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 I[1]

Naoki Yamazaki,[*ab] Masakazu Atobe,[b] Chihiro Kibayashi,[b] and Sakae Aoyagi[*b]

[a]Faculty of Pharmacy, Iwaki Meisei University, 5-5-1 Chuodai-Iino, Iwaki, Fukushima 970-8551, Japan
[b]School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

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

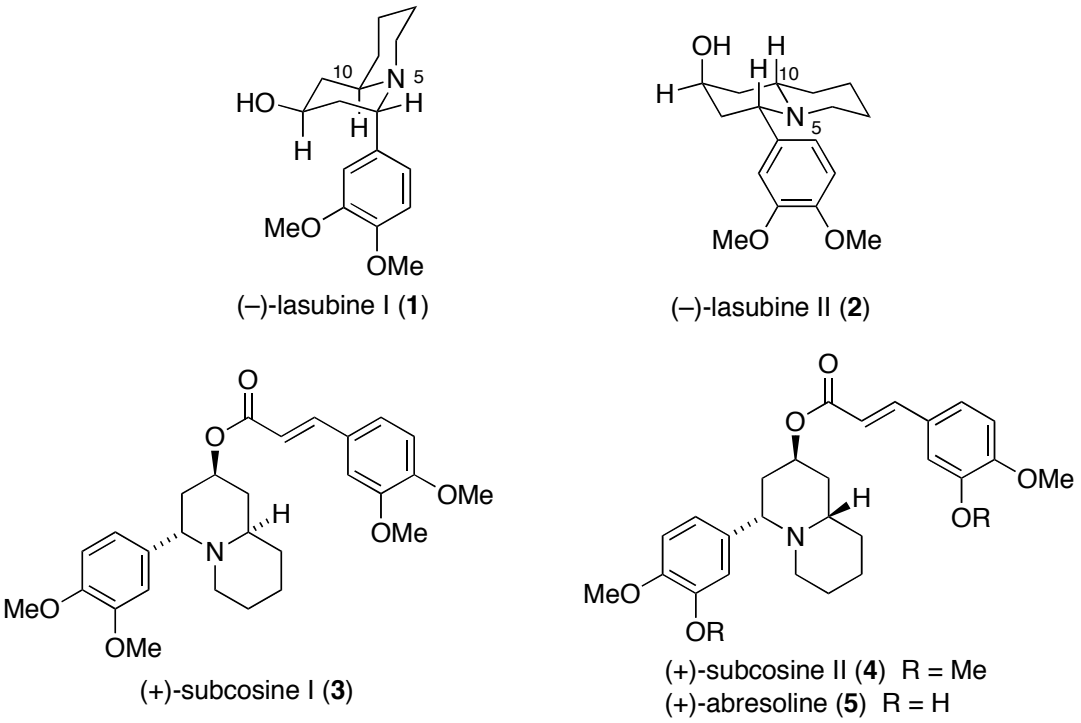
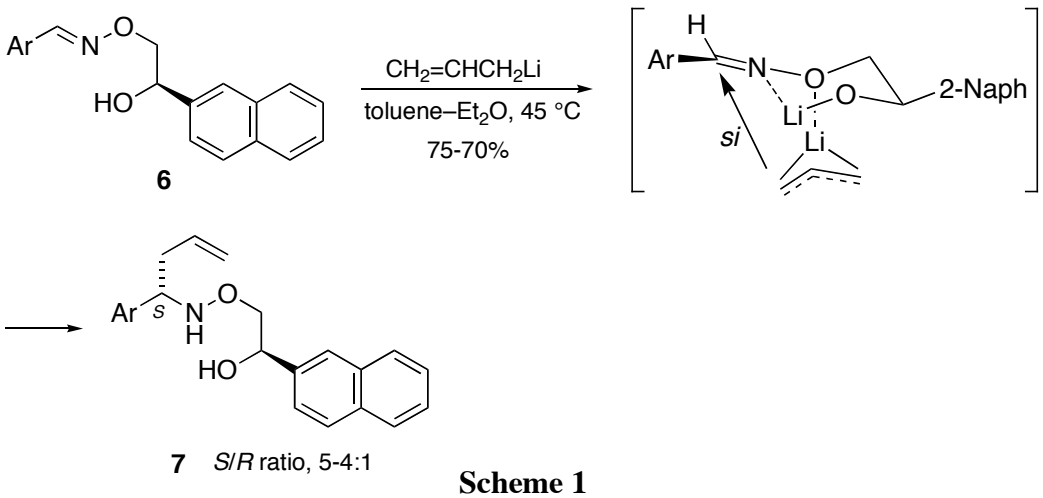


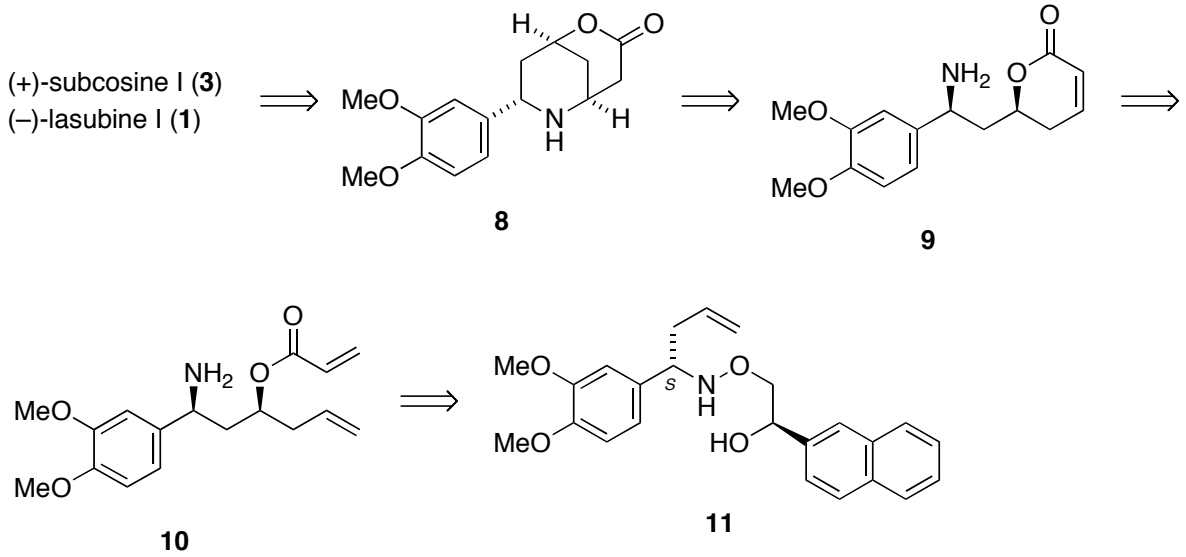
Figure 1. Structures of 4-arylquinolizidine alkaloids.



Scheme 1

Our synthetic strategy for *cis*-qunolizidine 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

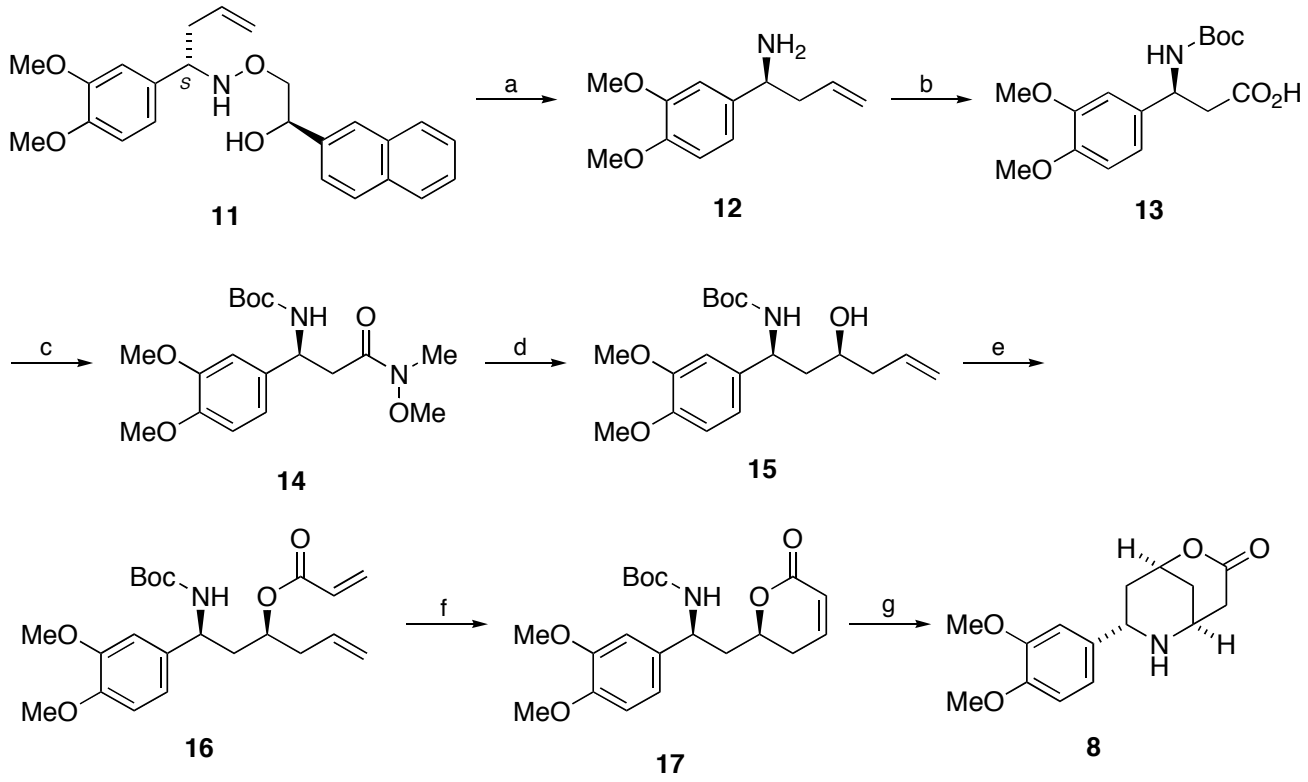
10 by ring-closing metathesis (RCM) (**10**→**9**) as illustrated in Scheme 2, starting with the (*S*)-1-(aryl)homoallylic amino derivative **11**.[9]



Scheme 2

RESULTS AND DISCUSSION

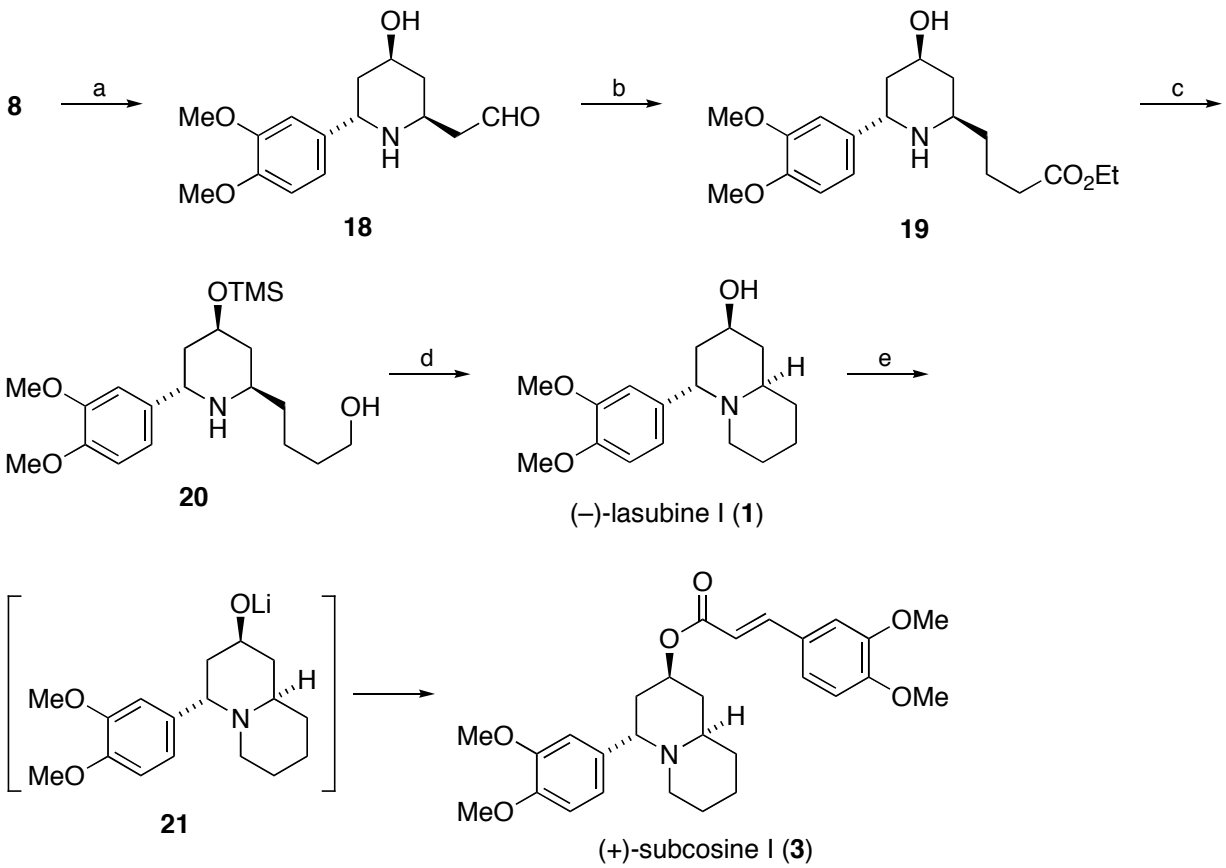
Reductive cleavage of the O-N bond of the (*S*)-1-(aryl)homoallylamine **11** proceeded successfully with zinc–AcOH in THF–H_2O at reflux to give the homoallylamine **12** in an 80% yield. This material showed levorotatory optical rotation, $[\alpha]^{20}_D$ –13.5 (*c* 0.5, $CHCl_3$) [lit.,[10] $[\alpha]^{20}_D$ –13.5 (*c* 0.5, $CHCl_3$)], 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 Et_3N to give the diene **16** in an yield of 75%. The RCM reaction of **16** with the second-generation Grubbs catalyst[12] (10 mol%) in CH_2Cl_2 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–H_2O (3:1), reflux, 80%; (b) (i) $(Boc)_2O$, NaOH, 92%; (ii) OsO_4, $NaIO_4$, THF–H_2O, 99%; (iii) $NaClO_2$, NaH_2PO_3, 94%; (c) MeO(Me)NH·HCl, CMPI, Et_3N, 99%; (d) (i) CH_2=$CHCH_2MgBr$, THF, 0 °C, 85%; (ii) LS-Selectride®, THF, –78 °C; (e) acryloyl chloride, Et_3N, CH_2Cl_2, 75%; (f) Grubbs catalyst, 2nd generation (10 mol %), 98%; (g) TFA, CH_2Cl_2, then saturated $NaHCO_3$, 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 $LiAlH_4$ to give the primary alcohol **20** in a 66% yield over two steps. Upon treatment of **20** with tetrabromomethane and triphenylphosphine[14] in CH_2Cl_2 at room temperature, intramolecular cyclization occurred to give a quinolizidine, which was exposed to tetrabutylammonium fluoride in THF to furnish (–)-lasubine I (**1**), $[\alpha]^{20}_D$ –7.66 (*c* 1.0, MeOH) [lit.,[4g] $[\alpha]^{23}_D$ –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 $[\alpha]^{20}_D$ +95.5 (*c* 1.0, MeOH) [lit.,[4g] $[\alpha]^{23}_D$ +93.6 (*c* 0.14, MeOH)] and to be identical to those of authentic subcosine I by IR, ^{1}H-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–$NaHCO_3$ 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, CH_2Cl_2, –78 °C, 99%; (b) (i) $(EtO)_2POCH_2CO_2Et$, KHMDS, 0 °C, 80%; (ii) H_2, Pd–C, 94%; (c) (i) TMS-imidazole, 81%; (ii) $LiAlH_4$, THF, 82%; (d) (i) Ph_3P, CBr_4, 92%; (ii) TBAF, 99%; (e) BuLi, THF, –78 °C, then 3.4-dimthoxycinnamic anhydride, 70%.

REFERENCES AND NOTES

1. This paper is dedicated to the great contribution to heterocyclic chemistry by the late Dr. John Daly, National Institutes of Health.
2. For isolation, see: K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.,* 1978, **26**, 2515.
3. For reviews of the lythraceae alkaloids, see: (a) W. M. Golebiewski and J. T. Wróbel, 'The Alkaloids,' Vol. 18, ed. by R. G. A. Rodrigo, Academic Press, New York, 1981, Chapter 4; (b) K. Fuji, 'The Alkaloids', Vol. 35, ed. by A. Brossi, Academic Press, San Diego, 1989, Chapter 3.

4. For racemic syntheses of lasubine I, see: (a) H. Iida, M. Tanaka, and C. Kibayashi, *J. Chem. Soc., Chem. Commun.,* 1983, 1143; (b) H. Iida, M. Tanaka, and C. Kibayashi, *J. Org. Chem.,* 1984, **49**, 1909; (c) H. Ent, H. De Koning, and W. N. Speckamp, *Heterocycles,* 1988, **27**, 237; (d) A. L. J. Beckwith, S. P. Joseph, and R. T. A. Mayadunne, *J. Org. Chem.,* 1993, **58**, 4198; (e) V. Bardot, D. Gardette, Y. Gelas-Mialhe, J.-C. Gramain, and R. Remuson, *Heterocycles,* 1998, **48**, 507; (f) B. Furman, and G. Lipner, *Tetrahedron*, 2008, **64**, 3464. For asymmetric syntheses of (–)-lasubine I, see: (g) D. L. Comins and D. H. LaMunyon, *J. Org. Chem.,* 1992, **57**, 5807; (h) P. Chalard, R. Remuson, Y. Gelas-Mialhe, and J.-C. Gramain, *Tetrahedron: Asymmetry,* 1998, **9**, 4361; (i) H. Ratoni and E. P. Kuendig, *Org. Lett.,* 1999, **1**, 1997; (j) F. A. Davis, A. Rao, and P. J. Carroll, *Org. Lett.,* 2003, **5**, 3855; (k) S. Liu, Y. Fan, X. Peng, W. Wang, W. Hua, H. Akber, and L. Liao, *Tetrahedron Lett.*, 2006, **47**, 7681.

5. For racemic syntheses of lasubine II, see: refs. 4a, b and R. A. Pilli, L. C. Dias, and A. O. Maldaner, *J. Org. Chem.,* 1995, **60**, 717 and references cited therein. For asymmetric syntheses of (–)-lasubine II, see: ref. 4h and T. G. Back, M. D. Hamilton, V. J. J. Lim, and M. Parvez, *J. Org. Chem.*, 2005, **70**, 967 and references cited therein. For a synthesis of 8-epi-(-)-lasubine II, see: J. Lim and G. Kim, *Tetrahedron Lett.,* 2008, **49**, 88. For a synthesis of antipodal (+)-lasubines, see: O. G. Mancheño, R. G. Arrayás, J. Adrio, and J. C. Carretero, *J. Org. Chem.*, 2007, **72**, 10294 and references cited therein.

6. For a racemic synthesis of subcosine I, see: refs. 4a, b.

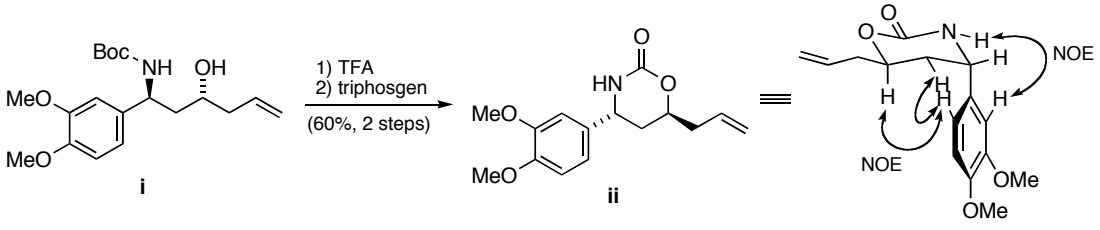
7. For an asymmetric synthesis of (+)-subcosine I, see: ref. 4g. For an asymmetric synthesis of (+)-subcosine II, see: ref. 4h.

8. M. Atobe, N. Yamazaki, and C. Kibayashi, *J. Org. Chem.,* 2004, **69**, 5595.

9. M. Atobe, N. Yamazaki, and C. Kibayashi, *Tetrahedron Lett.,* 2005, **46**, 2669.

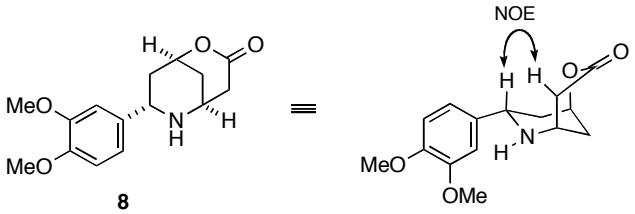
10. G. K. Friestad and H. Ding, *Org. Lett.*, 2004, **6**, 637.

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).



12. M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.

13. The selected NOESY correlation of the bicyclic lactone confirmed the structure **8** as shown below.



8

14. Y. Shishido and C. Kibayashi, *J. Org. Chem.*, 1992, **57**, 2876.