Enantioselective Total Syntheses of Indolizidine Alkaloids (-)-205A and (-)-235B

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Enantioselective total syntheses of indolizidine alkaloids (-)-**205A** and (-)-**235B** are described. The syntheses proceed via a common late-stage intermediate, α-aminonitrile **1**. Absolute stereochemical control over the C8 and C8a stereocenters in these materials was achieved by a stereoselective crotylation reaction between chiral acyliminium ion (*R*)-**3b** and crotylmagnesium chloride. The selectivity of this reaction, which produced the (future)-8*R*,8a*S* configuration was complementary to the result obtained by crotylation of acyliminium ion (*S*)-**3a** with *trans*-crotyltrimethylsilane, which produced predominantly an adduct with the (future)-8*S*,8a*S* configuration. This latter crotyl lactam was converted to two additional diastereomers of alkaloid **205A**. Comparison of the ^1H and ^{13}C NMR and optical rotation values of the four synthetic diastereomers of **205A** with literature values supported the proposed assignment of the absolute and relative configuration of (-)-**205A**. The ^{13}C spectrum of synthetic (5*R*,8*R*,8a*S*)-**235B** was identical with that of natural **235B** and supported the proposed assignment of relative configuration of the alkaloid. The optical rotation differed in sign and magnitude from the published value. Revised values of the optical rotations of (-)-**205A** and (-)-**235B** are suggested. This work constitutes the first enantioselective syntheses of **205A** and **235B**, which were prepared in 15 and 14 steps, respectively, from succinic anhydride, in an average overall yield of 17%.

The indolizidine alkaloids constitute a family of natural products that have been detected in extracts from the skins of neotropical frogs.[1] We have been interested in preparing various indolizidine alkaloids (a) because of their activity as noncompetitive inhibitors of the acetylcholine receptor complex, (b) to unambiguously confirm their proposed structures, and (c) as an instrument for evaluating transition-state geometries of nucleophilic addition to the carbon-nitrogen double bond in chiral environments.[2] Our previous paper[3] described enantioselective syntheses of the simplest indolizidine alkaloids: **167B** and **209D**. This paper details results of addition of crotyl metal reagents to chiral acyliminium ions **3**, assignment of the absolute and relative stereochemistry of the products, and conversion of the appropriate crotyl lactams to alkaloids (-)-**205A**[4] and (-)-**235B**.[4]

The utilization of acyliminium ions in the syntheses of many diverse alkaloid structural types has been well established.[5] The study of bimolecular nucleophilic addition reactions of prochiral acyliminium ions with chiral nucleophiles[6] and chiral acyliminium ions with achiral[2,7] and prochiral[8] nucleophiles is an area undergoing significant development.

The key aspect of our present study was to determine conditions to effect a diastereoselective reaction between chiral acyliminium ions **3** and a prochiral crotyl metal reagent. The product of this reaction was required to possess the (future) 8*R*,8a*S* configuration present in **205A** and **235B**. It was assumed that processing of this crotyl lactam intermediate according to the protocol developed earlier in our **167B** and **209D** syntheses[3] would provide the desired natural products **205A** and **235B** (Scheme I).

Crotylation Reactions of Chiral Acyliminium Ions. At the outset it was decided to screen the reactions of both *trans*- and *cis*-crotyltrimethylsilane with chiral acyliminium ions (*S*)-**3a-c** in a search for possible diastereoselection in this process. The preparation of the hydroxy lactams **4a-c** and their conversion to acyliminium ions (*S*)-**3a-c** has been described previously.[2] *cis*- and *trans*-crotyltrimethylsilane were prepared by metalation of *cis*- and *trans*-2-butene with Schlosser's base at -45 °C, followed by quenching the allylic anions with chlorotri-

Scheme I. Retrosynthetic Analysis

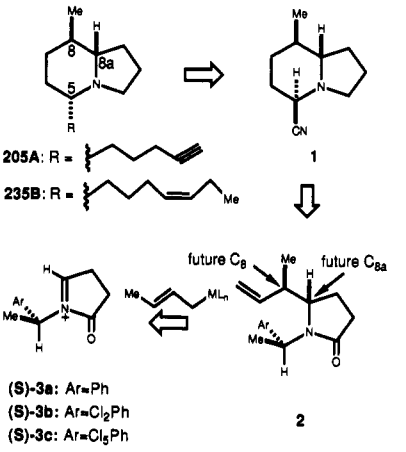
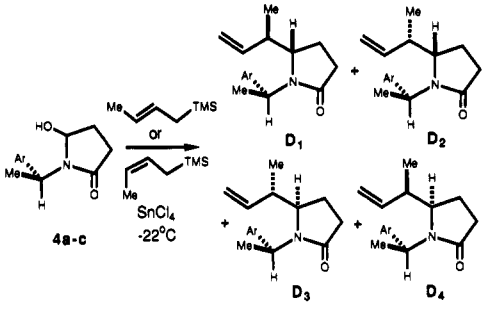


Table I



entry	Ar	silane	ratio (D_1:D_2:D_3:D_4)	yield %
1	Ph (**4a**)	(*E*)-crotyl-TMS	7:79:3:11	94
2	2,6-Cl_2Ph (**4b**)		5.5:20:13:61.5	90
3	Cl_5Ph (**4c**)		0:0:25:75	90
4	Ph (**4a**)	(*Z*)-crotyl-TMS	16.5:50.5:11:22	93
5	Cl_5Ph (**4c**)		0:0:60:40	90

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‡ Charles R. Hauser Fellow, 1989-1990.

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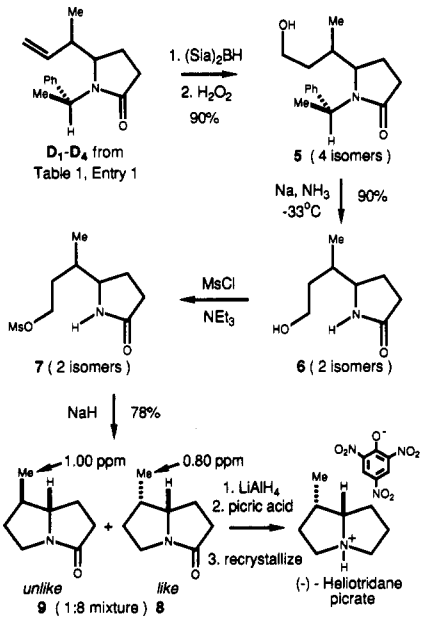
0022-3263/91/1956-4868$02.50/0

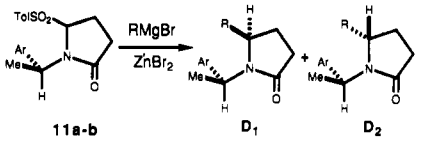
Scheme II



methylsilane.[9] The results of the crotylation reactions of acyliminium ions (*S*)-**3a–c** are presented in Table I.

Consideration of the stereoselection data reveals two trends. First, as expected,[2] chlorination of the aromatic nucleus appended to the resident stereogenic center of substrates **4** inverted the face selectivity of the intermediate acyliminium ions (*S*)-**3a–c**. It is evident from entries 1–3 that the major isomers changed from $D_1 + D_2$ to $D_3 + D_4$ with increasing chlorination of the aromatic ring in **4**. Second, *trans*-crotyltrimethylsilane tended to produce the undesired *like* (*l*) relative configuration[16] at the future C8,C8a stereocenters (isomers D_2 and D_4 in Table I), while *cis*-crotyltrimethylsilane reacted with **4a–c** to produce increased relative amounts of the desired *unlike* (*ul*) stereoisomers (D_1 and D_3 in Table I). However, even in the best reaction (entry 5, Table I) the stereoselection was only a modest 60:40. Consequently, we turned our attention to studying reactions of acyliminium ions **3a–c** with other crotyl metal reagents. Before describing those results, it is necessary to describe briefly how the configurations of various isomers D_1–D_4 appearing in Table I were assigned.

Table II

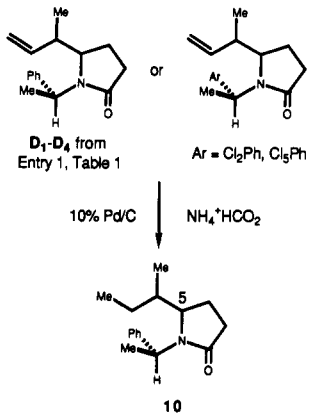


entry	Ar	R	ratio	yield (%)
1	Ph (**11a**)	allyl	40:60	80
2	2,6-Cl_2Ph (**11b**)	allyl	95:5	85
3	2,6-Cl_2Ph (**11b**)	2-propenyl	95:5	80

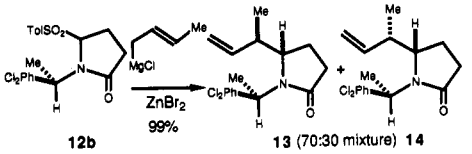
The crotyl lactam mixture generated according to entry 1 of Table I was hydroborated with disiamylborane[11] and then oxidized to afford a diastereomeric mixture of alcohols **5** in 90% yield (Scheme II). Dissolving metal reduction[12] of the α-phenethyl moiety of **5** produced pyrrolidinone **6**, which by virtue of removal of one of the stereogenic centers present in the substrate simplified to a mixture of two diastereoisomers. The primary alcohol of **6** was mesylated[13] and the resultant mesylate cyclized[14] to afford pyrrolizidinone **8** and its diastereomer **9**. As described by Hart,[15] these substances can be differentiated by distinct resonances of their methyl groups, which appear at 0.80 ppm for **8** and 1.00 ppm for **9**. The pyrrolizidinones displayed resonances at 0.80 and 1.00 ppm in a ratio of 8:1, implying that the major diastereomer resulting from entry 1 of Table I possessed the undesired *l* relative configuration. Reduction of lactams **8** + **9** with lithium aluminum hydride,[15] conversion of the resultant amines to their corresponding picrates, and separation of the diastereomeric picrates by recrystallization afforded (-)-heliotridane picrate. This result established that the predominant diastereomer produced according to entry 1 of Table I was D_2. The $[\alpha]_D$ value of -18.6° (*c* 0.9, acetone (lit.[10] -20.6° (*c* 0.9, acetone)) corresponds to an optical purity of 91%, implying that some resolution of the *l* diastereomer occurred during recrystallization. Analysis of the isomers D_1–D_4 from crotylation reactions of chlorinated hydroxy lactams **4b–c** was made after hydrogenation–hydrogenolysis[17] of these crotyl lactam mixtures over 10% Pd/C–NH_4HCO_2–MeOH and comparison of the reduced materials to the *sec*-butyl lactams **10** prepared by hydrogenation of crotyl lactams D_1–D_4 obtained from entry 1 of Table I. The full details of this diastereomer analysis are provided in the supplementary material.

We next directed our attention to the reaction[18] of hard nucleophiles with acyliminium ions (*S*)-**3**. Thus, toluenesulfonyl lactams[18a] **11a–b** were reacted with representative Grignard reagents (Table II). As documented in entries 2 and 3, the Grignard addition reactions to the acyliminium ion derived from **11b** displayed synthetically useful levels of stereoselection. The configurations of the products appearing in entries 1 and 2 of Table II were

(2) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215.
(3) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688.
(4) Isolation: Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643. A racemic synthesis of **205A** has appeared: Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696. During review of this manuscript full details of the **205A** synthesis and racemic syntheses of **235B** and **235B'** were published: Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393. Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F.; Baker, R.; Forbes, I. J.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 176. Also **209B**: Gneco, D.; Marazano, C.; Das, B. P. *Chem. Commun.* **1991**, 625.
(5) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1988; Vol. 32, Chapter 4. Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, J. W., Ed.; Wiley: New York, 1988; Vol. 6, Chapter 3.
(6) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shira, M. *Tetrahedron* **1990**, *46*, 6361 and previous papers cited therein.
(7) Wanner, K. T.; Praschak, I. *Heterocycles* **1989**, *29*, 29 and previous papers cited therein. Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891. Kiguchi, T., Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525. Thaning, M.; Wistrand, L. G. *J. Org. Chem.* **1990**, *55*, 1406. Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473.
(8) Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P. *J. Am. Chem. Soc.* **1985**, *107*, 3246.
(9) Mordini, A.; Palio, G.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1988**, *29*, 4991.
(10) Heliotridane: Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1941**, *63*, 228. Heliotridane picrate: Culvenor, C. C.; Smith, L. W. *Aust. J. Chem.* **1959**, *12*, 255.
(11) Brown, H. C.; Midland, M. M.; Molander, G. *Organic Syntheses via Boranes*; Wiley: New York, 1975.
(12) Ibuka, T.; Masaki, N.; Saji, I.; Tanaka, K.; Inubishi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2779.
(13) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(14) Heitz, M. P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.
(15) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209.
(16) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
(17) Ram, S.; EhrenKaufer, R. E. *Synthesis* **1988**, 91.
(18) (a) Brown, D. S.; Hansson, T.; Ley, S. V. *Syn. Lett.* **1990**, 48. (b) Yamada, J.; Sato, H.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 5611. (c) Skrinjar, M.; Wistrand, L. G. *Tetrahedron Lett.* **1990**, *31*, 1775.



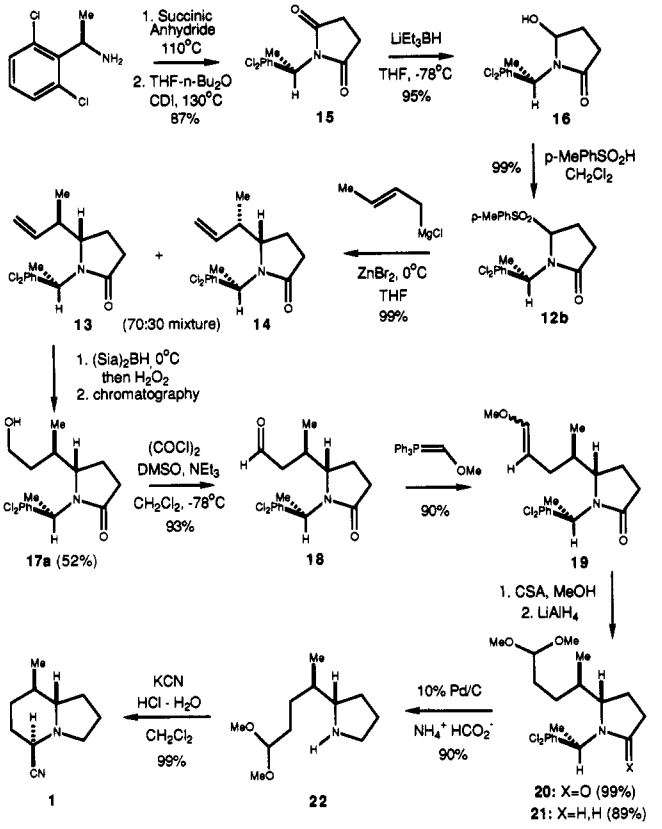
established by comparison of these mixtures to authentic samples whose absolute configurations were established rigorously by correlation with (*S*)- and (*R*)-2-pyrrolidinone-5-acetic acid.[2] Gratifyingly, when crotylmagnesium chloride was reacted with the toluenesulfonyl lactam **12b** (enantiomer of **11b**), only two diastereomeric



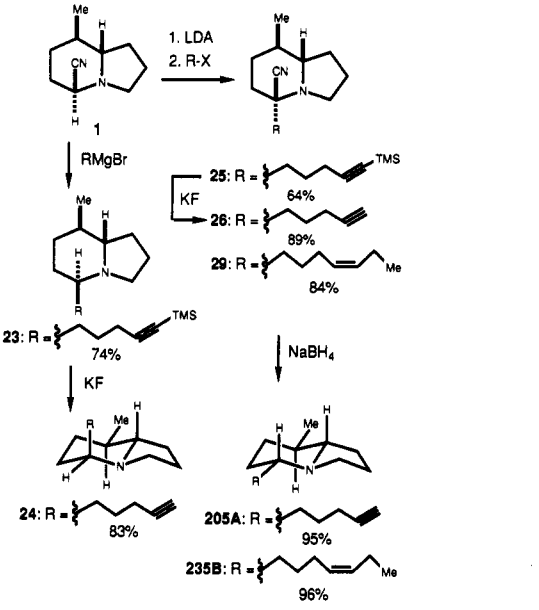
lactams were produced in a ratio of 70:30. Furthermore, the desired *ul* stereoisomer **13** represented the major isomer formed in the addition reaction. With this key result in hand, we initiated efforts to produce alkaloids **205A** and **235B**.

Total Syntheses of 205A and 235B. We have secured diastereomers of the proposed structure of (−)-**205A** for comparison to the natural material. The routes to the natural product **205A** of 5*R*,8*R*,8a*S* configuration and its 5*S*,8*R*,8a*S* diastereomer begin in Scheme III. Reduction of *N*-[(1*R*)-1-(2,6-dichlorophenyl)ethyl]succinimide[3] (**15**) with lithium triethylborohydride[19] produced hydroxy lactam **16** as a 95:5 mixture of diastereoisomers in 95% yield. Conversion of **16** to the *p*-toluenesulfonyl lactam **12b** with *p*-toluenesulfinic acid in dichloromethane was carried out according to Ley.[18a] This reaction produced a single diastereomer. We have not rigorously assigned the configuration of the ring stereogenic center. If the sulfonyl lactam **12b** represents the product of kinetic trapping of the intermediate acyliminium ion by *p*-toluenesulfinate, then it is highly likely that the configuration of the ring stereogenic center is *R*, by analogy to results obtained in other nucleophilic additions to such acyliminium ions.[2] Reaction of the sulfonyl lactam **12b** with crotylmagnesium chloride produced a mixture of two crotyl lactams **13** and **14** in 99% yield. The crotyl lactam mixture (**13** + **14**) was hydroborated with disiamylborane[11] to afford a mixture of primary alcohols **17a,b**. These diastereomers were readily separable by simple flash chromatography. Hence, the major isomer **17a** was obtained in 52% yield. The primary alcohol **17a** was oxidized by the method of Swern[20] to aldehyde **18**, which then underwent Wittig olefination with (methoxymethylidene)triphenylphosphorane[21] to afford enol ethers **19** as an inseparable mixture of *E* and *Z* configurational isomers. Simply stirring the enol ethers with anhydrous methanol containing camphorsulfonic acid produced the dimethyl

Scheme III



Scheme IV



acetal **20**. Reduction of the lactam to the corresponding pyrrolidine[15] **21** and subsequent hydrogenolysis[17] of the chiral directing group afforded amino acetal **22**. Hydrolysis of the acetal **32** in the presence of HCN[22] afforded the key intermediate, the α-amino nitrile **1**. The conversion of α-amino nitrile **1** to alkaloids **205A** and **235B** is reported in Scheme IV.

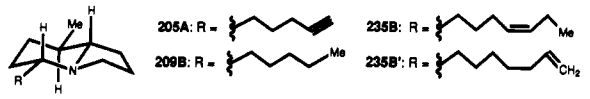
Bruylants' reaction[23] of [1-(trimethylsilyl)pent-1-yn-5-yl]magnesium chloride[24] with α-amino nitrile **1** followed

(19) Chen, J.; Browne, L. J.; Gonnela, N. C. *Chem. Commun.* **1986**, 905.
(20) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(21) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.
(22) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515.
(23) Bruylants, P. *Bull. Soc. Chim. Belg.* **1924**, *33*, 467.
(24) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611.

Table III

compd	C_1	C_2	C_3	C_5	C_6	C_7	C_8	C_{8a}	C_8-Me
indolizidine[27]	30.1	20.3	53.9	52.7	25.1	24.2	30.7	64.1	
1	28.8	20.1	51.3	51.2	28.5	29.3	36.5	64.6	18.3
23	29.6	20.7	49.0	54.8	26.9	27.8	37.5	61.6	19.0
24	29.6	20.7	49.1	54.8	26.8	27.9	37.5	61.5	19.0
25	30.5	20.1	48.0	62.1	37.7	34.0	36.4	66.3	18.5
26	30.5	20.1	48.0	62.1	37.7	34.1	36.4	66.3	18.5
27	26.9	20.4	52.3	64.5	32.0	25.8	29.5	67.7	12.2
28	22.2	20.8	50.3	53.8	26.9	31.7	31.3	64.3	18.0
29	30.5	20.1	48.0	62.3	38.2	34.1	36.4	66.2	18.5
205A	29.1	20.4	51.9	63.0	31.3	33.7	36.6	71.3	18.9
235B	29.1	20.4	51.9	63.5	31.3	33.8	36.7	71.4	19.0

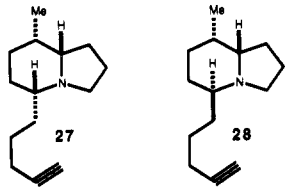
Table IV



alkaloid	$[\alpha]_D$	conditions
205A	-83.5,[a] -35[b]	(*c* 0.30, MeOH),[a] (*c* 0.24, MeOH)[b]
235B	-73.4,[a] 11.3[b]	(*c* 1, MeOH)[a,b]
209B	-94.3[c]	(*c* 1.85, MeOH)
235B'	-61[d]	(*c* 0.5, MeOH)

[a] This work. [b] Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643. [c] Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8676. [d] Edwards, M. W.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.

by removal of the trimethylsilyl group of **23** with aqueous potassium fluoride[24] afforded **24**, the 5*S*,8*R*,8a*S* configurational isomer of **205A**. Alternatively, alkylation[37,38] of amino nitrile **1** with 5-(trimethylsilyl)pent-4-yn-1-yl chloride[25] and subsequent desilylation[24] produced α-amino nitrile **26**. Reduction of the iminium ion derived from **26** with sodium borohydride[26] afforded alkaloid **205A** of 5*R*,8*R*,8a*S* configuration, which possessed both ^{1}H and ^{13}C NMR spectra that were identical with those reported for the natural product. The optical rotation of synthetic (5*R*,8*R*,8a*S*)-**205A** was $[\alpha]_D$ = -83.5° (*c* 0.30, MeOH), somewhat higher than the reported[4] value $[\alpha]_D$ = -35° (*c* 0.24, MeOH). Because of the anomaly observed in the optical rotation of (-)-**205A**, two additional diastereomers of the alkaloid **27** and **28** were prepared by a series of



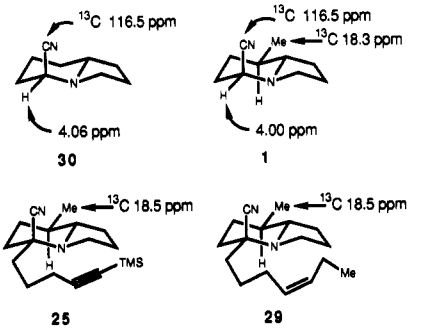
reactions similar to those in Schemes III and IV. Details are presented in the supplementary material. The ^{13}C data of the various stereoisomers of **205A** are reported in Table III. It appears that (5*R*,8*R*,8a*S*)-**205A** represents the naturally occurring configuration since the ^{13}C spectra of the three other **205A** diastereomers (**24**, **27**, and **28**) differ significantly from that of **205A** (Table III). Somewhat more surprising was the optical rotation displayed by alkaloid **235B**. The 5*R*,8*R*,8a*S* configurational isomer of **235B** was prepared (Scheme IV) from α-amino nitrile **1** by reactions analogous to those described for **205A**. The synthetic material had both ^{1}H and ^{13}C spectral data

Table V

compd	C_3-H_{eq}	C_3-H_{ax}	C_5-H	C_8-H	C_{8a}-H	C_8-Me
1	2.91	2.42	3.99	1.35	1.90	0.86
23	2.78	2.61	2.95	1.20	2.00	0.86
24	2.80	2.63	2.97	1.22	2.02	0.86
25	3.11	2.32		1.28	1.94	0.92
26	3.08	2.31		1.24	1.96	0.89
27	3.23	1.82	1.84	1.80	2.00	0.95
28	3.06	2.63	2.16	2.01	2.87	0.87
29	3.08	2.34		1.27	1.99	0.91
205A	3.24	1.95	1.86	1.24	1.48	0.84
235B	3.24	1.94	1.84	1.27	1.45	0.86

identical with that of the natural product, although its rotation $[\alpha]_D$ = -73.4° (*c* 1, MeOH) differed in both magnitude and sign from the published[4] value $[\alpha]_D$ = 11.3° (*c* 1, MeOH). At present, three indolizidine alkaloids of 5*R*,8*R*,8a*S* configuration have been prepared synthetically, and the rotation of a fourth natural product **235B'** is known. Alkaloid **235B'** is a positional isomer of **235B** in which the double bond in the C5 side chain is terminal rather than internal. The optical rotations for these various compounds are listed in Table IV. The $[\alpha]_D$ values for this series of compounds appear to be consistently levorotatory, in the range of -60 to -90°. We suggest that the values of the synthetic **205A** and **235B** reported here are correct. The discrepancy in the "natural" **235B** value may arise from an impurity in the isolated sample.

The trans-fused form of indolizidine has been estimated to be more stable than the cis-fused form by 2.4 kcal/mol.[28] Indolizidine derivatives **1**, **23**–**27**, **29**, **205A**, and **235B** appear to exist solely in the trans-fused form. The conformational features of the substituted indolizidines are best discussed in relation to their ^{13}C spectra (Table III), selected ^{1}H NMR (Table V), and IR absorptions. α-Amino nitrile **1** displayed Bohlmann bands at 2830 cm^{-1} consistent



with a trans ring fusion. According to the Bohlmann correlation,[29] an indolizidine will possess one or more low frequency C–H stretching absorptions when two or more

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hydrogens attached to carbon atoms adjacent to nitrogen are oriented trans and diaxial to the nitrogen lone electron pair. For α-amino nitrile **1** this stereoelectronic criterion can only be met when the ring fusion is trans. The proton chemical shifts of hydrogen nuclei attached to the C3, C5, and C8a positions of **1** are listed in Table V. The proton assignments were made based upon HETCOR[30] and APT[31] two-dimensional heteronuclear NMR experiments. The most downfield proton in **1** was assigned as the C5-H and it correlated with a methine carbon (C5). The nitrile moiety resident in **1** was assigned as axial by comparison of the chemical shift of the C5-H and the ^{13}C resonance of the nitrile carbon to the corresponding resonances of α-amino nitrile **30**, a compound of established configuration.[3] Further evidence consistent with the proposed configurations were the similarity in frequency and intensity of the Bohlmann bands displayed by **1** and **30**. The ^{13}C resonance of the C8 methyl group established that **1** possessed an equatorial methyl group (δ $^{13}C_{Me}$ 18.3).

Alkylation of α-amino nitrile **1** produced indolizidines **25** and **29**. The presence of a Bohlmann band in each alkylated derivative suggested that the indolizidines were trans-fused. The constancy of the chemical shifts of the C8 methyl groups in the alkylated derivatives relative to **1** suggested that the methyl groups in **25** and **29** retained their equatorial orientation. The small upfield shifts of the C8a carbon resonances in derivatives **25** and **29** were consistent with stereospecific equatorial alkylation[3] of the corresponding carbanions.

Reduction of indolizidines **26** and **29** with sodium borohydride afforded **205A** and **235B**. The presence of Bohlmann bands and constancy of the appropriate C8 methyl resonances suggested that these materials maintained the trans-fused conformation of their amino nitrile predecessors. We assume axial delivery of hydride to the intermediate iminium ions by analogy to Stevens.[32] The observed ^{13}C chemical shifts of C8a in **205A** and **235B** are consistent with the proposed structures, the ^{13}C shifts being calculated from the base value of indolizidine (Table V, entry 1) and ^{13}C substituent parameters developed by Eliel[33] in the *N*-methylpiperidine system.

In summary, an efficient, practical, general enantioselective synthesis of 5-substituted 8-methylindolizidines of 5*R*,8*R*,8a*S* configuration has been developed. Although it has been possible to achieve high face selection in addition of achiral nucleophiles[2] to acyliminium ions **3**, addition of prochiral crotyl metal nucleophiles resulted in only modest control in the production of two new vicinal stereogenic centers.

Experimental Section[34]

(5*S*,6*S*)-5-(2-But-3-enyl)-1-[(1*S*)-1-phenylethyl]-pyrrolidinone (D_2, Entry 1, Table I) and Diastereomers. Hydroxy lactam **4a**[2] (1.10 g, 5.37 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to −78 °C, *trans*-crotyltrimethylsilane (1.45 g, 2 equiv) was added, $SnCl_4$ (1.4 g, 1 equiv) was added, and the reaction was warmed to −22 °C. After 4 h, the reaction was quenched with 1 N HCl (50 mL) and extracted with CH_2Cl_2, the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, and the residue was flash chromatographed on silica with EtOAc, affording 1.23 g (94%) of a mixture of 4 diastereomers (IR (NaCl) 1690 (s) cm^{-1}); inspection of the spectra provided data for the major isomer D_2: ^1H NMR ($CDCl_3$) δ 7.45–7.19 (m, 5 H, ArH_5), 5.45 (m, 1 H, *H*C=CH_2), 5.30 (q, 1 H, J = 7 Hz, ArCH), 4.92 (dt, 1 H, J = 10.5, 1.5 Hz, C=C*H*H cis), 4.92 (dt, 1 H, J = 17.5, 1.5 Hz, C=CH*H* trans), 3.67 (dt, 1 H, J = 9, 3 Hz, C_5-H), 2.42–2.09 (m, 3 H), 1.96–1.65 (m, 2 H), 1.68 (d, 3 H, J = 7 Hz, ArCHC*H*$_3$), 0.86 (d, 3 H, J = 7 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 138.5, 136.6, 128.3, 127.5, 116.4, 61.6, 50.3, 37.9, 31.0, 19.1, 16.5, 15.5; mass spectrum (CI, NH_3) m/e 244 (MH^+). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.01; H, 8.65.

(5*R*)-(−)-[(1*R*)-1-(2,6-Dichlorophenyl)ethyl]-5-(*p*-toluenesulfonyl)pyrrolidinone (12b). Hydroxy lactam **16**[2] (1.41 g, 5.14 mmol) and toluenesulfinic acid (freshly prepared from the sodium salt) were dissolved in CH_2Cl_2 (50 mL), stirred 2 h, and quenched with 5% Na_2CO_3. The product was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated, affording 2.12 g (100%) of a single diastereomer: IR (CH_2Cl_2) 1710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (d, 2 H, J = 7 Hz, ArH_2), 7.41 (d, 2 H, J = 7 Hz, ArH_2), 7.40–7.10 (m, 3 H, ArH_3), 7.05 (t, 1 H, J = 7 Hz, ArH), 5.70 (q, 1 H, J = 7 Hz, ArCH), 5.10 (dd, 1 H, J = 7, 1.5 Hz, C_5-H), 2.46 (s, 3 H, $ArCH_3$), 2.40 (m, 2 H), 1.99 (m, 1 H), 1.58 (m, 1 H), 1.80 (d, 3 H, J = 7 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 146.0, 132.9, 130.5, 130.4, 129.4, 129.3, 128.2, 79.2, 51.8, 28.4, 22.7, 21.7, 16.0; mass spectrum (CI, NH_3) m/e 412 (MH^+); $[\alpha]_D$ = −158° (*c* 0.9, CH_2Cl_2). Anal. Calcd for $C_{19}H_{19}C_{12}NO_3S$: C, 55.35; H, 4.64. Found: C, 55.37; H, 4.70.

(5*S*,6*R*)-5-(2-But-3-enyl)-1-[(1*R*)-1-(2,6-dichlorophenyl)-ethyl]pyrrolidinone (13). Crotylmagnesium chloride (30 mL, 16 mmol, 0.53 M in Et_2O) was added to $ZnBr_2$ (8 mL, 8 mmol, 1 M in THF) in THF (70 mL) and cooled to 0 °C, and sulfonyl lactam **12b** (2.12 g, 5.14 mmol) in THF (25 mL) was added. After being stirred for 2 h, the reaction was quenched with 1 N HCl (70 mL) and extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, affording 1.61 g (100%) of an oil (70:30 mixture of **13**:**14**) IR (NaCl) 1695 (s) cm^{-1}); inspection of the spectra provided data for the major isomer **13**: ^1H NMR ($CDCl_3$) δ 7.26 (d, 2 H, J = 8 Hz, ArH_2), 7.07 (t, 1 H, J = 8 Hz, ArH), 5.78 (m, 1 H, C*H*=CH_2), 5.63 (q, 1 H, J = 7.5 Hz, ArCH), 5.18–5.06 (m, 2 H, CH=C*H*$_2$), 3.91 (dd, 1 H, J = 8.5, 3 Hz, C_5-H), 2.80 (m, 1 H), 2.43–1.78 (m, 6 H), 1.69 (d, 3 H, J = 7.5 Hz, ArCHC*H*$_3$), 1.00 (d, 3 H, J = 7 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 175.0, 140.1, 137.5, 129.3, 128.2, 115.4, 61.0, 50.6, 41.4, 30.9, 19.7, 16.5, 11.9; mass spectrum (CI, NH_3) m/e 312 (MH^+). Anal. Calcd for $C_{16}H_{19}Cl_2NO$: C, 61.55; H, 6.13. Found: C, 61.76; H, 6.25.

(5*S*,6*R*)-(−)-1-[(1*R*)-1-(2,6-Dichlorophenyl)ethyl]-5-(4-hydroxybut-2-yl)pyrrolidinone (17a). 2-Methyl-2-butene (1.08 g, 15.4 mmol) was added to borane (7.7 mL, 7.7 mmol, 1 M solution in THF) in THF (5 mL) at 0 °C and stirred for 2 h. Lactams **13** and **14** (1.20 g, 3.85 mmol) in THF (10 mL) were slowly added, the reaction was stirred 2 h, and H_2O (1.0 mL) was slowly added, followed by 3 M NaOH (2.0 mL), 30% H_2O_2 (2.0 mL), and finally H_2O (25 mL). After being stirred for 2 h, the aqueous solution was extracted with CH_2Cl_2, dried, filtered, and concentrated, affording 936 mg (74%) of a mixture of **17a** and **17b**. Flash chromatography on silica with 20:80 hexane–EtOAc afforded the major **17a** and minor **17b** diastereomers. **17a**: mp 145–146 °C; IR (NaCl) 3600 (br), 1680 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8 Hz, ArH_2), 7.09 (t, 1 H, J = 8 Hz, ArH), 5.60 (q, 1 H, J = 7.5 Hz, ArCH), 3.86 (dd, 1 H, J = 8, 2 Hz, C_5-H), 3.70 (m, 2 H, C*H*$_2$OH), 2.44–2.19 (m, 3 H), 2.04 (m, 1 H), 1.84 (m, 1 H), 1.69 (d, 3 H, J = 7.5 Hz, ArCHC*H*$_3$), 1.51 (m, 1 H), 0.90 (d, 3 H, J = 6.5 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 175.0, 137.3, 129.2, 128.1, 61.2, 60.2, 50.6, 36.5, 33.8, 31.0, 19.1, 16.4, 13.2; mass spectrum (CI, NH_3) m/e 330 (MH^+); $[\alpha]_D$ = −107° (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{21}Cl_2NO_2$: C, 58.19; H, 6.41. Found: C, 57.99; H, 6.29. **17b**: mp 151–153 °C; IR (NaCl) 3600 (br), 1680 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (d, 2 H, J = 8 Hz, ArH_2), 7.08 (t, 1 H, J = 8, ArH), 5.61 (q, 1 H, J = 7.5, ArCH), 3.83 (dd, 1 H, J = 8.5,

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2, C_5-H), 3.75 (m, 1 H, CH_2OH), 3.60 (m, 1 H, CH_2OH), 2.40–1.64 (m, 5 H), 1.69 (d, 3 H, J = 7.5, $ArCHCH_3$), 1.51 (m, 1 H), 1.26 (m, 1 H), 0.96 (d, 3 H, J = 7, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 175.0, 137.5, 129.3, 128.1, 62.7, 60.7, 50.8, 33.8, 32.4, 30.9, 19.3, 16.5, 16.4; mass spectrum (CI, NH_3) m/e 330 (MH^+); $[\alpha]_D$ = −115° (c 1.1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{21}Cl_2NO_2$: C, 58.19; H, 6.41. Found: C, 58.22; H, 6.43.

(5*S*,6*R*)-(-)-1-[(1*R*)-1-(2,6-Dichlorophenyl)ethyl]-5-(4-oxobut-2-yl)pyrrolidinone (18). Oxalyl chloride (303 mg, 2.4 mmol) was dissolved in CH_2Cl_2 (10 mL) stirring at −78 °C and stirred 10 min, DMSO (0.23 mL, 3.18 mmol) in CH_2Cl_2 (6 mL) was added, and the reaction was stirred 10 min. Alcohol **17a** (525 mg, 1.59 mmol) in CH_2Cl_2 (12 mL) was slowly added and the reaction stirred 20 min, and Et_3N (1.3 mL, 6 equiv) was added and the reaction stirred 30 min. at −78 °C and 1 h at ambient temperature. After being quenched with dilute NH_4OH (30 mL), the aqueous solution was extracted with CH_2Cl_2, dried, filtered, and concentrated. Flash chromatography on silica with EtOAc afforded 483 mg (93%) of an oil: IR (CH_2Cl_2) 1730 (m), 1680 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (t, 1 H, J = 1.5 Hz, CHO), 7.29 (d, 2 H, J = 8 Hz, ArH_2), 7.10 (t, 1 H, J = 8 Hz, ArH), 5.63 (q, 1 H, J = 7.5, ArCH), 3.86 (dd, 1 H, J = 8.5, 2, C_5-H), 2.75 (ddd, 1 H, J = 14, 7, 3 Hz, $COCH_a$), 2.43 (dd, 2 H, J = 7.5, 1.5 Hz, $HCOCH_2$), 2.40–2.21 (m, 2 H), 2.06 (m, 1 H), 1.80 (m, 1 H), 1.74 (d, 3 H, J = 7.5 Hz, $ArCHCH_3$), 0.94 (d, 3 H, J = 7 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 200.5, 174.6, 137.2, 129.3, 128.2, 60.4, 50.7, 48.0, 31.7, 30.7, 19.2, 16.5, 13.4; mass spectrum (CI, NH_3) m/e 328 (MH^+); $[\alpha]_D$ = −128° (c 1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{19}Cl_2NO_2$: C, 58.55; H, 5.83. Found: C, 58.24; H, 5.72.

(5*S*,6*R*)-(-)-5-(5,5-Dimethoxypent-2-yl)-1-[(1*R*)-1-(2,6-dichlorophenyl)ethyl]pyrrolidinone (20). (Methoxymethyl)-triphenylphosphonium chloride (1.51 g, 4.4 mmol) was suspended in Et_2O (20 mL) and cooled to 0 °C, t-BuLi (2.0 mL, 3.83 mmol, 1.95 M in THF) was slowly added, and the reaction was stirred 15 min. Aldehyde **18** (483 mg, 1.47 mmol) in THF (20 mL) was slowly added, and the reaction was stirred for 5 h and then quenched with 5% $NaHCO_3$. The product was extracted with CH_2Cl_2, the combined extracts were dried, filtered, and concentrated, and the residue was flash chromatographed on silica with 30:70 hexane–EtOAc, affording 471 mg (90%) of methyl enol ether **19**. The enol ether was dissolved in MeOH (50 mL), camphorsulfonic acid (313 mg, 1.05 equiv) was added, and the reaction was stirred for 15 h. After the mixture was quenched with saturated $NaHCO_3$ (40 mL), the product was extracted with CH_2Cl_2, and the combined organic layers were dried, filtered, and concentrated, affording 504 mg (98%) of **20** as an oil: IR (NaCl) 1690 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (d, 2 H, J = 8 Hz, ArH_2), 7.06 (t, 1 H, J = 8 Hz, ArH), 5.57 (q, 1 H, J = 7.5 Hz, ArCH), 4.32 (t, 1 H, J = 5.5 Hz, $CH(OMe)_2$), 3.81 (dd, 1 H, J = 9, 1.5 Hz, C_5-H), 3.30 (s, 6 H, OMe + OMe), 2.27 (m, 2 H, $COCH_2$), 1.99 (m, 2 H), 1.81 (m, 1 H), 1.65 (d, 3 H, J = 7.5, $ArCHCH_3$), 1.55 (m, 1 H), 1.28 (m, 2 H), 0.85 (d, 3 H, J = 7 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 174.7, 137.2, 129.3, 128.2, 104.5, 61.2, 52.9, 52.8, 50.7, 37.2, 31.0, 30.5, 28.7, 19.0, 16.6, 13.2; mass spectrum (CI, NH_3) m/e 388 (MH^+); $[\alpha]_D$ = −85.7° (c 1, CH_2Cl_2). Anal. Calcd for $C_{19}H_{27}Cl_2NO_3$: C, 58.77; H, 7.01. Found: C, 59.03; H, 6.93.

(2*S*,6*R*)-(-)-2-(5,5-Dimethoxypent-2-yl)-1-[(1*R*)-1-(2,6-dichlorophenyl)ethyl]pyrrolidine (21). Lactam **20** (292 mg, 1.20 mmol) was dissolved in THF (12 mL), $LiAlH_4$ (320 mg, 7 equiv) was added, and the reaction mixture was refluxed for 2 h. After the mixture was cooled to room temperature, Et_2O (30 mL) was added followed by water (0.40 mL), 3 M NaOH (0.40 mL), and additional water (1.20 mL). The solution was stirred for 1 h, filtered, and concentrated, affording an oil (89%): IR (NaCl) 1590 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (d, 2 H, J = 7.5 Hz, ArH_2), 7.03 (t, 1 H, J = 7.5 Hz, ArH), 4.51 (q, 1 H, J = 7 Hz, ArCH), 4.18 (t, 1 H, J = 5.5 Hz, $CH(OMe)_2$), 3.26 (s, 3 H, OMe), 3.24 (s, 3 H, OMe), 2.68 (m, 1 H), 2.54 (m, 2 H), 1.72–1.46 (m, 3 H), 1.50 (d, 3 H, J = 7, $ArCHCH_3$), 1.32 (m, 2 H), 1.06–0.83 (m, 2 H), 0.58 (d, 3 H, J = 6.5 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 141.0, 127.7, 104.6, 69.0, 60.0, 52.7, 52.2, 51.8, 35.7, 30.6, 29.8, 24.6, 24.4, 17.4, 13.3; mass spectrum (CI, NH_3) m/e 374 (MH^+); $[\alpha]_D$ = −23.6° (c 1, CH_2Cl_2). Anal. Calcd for $C_{19}H_{29}Cl_2NO_2$: C, 60.96; H, 7.81. Found: C, 60.77; H, 7.88.

(2*S*,6*R*)-(+)-2-(5,5-Dimethoxypent-2-yl)pyrrolidine (22). Acetal **21** (0.47 mmol) and ammonium formate (240 mg, 8 equiv) were dissolved in MeOH (12 mL), 10% Pd/C (80 mg) was added, and the mixture was stirred for 12 h. The suspension was filtered through Celite and concentrated, 1 NaOH (6 mL) was added, and the product was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, affording an oil (90%): IR (NaCl) 3350 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (t, 1 H, J = 5.5 Hz, $CH(OMe)_2$), 3.30 (s, 6 H, OMe + OMe), 2.99 (m, 1 H), 2.81 (m, 1 H), 2.72 (m, 1 H), 2.00–1.08 (m, 10 H), 0.88 (d, 3 H, J = 6.5, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 104.9, 64.5, 52.7, 46.8, 38.6, 30.0, 29.4, 25.5, 16.3; mass spectrum (CI, NH_3) m/e 374 (MH^+); $[\alpha]_D$ = +7.4° (c 1.1, CH_2Cl_2). Anal. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52. Found: C, 65.44; H, 11.35.

(5*R*,8*R*,8a*S*)-(-)-5-Cyano-8-methylindolizidine (1). Acetal **22** (0.41 mmol) was dissolved in CH_2Cl_2/H_2O (7 mL each), KCN (320 mg, 12 equiv) was added, and the pH was adjusted to 3–4 with concentrated HCl and stirred for 7 h. After basification with 2 N NaOH, the mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated, affording an oil (99%): IR (NaCl) 2240 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (t, 1 H, J = 3.5 Hz, C_5-H), 2.91 (td, 1 H, J = 8.5, 3 Hz, C_3-H_a), 2.42 (q, 1 H, J = 9, C_3-H_b), 2.01–1.58 (m, 7 H), 1.40–1.15 (m, 4 H), 0.86 (d, 3 H, J = 6, CH_3); ^{13}C NMR ($CDCl_3$) δ 116.5, 64.6, 51.3, 51.2, 36.5, 29.3, 28.8, 28.5, 20.1, 18.3; mass spectrum (CI, NH_3) m/e 165 (MH^+); $[\alpha]_D$ = −18.8° (c 1, CH_2Cl_2). Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82. Found: C, 73.30; H, 9.74.

(5*S*,8*R*,8a*S*)-(-)-5-[5-(Trimethylsilyl)pent-4-yn-1-yl]-8-methylindolizidine (23). Cyano amine **1** (30 mg, 0.18 mmol) was dissolved in Et_2O (2 mL) and cooled to 0 °C, [5-(trimethylsilyl)pent-4-yn-1-yl]magnesium chloride (3.1 mL, 6 equiv, 0.35 M in THF) was added, and the reaction was allowed to slowly warm to room temperature. After 14 h, the reaction was quenched with 1 N NaOH (8 mL) and extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, concentrated. The residue was flash chromatographed on silica with a gradient of EtOAc to 50:50 EtOAc–MeOH, affording an oil (74%): IR (NaCl) 2180 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, 1 H, J = 7 Hz, C_5-H), 2.78 (dd, 1 H, J = 8.5, 3 Hz, C_3-H_a), 2.61 (q, 1 H, J = 8.5 Hz, C_3-H_b), 2.20 (m, 2 H, $CH_2C{\equiv}C$), 2.00 (m, 1 H, C_{8a}-H), 1.93–0.96 (m, 13 H), 0.86 (d, 3 H, J = 6 Hz, CH_3), 0.11 (s, 9 H, TMS); ^{13}C NMR ($CDCl_3$) δ 107.4, 84.7, 61.6, 54.8, 49.0, 37.5, 29.6, 28.1, 27.9, 26.9, 21.5, 20.7, 20.2, 19.0, 0.2; mass spectrum (CI, NH_3) m/e 278 (MH^+); $[\alpha]_D$ = −10.8° (c 0.8, CH_2Cl_2). Anal. Calcd for $C_{17}H_{31}NSi$: C, 73.57; H, 11.26. Found: C, 73.36; H, 10.99.

(5*S*,8*R*,8a*S*)-(-)-5-(4-Pentynyl)-8-methylindolizidine (24). Indolizidine **23** (40.0 mg, 0.144 mmol) was dissolved in H_2O (1.5 mL) and DMF (9 mL), and cooled to 0 °C, KF (30 mg, 2 equiv) was added, and the reaction was allowed to slowly warm to room temperature. After 35 h, the reaction was quenched with 1 N NaOH (10 mL) and extracted with 50:50 hexane–Et_2O, and the combined organic extracts were dried, filtered, concentrated, affording an oil (83%): IR (NaCl) 2140 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (m, 1 H, C_5-H), 2.80 (td, 1 H, J = 8.5 Hz, 3, C_3-H_a), 2.63 (q, 1 H, J = 8.5 Hz, C_3-H_b), 2.20 (m, 2 H, $CH_2C{\equiv}C$), 2.02 (q, 1 H, J = 8.5 Hz, C_{8a}-H), 1.96–1.00 (m, 13 H), 0.86 (d, 3 H, J = 6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 84.5, 68.4, 61.5, 54.8, 49.1, 37.5, 29.6, 28.2, 28.0, 27.9, 26.8, 21.6, 20.7, 19.0, 18.8; mass spectrum (CI, NH_3) m/e 206 (MH^+); $[\alpha]_D$ = −7.3° (c 0.3, MeOH). Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29. Found: C, 81.74; H, 11.20.

(5*R*,8*R*,8a*S*)-(-)-5-Cyano-5-[5-(trimethylsilyl)pent-4-yn-1-yl]-8-methylindolizidine (25). Diisopropylamine (41 mg, 0.40 mmol) was dissolved in THF and cooled to 0 °C, n-BuLi (0.13 mL, 1 equiv, 2.2 M in hexane) was added, and the mixture was stirred for 30 min. After the solution was cooled to −78 °C, cyano amine **1** (32.5 mg, 0.198 mmol) in THF (2 mL) was added and the mixture was warmed to 0 °C and stirred for 30 min After the solution was again cooled to −78 °C, 5-(trimethylsilyl)pent-4-ynyl chloride (0.2 mL, 6 equiv) was added, and the reaction was warmed to 0 °C, stirred 30 min, and quenched with 1 N NaOH (8 mL). After extraction with CH_2Cl_2, the combined organic extracts were dried, filtered, and concentrated, affording an oil (64%): IR (NaCl) 2190 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (td, 1 H, J = 8.5, 3.5 Hz, C_3-H_a), 2.32 (m, 1 H, C_3-H_b), 2.26 (m, 2 H, $CH_2C{\equiv}C$), 2.04–1.19 (m, 14 H), 0.92 (d, 3 H, J = 6 Hz, CH_3), 0.08 (s, 9 H, TMS); ^{13}C NMR ($CDCl_3$) δ 118.8, 106.2, 85.4, 66.3, 62.1, 48.0, 37.7, 36.4, 34.0, 30.5, 29.1, 22.7, 20.1, 19.9, 18.5, 0.1; mass spectrum (CI, NH_3) m/e 276 ($(MH - HCN)^+$); $[\alpha]_D$ = −44.8° (c

1.1, CH_2Cl_2). Anal. Calcd for $C_{18}H_{30}N_2Si$: C, 71.46; H, 9.99. Found: C, 71.49; H, 9.98.

(5*R*,8*R*,8a*S*)-(−)-5-Cyano-5-(4-pentynyl)-8-methylindolizidine (26). Prepared according to the procedure for **24**, affording an oil (89%): IR (CH_2Cl_2) 2240 (w), 2130 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (td, 1 H, J = 8.5, 3.5 Hz, C_3-H_a), 2.31 (q, 1 H, J = 9, C_3-H_b), 2.43 (m, 1 H, C_5-H), 2.22 (m, 2 H, $CH_2C{\equiv}C$), 2.02–1.18 (m, 14 H), 0.89 (d, 3 H, J = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 118.8, 83.4, 69.2, 66.3, 62.1, 48.0, 37.7, 36.4, 34.1, 30.5, 29.1, 22.6, 20.1, 18.53, 18.49; mass spectrum (CI, NH_3) m/e 204 ((MH − HCN)$^+$); $[\alpha]_D$ = −56.1° (c 1, CH_2Cl_2). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63. Found: C, 78.37; H, 9.47.

(5*R*,8*R*,8a*S*)-(−)-5-(4-Pentynyl)-8-methylindolizidine (205A). Indolizidine **26** (0.13 mmol) was dissolved in EtOH (10 mL) and cooled to 0 °C, $NaBH_4$ (50 mg, 10 equiv) was added, and the reaction was allowed to slowly warm to room temperature. After 15 h, the reaction was quenched with 1 N NaOH (8 mL) and extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated affording an oil (85%): IR (NaCl) 2130 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (td, 1 H, J = 8.5, 2, C_3-H_a), 2.16 (td, 2 H, J = 6.5, 2.5 Hz, $CH_2C{\equiv}C$), 1.95 (q, 1 H, J = 9 Hz, C_3-H_b), 1.92–1.14 (m, 16 H), 0.94 (d, 3 H, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 84.5, 71.3, 68.4, 62.8, 51.9, 36.6., 33.8, 33.7, 31.3, 29.1, 24.8, 20.4, 18.9, 18.8; mass spectrum (CI, isobutane) m/e 206 (MH$^+$); $[\alpha]_D$ = −83.5° (c 0.30, MeOH) (lit.[4] $[\alpha]_D$ = −35° (c 0.24, MeOH).

(5*R*,8*R*,8a*S*)-(−)-5-Cyano-5-(7-hept-3-enyl)-8-methylindolizine (29). Prepared according to the procedure for **25**, from (*Z*)-1-chlorohept-4-ene, affording an oil (84%): IR (CH_2Cl_2) 2250 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.46–5.24 (m, 2 H, HC=CH), 3.08 (td, 1 H, J = 8.5, 3.5 Hz, C_3-H_a), 2.34 (q, 1 H, J = 9 Hz, C_3-H_b), 2.12–1.22 (m, 18 H), 0.96 (t, 3 H, J = 7.5, CH_2CH_3), 0.91 (d, 3 H, J = 6, C_8-CH_3); ^{13}C NMR ($CDCl_3$) δ 132.6, 128.0, 118.9, 66.2, 63.0, 48.0, 38.2, 36.4, 34.1, 30.6, 29.1, 27.0, 23.6, 20.6, 20.1, 18.5, 14.4; mass spectrum (CI, isobutane) m/e 261 (MH$^+$); $[\alpha]_D$ = −41.8° (c 0.9, CH_2Cl_2). Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84. Found: C, 78.61; H, 10.95.

(5*R*,8*R*,8a*S*)-(−)-5-(7-Hept-3-enyl)-8-methylindolizidine (235B). Prepared from **29** according to the procedure of **205A**, affording an oil (96%): IR (NaCl) 1460 (m) cm^{-1}; ^1H NMR ($CDCl_3$), δ 5.48–5.24 (m, 2 H, HC=CH), 3.24 (td, 1 H, J = 8.5, 2 Hz, C_3-H_a), 2.07–1.14 (m, 16 H), 0.94 (t, 3 H, J = 7.5, CH_2CH_3), 0.86 (d, 3 H, J = 6.5, C_8-CH_3); ^{13}C NMR ($CDCl_3$) δ 131.8, 129.0, 71.4, 63.5, 51.9, 36.7, 34.3, 33.8, 31.3, 29.1, 27.5, 26.0, 20.6, 20.4, 19.0, 14.4; mass spectrum (CI, NH_3) m/e 236 (MH$^+$); $[\alpha]_D$ = −73.4° (c 1, MeOH) (lit.[4] $[\alpha]_D$ = +11.3 (c 1, MeOH)).

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Registry No. **1**, 134457-78-6; **4a**, 65084-17-5; **4b**, 126017-80-9; **4c**, 126017-64-9; **5** (isomer 1), 134457-90-2; **5** (isomer 2), 134527-78-9; **5** (isomer 3), 134527-79-0; **5** (isomer 4), 134527-80-3; **6** (isomer 1), 134457-91-3; **6** (isomer 2), 134457-98-0; **8**, 134527-81-4; **9**, 134527-82-5; **10a**, 134457-83-3; **10b**, 134527-66-5; **10c**, 134527-67-6; **10d**, 134527-68-7; **11a**, 134457-94-6; **11b**, 134457-95-7; **12b**, 134457-72-0; **13**, 134527-62-1; **14**, 134527-63-2; **17a**, 134457-73-1; **17b**, 134527-64-3; **18**, 134457-74-2; **20**, 134457-75-3; **21**, 134457-76-4; **22**, 134457-77-5; **23**, 134457-79-7; **24**, 134527-65-4; **25**, 134457-80-0; **26**, 134457-81-1; **27**, 134527-77-8; **28**, 134527-74-5; **29**, 134457-82-2; **31** (isomer 1), 134457-86-6; **31** (isomer 2), 134527-69-8; **31** (isomer 3), 134527-70-1; **31** (isomer 4), 134527-71-2; **32**, 134457-87-7; **33**, 134457-88-8; **34**, 134457-89-9; **35**, 134527-72-3; **36**, 134527-73-4; **37**, 134527-75-6; **38**, 134527-76-7; D_1 (Ar = Ph), 134457-69-5; D_1 (Ar = 2,6-Cl_2Ph), 134457-70-8; D_2 (Ar = Ph), 134527-55-2; D_2 (Ar = 2,6-Cl_2Ph), 134527-58-5; D_3 (Ar = Ph), 134527-56-3; D_3 (Ar = 2,6-Cl_2Ph), 134527-59-6; D_3 (Ar = Cl_5Ph), 134457-71-9; D_4 (Ar = Ph), 134527-57-4; D_4 (Ar = 2,6-Cl_2Ph), 134527-60-9; D_4 (Ar = Cl_5Ph), 134527-61-0; (*E*)-MeCH=$CHCH_2$TMS, 17486-12-3; (*Z*)-MeCH=$CHCH_2$TMS, 17486-13-4; MeCH=$CHCH_2MgCl$, 6088-88-6; $Ph_3P^+CH_2OMeCl^-$, 4009-98-7; $ClMg(CH_2)_3{\equiv}CTMS$, 113893-39-3; (*Z*)-$Cl(CH_2)_3CH{=}CHCH_2CH_3$, 70732-49-9; $Cl(CH_2)_3C{\equiv}CTMS$, 77113-48-5; $BrMgCH{=}CHCH_3$, 14092-04-7; (−)-205A, 109175-46-4; (−)-235B, 109175-47-5; (5*R*,6*R*)-5-*sec*-butylpyrrolidone, 134457-84-4; (5*R*,6*S*)-5-*sec*-butylpyrrolidone, 134457-85-5; heliotridane, 517-24-8; heliotridane picrate, 134457-92-4; (5*S*,6*S*)-5-*sec*-butylpyrrolidone, 134457-93-5; (5*R*)-allyl-1-((1*R*)-phenylethyl)pyrrolidone, 126017-86-5; (5*S*)-allyl-1-((1*R*)-phenylethyl)pyrrolidone, 134457-96-8; (5*R*)-allyl-1-[((1*R*)-2,6-dichlorophenyl)ethyl]pyrrolidone, 126017-89-8; (5*R*)-1-propenyl-1-[((1*R*)-2,6-dichlorophenyl)ethyl]pyrrolidone, 134457-97-9.

Supplementary Material Available: Experimental procedures and analytical data for crotyl lactams derived from **4c**, compounds **5–9**, and heliotridane, a discussion of and experimental procedures for the correlations of crotyl lactams D_1–D_4 involving hydrogenation and subsequent dissolving metal reduction of the crotyl lactams, and discussion of and experimental procedures for syntheses of **27** and **28** from crotyl lactam mixture D_1–D_4 (Table I, entry 1) (9 pages). Ordering information is given on any current masthead page.