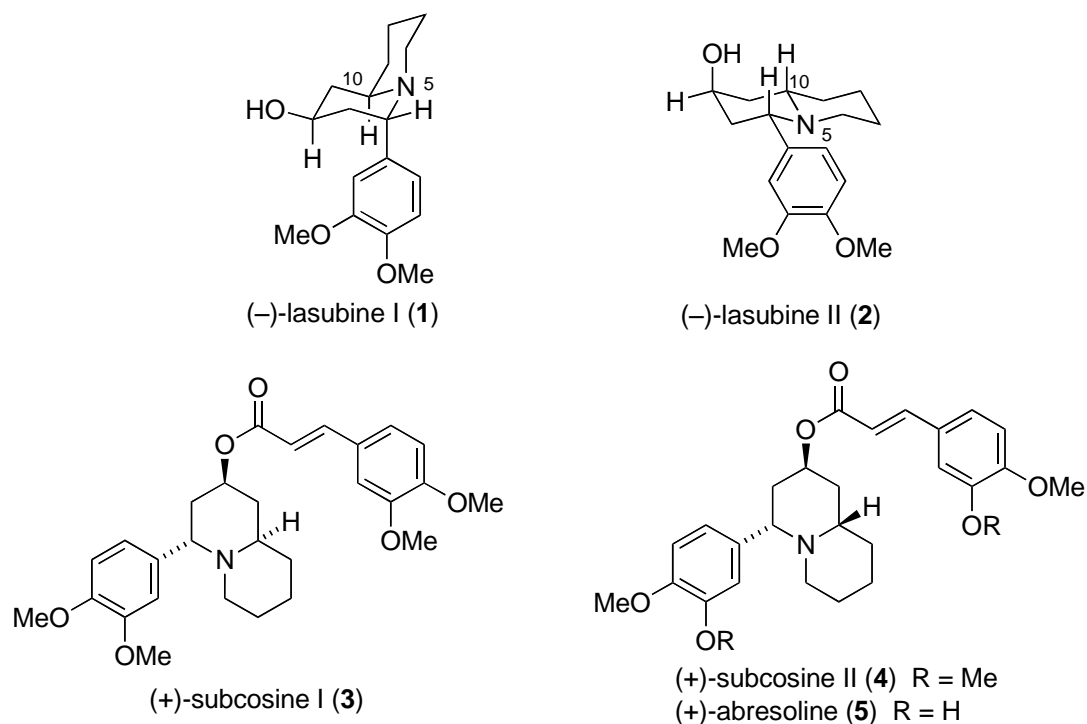
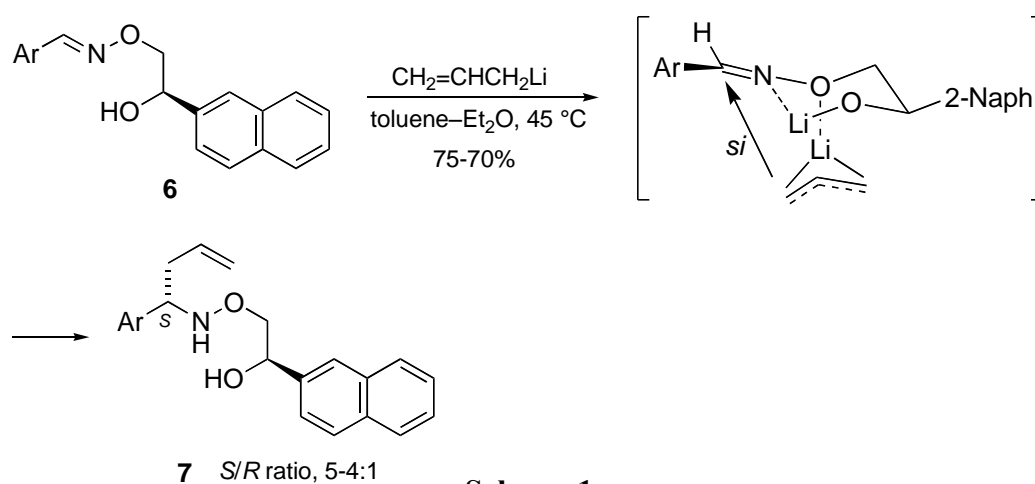
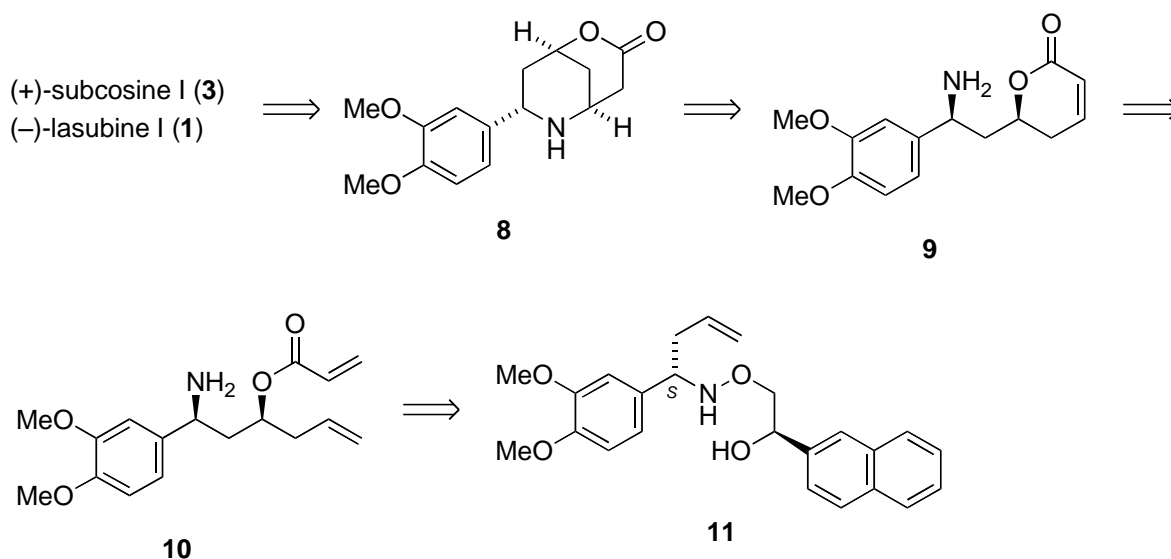


Figure 1. Structures of 4-arylquinolizidine alkaloids.



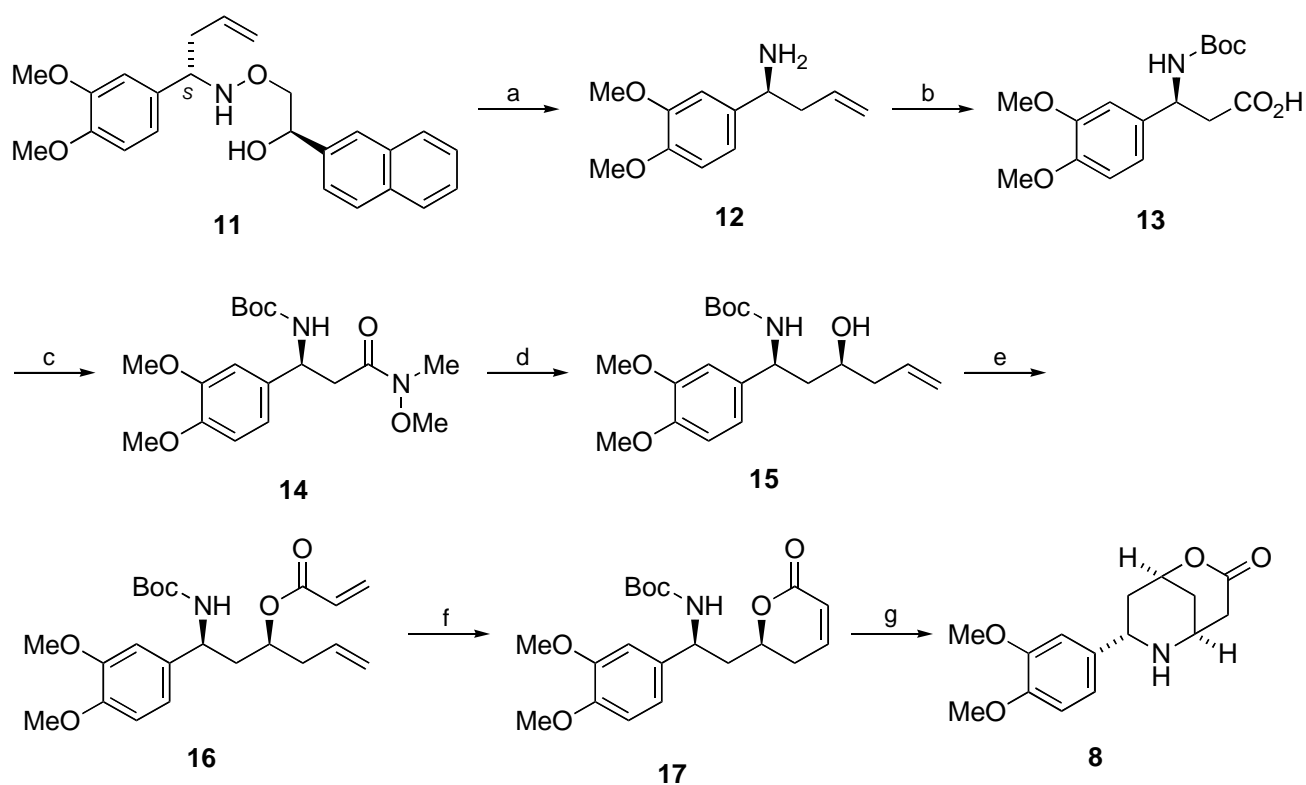
Our synthetic strategy for *cis*-quinolizidine alkaloids, **1** and **3**, involves preparation of the bicyclic lactone **8** having a *trans*-2,6-piperidine skeleton, which was obtained in a stereospecific manner by an intramolecular Michael-type addition (**9**→**8**) of the α,β -unsaturated lactone **9** and the cyclization of diene **10** by

ring-closing metathesis (RCM) (**10**→**9**) as illustrated in Scheme 2, starting with the (*S*)-1-(aryl)homoallylic amino derivative **11**.⁹



RESULTS AND DISCUSSION

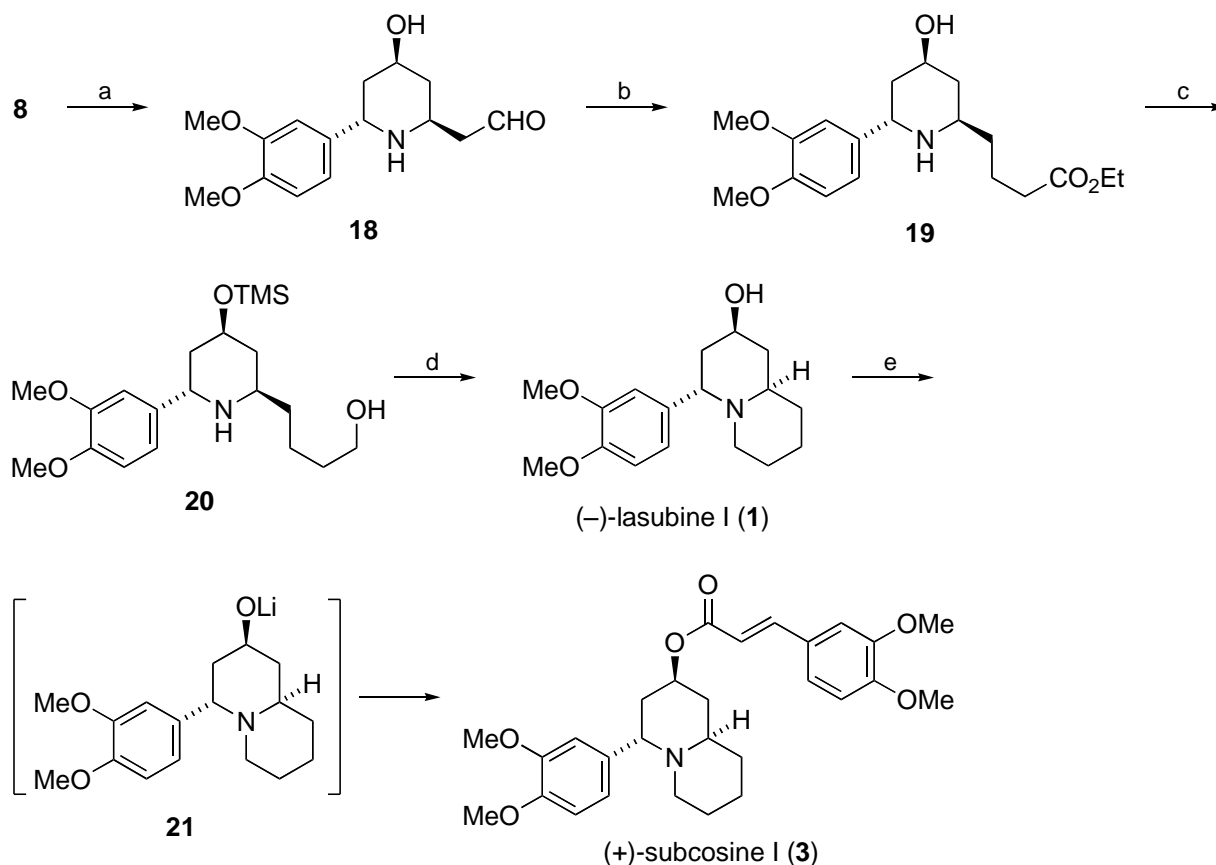
Reductive cleavage of the O-N bond of the (*S*)-1-(aryl)homoallylamine **11** proceeded successfully with zinc–AcOH in THF–H₂O at reflux to give the homoallylamine **12** in an 80% yield. This material showed levorotatory optical rotation, $[\alpha]_D^{20} -13.5$ (*c* 0.5, CHCl₃) [lit.,¹⁰ $[\alpha]_D^{20} -13.5$ (*c* 0.5, CHCl₃)], which coincided with the *S*-configuration at the benzylic position. Boc-protection of the primary amine **12** was followed by transformation of the vinyl group to the formyl group by oxidative cleavage, and then re-oxidation of the formyl group with sodium chlorite yielded the Boc-protected carboxylic acid **13** in an 86% yield over three steps. The carboxylic acid **13** was converted to the Weinreb amide **14** with *O,N*-dimethylhydroxylamine hydrochloride and 2-chloro-1-methylpyridinium iodide in a 99% yield. Treatment of **14** with allylmagnesium bromide gave the β,γ-unsaturated ketone, which was reduced diastereoselectively by chelation controlled hydride addition with LS-Selectride in THF at –78 °C to give the 1,3-*syn*-aminoalcohol **15** accompanied by a small amount of *anti*-isomer (*syn/anti* = 9.1:1) in a combined yield of 76%.¹¹ After separation of the *S*-isomer by column chromatography, esterification of **15** was affected with acryloyl chloride in the presence of Et₃N to give the diene **16** in an yield of 75%. The RCM reaction of **16** with the second-generation Grubbs catalyst¹² (10 mol%) in CH₂Cl₂ under reflux gave the α,β-unsaturated-δ-lactone **17** as a sole product in an excellent yield (98%). Deprotection of the *N*-Boc group of **17** by treatment of trifluoroacetic acid, followed by exposure to a saturated sodium bicarbonate solution, led to the Michael-type addition in a stereospecific manner to yield the bicyclic lactone **8** in an 88% yield as a single stereoisomer.¹³



Scheme 3. Reagents and conditions: (a) Zn–AcOH, THF–H₂O (3:1), reflux, 80%; (b) (i) (Boc)₂O, NaOH, 92%; (ii) OsO₄, NaIO₄, THF–H₂O, 99%; (iii) NaClO₂, NaH₂PO₃, 94%; (c) MeO(Me)NH·HCl, CMPI, Et₃N, 99%; (d) (i) CH₂=CHCH₂MgBr, THF, 0 °C, 85%; (ii) LS-Selectride[®], THF, –78 °C; (e) acryloyl chloride, Et₃N, CH₂Cl₂, 75%; (f) Grubbs catalyst, 2nd generation (10 mol %), 98%; (g) TFA, CH₂Cl₂, then saturated NaHCO₃, 88%.

With the bicyclic lactone having the desired stereochemistry in hand, we next examined its conversion to a *cis*-quinolizidine compound. Reduction of the bicyclic lactone **8** with DIBAL-H gave the 2,4,6-trisubstituted formylmethyl piperidine **18** in a 99% yield. The formyl substituent of **18** was elongated by Horner-Wadsworth-Emmons olefination and then hydrogenated to yield the (ethoxycarbonyl)propylpiperidine **19**. The secondary hydroxy group of **19** was protected as a TMS ether and then treated with LiAlH₄ to give the primary alcohol **20** in a 66% yield over two steps. Upon treatment of **20** with tetrabromomethane and triphenylphosphine¹⁴ in CH₂Cl₂ at room temperature, intramolecular cyclization occurred to give a quinolizidine, which was exposed to tetrabutylammonium fluoride in THF to furnish (–)-lasubine I (**1**), [α]_D²⁰ –7.66 (*c* 1.0, MeOH) [lit.,^{4g} [α]_D²³ –7.03 (*c* 0.37, MeOH)], in a 69% yield over two steps. Conversion of (–)-lasubine I (**1**) to (+)-subcosine I (**3**) was effected by lithiation of the secondary alcohol and then treatment with dimethoxycinnamic anhydride to yield (+)-subcosine I (**3**) in a 70% yield. Our synthetic material of **3** was found to have [α]_D²⁰ +95.5 (*c* 1.0, MeOH) [lit.,^{4g} [α]_D²³ +93.6 (*c* 0.14, MeOH)] and to be identical to those of authentic subcosine I by IR, ¹H-NMR, and mass spectra.^{4b,g}

In conclusion, we have established a new synthetic entry to (-)-lasubine I and (+)-subcosine I starting with the (*S*)-1-(aryl)homoallylic amine **11**. This route employs, as the key steps, the RCM reaction of the diene **16** to afford the Boc protected monocyclic lactone **17**, and the TFA–NaHCO₃ mediated intramolecular Michael-type addition for the elaboration of the bicyclic lactone **8** having the necessary stereochemistry for **1** and **3**.

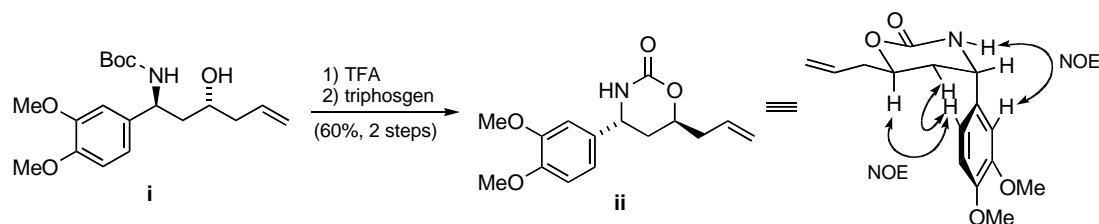


Scheme 4. Reagents and conditions: (a) DIBAL-H, CH₂Cl₂, -78 °C, 99%; (b) (i) (EtO)₂POCH₂CO₂Et, KHMDS, 0 °C, 80%; (ii) H₂, Pd-C, 94%; (c) (i) TMS-imidazole, 81%; (ii) LiAlH₄, THF, 82%; (d) (i) Ph₃P, CBr₄, 92%; (ii) TBAF, 99%; (e) BuLi, THF, -78 °C, then 3,4-dimethoxycinnamic anhydride, 70%.

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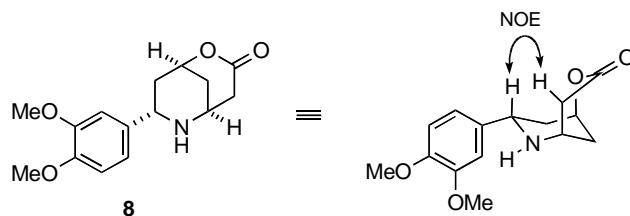
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11. The stereochemistry of the 1,3-*cis*-aminoalcohol **15** was assigned tentatively on the basis of the NOESY spectra of **ii**, which was obtained by the chemical transformation of the minor 1,3-*trans*-aminoalcohol **i** in two steps as shown below. Direct stereochemical assignment of the major isomer was performed by means of the NOESY spectra of the bicyclic lactone **8**, which was derived from **15** (vide infra).



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