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Total Synthesis of (−)-Lasubine II by the Conjugate Addition and Intramolecular Acylation of an Amino Ester with an Acetylenic Sulfone

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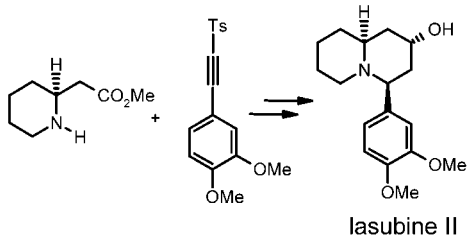
ABSTRACT



lasubine II

The conjugate addition of methyl (*S*)-(2-piperidyl)acetate (3) to 2-(3,4-dimethoxyphenyl)-1-(*p*-toluenesulfonyl)ethyne (4), followed by LDA-promoted intramolecular acylation, stereoselective reduction, and desulfonylation, afforded (−)-lasubine II.

Unsaturated sulfones have proven to be versatile synthetic reagents.[1] For example, the activating effects of the sulfone moiety enable these compounds to undergo conjugate additions, cycloadditions, and deprotonation and alkylation of the corresponding α-anions. Moreover, the sulfone group can be removed at the end of a synthetic sequence by a variety of reductive, alkylative, or oxidative methods.[2] We recently reported the synthesis of various types of nitrogen heterocycles by conjugate additions of cyclic or acyclic secondary amines bearing β- or γ-chloro substituents to acetylenic sulfones, followed by intramolecular alkylation[3] (Scheme 1). This methodology has been successfully applied to the enantioselective total synthesis of several dendrobatid alkaloids, including indolizidines (−)-167B, (−)-209D, (−)-209B, and (−)-207A.[3b] The decahydroquinoline (−)-pumiliotoxin C was obtained by a similar cyclization employing an exocyclic primary amine as the nucleophile, followed by intramolecular acylation of the resulting enamine (Scheme 1).[4] We now report a new variation of this protocol that provides a concise synthesis of the quinolizidine alkaloid (−)-lasubine II (**1**). Both **1** and several other quinolizidine alkaloids,[5] including (−)-lasubine I (the 10-epi derivative of **1**), and their respective 3,4-dimethoxycinnamate esters (+)-subcosine II and I have been isolated from plants of the *Lythraceae* family.[6] Whereas numerous racemic syntheses

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(1) For a general review of sulfones, see: (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) For acetylenic and allenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, *57*, 5263. (c) For vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (d) For dienyl sulfones, see: Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.

(2) For a review of desulfonylation, see: Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

(3) (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

(4) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566.

(5) For selected reviews of quinolizidine alkaloids, see: (a) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 28, Chapter 3. (b) Herbert, R. B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 3, Chapter 6. (c) Kinghorn, A. D.; Balandrin, M. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 2, Chapter 3. (d) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. See also earlier reviews by this author in this series, as cited therein.

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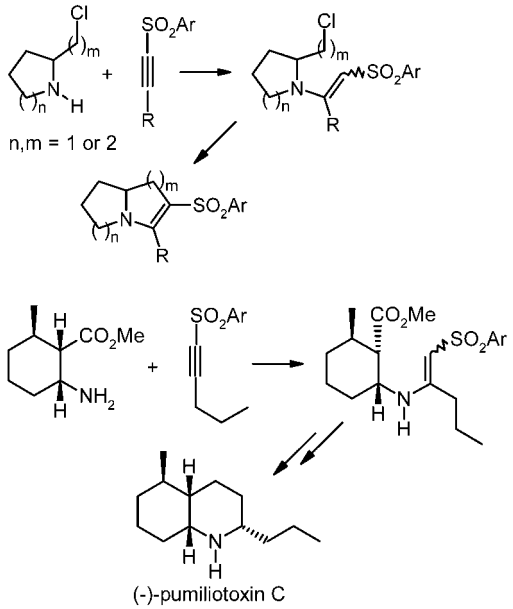
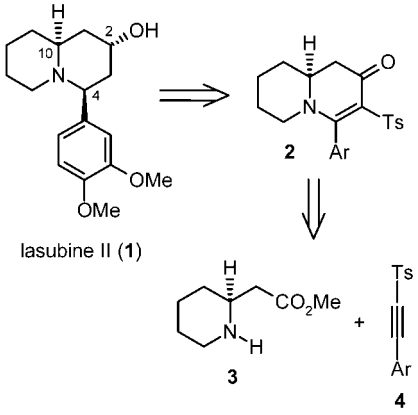
Scheme 1



of these and related compounds have been reported, only a few enantioselective syntheses have appeared.[7]

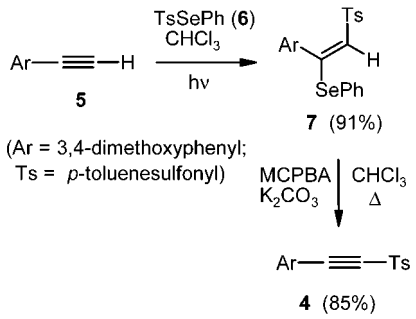
Our approach to **1** is illustrated retrosynthetically in Scheme 2, where enaminone **2** serves as a key intermediate

Scheme 2



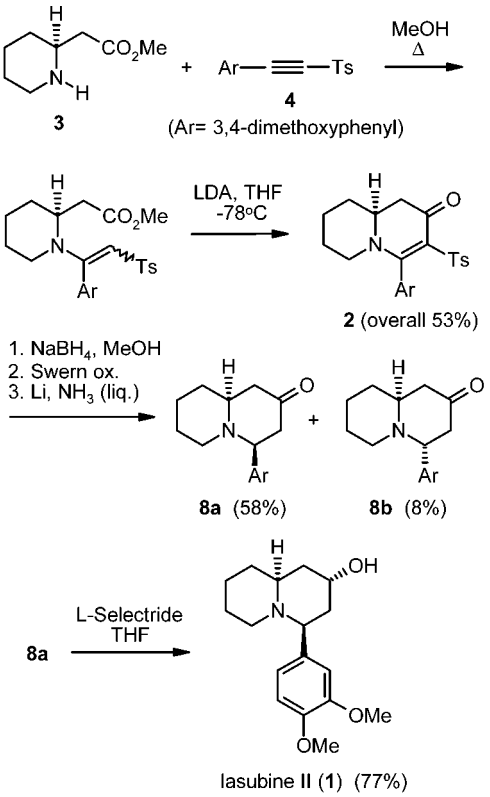
and is in turn prepared by the conjugate addition and intramolecular acylation of the piperidine **3** with acetylenic sulfone **4**. The pure (*S*)-enantiomer of **3** was obtained by a minor variation of the method of Chung et al.,[8] and the acetylenic sulfone **4** was prepared by photoinitiated free-radical selenosulfonation[9] of the known acetylene **5**[10] with *Se*-phenyl *p*-tolueneselenosulfonate (**6**),[11] followed by selenoxide elimination of the resulting adduct **7** (Scheme 3).

Scheme 3



The synthesis of **1** is summarized in Scheme 4. The conjugate addition of amino ester (*S*)-**3** to acetylenic sulfone

Scheme 4



4 was effected by refluxing in methanol for 4 h. The crude product was added in THF solution to 2.3 equiv of LDA in

(6) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull*. **1978**, *26*, 2515.

(7) For previous enantioselective syntheses of (−)-**1,** see: (a) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. (b) Ukaji, Y.; Ima, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. (c) Davis, F. A.; Chao, B. *Org. Lett*. **2000**, *2*, 2623. (d) Ma, D.; Zhu, W. *Org. Lett*. **2001**, *3*, 3927. For (−)-lasubine I, see ref 7a and (e) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (f) Ratni, H.; Kundig, E. P. *Org. Lett.* **1999**, *1*, 1997. For (+)-subcosine I, see ref 7e. For (+)-subcosine II, see ref 7a.

(8) Chung, H.-K.; Kim, H.-W.; Chung, K.-H. *Heterocycles* **1999**, *51*, 2983. These authors obtained the parent carboxylic acid derivative of **3** by hydrolytic cleavage of an oxazolidinone chiral auxiliary from the corresponding amide. In the present case, cleavage of the auxiliary with sodium methoxide in methanol afforded the methyl ester **3**.

THF at −78 °C, and the reaction was quenched after 1 min by filtration through alumina to afford enaminone **2** in 53% overall yield. The ring closure presumably involves intramolecular acylation of a sulfone-stabilized vinyl carbanion, in contrast to the enamine acylation employed in our earlier synthesis of pumiliotoxin C[4] (see Scheme 1), since in the present case a secondary amine was employed in the initial addition step instead of a primary amine. This is noteworthy because deprotonation of the vinyl sulfone, as required for ring closure, occurred preferentially over enolate formation from the ester moiety. It also suggests that acylations of carbanions derived from other vinyl sulfones may prove more generally useful in future synthetic applications.[12]

Treatment of **2** with sodium borohydride resulted in reduction of both the enamine and ketone moiety, affording a mixture of diastereomers, including both α- and β-epimers of the corresponding alcohol. Other reduction methods, including the use of sodium cyanoborohydride, various boranes, and catalytic hydrogenation, proved less chemo- and/or stereoselective or failed to achieve the desired transformation. The unseparated mixture from the sodium borohydride reduction was therefore subjected to Swern oxidation and desulfonylation with lithium in liquid ammonia to afford the easily separable ketones **8a** and **8b** in overall yields of 58% and 8%, respectively, from **2**. Finally, the stereoselective reduction of ketone **8a** to **1** was achieved with L-Selectride, in a variation of a literature procedure.[7a] Thus, the method depicted in Scheme 4 provides a concise and stereoselective synthesis of the quinolizidine alkaloid (−)-lasubine II (**1**). Since **1** has been previously converted into (+)-subcosine II,[7a] this method also represents a formal synthesis of the latter product.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra of **4** and (−)-**1**, and the ^{1}H NMR spectrum of **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For thermal selenosulfonation of acetylenes, see: (a) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1983**, *48*, 3077. (b) Miura, T.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1982**, 438. For a photochemical variation, see: (c) Back, T. G.; Krishna, M. V.; Muralidharan, K. R. *J. Org. Chem.* **1989**, *54*, 4146. For a recent review of selenosulfonation, including descriptions of procedures, see: (d) Back, T. G. In *Organoselenium Chemistry—A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 9, pp 176−178.

(10) Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775.

(11) For a recommended procedure for the preparation of **6**, see: (a) Back, T. G. In ref 9d, Chapter 6, p 105. For a general preparation of selenosulfonates, see: (b) Back, T. G.; Collins, S.; Krishna, M. V. *Can. J. Chem.* **1987**, *65*, 38.

(12) For examples of intramolecular acylations of alkyl as opposed to vinyl sulfones, see: (a) Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994**, *35*, 5369. (b) Grimm, E. L.; Coutu, M. L. Trimble, L. A. *Tetrahedron Lett.* **1993**, *34*, 7017.