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Synthesis of the Quinolizidine Alkaloids (−)-Lasubine II and (±)-Myrtine by Conjugate Addition and Intramolecular Acylation of Amino Esters with Acetylenic Sulfones

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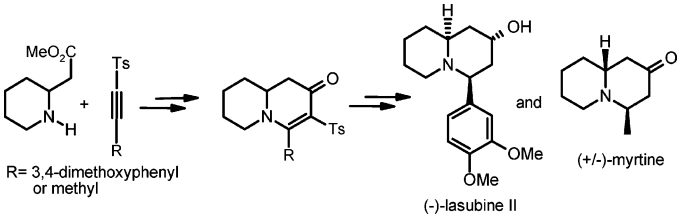
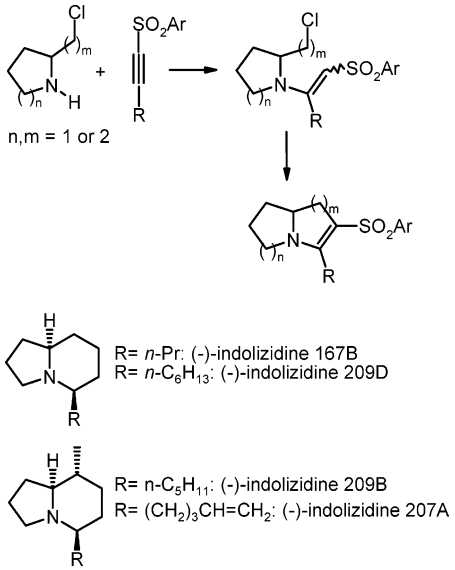


The conjugate additions of (2-piperidyl)acetate esters to acetylenic sulfones, followed by LDA-promoted intramolecular acylations, afforded cyclic enaminones that were readily converted into the corresponding 4-substituted 2-keto- or 2-hydroxyquinolizidines by stereoselective reduction and desulfonylation. This procedure was applied to the total synthesis of (−)-lasubine II from methyl (*S*)-(2-piperidyl)acetate and 2-(3,4-dimethoxyphenyl)-1-(*p*-toluenesulfonyl)ethyne. Similarly, methyl (±)-(2-piperidyl)acetate and 1-(*p*-toluenesulfonyl)propyne provided (±)-myrtine.

Introduction

The chemistry of unsaturated sulfones continues to be widely exploited in organic synthesis.[1,2] For example, the electron-withdrawing sulfone group activates adjacent alkene, allene, and acetylene moieties in diverse conjugate addition and cycloaddition reactions. Moreover, the α-protons of vinyl and alkyl sulfones are relatively acidic, thereby permitting the generation of sulfone-stabilized anions,[3] which can in turn be alkylated or acylated with appropriate electrophilic reagents. Finally, the sulfone group can be removed at the end of a synthetic sequence by a variety of reductive, alkylative, or oxidative methods.[4] We have found that conjugate additions of suitably functionalized amines to acetylenic sulfones can be used in tandem with intramolecular alkylations or acylations, resulting in a novel cyclization protocol that leads to a broad range of nitrogen heterocycles (Scheme 1). This general protocol has been employed with both cyclic and acyclic secondary amines containing β- or γ-chloro substituents, leading to substituted piperidines, pyrrolizidines, indolizidines, and quinolizidines,[5] including the dendrobatid alkaloids indolizidines (−)-167B, (−)-209D,

SCHEME 1



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(1) For a general review of sulfones, see: Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

(2) (a) For acetylenic and allenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, *57*, 5263. (b) For vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, 46, 6951. (c) For dienyl sulfones, see: Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.

(3) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978; Chapter 2.

(4) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

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

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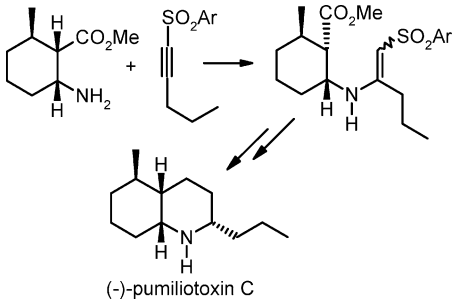
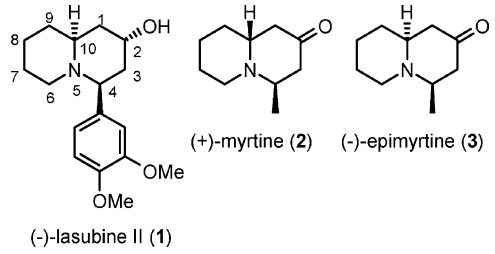
SCHEME 2



(−)-209B, and (−)-207A[5b] (Scheme 1). Similarly, conjugate additions of amino esters to acetylenic sulfones, followed by intramolecular acylation, have been exploited in the synthesis of both naturally occurring and unnatural quinolones,[6] as well as in the preparation of the dendrobatid alkaloid (−)-pumiliotoxin C[7] (Scheme 2). We now report that the similar reactions of methyl (2-piperidyl)acetate with the appropriate acetylenic sulfones provide a concise new route to the corresponding 4-substituted 2-keto- or 2-hydroxyquinolizidines, and we illustrate the method by its application to the total synthesis of the alkaloids (−)-lasubine II (**1**)[8] and (±)-myrtine (**2**).

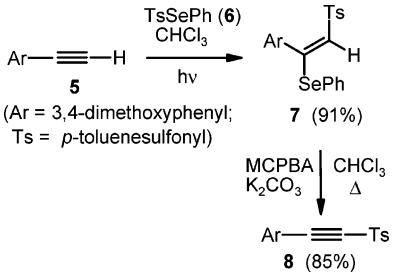
Results and Discussion

(−)-Lasubine II and related quinolizidine alkaloids[9] such as (−)-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.[10] (+)-Myrtine (**2**) and (−)-epimyrtine (**3**) are found in *Vaccinium myrtillus*.[11] Several earlier syntheses of **1** and **2** and their congeners have been reported.[12,13]

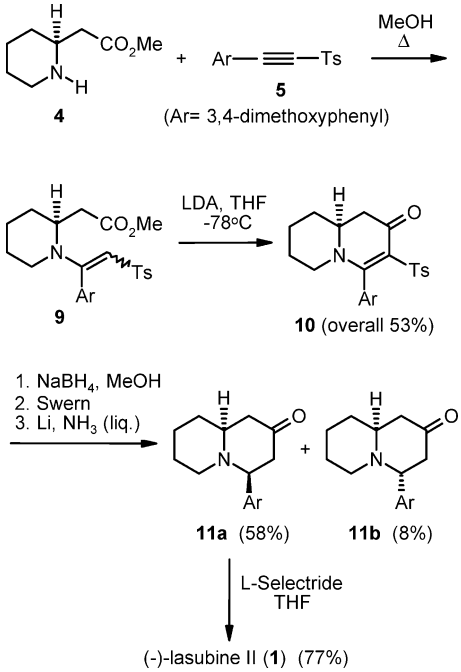


For the synthesis of (−)-**1**, we required methyl (*S*)-(2-piperidyl)acetate (**4**) as well as acetylenic sulfone **8**. The former was obtained by a minor variation of the method

SCHEME 3



SCHEME 4



of Chung et al.,[14] while **8** was obtained by the free-radical selenosulfonation[15] of acetylene **5**[16] with *Se*-phenyl *p*-tolueneselenosulfonate (**6**).[17] The adduct **7** was then subjected to selenoxide elimination to afford the required acetylenic sulfone **8** (Scheme 3).

The synthesis of **1** is summarized in Scheme 4. The conjugate addition of **4** to **5** proceeded smoothly, and the

(6) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223.

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

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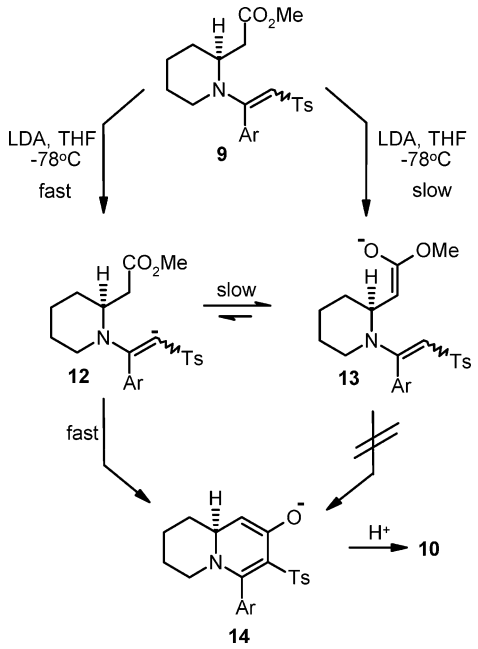
(11) (a) Slosse, P.; Hootelé, C. *Tetrahedron Lett.* **1978**, 397. (b) Slosse, P.; Hootelé, C. *Tetrahedron* **1981**, *37*, 4287.

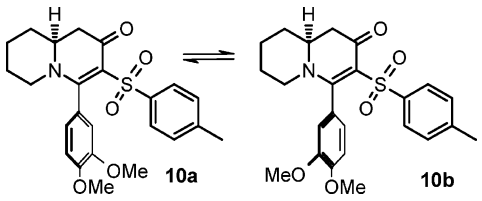
(12) For previous syntheses of (−)-lasubine II, see: (a) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. (b) Ukaji, Y.; Ima, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. (c) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (d) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (e) Gracias, V.; Zeng, Y.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999. For syntheses of (±)-lasubine II, see: (f) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1998**, *48*, 507. (g) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (h) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729. (i) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (j) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525. (k) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1986**, 1823. (l) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 1909. (m) Takano, S.; Shishido, K. *Chem. Pharm. Bull.* **1984**, *32*, 3892. (n) Quick, J.; Ramachandra, R. *Tetrahedron* **1980**, *36*, 1301. For syntheses of (−)-lasubine I, see: ref 12a and (o) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855. (p) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (q) Ratni, H.; Kundig, E. P. *Org. Lett.* **1999**, *1*, 1997. For syntheses of (±)-lasubine I, see: ref 12f,l and (r) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198. (s) Ent, H.; De Koning, H.; Speckamp, W. N. *Heterocycles* **1988**, *27*, 237. (t) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1143. For a synthesis of (+)-subcosine I, see ref 12p, and for a synthesis of (±)-subcosine I, see ref 12l,t. For a synthesis of (+)-subcosine II, see ref 12a.

SCHEME 5

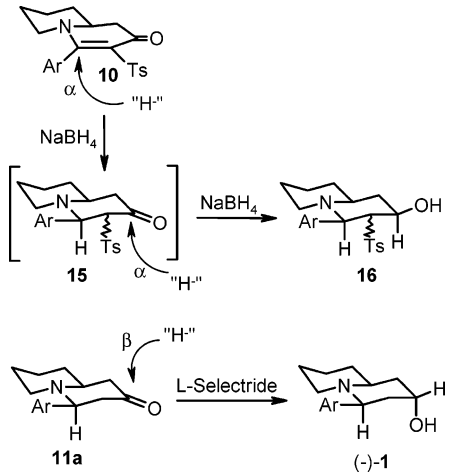


adduct **9** was immediately cyclized by treatment with LDA at −78 °C. The kinetic deprotonation and intramolecular acylation of alkyl sulfones (pK_a = ca. 30)[18] in the presence of esters (pK_a = ca. 25)[19] has been reported previously.[20] Similarly, the desired intramolecular acylation of the sulfone-stabilized vinyl anion **12**, produced from **9**, competed effectively with formation of the corresponding ester enolate **13** (Scheme 5), and ring closure proceeded faster than proton transfer between **12** and **13**. These considerations are significantly different from those in Scheme 2, where a primary amine was used in the initial conjugate addition and where subsequent abstraction of the remaining N−H proton generated a delocalized enamidyl anion instead of a less stable vinyl anion. The use of excess LDA and low temperatures was necessary in the present case to suppress undesired proton-transfer processes between **12** and **13** and between the product **10** (which is presumably converted into its enolate **14** in the presence of excess base) and the anion **12**. It is also worth noting that **9** was obtained as

SCHEME 6



SCHEME 7



an *E*/*Z* mixture but that both isomers reacted to afford **10**, suggesting that interconversion of the geometrical isomers is rapid under these conditions.

Both the ^{1}H and ^{13}C NMR spectra of **10** at room temperature suggested that it exists as two distinct rotamers, i.e., **10a** and **10b** (Scheme 6), as many of the peaks were duplicated, most obviously the *m*-methoxy peak of the aromatic ring. The rotational barrier is likely due to steric interactions between the 3,4-dimethoxyphenyl and the *p*-toluenesulfonyl groups. Variable-temperature ^{1}H NMR experiments (see the Supporting Information) revealed that coalescence of the twinned signals occurred at 400 K, indicating that the energy of the rotational barrier is 88.0 kJ/mol.[21]

The reduction of the enaminone moiety of **10** with sodium borohydride proceeded selectively via the α-face to afford **15**, where the bulky aryl substituent occupies the equatorial position. Simultaneous reduction of the ketone occurred to afford the corresponding equatorial alcohol **16** (Scheme 7), which possesses the 2-epi configuration relative to **1**. Other reduction methods, includ-

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(14) Chung, H.-K.; Kim, H.-W.; Chung, K.-H. *Heterocycles* **1999**, *51*, 2983.

(15) 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.

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

(17) Back, T. G.; Collins, S.; Krishna, M. V. *Can. J. Chem.* **1987**, *65*, 38.

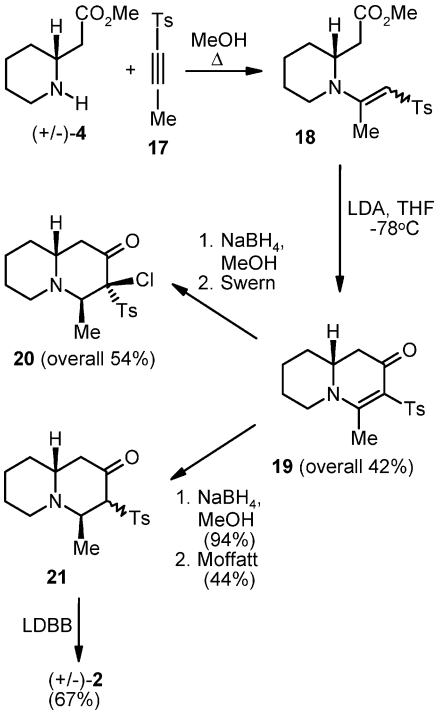
(18) (a) Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883. (b) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326. (c) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(19) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; p 331.

(20) (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.

(21) Lambert, J. B.; Mazzola, E. P. *Nuclear Magnetic Resonance Spectroscopy*; Pearson Education: Upper Saddle River, NJ, 2004; pp 136−143.

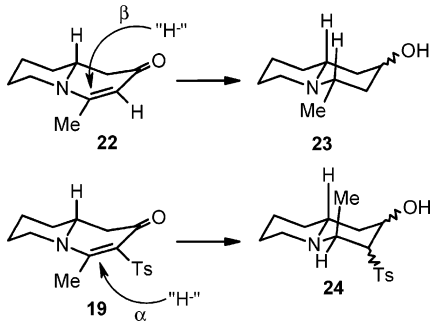
SCHEME 8



ing the use of sodium cyanoborohydride, various boranes, and catalytic hydrogenation, proved less chemo- and/or stereoselective or failed to achieve the desired transformation. Thus, alcohol **16** was subjected to a Swern oxidation[22] to produce the corresponding ketone, followed by desulfonylation with lithium in liquid ammonia to afford an 88:12 mixture of the corresponding C-4 epimers **11a** and **11b** (Scheme 4). Finally, reduction of **11a** with lithium tri-*sec*-butylborohydride (L-Selectride)[23] occurred from the β-face (equatorial approach) to produce (−)-lasubine II (**1**), containing the necessary axial alcohol (Schemes 4 and 7).

The synthesis of the myrtine−epimyrtine system was approached in a similar manner, with the expectation that epimyrtine (**3**) would be the dominant stereoisomer, by analogy to the formation of **1** in Scheme 4. In this case, amino ester (±)-**4** (arbitrarily shown as the *R*-enantiomer) was added to 1-(*p*-toluenesulfonyl)propyne (**17**), followed by intramolecular acylation of **18** with excess LDA (Scheme 8). The sulfone **17** was prepared by a protocol similar to that shown in Scheme 3, except that a chloroform solution of **6** was saturated with propyne, followed by irradiation with UV light. In contrast to Scheme 4, where deprotonation of **9** produced a vinyl anion, the methyl-substituted adduct **18** presumably underwent acylation via the corresponding allyl anion. The enaminone **19** was then reduced with sodium borohydride to furnish 94% of a single diastereomer of a saturated alcohol product with undetermined stereochemistry at C-3 and C-4. The alcohol was subjected to a Swern oxidation (as in the preparation of **11** in Scheme 4) to afford **20**, in which the expected ketone underwent a subsequent α-chlorination at C-3. Product **20** was

SCHEME 9



subjected to X-ray crystallography (see the Supporting Information), thereby confirming its structure unequivocally and clearly indicating the presence of an axial C-4 methyl substituent located *cis* to the hydrogen atom at C-10. The observed stereochemistry was in contrast to that observed in the reduction of enaminone **10** in Scheme 4, where the dominant epimer contained the C-4 substituent *trans* to the C-10 hydrogen atom. α-Chlorinations accompanying Swern oxidations have been reported previously.[24] Presumably, this process was not observed during the preparation of **11** because of the greater steric hindrance imposed by the bulky aryl group at C-4. Of several other standard oxidation procedures investigated (e.g., PDC, PCC, Dess−Martin periodinane), the Moffatt oxidation[25] afforded the best, albeit still modest, yield of the corresponding ketone **21**. Finally, reductive desulfonylation of **21** with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB)[26] produced (±)-myrtine (**2**). Its identity was confirmed by comparing its NMR spectra with those reported in the literature[11,13] for both myrtine (**2**) and epimyrtene (**3**).

It is interesting to note that the stereochemical outcome of the enaminone reduction of **19** in Scheme 8 was the opposite to that of **10** in Scheme 4. Thus, while incorporation of hydride at C-4 occurred predominantly *cis* to the ring-fusion hydrogen at C-10 in **10**, the similar reduction of **19** resulted in *trans* addition. The stereochemistry of nucleophilic additions to enaminones and the corresponding iminium species has been widely studied in other systems.[27] In general, both steric and stereoelectronic factors can play a role in determining facial selectivity. Slosse and Hootelé[11b] have reported that the reduction of the similar enaminone **22** with lithium aluminum hydride afforded chiefly the epimyrtine derivative **23** (Scheme 9), with the opposite stereochemistry at C-4 to that observed in the reduction of **19** with sodium borohydride to afford **24**, but similar to that obtained in the reduction of **10** shown in Scheme 4. They attributed their observation to a preferred chairlike transition state leading to the formation of **23**. Since the principal

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(23) Quick, J.; Meltz, C.; Ramachandra, R. *Org. Prep. Proc. Int.* **1979**, *11*, 111.
(24) For example, see: Beck, B. J.; Aldrich, C. C.; Fecik, R. A.; Reynolds, K. A.; Sherman, D. H. *J. Am. Chem. Soc.* **2003**, *125*, 12551.
(25) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027. (b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661. (c) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.
(26) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091.
(27) For reviews of stereoelectronic effects in additions to enaminones and related iminium species, see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 211−221. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

difference in the structures of **22** and **19** is the presence of the sulfone substituent at C-3 in the latter, this group may play a role in determining the stereochemistry. It has also been reported that myrtine and epimyrtine equilibrate under both acid- and base-catalyzed conditions, most probably via retro-Michael and/or retro-Mannich processes followed by recyclization.[11b] Since these processes are likely to be facilitated by the presence of the sulfone moiety at C-3, similar isomerizations of the initial reduction products of **10** and **19** might also affect the stereochemistry found in their respective products. The greater steric bulk of the C-4 aryl group in **10** compared to the methyl substituent in **19** is consistent with its greater propensity to occupy the equatorial position in the reduced product.[28] Because the above equilibration experiments demonstrated that epimyrtine is thermodynamically favored over myrtine,[11b] it is plausible that the myrtine analogue **24** is the kinetic product of reduction of **19**, while the similar reduction of **10** is under thermodynamic control, thereby resulting in the opposite stereochemistry at C-4. However, the conformational mobility of quinolizidinones such as myrtine and epimyrtine,[11b,13a] as well as uncertainty about the precise effect of the sulfone group upon the stereochemistry, precludes more precise conclusions at this time.

In summary, the quinolizidine alkaloid (−)-**1** was obtained with high stereoselectivity in just six steps and 24% overall yield from amino ester **4** and acetylenic sulfone **5**, as shown in Scheme 4. Since (−)-**1** has been previously converted into (+)-subcosine II,[12a] this also represents a formal synthesis of the latter product. Similarly, despite a relatively low overall yield of 12%, the synthesis shown in Scheme 8 comprises a concise approach to (±)-**2** from (±)-**4** and acetylenic sulfone **17** in five steps. The different C-4 stereochemistry that was obtained in products **1** and **2** from enaminones **10** and **19** by very similar synthetic procedures is also noteworthy.

Experimental Section

Experimental procedures for the synthesis of (−)-lasubine II (**1**) via Schemes 3 and 4 are available in the Supporting Information accompanying our preliminary communication.[8] *Se*-Phenyl *p*-tolueneselenosulfonate (**6**)[17] was prepared by a literature procedure.

Methyl (±)-(2-Piperidyl)acetate (4). 2-(2-Piperidyl)ethanol was converted to (2-piperidyl)acetic acid by Jones oxidation.[29] The product (1.83 g, 12.8 mmol) in HCl-saturated methanol (20 mL) was refluxed for 2 h and stirred at room temperature for 16 h. The solvent was removed in vacuo to give the hydrochloride salt of **4** as a fine white powder. This solid was dissolved in saturated $NaHCO_3$ solution (10 mL) and was extracted with dichloromethane. The combined, dried, and concentrated organic extracts gave (±)-**4**[30] as a pale yellow liquid (2.05 g, quantitative): ^{1}H NMR (200 MHz) δ 3.67 (s, 3 H), 3.11−2.84 (m, 2 H), 2.65 (dt, J = 11.5 and 3.2 Hz, 1 H), 2.40−2.34 (m, 2 H), 2.04 (br s, 1 H), 1.85−1.05 (m, 6 H); mass spectrum (ESI) *m/z* (relative intensity) 158 (M^+ + 1, 100), 96 (80), 84 (81).

The pure (*S*)-enantiomer of **4** was prepared by a variation of the procedure of Chung et al.[14] These authors resolved the *N*-Cbz-protected parent carboxylic acid derivative by forming an amide with a chiral oxazolidinone, followed by hydrolytic cleavage of the resolving agent. In the present case, cleavage of the resolving agent was achieved with sodium methoxide in methanol to afford the methyl ester (*S*)-**4** directly.

1-(*p*-Toluenesulfonyl)propyne (17). Acetylenic sulfone **17** was prepared by a modification of the general selenosulfonation procedure described previously.[15d] Propyne was bubbled through a solution of *Se*-phenyl *p*-tolueneselenosulfonate (4.34 g, 14.0 mmol) in chloroform (40 mL) at 0 °C for 10 min. The solution was irradiated in a Rayonet reactor containing six 300 nm lamps for 1.5 h. The solvent was removed in vacuo, and the residue was chromatographed over silica gel using 15% ethyl acetate−hexane to afford the corresponding β-(phenylseleno)vinyl sulfone as a white solid (4.35 g, 89%). The latter product (1.70 g, 4.84 mmol) in dichloromethane (30 mL) was stirred with K_2CO_3 (0.81 g, 5.9 mmol) and purified *m*-CPBA[31] (0.94 g, 5.5 mmol) for 20 min. The solution was then washed with water, 1.0 M K_2CO_3 solution, and brine. It was dried and concentrated in vacuo to give the corresponding crude selenoxide as a yellow oil, which was dissolved in chloroform (125 mL) and refluxed under Ar for 3.5 h. The solvent was removed in vacuo, and chromatography over silica gel (25% ethyl acetate−hexane) provided **17** as a pale yellow solid (600 mg, 64%): mp 97−99 °C (lit.[32] mp 96−97 °C); IR (film) 2203, 1324, 1150 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.88 (d, J = 8.2 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 2.47 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (75 MHz) δ 145.3, 139.1, 130.0, 127.5, 93.3, 77.9, 21.8, 4.4.

(±)-4-Methyl-3-(*p*-toluenesulfonyl)-3,4-dehydroquinolizidin-2-one (19). Amino ester (±)-**4** (1.428 g, 9.10 mmol) and acetylenic sulfone **17** (0.872 g, 4.49 mmol) were dissolved in dry MeOH (45 mL) and stirred at room temperature for 20 h. The solvent was removed in vacuo to give the crude enamine **18** as a yellow oil, which was used directly in the next step.

The above enamine was dissolved in dry THF (20 mL) and added to a solution of LDA (11 mmol) in dry THF (30 mL) at −78 °C over 5 min. The dark red solution was filtered through neutral alumina, which was subsequently washed with THF (30 mL) and acetone (30 mL). The dark red filtrate was concentrated in vacuo and chromatographed over silica gel (50% acetone−hexanes) to give enaminone **19** as a yellow oil (599 mg, 42%): IR (film) 1641, 1279, 1136 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.84 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 4.09 (br d, J = 14.0 Hz, 1 H), 3.57−3.44 (m, 1 H), 3.07 (br t, J = 11.8 Hz, 1 H), 2.64−2.54 (m, 1 H), 2.61 (s, 3 H), 2.34 (s, 3 H), 2.20 (dd, J = 16.6, 7.4 Hz, 1 H), 1.88−1.77 (m, 2 H), 1.65−1.47 (m, 4 H); ^{13}C NMR (75 MHz) δ 185.0, 165.6, 142.6, 141.8, 129.0, 127.2, 112.5, 58.3, 49.8, 42.1, 30.6, 26.1, 23.3, 21.6, 17.9; mass spectrum *m/z* (relative intensity) 319 (M^+, 1), 275 (4), 254 (100).

(±)-3-Chloro-4-methyl-3-(*p*-toluenesulfonyl)quinolizidin-2-one (20). Enaminone **19** (294 mg, 0.922 mmol) and sodium borohydride (178 mg, 4.68 mmol) were stirred in methanol (20 mL) at room temperature for 30 min and then concentrated in vacuo to afford a solid foam. This was partitioned between dichloromethane and 1 M KOH solution. The aqueous portions were combined and extracted with dichloromethane. The organic portions were combined, dried, and concentrated in vacuo to give the corresponding amino alcohol, which was used directly in the next step.

Oxalyl chloride (121 μL, 1.39 mmol) was added to dry dichloromethane (20 mL) under Ar and cooled to −78 °C. DMSO (196 μL, 2.76 mmol) was added, and the solution was stirred at −78 °C for 30 min. A solution of the above amino alcohol in dichloromethane (8 mL) was added, and the mixture was stirred at −78 °C for 30 min. Triethylamine (866 μL, 6.22

(28) The differences in the conformational energies of axial and equatorial substituents are reflected in their *A* values, which are 1.74 and 2.8 kcal mol^{-1} for methyl and phenyl groups, respectively: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

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(31) MCPBA was purified by washing with a pH 7.5 buffer and was assumed to be 100% pure; see: Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

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mmol) was added, and the resulting solution was stirred at room temperature for 18 h. The mixture was partitioned between ether and 1 M KOH solution, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and concentrated in vacuo to a yellow oil. Chromatography over silica gel (10% ethyl acetate−hexanes) afforded the α-chloro-β-keto sulfone as a pale yellow solid (178 mg, 54%): mp 130−132 °C (from ethyl acetate−hexanes); IR (film) 1725, 1324, 1143 cm^{-1}; ^1H NMR (400 MHz) δ 7.69 (d, J = 8.1 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 3.78 (q, J = 6.8 Hz, 1 H), 3.09 (m, 1 H), 2.82−2.73 (m, 3 H), 2.51−2.44 (m, 1 H), 2.45 (s, 3 H, Me), 1.79−1.65 (m, 4 H), 1.55−1.42 (m, 1 H), 1.23−1.14 (m, 1 H), 1.09 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 196.3, 145.4, 133.7, 130.3, 129.3, 92.9, 63.7, 52.2, 51.7, 47.0, 33.7, 25.5, 23.4, 21.7, 7.8; mass spectrum *m/z* (relative intensity) 355 (M^+, 32), 200 (100), 185 (22), 164 (30), 124 (38), 110 (70), 91 (46), 55 (39); exact mass calcd for $C_{17}H_{22}{}^{35}ClNO_3S$ 355.1009, found 355.0997. For X-ray crystallographic data for **20**, see the Supporting Information.

(±)-4-Methyl-3-(*p*-toluenesulfonyl)quinolizidin-2-one (21). Enaminone **19** (282 mg, 0.884 mmol) was reduced with sodium borohydride (138 mg, 3.63 mmol) as in the preceding procedure to afford the corresponding amino alcohol as a beige solid foam (268 mg, 94%), which was used directly in the next step.

The above product and DCC (694 mg, 3.37 mmol) were dissolved in benzene (4 mL). To this solution were added DMSO (0.7 mL, 10 mmol) and pyridine (94 μL, 1.16 mmol). The mixture was cooled to 0 °C, trifluoroacetic acid (45 μL, 0.58 mmol) was added, and the resulting solution was stirred at room temperature for 18 h. The mixture was filtered, and the resulting dark orange solution was concentrated in vacuo and subjected to column chromatography over silica gel (35% ethyl acetate−hexanes) to afford keto sulfone **21** as a slightly yellow oil (117 mg, 44%): IR (film) 1718, 1318, 1285, 1143 cm^{-1}; ^1H NMR (400 MHz) δ 7.73 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 3.94 (q, J = 6.9 Hz, 1 H), 3.61 (d, J = 1.4 Hz, 1 H), 2.75 (d, J = 11.0 Hz, 1 H), 2.69−2.59 (m, 2 H), 2.46−2.30 (m, 2 H), 2.43 (s, 3 H), 1.71−1.55 (m, 4 H), 1.24−1.11 (m, 2 H), 0.98 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz) δ 200.7, 145.0, 136.4, 129.7, 129.0, 80.2, 57.2, 52.3, 51.2, 46.8, 34.1, 25.7, 23.4, 21.6, 10.0; mass spectrum *m/z* (relative intensity) 321 (M^+, 18), 306 (84), 165 (100); exact mass calcd for $C_{17}H_{23}NO_3S$ 321.1399, found 321.1396.

(±)-Myrtine (2). A solution of LDBB was prepared by dissolving di-*tert*-butylbiphenyl (1.45 g, 5.44 mmol) in dry tetrahydrofuran (10 mL) and adding finely cut pieces of lithium metal (43 mg, 6.2 mmol). The mixture was stirred under Ar until it turned dark green, at which point it was cooled to 0 °C and stirring was continued for 4 h. The LDBB solution was added dropwise via syringe to a solution of keto sulfone **21** (117 mg, 0.364 mmol) in dry tetrahydrofuran (10 mL) until the green color persisted. After 2 min, the reaction was quenched by adding saturated ammonium chloride to give a yellow solution. The mixture was partitioned between ethyl acetate and 0.5 M KOH solution. The aqueous phase was extracted with ethyl acetate, and the combined organic portions were dried and concentrated in vacuo to give a white residue. Chromatography over silica gel (ethyl acetate) gave (±)-myrtine **(2)** as a pale yellow residue (41 mg, 67%): IR (film) 1718 cm^{-1}; ^1H NMR (400 MHz) δ 3.39 (d of quintets, J = 6.4 and 1.9 Hz, 1 H), 2.90−2.76 (m, 2 H), 2.70−2.61 (m, 1 H), 2.48 (dt, J = 11.4, 2.8 Hz, 1 H), 2.30−2.16 (m, 3 H), 1.79−1.55 (m, 4 H), 1.40−1.17 (m, 2 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 209.4, 57.1, 53.5, 51.4, 48.6, 48.0, 34.2, 25.8, 23.4, 11.1; mass spectrum *m/z* (relative intensity) 167 (M^+, 40), 152 (100).

For comparison, the following IR, NMR, and mass spectral data for (±)-myrtine (**2**) were reported in the literature:[12g] IR (film) 1714 cm^{-1}; ^1H NMR (300 MHz) δ 3.39 (dqt, J = 6.3, 2.4 Hz, 1 H), 2.90−2.74 (m, 2 H), 2.72−2.62 (m, 1 H), 2.49 (dt, J = 11.5, 3.0 Hz, 1 H), 2.31−2.16 (m, 3 H), 1.90−1.55 (m, 4 H), 1.45−1.15 (m, 2 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.2 MHz) δ 210.0, 57.2, 53.6, 51.5, 48.8, 48.1, 34.3, 25.9, 23.5, 11.1; mass spectrum *m/z* (relative intensity) 167 (M^+, 39), 152 (100). Similarly, the following spectra were reported for (−)-epimyrtine (**3**):[13a] IR 1750 cm^{-1}; ^1H NMR (400 MHz) δ 3.34 (br d, J = 11.0 Hz, 1 H), 2.50−2.25 (m, 4 H), 2.24−2.12 (m, 1 H), 1.90−1.55 (m, 6 H), 1.50−1.25 (m, 2 H), 1.20 (d, J = 5.7 Hz, 3 H); ^{13}C NMR (100 MHz) δ 208.7, 62.4, 59.6, 51.3, 50.0, 49.0, 34.4, 26.2, 24.2, 21.0.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **19**, **20**, **21**, and **2**, variable-temperature NMR spectra of **10**, and X-ray crystallographic data for **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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