A Convenient New Route to Piperidines, Pyrrolizidines, Indolizidines, and Quinolizidines by Cyclization of Acetylenic Sulfones with β- and γ-Chloroamines. Enantioselective Total Synthesis of Indolizidines (−)-167B, (−)-209D, (−)-209B, and (−)-207A

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The methyl esters of (L)-phenylalanine and (L)-methionine underwent conjugate additions via their free amino groups to 1-(*p*-toluenesulfonyl)hexyne, followed by intramolecular acylation of the corresponding enamide anions and tautomerization to afford 2-benzyl-5-*n*-butyl-3-hydroxy-4-(*p*-toluenesulfonyl)pyrrole and 5-*n*-butyl-3-hydroxy-2-(2-methylthioethyl)-4-(*p*-toluenesulfonyl)pyrrole, respectively. The conjugate additions of a series of acyclic and cyclic secondary β- and γ-chloroamines to acetylenic sulfones proceeded similarly under mild conditions. The resulting adducts were deprotonated with LDA in THF at −78 °C, and the resulting sulfone-stabilized carbanions underwent intramolecular alkylation to afford cyclic enamine sulfones. Thus, acyclic γ-chloroalkylbenzylamines afforded the corresponding 2- or 2,6-disubstituted piperidines, while 2-(chloromethyl)pyrrolidines, 2-(2-chloroethyl)pyrrolidines, 2-(chloromethyl)piperidines, and 2-(2-chloroethyl)piperidines produced the corresponding 3-substituted pyrrolizidines, 5- or 3-substituted indolizidines, and 4-substituted quinolizidines, respectively. 8-Methyl-5-substituted indolizidines were also prepared from the appropriate methyl-substituted chloroamine precursor. Enantioselective syntheses were achieved by employing chiral chloroamines derived from amino acids or other enantiopure precursors. Further transformations of several of the products provided concise syntheses of four dendrobatid alkaloids. Thus, reduction of (8a*S*)-5-*n*-propyl-6-(*p*-toluenesulfonyl)-$\Delta^{5,6}$-indolizidine with sodium cyanoborohydride in trifluoroacetic acid, followed by reductive desulfonylation, afforded (−)-indolizidine **167B**. The corresponding 5-*n*-hexyl derivative similarly produced (−)-indolizidine **209D**, while (−)-(8*R*,8a*S*)-8-methyl-5-*n*-pentyl-6-(*p*-toluenesulfonyl)-$\Delta^{5,6}$-indolizidine furnished (−)-indolizidine **209B**. Finally, the similar reduction and debenzylation of (−)-(8*R*,8a*S*)-5-(2-benzyloxyethyl)-8-methyl-6-(*p*-toluenesulfonyl)-$\Delta^{5,6}$-indolizidine produced the corresponding 5-hydroxyethyl indolizidine. This was subjected to chlorination of the alcohol group with thionyl chloride and substitution with a higher order allyl cuprate reagent to afford (−)-indolizidine **207A**.

Acetylenic sulfones **1** have many synthetic applications.[1] Because of the electron-withdrawing effect of the sulfone moiety, unsaturated sulfones such as **1** function as efficient dienophiles and dipolarophiles in cycloadditions.[2] Acetylenic sulfones can also undergo single or double conjugate additions at the β-position with a variety of nucleophiles, while the resulting vinyl or saturated alkyl sulfones afford sulfone-stabilized α-carbanions when deprotonated with strong bases.[3] Thus, it is in principle possible to introduce one or two nucleophiles and one or two electrophiles, at the β- and α-positions, respectively. Moreover, since the sulfone group can be subsequently removed by a variety of reductive, oxidative, or alkylative methods,[4] the original acetylenic sulfone functions as the synthetic equivalent of hypothetical dipole or multipole species (Scheme 1). Intramolecular acylations or alkylations of sulfone-stabilized anions have been employed in several previous ring-closure techniques.[5] We recently reported[6] that the conjugate addition of primary β-amino ester **2** to acetylenic sulfone **1** (R = *n*-Pr), followed by intramolecular acylation of the corresponding anion, afforded the enaminone **3**, which then served as a key intermediate in the synthesis of (−)-pumiliotoxin C (**4**) (Scheme 2). We now describe variations of this cyclization protocol that sig-

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(1) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 15.

(2) For reviews, see: (a) ref 1a, Chapter 6. (b) De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755. For lead references, see: (c) Back, T. G.; Bethell, R. J.; Parvez, M.; Taylor, J. A.; Wehrli, D. *J. Org. Chem.* **1999**, *64*, 7426. (d) Shen, M.; Schultz, A. G. *Tetrahedron Lett.* **1981**, *22*, 3347.

(3) For reviews of sulfone-stabilized carbanions, see: (a) ref 1a, Chapter 3. (b) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978; Chapter 2. (c) Nájera, C.; Sansano, J. M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 637. For examples of sulfone-stabilized vinyl carbanions, see: (d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3279. (e) Kleijn, H.; Vermeer, P. *J. Organomet. Chem.* **1986**, *302*, 1. (f) Nájera, C.; Yus, M. *J. Org. Chem.* **1988**, *53*, 4708. (g) Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775. (h) Caturla, F.; Nájera, C. *Tetrahedron* **1997**, *53*, 11449.

(4) (a) See ref 1a, Chapter 9. (b) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

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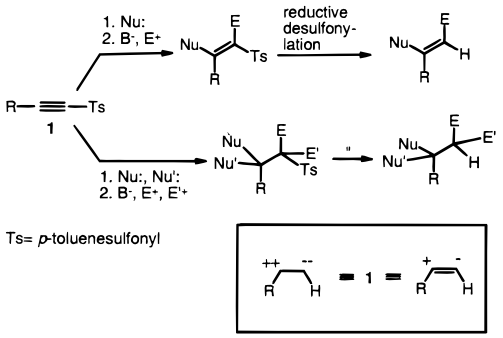
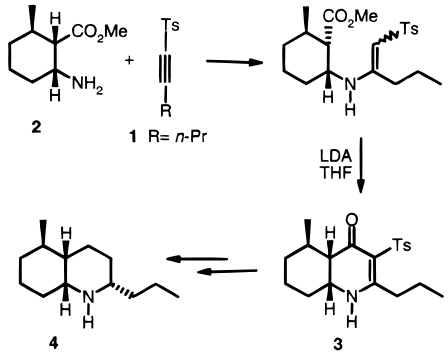
Scheme 1



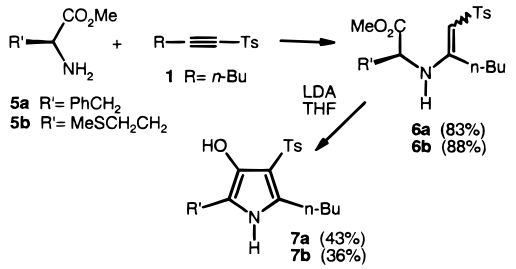
Scheme 2



nificantly extend the scope of the original method. In particular, the use of readily available chloroamines in place of amino esters provides access to a variety of nitrogen heterocycles,[7] including the four dendrobatid alkaloids of the title.

Dendrobatid alkaloids[8] are contained in the toxic skin secretions of certain neotropical frogs and other species. These compounds serve as a defense against predation and have been employed by hunters in the rain forests of Central and South American as blow-gun dart poisons. The structures and toxicity of the dendrobatid alkaloids vary widely. For example, some of the indolizidines in this class are noncompetitive blockers of nicotinic receptor channels, thus making them of pharmacological and medicinal interest. Furthermore, the very limited amounts available from natural sources make the development of synthetic approaches to these compounds necessary for procuring adequate amounts for biological studies. The application of our sulfone-based cyclization procedure to the synthesis of several dendrobatid alkaloids of the indolizidine class was therefore also investigated.

Scheme 3



Results and Discussion

During the cyclization leading to **3**, and in several other examples that were subsequently investigated with other β-amino esters,[9a] we observed varying degrees of competing proton transfer from the α-position of the ester to that of the sulfone.[9b] This resulted in the recovery of significant amounts of the unreacted enamine sulfone and decreased the efficiency of the desired ring-closure step. When α-amino esters **5a** and **5b** were similarly employed with acetylenic sulfone **1** (R = *n*-Bu), cyclization occurred efficiently but was accompanied by enolization and aromatization to afford the corresponding pyrroles **7a** and **7b** via the conjugate addition products **6a** and **6b**, respectively (Scheme 3). To circumvent proton transfer and aromatization, we next investigated the use of β- and γ-chloroamines in a variation of the original technique, where ring closure occurs via intramolecular alkylation instead of acylation (Scheme 4).

The required chloroamines in Scheme 4 were prepared by chlorination of the corresponding amino alcohols with thionyl chloride. Products **8a**,[10] **8c**,[11] **8e**,[12] and **8f**[12] were prepared as reported in the literature. Thus, enantiopure chloroamine **8c** was obtained from (L)-proline, while **8e** and **8f** were employed as racemic mixtures. Arndt–Eistert homologation[13] of (L)-proline[14a] followed by reduction afforded the known amino alcohol precursor of **8d**.[14b,14c] Similar homologation of (L)-alanine provided the known ester **9**,[15] which was transformed into **8b** as shown in Scheme 5. Ester **11** was obtained from (*R*)-α-methylbenzylamine by literature methods[16] and was converted into **8g** as shown in Scheme 5. Both **8b** and **8g** were thus

(5) For illustrative examples, see: (a) Ghera, E.; Maurya, R.; Ben-David, Y. *J. Org. Chem.* **1988**, *53*, 1912. (b) Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994**, *35*, 5369. (c) Grimm, E. L.; Coutu, M. L.; Trimble, L. A. *Tetrahedron Lett.* **1993**, *34*, 7017. (d) Gamble, M. P.; Giblin, G. M. P.; Taylor, R. J. K. *Synlett* **1995**, 779. (e) Magnus, P.; Booth, J.; Magnus, N.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett.* **1995**, *36*, 5331. (f) McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, *28*, 4123. (g) Date, M.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 902. (h) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1995**, *60*, 6000. (i) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993. (j) Carretero, J. C.; Arrayás, R. G.; Storch de Garcia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (k) Carretero, J. C.; Arrayás, R. G. *Synlett* **1999**, 49. (l) Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139.

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

(7) Preliminary communication: Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261.

(8) For general reviews of dendrobatid alkaloids, see: (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (b) Witkop, B.; Gössinger, E. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Science, New York, 1983; Vol. 21, Chapter 5. (c) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. (d) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189. (e) Daly, J. W.; Myers, C. W. Whittaker, N. *Toxicon* **1987**, *25*, 1023.

(9) (a) Nakajima, K. Ph.D. Thesis, University of Calgary, 2000. (b) The success of intramolecular acylations of sulfone-stabilized carbanions can be attributed to the greater kinetic acidity of the sulfone moiety, despite the generally higher pK_a values of sulfones compared to esters.

(10) Dolfini, J. E.; Dolfini, D. M. *Tetrahedron Lett.* **1964**, 2103.

(11) Piper, J. R.; Johnston, T. P. *J. Org. Chem.* **1963**, *28*, 981.

(12) Norton, T. R.; Seibert, R. A.; Benson, A. A.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1946**, *68*, 1572.

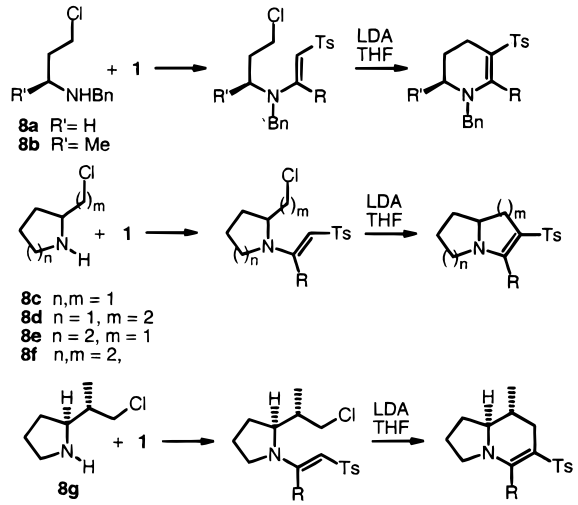
(13) For lead references, see March, J. In *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 1083–1085.

(14) For the Arndt–Eistert homologation of (L)-proline, see: (a) Cassal, J.-M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1976**, *59*, 1917. The preparation of racemic **8d** has also been reported; see: (b) Sandoz Ltd., Neth. Appl. Patent 6,600,184; July, 13, 1966 via *Chem. Abstr.* **1967**, *66*, 2580r. (c) Mahesh, V. K.; Sharma, R.; Maheshwari, M. *Indian J. Chem, Sect. B* **1984**, *23*, 486.

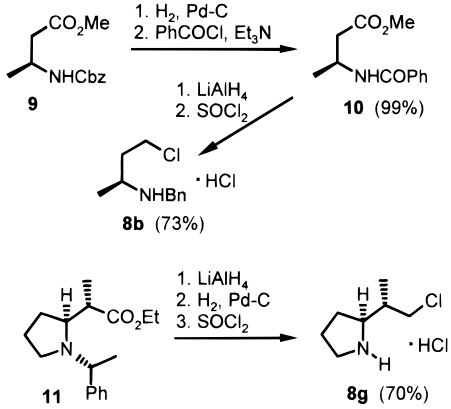
(15) Drey, C. N. C.; Mtetwa, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1587.

(16) Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189.

Scheme 4



Scheme 5



obtained as essentially pure enantiomers. All of the chloroamines shown in Scheme 4 were isolated and stored as their hydrochloride salts, which are stable for prolonged periods at −20 °C.

Acetylenic sulfone **1a** was prepared by a literature method[17] from bis(trimethylsilyl)acetylene. Compounds **1b**−**1i** were obtained by selenosulfonation of the corresponding acetylenes,[18] followed by selenoxide elimination (Scheme 6). The selenosulfonation step was performed after O-benzylation of the corresponding acetylenic alcohols in the synthesis of **1h** and **1i** but was more effectively carried out directly on 3-butyn-1-ol, followed by silylation and selenoxide elimination in the preparation of **1g**. Enyne **1j** was prepared as described earlier.[19]

Scheme 6

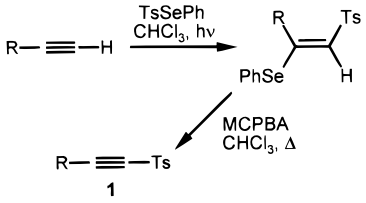
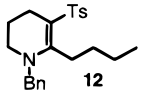
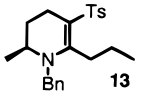
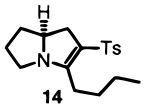
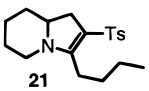


Table 1. Cyclizations of Chloroamines with Acetylenic Sulfones

Entry	Reactants		Conditions for Conjugate Addition[a]	Product	Yield (%)
1	**8a**	**1c**	C_6H_6, Δ, 18.5	 **12**	94[b]
2	**8b**	**1b**	EtOH, RT, 24	 **13**	88[b]
3	**8c**	**1c**	CH_2Cl_2, RT, 21.5	 **14**	75[b]
4	**8d**	**1b**	CH_2Cl_2, RT, 5	**15** R= *n*-Pr	94[b], 84[c]
5	**8d**	**1c**	CH_2Cl_2, RT, 22	**16** R= *n*-Bu	86[b]
6	**8d**	**1e**	CH_2Cl_2, RT, 40	**17** R= *n*-C_6H_{13}	86[c]
7	**8g**	**1d**	CH_2Cl_2, RT, 19	**18** R= *n*-C_5H_{11}	74[c]
8	**8g**	**1h**	CH_2Cl_2, RT, 21	**19** R= $(CH_2)_2OBn$	73[c]
9	**8g**	**1i**	CH_2Cl_2, RT, 24	**20** R= $(CH_2)_3OBn$	82[c]
10	**8e**	**1c**	THF, Δ, 18.5	 **21**	77[b]
11	**8f**	**1a**	THF, Δ, 8	**22** R= H	64[b]
12	**8f**	**1c**	THF, Δ, 20.5	**23** R= n-Bu	84[b]
13	**8f**	**1f**	THF, Δ, 16.5	**24** R= Ph	78[b]
14	**8f**	**1g**	THF, Δ, 16	**25** R= $(CH_2)_2OTBDMS$	81[b]
15	**8f**	**1j**	THF, Δ, 16, then C_6H_6, Δ, 23	**26** R= 	80[b]

[a] Solvent, temperature (Δ = reflux; RT = room temperature), and time (h) are given for the conjugate addition step. All cyclization steps were performed in THF at −78 °C for 5−45 min in the presence of excess LDA. [b] A small excess (1.1−1.2 equiv) of the chloroamine hydrochloride was employed; the yield is based on the acetylenic sulfone. [c] Equimolar amounts of the chloroamine hydrochloride and acetylenic sulfone were used.

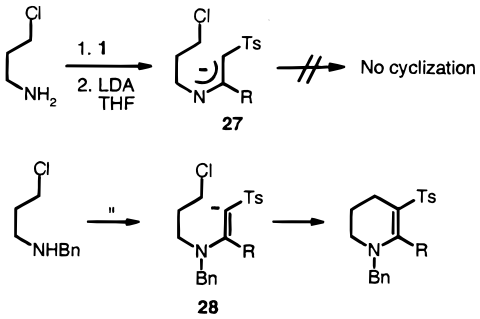
The results of the cyclizations of chloroamines **8** with acetylenic sulfones **1** are listed in Table 1. In general, the chloroamines were liberated from their hydrochloride salts just prior to use by treatment with aqueous potassium hydroxide. The conjugate additions of the corresponding free bases[20] proceeded smoothly in solvents such as benzene, dichloromethane, or THF at room tempera-

(17) Chen, Z.; Trudell, M. L. *Synth. Commun.* **1994**, *24*, 3149.

(18) For the preparation of acetylenic sulfones by selenosulfonation, see: (a) Back, T. G. In *Organoselenium Chemistry−A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 9. (b) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1983**, *48*, 3077. (c) Miura, T.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1982**, 438.

(19) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. *J. Org. Chem.* **1990**, *55*, 4595.

Scheme 7



ture or at reflux. The addition in entry 2 proceeded slowly in these solvents, but the rate was enhanced in ethanol. The adducts were typically obtained as pure *E*-isomers (NMR), as expected from precedents with other additions of secondary amines to acetylenic sulfones.[20a,d,f] The cyclization step was then conducted by evaporation of the solvent (if other than THF) and treatment of the crude adduct with LDA in THF at −78 °C for a few minutes. The products were isolated in the yields indicated in Table 1. In some cases, it was expedient to employ a small excess of the chloroamine to compensate for losses during its liberation from the corresponding hydrochloride. In such cases the yield in Table 1 is calculated on the basis of the acetylenic sulfone. Thus, in entry 4, a modest improvement in the yield of **15** from 84% to 94% was observed when 1.1 equiv of the chloroamine **8d** was employed. When primary chloroamines were similarly investigated, the conjugate addition step proceeded in the normal manner, but attempts at subsequent cyclizations failed, resulting in the recovery of the enamine sulfone intermediate. This can be attributed to the lower reactivity in the intramolecular alkylation of the enamide anion **27**, derived from a primary amine, compared to that of the sulfone-stabilized vinyl carbanion **28**, which was generated from a secondary amine (Scheme 7). Thus, N-benzylation of the chloroamine was necessary in entries 1 and 2 to obtain the desired products **12** and **13**.

The examples in Table 1 indicate that the method is applicable to the synthesis of a variety of nitrogen heterocycles containing the enamine sulfone moiety. These include 2- or 2,6-disubstituted piperidines (entries 1 and 2), a 3-substituted pyrrolizidine (entry 3), 5-, 5,8-, or 3-substituted indolizidines (entries 4−6, 7−9 and 10, respectively), and 4-substituted quinolizidines (entries 11−15).[21] It is worth noting that the substituent originating from the acetylenic sulfone can be incorporated into either the 5- or 3-position of the corresponding indolizidine products (i.e., entries 4−9 and 10, respectively). This was achieved by choosing either a pyrrolidine with a pendant 2-chloroethyl side chain (i.e., **8d** or **8g**) or a piperidine with a chloromethyl substituent (i.e., **8e**), respectively, as the starting chloroamine. Moreover, since the chloroamines can be prepared from α-amino acids or other enantiopure precursors (vide supra), enantioselective syntheses of the product heterocycles are possible, as illustrated by entries 2−9.

Further stereoselective transformations of the enamine sulfone moieties of the products are also possible. This was exemplified in our earlier synthesis of pumiliotoxin C[6] by preferential hydrogenation and hydrogenolysis of the enol triflate of **3** from the exo side, followed by reductive desulfonylation. We now report that the enamine sulfone groups in several of the products in Table 1 were reduced with high α-stereoselectivity with sodium cyanoborohydride in acidic media, via the corresponding iminium ions.[22,23] This process, followed by reductive desulfonylation, therefore provides a short enantioselective route to dendrobatid alkaloids of the indolizidine class that contain substituents in the 5- or 5,8-positions.

Thus, the enamine moieties of cyclized products **15** and **17** were reduced with sodium cyanoborohydride in the presence of trifluoroacetic acid, followed by desulfonylation with sodium in liquid ammonia.[24] Although no significant formation of the corresponding 5-epimers was detected, the crude products contained traces (<5%) of unsaturated byproducts, tentatively identified by NMR analysis as the corresponding $\Delta^{6,7}$ analogues **29** and **30**, respectively. The latter compounds were presumably formed by a competing base-catalyzed elimination of *p*-toluenesulfinic acid in the desulfonylation step. The entire crude mixture was therefore hydrogenated to reduce the byproducts, thereby affording the desired alkaloids (−)-indolizidine **167B** (**31**, R = *n*-Pr)[25] and (−)-indolizidine **209D** (**32**, R = *n*-C_6H_{13})[26] in overall yields of 60% and 74%, respectively (Scheme 8). Enamine sulfone **18** was similarly converted into (−)-indolizidine **209B**

(20) For examples of conjugate additions of amines to acetylenic sulfones, see: (a) Truce, W. E.; Brady, D. G. *J. Org. Chem*. **1966**, *31*, 3543. (b) Truce, W. E.; Markley, L. D. *J. Org. Chem*. **1970**, *35*, 3275. (c) Truce, W. E.; Onken, D. W. *J. Org. Chem*. **1975**, *40*, 3200. (d) Stirling, C. J. M. *J. Chem. Soc*. **1964**, 5863. (e) Pink, R. C.; Spratt, R.; Stirling, C. J. M. *J. Chem. Soc*. **1965**, 5714. (f) McMullen, C. H.; Stirling, C. J. M. *J. Chem. Soc. B* **1966**, 1217. (g) McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 351. (h) Cossu, S.; De Lucchi, O.; Durr, R. *Synth. Commun*. **1996**, *26*, 4597. (i) Cinquini, M.; Cozzi, F.; Pelosi, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1430. (j) Back, T. G.; Collins, S.; Law, K.-W. *Can. J. Chem*. **1985**, *63*, 2313. (k) Back, T. G.; Bethell, R. J.; Parvez, M.; Wehrli, D. *J. Org. Chem*. **1998**, *63*, 7908.

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(22) For the stereoselective reduction of other enamines via their iminium ions with $NaBH_3CN$−TFA, see: Comins, D. L.; Weglarz, M. A. *J. Org. Chem*. **1991**, *56*, 2506.

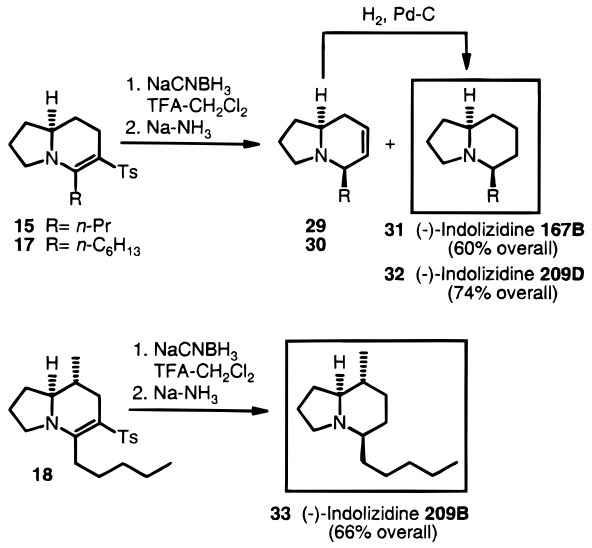
(23) The generally high stereoselectivity of hydride reductions of similar bicyclic iminium ions has been rationalized on the basis of conformational and stereoelectronic effects: Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

(24) For a general procedure for reductive desulfonylation with Na−liquid NH_3, see: Marshall, J. A.; Cleary, D. G. *J. Org. Chem*. **1986**, *51*, 858.

(25) For previous syntheses of (−)-indolizidine **167B** (**31**), see: (a) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (b) Angle, S. R.; Henry, R. M. *J. Org. Chem*. **1997**, *62*, 8549. (c) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett*. **1996**, *37*, 1445. (d) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron Asymmetry* **1992**, *3*, 695. (e) Fleurant, A.; Saliou, C.; Célérier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem*. **1995**, *32*, 255. (f) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett*. **1993**, *34*, 3119. (g) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc*. **1991**, *113*, 3513. (h) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem*. **1990**, *55*, 4688.

(26) For previous syntheses of (−)-indolizidine **209D** (**32**), see: refs 25c, 25f, 25h, and (a) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 398. (b)Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747. (c) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511. (d) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289.

Scheme 8

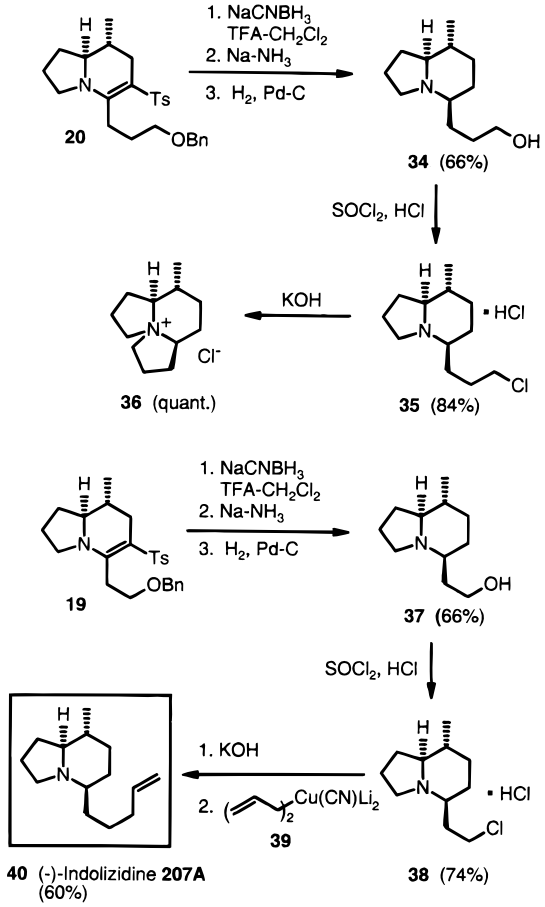


(**33**)[27] in 66% overall yield, without the appearance of unsaturated byproducts, thereby obviating the hydrogenation step.

We next attempted to prepare (−)-indolizidine **207A** (**40**),[28] an unsaturated analogue of **33**, via substitution of the corresponding chloride **35** with a vinyl cuprate reagent. The alcohol **34** was obtained from enamine sulfone **20** in the usual manner (Scheme 9). However, conversion of the latter into the free base of the corresponding chloride **35** resulted in spontaneous cyclization to **36**. When the procedure was repeated with the homologue **19**, where similar cyclization was expected to be less favorable as a result of the formation of a four-membered ring, the corresponding chloride **38** was easily obtained from alcohol **37**. Treatment of **38** with the higher order cuprate **39**[29] then afforded the desired product **40** (Scheme 9).

In conclusion, the conjugate additions of acyclic or cyclic secondary β- or γ-chloroamines to acetylenic sulfones proceed smoothly under mild conditions. The crude products undergo cyclization when treated with LDA, via intramolecular alkylation of the corresponding sulfone-stabilized vinyl carbanions. The products thus obtained include variously substituted piperidines, pyrrolizidines, indolizidines, and quinolizidines, all containing the enamine sulfone moiety. Since the required chloroamines can be obtained from α-amino acids or other enantiopure precursors, the products can be prepared enantioselectively. The cyclic enamine sulfones that are obtained in this manner can be reduced stereoselectively and desulfonylated. The utility of this protocol was illustrated by the enantioselective synthesis of four dendrobatid alkaloids: (−)-indolizidines **167B**, **209D**, **209B**, and **207A**. Further opportunities exist for modifying the enamine sulfone functionality in a synthetically useful manner and these are under continued investigation.

Scheme 9



Experimental Section

NMR spectra were recorded in deuteriochloroform and are reported relative to residual chloroform or TMS as the internal standard. Where ^{13}C NMR signals are assigned as C, CH, CH_2, or CH_3, the assignments are based on DEPT experiments. Chromatography refers to flash chromatography on silica gel (230−400 mesh), unless otherwise noted.

2-Benzyl-5-*n*-butyl-3-hydroxy-4-(*p*-toluenesulfonyl)-pyrrole (7a). A solution of (L)-phenylalanine methyl ester (**5a**) (228 mg, 1.27 mmol) and 1-(*p*-toluenesulfonyl)-1-hexyne[30] (**1c**) (255 mg, 1.08 mmol) in 2 mL of benzene was refluxed for 3 h and concentrated in vacuo. The residual oil was chromatographed over neutral alumina. Elution with 25% ethyl acetate−hexanes furnished 372 mg (83% based on **1c**) of a 1:2 *E*,*Z* mixture (NMR) of the corresponding conjugate addition product **6a** as a yellow oil, which was used directly in the next step.

A solution of the above enamine sulfone **6a** (155 mg, 0.373 mmol) in 1.0 mL of THF was added to LDA (0.37 mmol) in 2.0 mL of THF at −78 °C. It was stirred at −78 °C for 40 min and then at room temperature for 24 h. The concentrated crude product was chromatographed without further manipulation. Elution with 50% ethyl acetate−hexanes afforded 62 mg (43%) of **7a** as a yellow oil, which crystallized from dichloromethane−hexanes to give white needles: mp 184−186 °C; IR (KBr) 3390, 3188, 1678, 1283, 1137 cm^{-1}; ^1H NMR[31] (400 MHz) δ 8.81 (br s, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.02 (t, J = 7.4 Hz, 1 H), 6.97 (d, J = 7.4 Hz, 2 H), 6.87 (t,

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(28) For previous syntheses of (−)-indolizidine **207A** (**40**), see: ref 27d and (a) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182. (b) Taber, D. F.; Rahimizadeh, M.; You, K. K. *J. Org. Chem.* **1995**, *60*, 529.

(29) (a) Lipshutz, B. H.; Crow, R.; Dimock, S. H.; Ellsworth, E. L.; Smith, R. A. J.; Behling, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 4063. (b) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; p 315.

(30) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1987**, *52*, 4265; the general method of ref 18 was used in the preparation of **1c**.

J = 7.6 Hz, 2 H), 6.03 (br s, 1 H), 3.34 (d, J = 13.2 Hz, 1 H), 3.24 (d, J = 13.1 Hz, 1 H), 3.02−2.92 (m, 1 H), 2.69−2.59 (m, 1 H), 2.46 (s, 3 H), 1.35−1.10 (m, 4 H), 0.80 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 193.6 (C), 183.0 (C), 143.1 (C), 140.4 (C), 132.7 (C), 130.0 (CH), 129.3 (CH), 127.9 (CH), 126.7 (CH), 126.4 (CH), 105.9 (C), 88.5 (C), 42.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 13.6 (CH_3); MS(EI) *m/z* (%) 383 (M^+, 5), 381 (37), 91 (100); HRMS calcd for $C_{22}H_{25}NO_3S$ 383.1555, found 383.1517.

5-*n*-Butyl-3-hydroxy-2-(2-methylthioethyl)-4-(*p*-toluenesulfonyl)pyrrole (7b). Following the preceding procedure, the conjugate addition of methionine methyl ester (**5b**) (1.2 equiv) to **1c**[30] provided 88% (based on **1c**) of **6b** as an oil, which was directly subjected to the LDA-mediated cyclization to afford 36% of **7b** as a solid: mp 145−147 °C (from dichloromethane−hexanes); IR (KBr) 3242, 1674, 1282, 1137, 1082 cm^{-1}; ^{1}H NMR[31] (400 MHz) δ 8.45 (br s, 1 H), 7.82 (d, J = 7.6 Hz, 2 H), 7.26 (d, J = 7.2 Hz, 2 H), 5.40 (br s, 1 H), 3.14−3.00 (m, 1 H), 2.98−2.83 (m, 1 H), 2.45−2.33 (m, 1 H), 2.40 (s, 3 H), 2.33−2.22 (m, 1 H), 2.19−2.09 (m, 1 H), 2.06−1.98 (m, 1 H), 1.94 (s, 3 H), 1.75−1.60 (m, 2 H), 1.50−1.38 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz) δ 193.3 (C), 182.5 (C), 143.5 (C), 140.4 (C), 129.4 (CH), 126.2 (CH), 105.5 (C), 87.7 (C), 35.4 (CH_2), 29.34 (CH_2), 29.28 (CH_2), 27.1 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 15.2 (CH_3), 13.6 (CH_3); MS(EI) *m/z* (%) 367 (M^+, 11), 365 (52), 210 (100), 91 (80), 61 (92); HRMS calcd for $C_{18}H_{25}NO_3S_2$ 367.1276, found 367.1241.

Methyl (−)-(3*S*)-3-(Benzoylamino)butanoate (10). A mixture of *N*-Cbz amino ester **9**[15] (5.095 g, 20.30 mmol) and *p*-toluenesulfonic acid monohydrate (4.241 g, 22.32 mmol) in methanol (50 mL) was hydrogenated over 10% palladium on charcoal (516 mg) at room temperature and at 1 atm for 16.5 h. It was then filtered through Celite, and the filtrate was concentrated to give a yellow oil. This was dissolved in dichloromethane (50 mL) and triethylamine (11.5 mL, 82.6 mmol). Benzoyl chloride (2.36 mL, 20.3 mmol) was slowly added. The resulting mixture was stirred at room temperature for 30 min, washed with aqueous KOH, dried ($MgSO_4$), and concentrated in vacuo. The solid residue was further washed with hexane to provide 4.455 g (99%) of **10** as a white solid: mp 106−108 °C (from dichloromethane−hexanes); lit.[32] 108−109 °C; $[\alpha]^{20}_D$ −42.1 (*c* 0.86, $CHCl_3$); lit.[32] $[\alpha]_D$ −42.0 (*c* 0.77, $CHCl_3$).

(+)-(3*S*)-3-Benzylamino-1-chlorobutane Hydrochloride (8b). A solution of **10** (4.570 g, 20.68 mmol) in 35 mL of THF was added dropwise over 5 min to a suspension of lithium aluminum hydride (3.924 g, 103.3 mmol) in 150 mL of ether at 0 °C. The resulting mixture was stirred at room temperature for 47 h. Excess lithium aluminum hydride was destroyed by the cautious addition of water, and the precipitate was removed by filtration. The aqueous layer was basified with KOH, and the product was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo to give the corresponding amino alcohol[33] as a light yellow oil: ^{1}H NMR (200 MHz) δ 7.40−7.25 (m, 5 H), 3.95−3.73 (m, 4 H), 3.10−2.92 (m, 1 H), 1.85−1.68 (m, 1 H), 1.67−1.48 (m, 1 H), 1.21 (d, J = 6.3 Hz, 3 H). The product was dissolved in chloroform (30 mL), and HCl gas was bubbled through the solution while cooling at 0 °C. Thionyl chloride (3.0 mL, 41 mmol) was added dropwise over 5 min at 0 °C, and the resulting solution was refluxed for 2 h and concentrated in vacuo. The residue was triturated with methanol (30 mL), and a small amount of decolorizing charcoal was added. The mixture was refluxed for 30 min, filtered through Celite, and the filtrate was concentrated in vacuo to give a light yellow solid. Recrystallization from ethanol−ether provided 3.547 g (73%) of the hydrochloride salt of **8b** as white crystals: mp 140−141 °C; $[\alpha]^{20}_D$ +1.8 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NCl_2$: C, 56.42; H, 7.32; N, 5.98. Found: C, 56.38; H, 7.24; N, 5.96. The free base of **8b** was obtained as a yellow oil by treatment with aqueous KOH, extraction with dichloromethane, drying ($MgSO_4$), and concentration in vacuo: ^{1}H NMR (200 MHz) δ 7.45−7.20 (m, 5 H), 3.87 (d, J = 13.0 Hz, 1 H), 3.76 (d, J = 13.0 Hz, 1 H), 3.70 (dt, J = 10.7, 7.0 Hz, 1 H), 3.62 (dt, J = 11.1, 6.8 Hz, 1 H), 2.93 (sextet, J = 6.3 Hz, 1 H), 2.05−1.73 (m, 2 H), 1.15 (d, J = 6.3 Hz, 3 H). The free base was used immediately without storage.

(+)-(2*S*)-2-(2-Chloroethyl)pyrrolidine Hydrochloride (8d). Chlorination of (2*S*)-2-(2-hydroxyethyl)pyrrolidine[14] was carried out according to the procedure used for the preparation of **8b**. Hydrochloride salt of **8d**: mp 99−100 °C; $[\alpha]^{23}_D$ +14.7 (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_6H_{13}NCl_2$: C, 42.37; H, 7.71; N, 8.24. Found: C, 42.14; H, 7.48; N, 8.05. The free base of **8d** was obtained by treatment with aqueous KOH as in the case of **8b** and was used immediately: ^{1}H NMR (200 MHz) δ 3.64 (t, J = 6.7 Hz, 2 H), 3.32−3.12 (m, 1 H), 3.08−2.78 (m, 2 H), 2.07−1.64 (m, 6 H), 1.41−1.20 (m, 1 H).

(+)-(2*S*,2′*S*)-2-[2′-(1′-Chloropropyl)]pyrrolidine Hydrochloride (8g). A solution of ester **11**[16] (5.059 g, 18.40 mmol) in 50 mL of ether was added to a suspension of lithium aluminum hydride (2.864 g, 75.37 mmol) in 200 mL of ether at 0 °C, and the mixture was stirred at room temperature for 1 h. Excess lithium aluminum hydride was destroyed by the cautious addition of water, and the white precipitate was removed by filtration. The filtrate was washed with aqueous KOH, dried ($MgSO_4$), and concentrated in vacuo to give 4.944 g of the corresponding alcohol as a light yellow oil: ^{1}H NMR (200 MHz) δ 7.45−7.20 (m, 5 H), 3.65 (q, J = 6.6 Hz, 1 H), 3.45 (dd, J = 10.9, 3.5 Hz, 1 H), 3.26 (dd, J = 10.8, 9.7 Hz, 1 H), 3.10−2.75 (m, 3 H), 1.90−1.65 (m, 3 H), 1.64−1.45 (m, 2 H), 1.40 (d, J = 6.5 Hz, 3 H), 0.60 (d, J = 6.8 Hz, 3 H).

The above product was hydrogenated over 1.373 g of 10% palladium on charcoal in 60 mL of ethanol at 1 atm at room temperature for 6 days. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residual oil was triturated with chloroform, washed with aqueous KOH, dried ($MgSO_4$), and concentrated in vacuo to give 2.52 g of the corresponding secondary amine as a yellow oil: ^{1}H NMR (200 MHz) δ 4.25 (br m, 2 H), 3.63 (dd, J = 10.8, 3.6 Hz, 1 H), 3.51 (dd, J = 10.8, 8.7 Hz, 1 H), 3.07−2.70 (m, 3 H), 2.00−1.67 (m, 2 H), 1.66−1.35 (m, 3 H), 0.80 (d, J = 6.8 Hz, 3 H).

The product was dissolved in 40 mL of chloroform, and HCl gas was bubbled through the mixture at 0 °C. Thionyl chloride (5.4 mL, 74 mmol) was added dropwise over 5 min at 0 °C, and the resulting solution was refluxed for 3 h and concentrated in vacuo. The residue was triturated with methanol (20 mL), refluxed for 30 min with a small amount of decolorizing charcoal, and filtered through Celite. The filtrate was concentrated in vacuo, and the decolorizing procedure was repeated to give a light yellow solid, which was recrystallized from ethanol−ether to give 2.357 g (70%) of the hydrochloride salt of **8g** as a pale yellow solid: mp 109−110 °C; $[\alpha]^{18}_D$ +15.0 (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_7H_{15}NCl_2$: C, 45.67; H, 8.21; N, 7.61. Found: C, 45.42; H, 8.48; N, 7.47. The free base of **8g** was obtained by treatment with aqueous KOH solution as in the case of **8b** and was used immediately: ^{1}H NMR (200 MHz) δ 3.67 (d, J = 4.6 Hz, 2 H), 3.07−2.81 (m, 3 H), 2.20 (br s, 1 H), 2.02−1.60 (m, 4 H), 1.47−1.22 (m, 1 H), 1.03 (d, J = 6.7 Hz, 3 H).

(31) The diastereotopic methylene protons in the substituents at C-2 and C-5 in the ^{1}H NMR spectra of **7a** and **7b** suggest the predominance of the keto tautomers in these compounds. However, the presence of seven quaternary carbon and only five CH signals in the DEPT spectrum of **7a** and of six quaternary carbon and only two CH signals in that of **7b** is consistent with their enol tautomers, as is the absence of a signal in their ^{1}H NMR spectra attributable to the proton at the stereocenter (C-2) of the keto tautomer. The diastereotopic nature of the methylene protons in **7a** and **7b** is possibly due to asymmetry caused by intramolecular hydrogen bonding between the sulfone oxygen atoms and the hydroxyl groups of the enol tautomers, resulting in torsion of the arylsulfonyl moieties relative to the pyrrole rings. The averaging of NMR signals of the keto and enol forms would occur if equilibration of the tautomers was sufficiently rapid on the NMR time scale. This appears to be unlikely but cannot be completely ruled out. For a kinetic study of the tautomerization of other 3-hydroxypyrroles, see: Capon, B.; Kwok, F. *J. Am. Chem. Soc.* **1989**, *111*, 5346.

(32) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824.

(33) The racemic amino alcohol is a known compound: Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.

1-(*p*-Toluenesulfonyl)-1-heptyne (1d) and Acetylenic Sulfones 1b, 1e, 1f, and 1j. A solution of 1-heptyne (1.02 mL, 7.79 mmol) and *Se*-phenyl *p*-tolueneselenosulfonate[34] (1.216 g, 3.910 mmol) in 10 mL of chloroform was irradiated in a Rayonet minireactor equipped with 300 nm lamps for 1 h. MCPBA (1.350 g, 7.824 mmol) was added, and the mixture was stirred at room temperature for 10 min. It was washed with aqueous KOH, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 10 mL of chloroform, and the mixture was refluxed for 1 h and concentrated in vacuo. Chromatography of the crude product (elution with 5% ethyl acetate−hexanes) afforded 799 mg (82%) of **1d**[35] as a light yellow oil: ^{1}H NMR (200 MHz) δ 7.88 (d, J = 8.4 Hz, 2 H), 7.37 (d, J = 8.0 Hz, 2 H), 2.47 (s, 3 H), 2.35 (t, J = 7.1 Hz, 2 H), 1.65−1.45 (m, 2 H), 1.42−1.18 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (50 MHz) δ 144.8, 138.9, 129.6, 126.8, 97.2, 78.1, 30.5, 26.4, 21.7, 21.4, 18.6, 13.5; MS(EI) *m*/*z* (%) 250 (M^+, 0.5), 139 (50), 95 (94), 91 (100).

Compound **1e** was prepared similarly from 1-octyne in 87% yield and had spectroscopic properties in accord with those reported for a sample prepared by a different method.[36] Compounds **1b**,[6,18a] **1f**,[18b] and **1j**[19] were prepared by selenosulfonation of the corresponding acetylenes as described previously.

4-(*tert*-Butyldimethylsilyloxy)-1-(*p*-toluenesulfonyl)-1-butyne (1g). A solution of 3-butyn-1-ol (102 mg, 1.46 mmol) and *Se*-phenyl *p*-tolueneselenosulfonate[34] (224 mg, 0.720 mmol) in 3.0 mL of chloroform was irradiated at 300 nm for 2 h as in the preparation of **1d**. The mixture was concentrated in vacuo, and chromatography of the residue (elution with 25% ethyl acetate−hexanes) furnished the selenosulfonation adduct as a light yellow oil (237 mg). This was dissolved in 3.0 mL of DMF, imidazole (86 mg, 1.3 mmol) and *tert*-butyldimethylsilyl chloride (182 mg, 1.21 mmol) were added, and the mixture was stirred at room temperature for 2 h. The solution was diluted with 10% aqueous HCl, extracted with ether, dried ($MgSO_4$), concentrated, and chromatographed. Elution with 2% ethyl acetate−hexanes afforded the corresponding silyl ether as a yellow oil (295 mg). This was treated with MCPBA (210 mg, 1.22 mmol) and subjected to selenoxide elimination as in the preparation of **1d**. Chromatography (elution with 5% ethyl acetate−hexanes) provided 155 mg (64%) of **1g** as a colorless oil: IR (film) 2202, 1253, 1155 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.88 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 3.74 (t, J = 6.4 Hz, 2 H), 2.57 (t, J = 6.5 Hz, 2 H), 2.47 (s, 3 H), 0.85 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (50 MHz) δ 145.1, 138.9, 129.8, 127.3, 94.3, 79.1, 59.9, 25.7, 23.4, 21.6, 18.1, −5.5; MS(EI) *m*/*z* (%) 323 (M^+ − Me, 12), 281 (100); HRMS calcd for $C_{17}H_{26}O_3SSi$ − Me 323.1137, found 323.1156.

4-Benzyloxy-1-(*p*-toluenesulfonyl)-1-butyne (1h) and 5-Benzyloxy-1-(*p*-toluenesulfonyl)-1-pentyne (1i). 3-Butyn-1-ol (4.026 g, 57.51 mmol) was added to a suspension of sodium hydride (60 wt. % in mineral oil) (5.577 g, 139.4 mmol) in 40 mL of DMF, and the mixture was stirred at 0 °C for 45 min. Benzyl bromide (10.3 mL, 86.6 mmol) was added, and stirring was continued at 0 °C for 40 min. The mixture was diluted with ether, washed with 10% aqueous HCl, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. This was dissolved in 50 mL of chloroform, *Se*-phenyl *p*-tolueneselenosulfonate[34] (8.827 g, 28.38 mmol) was added, and the mixture was subjected to selenosulfonation and selenoxide elimination as in the preparation of **1d** to afford 4.538 g (51%) of **1h**: mp 54−55 °C (from dichloromethane−hexanes); IR (KBr) 2206, 1293, 1161 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.89 (d, J = 8.5 Hz, 2 H), 7.42−7.23 (m, 7 H,), 4.51 (s, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 2.67 (t, J = 6.7 Hz, 2 H), 2.46 (s, 3 H); ^{13}C NMR (50 MHz) δ 144.9, 138.6, 137.3, 129.6, 128.1, 127.4, 127.2, 126.9, 94.0, 78.7, 72.6, 66.0, 21.4, 20.2; MS(EI) *m*/*z* (%) 314 (M^+, 4), 207 (44), 91 (100). Anal. Calcd for $C_{18}H_{18}O_3S$: C, 68.76; H, 5.77. Found: C, 68.58; H, 5.95.

Compound **1i** was prepared in the same manner from 4-pentyn-1-ol in 75% yield as an oil: IR (film) 2209, 1293, 1156 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.87 (d, J = 8.4 Hz, 2 H), 7.41−7.27 (m, 7 H), 4.46 (s, 2 H), 3.49 (t, J = 5.9 Hz, 2 H), 2.51 (t, J = 7.1 Hz, 2 H), 2.46 (s, 3 H), 1.85 (quintet, J = 6.5 Hz, 2 H); ^{13}C NMR (50 MHz) δ 144.9, 138.9, 137.9, 129.7, 128.1, 127.4, 127.3, 127.0, 96.5, 78.4, 72.8, 67.8, 27.1, 21.5, 15.7; MS(EI) *m*/*z* (%) 328 (M^+, 4), 173 (76), 171 (98), 91 (100); HRMS calcd for $C_{19}H_{20}O_3S$ 328.1133, found 328.1133.

Cyclization of Chloroamines with Acetylenic Sulfones (see Table 1). A sample procedure is provided below for the preparation of **12** in entry 1, as well as characterization data for the other products. The other entries in the Table were carried out in the same manner as entry 1, except for changes in conditions during the conjugate addition step as listed in the table.

1-Benzyl-2-*n*-butyl-3-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridine (12). Chloroamine **8a**[10] was liberated from its hydrochloride (131 mg, 0.595 mmol) by treatment with aqueous KOH solution, extraction with dichloromethane, drying ($MgSO_4$), and concentration by rotatory evaporator without heating. A solution of the resulting free base and 1-(*p*-toluenesulfonyl)-1-hexyne (**1c**) (126 mg, 0.534 mmol) in 3 mL of benzene was refluxed for 18.5 h and concentrated in vacuo. The residue was dissolved in 3 mL of THF and added to 1.07 mmol of LDA in 3 mL of THF at −78 °C. The mixture was stirred at −78 °C for 15 min and was then quenched by filtration through neutral alumina. The filtrate was concentrated in vacuo, and the residue was chromatographed (elution with 10% ethyl acetate−hexanes) to afford 211 mg (94%) of **12** (based on **1c**) as an oil: IR (film) 1566, 1276, 1127 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.76 (d, J = 8.2 Hz, 2 H), 7.39−7.25 (m, 5 H), 7.13 (d, J = 7.1 Hz, 2 H), 4.40 (s, 2 H), 3.08 (t, J = 5.6 Hz, 2 H), 2.84−2.72 (m, 2 H), 2.52 (t, J = 6.3 Hz, 2 H), 2.42 (s, 3 H), 1.82−1.72 (m, 2 H), 1.50−1.38 (m, 2 H), 1.37−1.22 (m, 2 H), 0.85 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) 155.6, 142.1, 141.7, 137.3, 129.0, 128.5, 127.1, 126.1, 125.8, 100.1, 53.5, 48.5, 31.3, 28.3, 24.7, 22.6, 21.3, 21.1, 13.4; MS(EI) *m*/*z* (%) 383 (M^+, 34), 277 (100), 228 (84); HRMS calcd for $C_{23}H_{29}NO_2S$ 383.1919, found 383.1927.

(+)-(6*S*)-1-Benzyl-6-methyl-2-*n*-propyl-3-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridine (13): oil; IR (film) 1557, 1280, 1127 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.76 (d, J = 8.4 Hz, 2 H), 7.42−7.24 (m, 5 H), 7.13 (d, J = 8.2 Hz, 2 H), 4.66 (d, J = 16.4 Hz, 1 H), 4.21 (d, J = 16.9 Hz, 1 H), 3.39−3.22 (m, 1 H), 3.09 (ddd, J = 14.4, 10.3, 5.1 Hz, 1 H), 2.70−2.29 (m, 3 H), 2.42 (s, 3 H), 1.75−1.32 (m, 4 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz) δ 153.9, 142.0, 141.6, 137.7, 128.9, 128.4, 127.0, 125.9, 125.7, 98.9, 51.6, 51.1, 30.5, 26.3, 22.6, 21.1, 20.4, 16.8, 13.8; MS(EI) *m*/*z* (%) 383 (M^+, 24), 228 (62), 200 (55), 91 (100); HRMS calcd for $C_{23}H_{29}NO_2S$ 383.1919, found 383.1932; $[\alpha]^{18}_D$ +68.5 (*c* 1.53, $CHCl_3$).

(−)-(7a*S*)-3-*n*-Butyl-2-(*p*-toluenesulfonyl)-$\Delta^{2,3}$-pyrrolizidine (14): mp 78−79 °C (from dichloromethane−hexanes); IR (KBr) 1567, 1282, 1123 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.69 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 3.77−3.66 (m, 1 H), 3.22 (dt, J = 10.9, 7.6 Hz, 1 H), 3.18−3.04 (m, 2 H), 2.76−2.62 (m, 2 H), 2.39 (s, 3 H), 2.20−2.10 (m, 1 H), 1.90−1.67 (m, 3 H), 1.62−1.48 (m, 1 H), 1.47−1.29 (m, 4 H), 0.91 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz) 163.1, 142.3, 140.5, 129.3, 126.3, 104.2, 62.6, 46.4, 33.3, 31.0, 30.3, 25.8, 24.9, 22.6, 21.4, 13.8; MS(EI) *m*/*z* (%) 319 (M^+, 37), 290 (42), 213 (100), 120 (99), 91 (75); $[\alpha]^{19}_D$ −356.7 (*c* 1.19, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.39. Found: C, 67.39; H, 7.94; N, 4.39.

(−)-(8a*S*)-5-*n*-Propyl-6-(*p*-toluenesulfonyl)-$\Delta^{5,6}$-indolizidine (15): mp 95−96 °C (from dichloromethane−hexanes); IR (KBr) 1551, 1282, 1123 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.72 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 3.58−3.42 (m, 1 H), 3.40−3.15 (m, 2 H), 2.98−2.78 (m, 1 H), 2.68−2.22 (m, 3 H), 2.39 (s, 3 H), 2.21−2.00 (m, 2 H), 1.99−1.09 (m, 6 H), 0.97

(34) (a) Back, T. G. In *Organoselenium Chemistry−A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 5, p 105. (b) Back, T. G.; Collins, S.; Krishna, M. V. *Can. J. Chem.* **1987**, *65*, 38.

(35) Compound **1d** was reported previously (ref 18c), but no spectroscopic data was provided.

(36) Iwata, N.; Morioka, T.; Kobayashi, T.; Asada, T.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1379.

(t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz) δ 154.6, 142.2, 141.4, 128.9, 125.8, 97.0, 57.9, 46.9, 32.0, 27.4, 25.1, 23.6, 22.3, 21.2, 14.2; MS(EI) *m*/*z* (%) 319 (M^+, 40), 227 (91), 164 (100), 91 (68); $[\alpha]^{20}_D$ −246.7 (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.39. Found: C, 67.91; H, 7.80; N, 4.42.

(−)-(8a*S*)-5-*n*-Butyl-6-(*p*-toluenesulfonyl)-Δ^{5,6}-indolizidine (16): mp 109−110 °C (from dichloromethane−hexanes); IR (KBr) 1541, 1281, 1128 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.69 (d, J = 8.2 Hz, 2 H), 7.21 (d, J = 8.1 Hz, 2 H), 3.47 (br t, J = 8.8 Hz, 1 H), 3.33−3.25 (m, 1 H), 3.25−3.15 (m, 1 H), 2.89−2.78 (m, 1 H), 2.58 (br dd, J = 16.1, 3.9 Hz, 1 H), 2.51−2.41 (m, 1 H), 2.37 (s, 3 H), 2.37−2.29 (m, 1 H), 2.16−2.02 (m, 2 H), 1.98−1.88 (m, 1 H), 1.87−1.72 (m, 1 H), 1.60−1.30 (m, 5 H), 1.28−1.13 (m, 1 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz) 155.0, 142.5, 141.6, 129.1, 126.0, 97.4, 58.1, 47.0, 32.2, 31.0, 30.0, 27.6, 25.2, 23.7, 23.0, 21.3, 13.7; MS(EI) *m*/*z* (%) 333 (M^+, 18), 227 (100); $[\alpha]^{20}_D$ −245.4 (*c* 1.31, $CHCl_3$). Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16; N, 4.20. Found: C, 68.12; H, 7.89; N, 4.11.

(−)-(8a*S*)-5-*n*-Hexyl-6-(*p*-toluenesulfonyl)-Δ^{5,6}-indolizidine (17): mp 75−76 °C (from dichloromethane−hexanes); IR (KBr) 1559, 1291, 1149 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.72 (d, J = 8.1 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 3.55−3.45 (m, 1 H), 3.38−3.17 (m, 2 H), 2.95−2.79 (m, 1 H), 2.67−2.56 (m, 1 H), 2.52−2.30 (m, 2 H), 2.39 (s, 3 H), 2.18−2.02 (m, 2 H), 2.00−1.90 (m, 1 H), 1.88−1.73 (m, 1 H), 1.63−1.15 (m, 10 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (50 MHz) δ 154.9, 142.4, 141.5, 129.0, 125.9, 97.2, 58.0, 46.9, 32.1, 31.3, 30.2, 29.5, 28.9, 27.5, 25.2, 23.6, 22.4, 21.2, 13.9; MS(EI) *m*/*z* (%) 361 (M^+, 23), 227 (100), 206 (61), 136 (61), 91 (60); HRMS calcd for $C_{21}H_{31}NO_2S$ 361.2076, found 361.2105; $[\alpha]^{19}_D$ −224.1 (*c* 0.83, $CHCl_3$).

(−)-(8*R*,8a*S*)-8-Methyl-5-*n*-pentyl-6-(*p*-toluenesulfonyl)-Δ^{5,6}-indolizidine (18): oil; IR (film) 1561, 1283, 1127 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.72 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 7.9 Hz, 2 H), 3.60−3.45 (m, 1 H), 3.40−3.22 (m, 1 H), 2.95−2.75 (m, 2 H), 2.58 (dd, J = 15.8, 4.7 Hz, 1 H), 2.52−2.45 (m, 1 H), 2.39 (s, 3 H), 2.21−1.75 (m, 3 H), 1.65−1.18 (m, 9 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.88 (br t, J = 6.9 Hz, 3 H); ^{13}C NMR (50 MHz) δ 154.6, 142.4, 141.4, 128.9, 125.8, 97.0, 63.7, 47.2, 33.4, 32.4, 31.9, 31.0, 30.0, 28.5, 23.6, 22.1, 21.2, 17.8, 13.8; MS(EI) *m*/*z* (%) 361 (M^+, 1), 240 (100); HRMS calcd for $C_{21}H_{31}NO_2S$ 361.2076, found 361.2053; $[\alpha]^{23}_D$ −190.0 (*c* 1.26, $CHCl_3$).

(−)-(8*R*,8a*S*)-5-(2-Benzyloxyethyl)-8-methyl-6-(*p*-toluenesulfonyl)-Δ^{5,6}-indolizidine (19): oil; IR (film) 1547, 1284, 1147 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.49 (d, J = 8.1 Hz, 2 H), 7.40−7.25 (m, 5 H), 7.23 (d, J = 8.0 Hz, 2 H), 4.56 (d, J = 12.0 Hz, 1 H), 4.52 (d, J = 12.0 Hz, 1 H), 3.86−3.75 (m, 1 H), 3.74−3.60 (m, 2 H), 3.40−3.25 (m, 2 H), 3.00−2.81 (m, 2 H), 2.54 (dd, J = 15.9, 4.5 Hz, 1 H), 2.40 (s, 3 H), 2.20−2.10 (m, 1 H), 2.03−1.85 (m, 2 H), 1.82−1.65 (m, 1 H), 1.45−1.18 (m, 2 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 151.2, 142.1, 141.9, 138.6, 129.3, 128.3, 127.6, 127.5, 126.2, 98.5, 73.0, 70.0, 64.1, 48.2, 33.5, 32.5, 31.3, 30.9, 23.7, 21.4, 17.9; MS(EI) *m*/*z* (%) 425 (M^+, 0.1), 264 (26), 252 (100), 162 (75), 107 (81); HRMS calcd for $C_{25}H_{31}NO_3S$ 425.2025, found 425.2031; $[\alpha]^{21}_D$ −161.1 (*c* 1.00, $CHCl_3$).

(−)-(8*R*,8a*S*)-5-(3-Benzyloxypropyl)-8-methyl-6-(*p*-toluenesulfonyl)-Δ^{5,6}-indolizidine (20): oil; IR (film) 1562, 1283, 1127 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.42−7.30 (m, 5 H), 7.23 (d, J = 7.9 Hz, 2 H), 4.53 (s, 2 H), 3.68−3.48 (m, 3 H), 3.40−3.25 (m, 1 H), 3.08−2.78 (m, 2 H), 2.72−2.49 (m, 2 H), 2.40 (s, 3 H), 2.25−1.68 (m, 6 H), 1.50−1.19 (m, 2 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 154.1, 142.1, 141.4, 138.3, 129.0, 128.0, 127.1, 127.1, 125.7, 97.2, 72.4, 69.7, 63.7, 47.2, 33.3, 32.3, 30.9, 29.0, 27.0, 23.5, 21.1, 17.7; MS(EI) *m*/*z* (%) 439 (M^+, 0.6), 240 (100); HRMS calcd for $C_{26}H_{33}NO_3S$ 439.2181, found 439.2191; $[\alpha]^{19}_D$ −150.5 (*c* 2.11, $CHCl_3$).

(±)-3-*n*-Butyl-2-(*p*-toluenesulfonyl)-Δ^{2,3}-indolizidine (21): mp 118−119 °C (from dichloromethane−hexanes); IR (KBr) 1556, 1286, 1136 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 3.50 (br d, J = 13.5 Hz, 1 H), 3.41−3.29 (m, 1 H), 2.80 (dd, J = 13.3, 10.3 Hz, 1 H), 2.80−2.53 (m, 3 H), 2.39 (s, 3 H), 2.27 (dd, J = 13.3, 9.7 Hz, 1 H), 1.88−1.78 (m, 1 H), 1.77−1.61 (m, 2 H), 1.50−1.32 (m, 7 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz) 160.7, 141.5, 141.1, 128.9, 125.6, 98.2, 61.3, 44.1, 34.5, 31.1, 29.9, 25.4, 23.7, 23.4, 22.5, 21.0, 13.4; MS(EI) *m*/*z* (%) 333 (M^+, 19), 227 (100), 178 (46). Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16; N, 4.20. Found: C, 68.10; H, 8.29; N, 4.15.

(±)-3-(*p*-Toluenesulfonyl)-Δ^{3,4}-quinolizidine (22): mp 127−129 °C (from dichloromethane−hexanes); IR (KBr) 1617, 1282, 1159 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 9.4 Hz, 2 H), 7.17 (s, 1 H), 3.33 (br d, J = 12.7 Hz, 1 H), 3.01 (dt, J = 12.5, 2.8 Hz, 1 H), 2.92−2.82 (m, 1H), 2.40 (s, 3 H), 2.25−2.12 (m, 2 H), 1.93−1.80 (m, 2 H), 1.74−1.64 (m, 2 H), 1.63−1.34 (m, 3 H), 1.32−1.28 (m, 1 H); ^{13}C NMR (100 MHz) 144.6, 142.2, 139.4, 129.3, 126.8, 102.4, 53.9, 52.9, 31.4, 28.6, 25.8, 23.9, 21.3, 19.0; MS(EI) *m*/*z* (%) 291 (M^+, 59), 136 (100), 91 (32). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26; N, 4.81. Found: C, 65.97; H, 7.04; N, 4.71.

(±)-4-*n*-Butyl-3-(*p*-toluenesulfonyl)-Δ^{3,4}-quinolizidine (23): mp 102−103 °C (from dichloromethane−hexanes); IR (KBr) 1548, 1283, 1183, 1124 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.1 Hz, 2 H), 3.76 (br d, J = 13.5 Hz, 1 H), 3.07−2.99 (m, 1 H), 2.81−2.50 (m, 3 H), 2.58−2.42 (m, 2 H), 2.40 (s, 3 H), 1.90−1.80 (m, 2 H), 1.72−1.22 (m, 10 H), 0.86 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) 155.3, 142.4, 141.6, 129.0, 125.7, 101.0, 56.6, 47.8, 32.1, 30.7, 28.4, 28.2, 26.4, 24.2, 22.5, 22.0, 21.1, 13.5; MS(EI) *m*/*z* (%) 347 (M^+, 27), 241 (100), 192 (88), 150 (79), 91 (77). Anal. Calcd for $C_{20}H_{29}NO_2S$: C, 69.12; H, 8.41; N, 4.03. Found: C, 69.48; H, 8.27; N, 3.98.

(±)-4-Phenyl-3-(*p*-toluenesulfonyl)-Δ^{3,4}-quinolizidine (24): mp 123−126 °C (from dichloromethane−hexanes); IR (KBr) 1566, 1294, 1148 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.38−7.20 (m, 3 H), 7.34 (d, J = 8.2 Hz, 2 H), 7.15−7.02 (m, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 3.20−3.10 (m, 1 H), 2.97 (br d, J = 13.3 Hz, 1 H), 2.70 (ddd, J = 15.9, 6.8, 4.8 Hz, 1 H), 2.59 (ddd, J = 15.8, 8.5, 4.8 Hz, 1 H), 2.48 (dt, J = 13.0, 2.3 Hz, 1 H), 2.37 (s, 3 H), 2.02−1.90 (m, 1 H), 1.87−1.75 (m, 1 H), 1.74−1.56 (m, 2 H), 1.52−1.33 (m, 3 H), 1.30−1.15 (m, 1 H); ^{13}C NMR (100 MHz) 154.3, 141.6, 141.6, 134.7, 129.8, 128.9, 128.8, 128.2, 127.5, 127.4, 126.4, 103.9, 56.6, 49.4, 32.4, 28.8, 26.2, 24.2, 21.8, 21.3; MS(EI) *m*/*z* (%) 367 (M^+, 48), 212 (64), 210 (100), 91 (43). Anal. Calcd for $C_{22}H_{25}NO_2S$: C, 71.90; H, 6.86; N, 3.81. Found: C, 71.81; H, 6.59; N, 3.79.

(±)-4-(2-*tert*-Butyldimethylsilyloxy)ethyl-3-(*p*-toluenesulfonyl)-Δ^{3,4}-quinolizidine (25): oil; IR (film) 1561, 1283, 1178 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 4.01 (br d, J = 13.4 Hz, 1 H), 3.77−3.63 (m, 2 H), 3.18−2.90 (m, 3 H), 2.73 (dt, J = 12.9, 2.1 Hz, 1 H), 2.50−2.42 (m, 2 H), 2.40 (s, 3 H), 1.88−1.77 (m, 2 H), 1.71−1.64 (m, 1 H), 1.63−1.27 (m, 5 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) 152.2, 142.1, 142.0, 129.3, 126.1, 102.5, 62.6, 57.1, 48.6, 32.5, 32.1, 28.7, 26.7, 26.0, 24.5, 22.3, 21.4, 18.3, −5.3; MS(EI) *m*/*z* (%) 449 (M^+, 1), 252 (97), 160 (100); HRMS calcd for $C_{24}H_{39}NO_3SiS$ 449.2420, found 449.2417.

(±)-4-(1-Cyclohexenyl)-3-(*p*-toluenesulfonyl)-Δ^{3,4}-quinolizidine (26): oil; IR (film) 1554, 1285, 1131 cm^{-1}; ^{1}H NMR (400 MHz) separate signals attributed to *cisoid* and *transoid* conformers of **26** were present in a ca. 1:1 ratio, δ 7.63 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H), 5.19 (br s, 1 H), 5.14 (br s, 1 H); other signals overlapped; ^{13}C NMR (100 MHz) signals of the two conformers could not be unequivocally assigned and are listed together, δ 157.3, 156.6, 143.1, 142.9, 141.3, 133.1, 132.8, 129.1, 128.7, 128.6, 128.2, 126.0, 100.8, 99.8, 56.3, 55.3, 48.4, 48.3, 32.5, 32.3, 29.5, 29.0, 28.9, 27.9, 26.6, 26.3, 24.9, 24.2, 22.0, 21.9, 21.2, 21.1, 21.0; MS(EI) *m*/*z* (%) 371 (M^+, 4), 216 (44), 83 (100); HRMS calcd for $C_{22}H_{29}NO_2S$ 371.1919, found 371.1903.

(−)-Indolizidine 167B (31). Trifluoroacetic acid (1.0 mL, 13 mmol) was added dropwise to a suspension of **15** (422 mg, 1.32 mmol) and sodium cyanoborohydride (835 mg, 13.3 mmol) in 15 mL of dichloromethane, and the mixture was stirred at room temperature for 30 min and refluxed for 30 min. It was washed with aqueous KOH solution, dried ($MgSO_4$), and concentrated in vacuo to provide a yellow oil. This was dissolved in 3.5 mL of THF and 30 mL of liquid ammonia. Sodium (912 mg, 39.7 mg-atom) was added, and the mixture

was stirred at −33 °C for 15 min. Solid ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was dissolved in 10% HCl solution and washed with ether. The aqueous layer was basified with KOH, and the product was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo to provide crude **31**, containing ca. 5% of a byproduct tentatively assigned as the $\Delta^{6,7}$-derivative **29**, on the basis of the observation of its olefinic signals in the ^{1}H NMR spectrum. The mixture was hydrogenated in 4 mL of ethanol over 10% palladium on charcoal (32 mg) at room temperature and at 1 atm for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was treated with 3.0 mL of 1 M HCl−ether, and the resulting solid was recrystallized from ethanol−ether, basified with aqueous KOH solution, extracted with dichloromethane, dried ($MgSO_4$), and concentrated in vacuo to afford 132 mg (60%) of (−)-indolizidine **167B** (**31**) as a yellow oil: ^{1}H NMR (200 MHz) δ 3.26 (dt, J = 8.3, 2.2 Hz, 1 H), 2.05−1.55 (m, 10 H), 1.54−1.02 (m, 7 H), 0.90 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 64.9, 63.6, 51.5, 36.8, 30.9, 30.8, 30.5, 24.6, 20.3, 19.0, 14.4; MS(EI) m/z (%) 167 (M^+, 4), 124 (100); $[\alpha]^{20}_D$ −106.9 (*c* 1.10, CH_2Cl_2); lit.[25b] $[\alpha]^{25}_D$ −116.6 (*c* 0.0042, CH_2Cl_2); lit.[25c] $[\alpha]^{24}_D$ −112 (*c* 1.25, CH_2Cl_2); lit.[25e] $[\alpha]^{20}_D$ −115 (*c* 1.16, CH_2Cl_2); lit.[25h] $[\alpha]_D$ −111.3 (*c* 1.3, CH_2Cl_2).

(−)-Indolizidine 209D (32). Following the preceding procedure, cyclic enamine **17** was reduced to crude **32** containing a trace of the corresponding $\Delta^{6,7}$ unsaturated derivative **30**. Hydrogenation and chromatography of the crude product (elution with 17% ether−hexanes) afforded 74% of (−)-indolizidine **209D** (**32**) as a colorless oil: ^{1}H NMR (200 MHz) δ 3.27 (dt, J = 8.4, 2.1 Hz, 1 H), 2.05−1.55 (m, 10 H), 1.54−1.05 (m, 13 H), 0.88 (t, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz) δ 65.0, 63.9, 51.5, 34.6, 31.8, 31.0, 30.9, 30.5, 29.7, 25.8, 24.7, 22.6, 20.4, 14.1; MS(EI) m/z (%) 209 (M^+, 0.7), 124, 100); $[\alpha]^{19}_D$ −84.9 (*c* 0.98, CH_2Cl_2); lit.[25c] $[\alpha]^{26}_D$ −80.6 (*c* 1.15, CH_2Cl_2); lit.[26b] $[\alpha]_D$ −83.6 (*c* 0.77, CH_2Cl_2); lit.[25f] $[\alpha]^{20}_D$ −76.5 (*c* 0.74, CH_2Cl_2); lit.[25h] $[\alpha]_D$ −80.4 (*c* 1, CH_2Cl_2); lit.[26c] $[\alpha]^{20}_D$ −87.6 (*c* 1, CH_2Cl_2); lit.[26d] $[\alpha]^{25}_D$ −89.64 (*c* 1.880, CH_2Cl_2).

(−)-Indolizidine 209B (33). Following the procedure described for the preparation of **31**, cyclic enamine **18** was reduced to crude **33**, which did not contain any of the corresponding $\Delta^{6,7}$ unsaturated derivative. Chromatography (elution with 2% triethylamine−hexanes) afforded 66% of (−)-indolizidine **209B** (**33**) as a pale yellow oil: ^{1}H NMR (400 MHz) δ 3.27 (dt, J = 8.7, 2.0 Hz, 1 H), 2.01−1.82 (m, 3 H), 1.88−1.55 (m, 5 H), 1.54−1.15 (m, 11 H), 1.02−0.92 (m, 1 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 71.3, 63.5, 51.8, 36.5, 34.6, 33.7, 32.2, 31.2, 29.0, 25.4, 22.6, 20.3, 18.8, 14.0; MS(EI) m/z (%) 209 (M^+, 1.4), 138 (100); $[\alpha]^{21}_D$ −87.7 (*c* 1.26, MeOH); lit.[27b] $[\alpha]_D$ −96.5 (*c* 0.62, MeOH); lit.[26b] $[\alpha]_D$ −91.0 (*c* 0.55, MeOH); lit.[27c] $[\alpha]^{24}_D$ −90.1 (*c* 1.38, MeOH); lit.[16] $[\alpha]^{20}_D$ −95 (*c* 0.585, MeOH); lit.[27d] $[\alpha]^{28}_D$ −91.3 (*c* 0.58, MeOH); lit.[27e] $[\alpha]^{20}_D$ −94.3 (*c* 1.85, MeOH).

(−)-(5*S*,8*R*,8a*S*)-5-(3-Hydroxypropyl)-8-methylindolizidine (34). Following the procedure described for the preparation of **31**, cyclic enamine **20** was reduced to crude **34** containing a trace of the corresponding $\Delta^{6,7}$ unsaturated derivative. After hydrogenation, the product was subjected to Kugelrohr distillation (bp 130−140 °C at 0.05 mmHg) to afford 66% of **34** as a colorless oil: IR (film) 3287 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.75−3.45 (m, 2 H), 3.28 (dt, J = 8.5, 2.2 Hz, 1 H), 2.15−1.18 (m, 16 H), 1.10−0.91 (m, 1 H), 0.86 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz) δ 71.0, 62.5, 61.9, 51.5, 35.8, 33.3, 31.3, 29.6, 28.6, 28.0, 19.9, 18.6; MS(EI) m/z (%) 196 ($M^+ - 1$, 0.2), 138 (100); HRMS calcd for $C_{12}H_{22}NO$ ($M^+ - 1$) 196.1701, found 196.1697; $[\alpha]^{18}_D$ −65.4 (*c* 1.10, $CHCl_3$).

(−)-(5*S*,8*R*,8a*S*)-5-(3-Chloropropyl)-8-methylindolizidine Hydrochloride (35) and Its Cyclization to the Quaternary Ammonium Salt 36. HCl gas was bubbled through a solution of alcohol **34** (560 mg, 2.84 mmol) in 8 mL of chloroform at 0 °C. Thionyl chloride (0.630 mL, 8.63 mmol) was then added, and the mixture was refluxed for 4 h and concentrated in vacuo. The residue was triturated with methanol (5.0 mL) and refluxed with a small amount of decolorizing charcoal for 30 min. It was filtered through Celite, and the filtrate was concentrated in vacuo to give a yellow solid, which was recrystallized from ethanol−ether to afford 599 mg (84%) of the hydrochloride salt **35** as white crystals: mp 265−267 °C; $[\alpha]^{23}_D$ −27.2 (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{12}H_{23}NCl_2$: C, 57.14; H, 9.19; N, 5.56. Found: C, 56.79; H, 9.07; N, 5.54.

Basification of **35** with aqueous KOH solution, extraction with chloroform, drying ($MgSO_4$), and concentration in vacuo provided a quantitative yield of the quaternary salt **36** as a colorless oil: ^{1}H NMR (400 MHz) δ 4.52−4.39 (m, 1 H), 4.10−3.97 (m, 1 H), 3.82 (dt, J = 12.0, 5.6 Hz, 1 H), 3.70 (t, J = 9.6 Hz, 1 H), 3.53−3.39 (m, 1 H), 3.35−3.20 (m, 1 H), 2.45−2.15 (m, 6 H), 2.00−1.80 (m, 4 H), 1.78−1.48 (m, 3 H), 1.03 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 74.0, 69.7, 61.4, 49.4, 30.9, 28.9, 27.7, 27.4, 25.0, 18.3, 17.9, 17.8.

(−)-(5*S*,8*R*,8a*S*)-5-(2-Hydroxyethyl)-8-methylindolizidine (37). Following the procedure described for the preparation of **31**, cyclic enamine **19** was reduced to crude **37** containing a trace of the corresponding $\Delta^{6,7}$ unsaturated derivative. After hydrogenation, the crude product was subjected to Kugelrohr distillation (bp 110−130 °C at 0.05 mmHg) to afford 66% of **37** as a colorless oil: IR (film) 3600−3100 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.15 (br s, 1 H), 3.97 (dt, J = 10.5, 4.4 Hz, 1 H), 3.77−3.62 (m, 1 H), 3.47 (dt, J = 8.5, 2.7 Hz, 1 H), 2.38−2.21 (m, 1 H), 2.18−1.18 (m, 12 H), 1.15−0.95 (m, 1 H), 0.88 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz) δ 71.3, 61.0, 59.5, 51.9, 35.9, 34.8, 33.2, 29.8, 28.7, 19.9, 18.6; MS(EI) m/z (%) 183 (M^+, 0.7), 182 (1), 138 (100); HRMS calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1622; $[\alpha]^{21}_D$ −42.4 (*c* 1.32, $CHCl_3$).

(−)-(5*S*,8*R*,8a*S*)-5-(2-Chloroethyl)-8-methylindolizidine Hydrochloride (38). Following the procedure for the preparation of **35**, the hydrochloride salt of **38** was obtained as a white solid in 74% yield: mp 153−154 °C (from ethanol−ether); $[\alpha]^{21}_D$ −70.0 (*c* 0.40, $CHCl_3$). Anal. Calcd for $C_{11}H_{21}NCl_2$: C, 55.46; H, 8.89; N, 5.88. Found: C, 55.12; H, 8.78; N, 5.83. The free base of **38** was used immediately in the next step: ^{1}H NMR (200 MHz) δ 3.72−3.45 (m, 2 H), 3.23 (dt, J = 8.2, 2.6 Hz, 1 H), 2.28−1.18 (m, 13 H), 1.11−0.92 (m, 1 H), 0.87 (d, J = 6.3 Hz, 3 H).

(−)-Indolizidine 207A (40). Diallyl dilithium cyanocuprate (**39**) was prepared according to a literature procedure.[29] An ethereal solution of methyllithium (6.0 mL, 1.4 M, 8.4 mmol) was added to a suspension of copper(I) cyanide (379 mg, 4.23 mmol) in 4.0 mL of THF at −78 °C, and the resulting clear solution was stirred at 0 °C for 5 min. Allyltri-*n*-butylstannane (2.68 mL, 8.65 mmol) was then added, and the resulting yellow mixture was stirred at 0 °C for 50 min. The hydrochloride salt of **38** (101 mg, 0.424 mmol) was dissolved in dichloromethane, washed with aqueous KOH solution, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. It was dissolved in THF (3 mL) and added to the solution containing the cuprate at −78 °C. After 15 min, the mixture was warmed to 0 °C and stirred for 1 h. It was diluted with 10% HCl and washed with ether. The aqueous layer was basified with KOH, and the product was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (elution with 5% triethylamine−hexanes) provided 53 mg (60%) of (−)-indolizidine **207A** (**40**) as a light yellow oil: ^{1}H NMR (400 MHz) δ 5.81 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 5.01 (br d, J = 17.1 Hz, 1 H), 4.95 (br d, J = 10.2 Hz, 1 H), 3.27 (dt, J = 8.3, 2.4 Hz, 1 H), 2.15−1.82 (m, 5 H), 1.81−1.59 (m, 5 H), 1.55−1.18 (m, 7 H), 1.10−0.91 (m, 1 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 138.8, 114.4, 71.3, 63.3, 51.8, 36.5, 34.1, 33.7, 31.3, 29.1, 25.1, 20.3, 18.8; MS(EI) m/z (%) 207 (M^+, 2.4), 138 (100); $[\alpha]^{21}_D$ −83.5 (*c* 1.36, $CHCl_3$); lit.[28a] $[\alpha]^{22.5}_D$ −103.2 (*c* 0.47, $CHCl_3$); lit.[28b] $[\alpha]_D$ −85.25 (*c* 0.174, EtOH); lit.[27d] $[\alpha]^{28}_D$ −86.5 (*c* 0.95, $CHCl_3$).

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Supporting Information Available: ^{1}H- and ^{13}C NMR spectra of new compounds that do not have elemental analyse and of (−)-indolizidines **167B**, **209D**, **209B** and **207A** (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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