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

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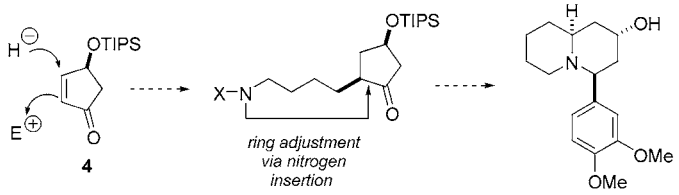
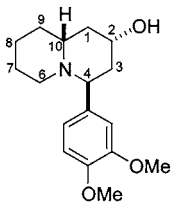
ABSTRACT

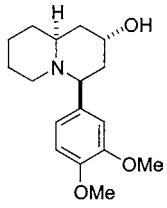


The application of two nitrogen ring expansion reactions to lasubine alkaloid synthesis is reported. The approach involves a conjugate reduction/alkylation sequence carried out on triisopropylsilyl-protected (*S*)-4-(−)-hydroxycyclopentenone, the formation of the quinolizidone ring system through nitrogen 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



(−)-Lasubine I (**1**)



(−)-Lasubine II (**2**)

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]

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

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(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 enatioselective 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.

(4) Noyori, R.; Suzuki, M. *Angew. Chem.* **1984**, *96*, 854−882.

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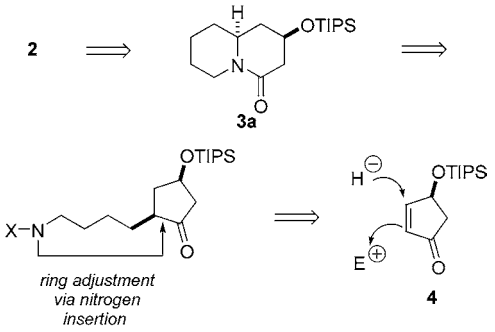
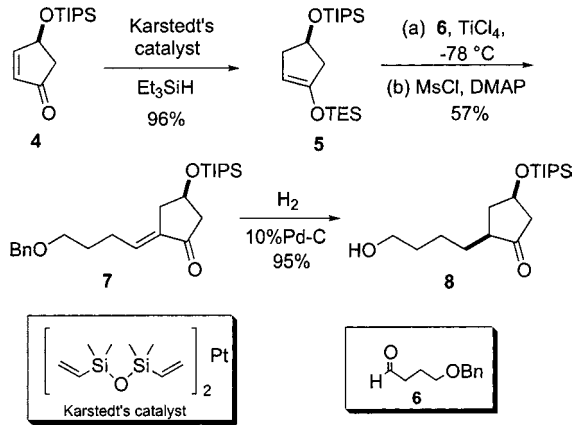
Scheme 1



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**

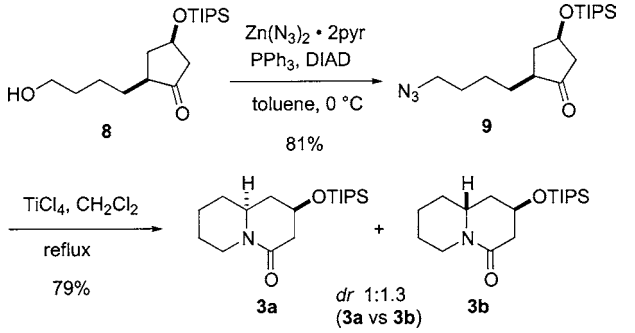
Scheme 2



with aldehyde **6**[8] followed by dehydration afforded the E enone **7** in 57% overall yield.[9,10] Catalytic hydrogenation of **7** with 10% Pd/C in ethanol resulted in reduction as well as 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, $BF_3{\cdot}OEt_2$, 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 stereoselective[11]).

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-benzyloxylcarbonyl (Cbz)-protected hydroxylamine **10** under modified Mitsunobu conditions (Scheme 4).[15] Subsequent

(5) (a) Elliott, J. D.; Hetmanski, M.; Palfreyman, M. N.; Purcell, N.; Stoodley, R. J. *Tetrahedron Lett.* **1983**, *24*, 965−968. (b) Essig, S.; Scheffold, R. *Chimia* **1991**, *45*, 30−32. (c) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5911−5912. (d) Jaroszewski, J. W.; Olafsdottir, E. S.; Cornett, C.; Schaumburg, K. *Acta Chem. Scand. B* **1987**, *B41*, 410−421. (e) Nagaoka, H.; Miyaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1990**, *31*, 1573−1576.

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(11) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

(12) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130−132.

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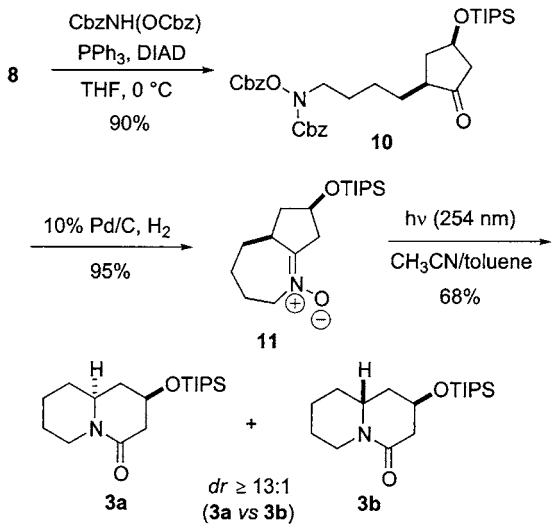
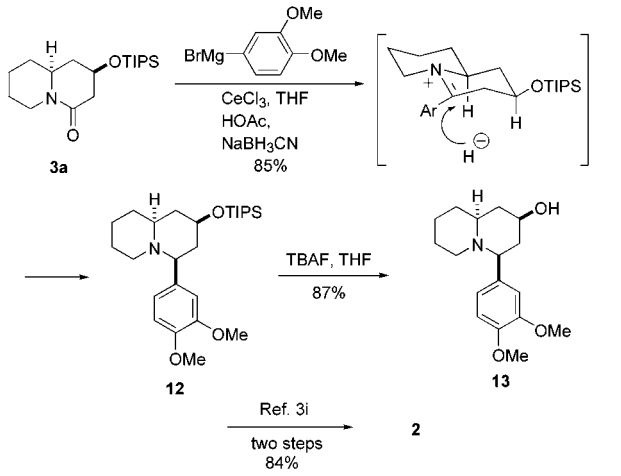
(14) Zeng, Y.; Smith, B. T.; Hershberger, J.; Aubé, J. *J. Org. Chem.* **2003**, *68*, 8065−8067.

(15) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593−2595.

Scheme 4



Scheme 5



hydrogenation over 10% Pd−C effected both hydroxylamine deprotection and cyclization to afford the nitrone **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 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 nitrone-based ring adjustment sequence as an alternative to the intramolecular Schmidt reaction has been demonstrated.

Acknowledgment. We thank the National Institutes of Health (GM-49093) for support of this work.

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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