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Enantiodivergent Synthetic Entry to the Quinolizidine Alkaloid Lasubine II

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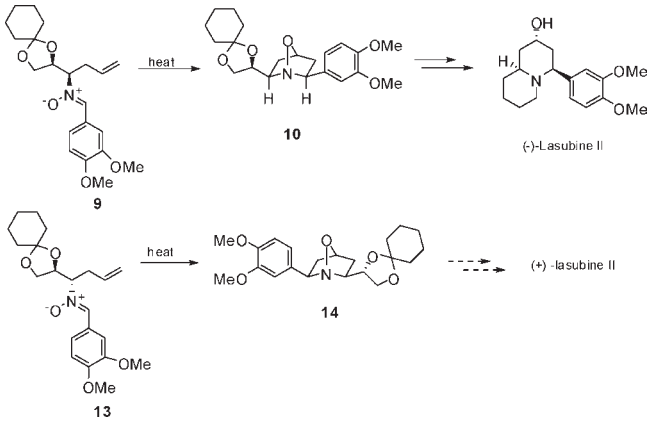
ABSTRACT



Intramolecular cycloaddition of the *syn*- and the *anti*-nitrone 9 and 13 leads stereoselectively to the azabicyclic compounds 10 and 14 which may provide access to both enantiomers of the quinolizidine alkaloid lasubine II.

The piperidine ring system constitutes part of many naturally occurring and biologically interesting compounds.[1] In particular, 2,6-disubstituted piperidine derivatives have attracted more attention because of their frequent appearance in various naturally occurring ring forms such as quinolizidines, indolizidines, and others.[2,3] Most of these compounds are known to display a broad range of useful biological activities. A major challenge in their synthesis is the strategic placement of the ring functionalities with the desired stereochemistry. As a consequence, synthetic methodologies continue to be developed for the stereoselective synthesis of both *cis*-[4] and *trans*-2,6-disubstituted piperidines.[5]

Among this class of compounds, the *cis*-2,6-disubstituted 4-piperidinol motif is present in important alkaloids such as lasubine II,[6] subcosine II,[6] alkaloid 241D,[7] and *epi*-myrtine[8] (Figure 1). Of these, lasubine II has received considerable attention and its several elegant syntheses have been reported. However, synthetic entry to both enantiomers of lasubine II from a common source remains

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important.[6c] Herein, we report an enantiodivergent synthetic route to lasubine II.

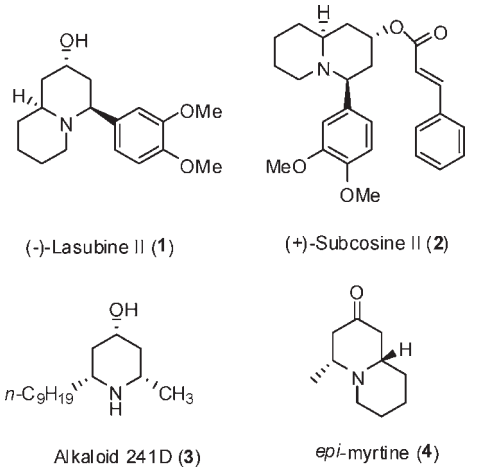
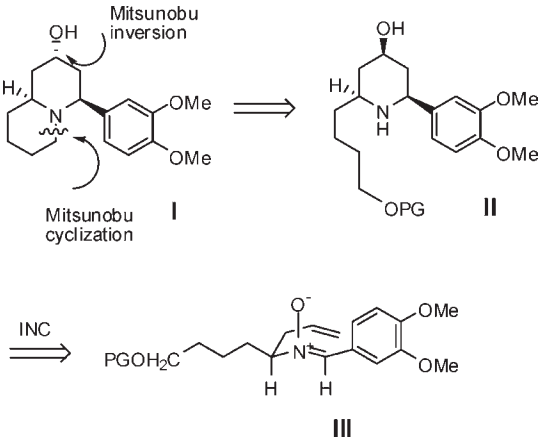


Figure 1. Selected natural products accommodating the *cis*-2, 6-disubstituted piperidine ring system.

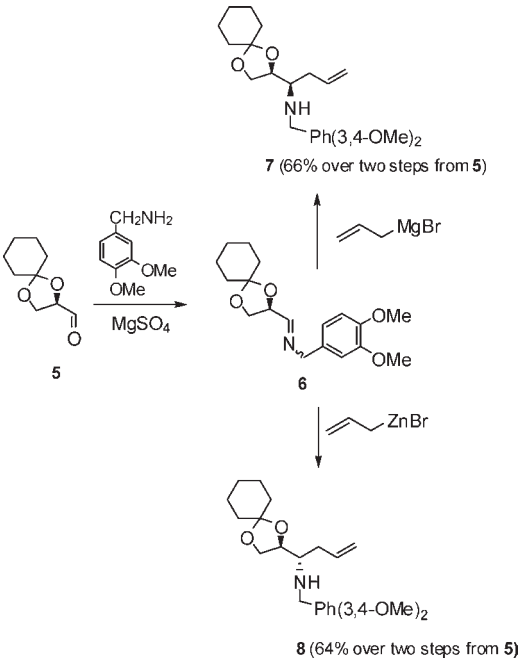
Our retrosynthetic analysis (Scheme 1) of lasubine II relied on using two simultaneous or sequential Mitsunobu reactions involving hydroxyl group inversion and azabicycle formation in either order leaving the substructure II as the prime target. The desired stereochemistry in II as well as the key ring formation from an acyclic precursor was thought to be obtainable from the Intramolecular Nitrone Cycloaddition (INC)[10] of an optically pure nitrone of the type III.

Scheme 1. Retrosynthetic Analysis of Lasubine II



We have recently reported[9] a diastereoselective synthesis of homoallylic amines by the addition of a suitable allyl metal to an imine derived from *R*-2,3-*O*-cyclohexylideneglyceraldehyde (**5**, Scheme 2). We adopted this methodology with some modifications to prepare the homoallylic *syn*- and *anti*-amines **7** and **8** from the imine **6**, obtained by dehydrative condensation of 3,4-dimethoxybenzyl amine with **5**. Thus, addition of allylmagnesium bromide to **6** delivered a separable mixture of the major *syn*-isomer **7** and the minor *anti*-isomer whereas addition of allylzinc bromide to **6** resulted in the formation of **8** as the major product.

Scheme 2. Preparation of the Homoallylic Amines **7** and **8**



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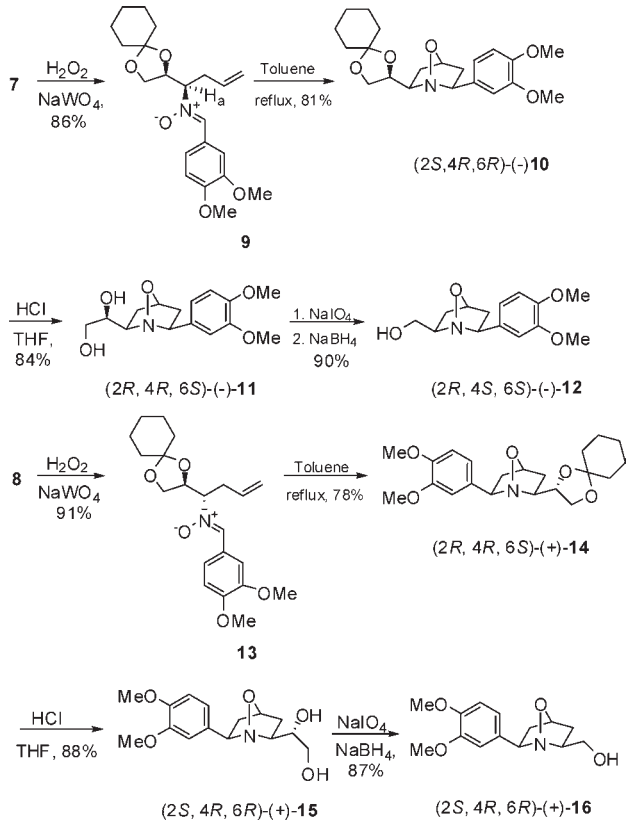
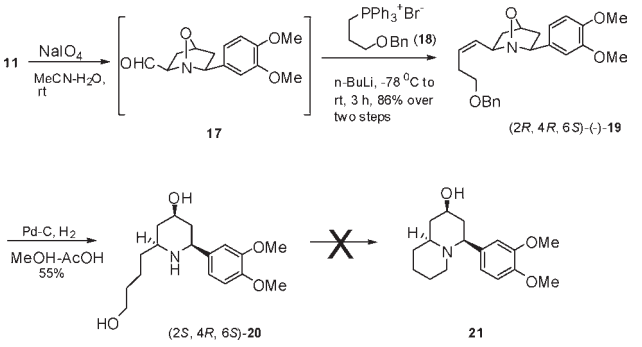
Scheme 3. Enantiodivergent Synthesis of the Azabicyclic Compounds **12** and **16**



Intramolecular 1,3-dipolar cycloaddition of *N*-alkenyl nitrones has been used[11] in the stereoselective preparation of various heterocyclic systems including piperidine derivatives. We therefore explored the utility of the chiral homoallylic amines **7** and **8** in the stereoselective construction of piperidine derivatives related to the synthesis of lasubine II. The *syn*-amine **7** was converted to the corresponding nitrone **9** (Scheme 3) using a hydrogen peroxide–sodium tungstate combination.[12] Compound **9** was obtained in high yield and as a single isomer assigned as the thermodynamically more stable *Z*-isomer. This assignment was further supported by NOESY experiments which revealed a correlation between the C_α-proton (δ3.89) and the azomethine proton (δ 8.41). Intramolecular cycloaddition of the nitrone **9** proceeded smoothly in refluxing toluene to give a single isolable product in 81% yield, but examination of the crude mixture by HPLC-MS indicated the possibility of the existence of an isomeric compound (7%) which could not be obtained in pure form. The major product was assigned structure **10** based on the assumption that an *endo* approach of the double bond to the *Re* face of the nitrone would be favorable.[13] Hydrolytic removal of the cyclohexylidene moiety followed by a two-step conversion of the resulting diol **11** involving oxidative cleavage of the diol unit and subsequent reduction of the resulting formyl group to the primary alcohol **12** proceeded smoothly under conventional conditions.

Similarly, the *anti*-amine derivative **8** produced the corresponding nitrone **13** also as the *Z*-isomer. Cycloaddition of **13** in refluxing toluene proceeded smoothly to deliver the cycloadduct **14** formed in an analogous manner by *Re* face addition to the nitrone in an *endo* approach. Compound **14** was then converted to the bicyclic piperidine derivative **16** following the three-step conversion detailed above for the conversion **10**→**12**, i.e. acid mediated opening to the diol **15** followed by its redox manipulation leading to the primary alcohol **16**. Compound **16** was found, as expected, to be enantiomeric to compound **12** from spectroscopic and optical measurement data.

Scheme 4



Having established an enantiodivergent route to the all *cis*-2,4,6-trisubstituted piperidine derivatives **12** and **16** (*ent*-**12**), we focused on the conversion of **11** to lasubine II along the projected pathway. Thus, the diol **11** was oxidatively cleaved to the aldehyde **17**, which was used without purification in the subsequent three-carbon Wittig homologation with the salt **18** to obtain the *cis*-olefin **19** as the only isomer in an overall yield of 86% over two steps (Scheme 4). Catalytic hydrogenation of the latter effected the desired three reductions to directly yield the amino-diol **20** in good yield. However, attempts to cyclize this to

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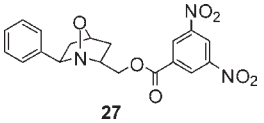
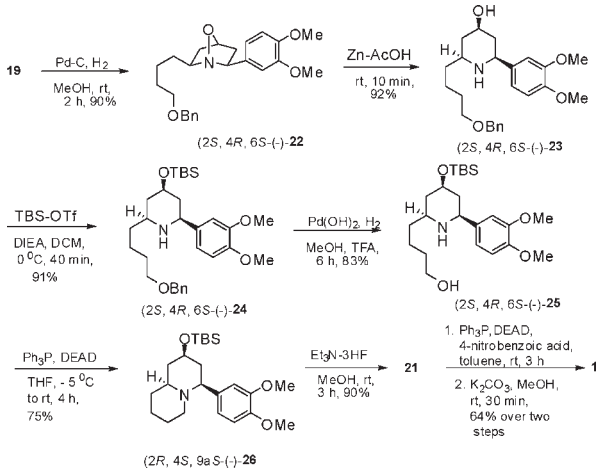
(13) This was supported by theoretical calculations as well as by X-ray analysis of model compound (**27**); CCDC No. 835450.



epi-lasubine **21** involving displacement of the derived primary OTs group by a ring nitrogen,[6d] or by Mitsunobu-type cyclization, proved to be unsuccessful; the solubility of compound **20** in the desired solvents was the major impediment.

Scheme 5. Synthesis of (−)-Lasubine II



In an alternative approach (Scheme 5), selective hydrogenation of the olefinic bond in **19** leading to **22** and its subsequent Zn-mediated opening of the bicyclic ring delivered the 4-hydroxypiperidine derivative **23**, which was protected as its OTBS-derivative **24** under conventional conditions. Hydrogenolytic removal of the benzyl group followed by cyclization of the resulting alcohol **25** under a Mitsunobu protocol proceeded in a facile manner leading to the formation of the quinolizidine derivative **26** in good yield. Removal of the OTBS group in the latter using $Et_3N{-}HF$ then provided 2-*epi*-lasubine II (**21**) in an overall yield of 14% over 11 steps in a convenient manner. Conversion of **21** to lasubine II was achieved using a second Mitsunobu reaction as described previously.[6k] Compounds **21** and **1** (overall yield 9% over 12 steps) showed spectroscopic and optical rotation data in close agreement with those reported for 2-*epi*-lasubine II[6j] and (−)-lasubine II respectively.[6k,l,14]

In conclusion, we have developed an enantiodivergent approach to the quinolizidine ring system culminating in the total synthesis of the alkaloid (−)-lasubine II. Although *ent*-lasubine II was not synthesized, it could be achieved starting with the diol **15**. The methodology may prove to be useful for the preparation of related compounds.

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Supporting Information Available. Experimental procedures, characterization data and copies of ^1H and ^{13}C NMR spectra for all new compounds, and ORTEP diagram of model compound **27** are provided in the Supporting Information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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