

Ring Expansive Routes to Quinolizidine
Alkaloids: Formal Synthesis of
(–)-Lasubine II

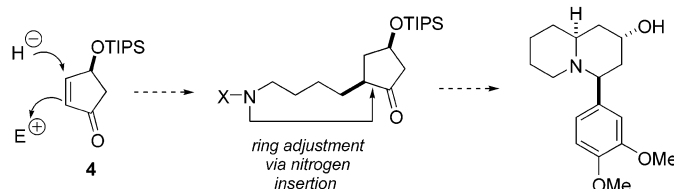
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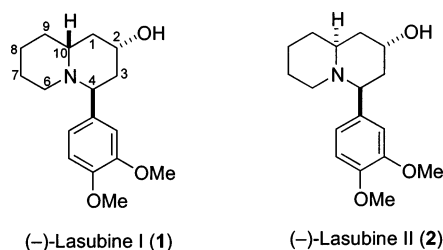
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ABSTRACT



The application of two nitrogen ring expansion reactions to lasubine alkaloid synthesis is reported. The approach involves a conjugate reduction/alkylation sequence carried out on triisopropylsilyl-protected (S)-4-(–)-hydroxycyclopentenone, the formation of the quinolizidone ring system through nitrogen ring expansion, and the addition of an arylmetallic species to the resulting lactam. This work resulted in the preparation of 2-*epi*-lasubine II and a formal synthesis of lasubine II.

Lasubine I (**1**) and its C10-epimer lasubine II (**2**) belong to a class of lythraceae alkaloids isolated from the leaves of



Lagerstroemia subcostata Koehne, widely distributed in the Amani islands, Taiwan, and China.¹ Although only of modest biological interest, these quinolizidine alkaloids have attracted significant interest among organic chemists for the validation of new methodologies for alkaloid synthesis. This has resulted in a number of syntheses of these alkaloids in either racemic or enantiomerically pure form.^{2,3}

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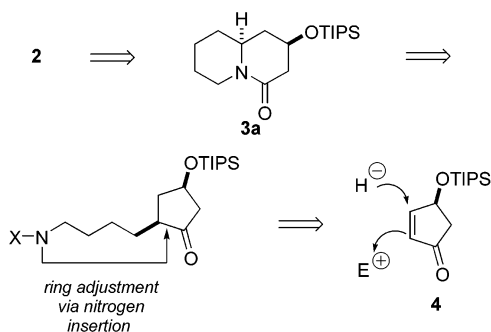
We envisioned that a protected cyclopentenone **4**, a familiar precursor to prostaglandins⁴ and other cyclopentane-containing natural products,⁵ would be a suitable chiral starting material for quinolizidine alkaloid synthesis (Scheme

(2) For lasubine I (racemic syntheses): (a) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1143. (b) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 1909–1912. (c) Ent, H.; De Koning, H.; Speckamp, W. N. *Heterocycles* **1988**, *27*, 237–243. (d) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198–9. (e) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1998**, *48*, 507–518. Enantioselective syntheses: (f) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807–5809. (g) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361–4368. (h) Ratni, H.; Kuendig, E. P. *Org. Lett.* **1999**, *1*, 1997–1999. (i) Davis, F. A.; Rao, A.; Carroll, P. *J. Org. Lett.* **2003**, *5*, 3855–3857.

(3) For lasubine II (racemic syntheses), see ref 2e and: (a) Narasaka, K.; Yamazaki, S.; Ukaji, Y. *Chem. Lett.* **1985**, 1177–1178. (b) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1986**, 1823–1836. (c) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525–533. (d) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445–7447. (e) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729–2732. (f) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717–722. For enantioselective syntheses, see ref 2g and: (g) Ukaji, Y.; Ima, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563–566. (h) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623–2625. (i) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927–3929. (j) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779–1781.

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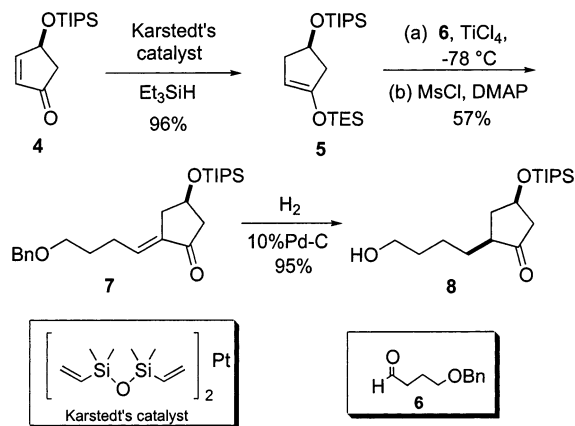
Scheme 1



1). In the present case, this would require a conjugate reduction/alkylation sequence, in contrast to the conjugate addition/trapping protocol more commonly associated with such enones.^{4,6} In addition, an efficient ring adjustment sequence would also be required. Herein, we report the successful application of this strategy to lasubine alkaloid synthesis.

The TIPS-protected 4-(*S*)-(-)-hydroxy-2-cyclopentenone (**4**) was synthesized according to literature procedures established for the known TBS derivative.⁷ The change of protecting group was necessitated by the lability of the TBS group in a later Lewis acid-promoted step (see below). Reductive alkylation of **4** using platinum divinyltetramethyl disiloxane complex (Karstedt's catalyst) in the presence of triethylsilane afforded enol ether **5** as a single regioisomer in 96% yield (Scheme 2).⁶ Mukaiyama aldol reaction of **5**

Scheme 2



with aldehyde **6**⁸ followed by dehydration afforded the enone **7** in 57% overall yield.^{9,10} Catalytic hydrogenation of **7** with 10% Pd/C in ethanol resulted in reduction as well as

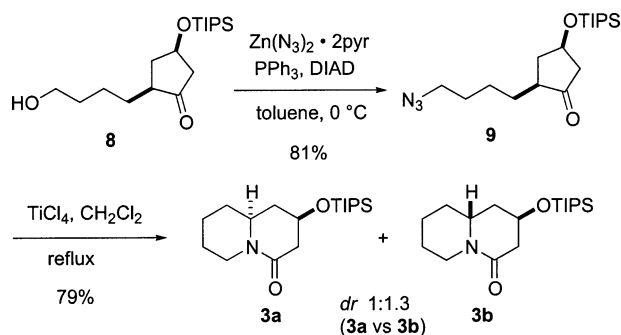
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debenzylation to furnish alcohol **8** as a single stereoisomer (NMR) in 95% yield. NOE studies revealed the *cis* diastereomer of the alcohol as the predominant product.

Our original intention was to simultaneously convert the cyclopentanone into a six-membered ring while forming the second ring using the intramolecular Schmidt reaction developed in these laboratories.¹¹ To accomplish this, a modified Mitsunobu reaction on **8** afforded azide **9**; no epimerization was apparent in this step (Scheme 3).¹² When

Scheme 3



9 was subjected to the standard Schmidt reaction conditions (TFA , $\text{BF}_3 \cdot \text{OEt}_2$, or TiCl_4 in CH_2Cl_2 at room temperature), no reaction was observed. Eventually, it was found that treatment with TiCl_4 in refluxing CH_2Cl_2 reluctantly afforded lactams **3a** and **3b** in a 1:1.3 ratio. Treatment of the diastereomerically pure 2-(4'-chlorobutyl) analogue of **9** resulted in complete epimerization at the α stereogenic center, which suggested that the formation of isomers **3a** and **3b** resulted from Lewis acid-promoted enolization and epimerization prior to the nitrogen insertion step (which has been shown to be stereoselective¹¹).

To avoid this Lewis acid-promoted epimerization, alternative ring expansion routes were considered. We have recently identified the photochemical rearrangement of endocyclic nitrones as an alternative to the intramolecular Schmidt reaction.^{13,14} We hypothesized that such a reaction may proceed without epimerization because Lewis or protic acids are not required. Thus, alcohol **8** was converted into the bis-benzyloxycarbonyl (Cbz)-protected hydroxylamine **10** under modified Mitsunobu conditions (Scheme 4).¹⁵ Subsequent

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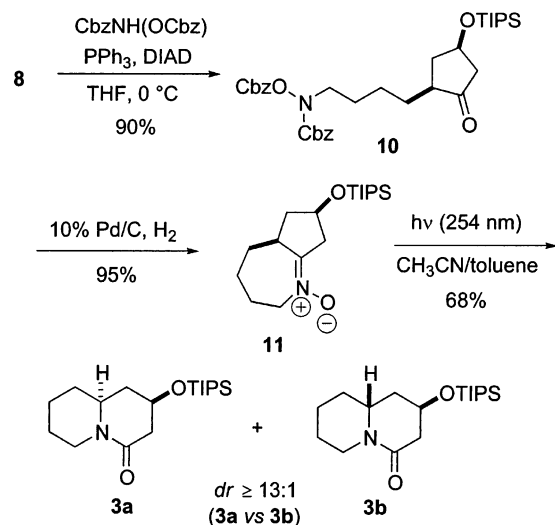
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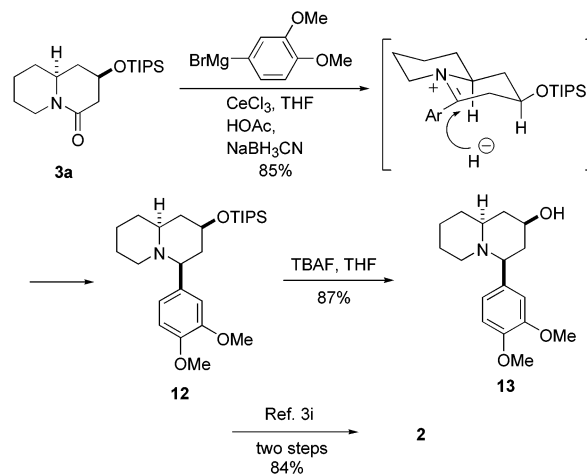
Scheme 4



hydrogenation over 10% Pd–C effected both hydroxylamine deprotection and cyclization to afford the nitron 11 directly. Photolysis of 11 gave a 13:1 mixture of 3a and 3b in 60% yield over two steps (GC).

A formal synthesis of lasubine II was completed as shown in Scheme 5. Thus, treatment of 3a with a Grignard reagent derived from 4-bromoveratrole in the presence of anhydrous CeCl_3 and acidification, followed by NaBH_3CN reduction, afforded quinolizidine 12 as a single diastereomer in 85% yield. The CeCl_3 was included to prevent competing elimination of the OTIPS group.¹⁶ The attack of hydride occurred from the pseudoaxial direction as predicted by the Stevens paradigm.¹⁷ The relative stereochemistry of 12 was assigned on the basis of NOE experiments and Bohlmann bands in

Scheme 5



the IR spectrum at 2786 and 2747 cm^{-1} .¹⁸ Finally, deprotection of TIPS group with TBAF in THF afforded (–)-2-*epi* lasubine II 13 in 87% yield. All spectroscopic and physical data of compound 13 were in agreement with the published data. This epimer can be readily converted to (–)-lasubine II via a Mitsunobu reaction as reported by Ma et al.³ⁱ

This work establishes cyclopentenone 4 as a precursor to quinolizidine alkaloids. In addition, the utility of a nitron-based ring adjustment sequence as an alternative to the intramolecular Schmidt reaction has been demonstrated.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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