Enantiospecific Synthesis of (−)-Slaframine and Related Hydroxylated Indolizidines. Utilization of a Nucleophilic Alaninol Synthon Derived from Serine[1]

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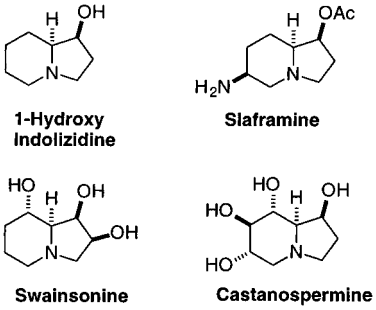
A general methodology for the synthesis of indolizidine alkaloids δ-coniceine (**12**), 1-hydroxyindolizidine (**20**), desacetoxy slaframine (**24**), slaframine (**34**), and an analogue (**37**) has been developed. This convergent approach utilizes the available chirality in proline and serine and is conceptually different from other approaches. A highly stereoselective coupling of the prolinals with a nucleophilic alaninol synthon provides the precursors for the key cyclization. A novel thermolytic annulation of an oxazolidinone is the key step in the formation of the six-membered piperidine ring. Further elaboration provides the target natural products **24**, **34**, and **37** in good overall yields.

Hydroxylated indolizidine alkaloids have gained interest as synthetic targets due to their diverse and potent biological activities.[2] Of the many naturally occurring members of this family, slaframine, swainsonine, and castanospermine have received notable attention. The



alkaloid slaframine, a mycotoxin produced by the fungus *Rhizoctonia leguminicola*, and swainsonine have been shown to arise from a common biosynthetic precursor.[3] These two compounds are involved in "slobbers syndrome",[4] a process which leads to excess salivation in cattle when they graze on fungus-infested feeds.[5] Swainsonine has also been found to be a potent α-mannosidase inhibitor.[6] Castanospermine, an alkaloid isolated from a variety of legumes as well as the Moreton Bay chestnut *Castanospermum australe*, is one of the actively studied targets due to its ability to interrupt the functions of the glycoprotein envelope surrounding the human immunodeficiency virus (HIV) responsible for the disease AIDS.[7] Its potential for use as an anti-viral and anti-cancer agent has also been proposed.[8] The wide range of bioactivity of these indolizidines makes them ideal targets for the development of new strategies for their efficient synthesis.

A variety of methods have been reported for the synthesis of indolizidine alkaloids.[9] The objective of this study was to develop a general synthetic methodology whereby a host of related indolizidine alkaloids could be prepared by a common route. In particular the synthesis of the parent indolizidine δ-coniceine,[10] 1-hydroxyindolizidine,[11] and slaframine[12,13] were of primary concern. Our convergent approach which uses the available chirality in proline and serine is conceptually different from other approaches and involves the annulation of the six-

(1) Taken in part from the Ph.D. Thesis of J. W. Christensen, North Dakota State University, 1994.

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(11) 1-Hydroxyindolizidine synthesis: (a) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 763. (b) Takahata, H.; Tajima, M.; Banba, Y.; Momose, T. *Chem. Pharm. Bull.* **1989**, *37*, 2550. (c) ref 3 a and b. (d) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1997**, *51*, 2865.

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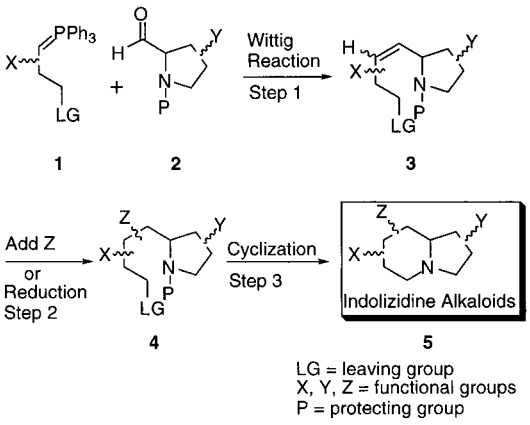
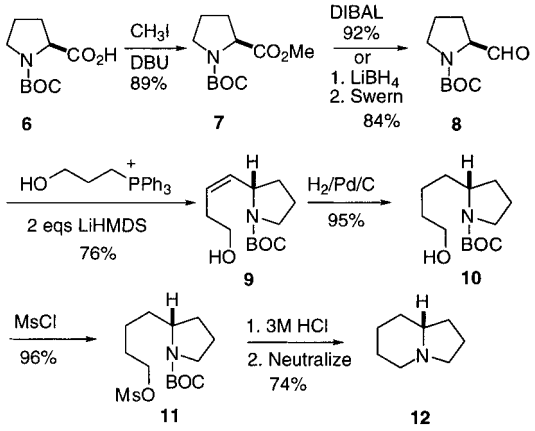
Scheme 1



Scheme 2



membered piperidine ring onto a hydroxylated proline as the key step in the methodology and further elaboration to the various natural products and their analogues (Scheme 1). In this manner, one can envision the synthesis of a variety of indolizidine alkaloids depending on the nature of the proline ring and the three-carbon synthon. The introduction of the three-carbon fragment involves a Wittig condensation with an appropriately substituted prolinal synthon to produce an alkene with control over the olefin geometry (step 1). Reduction or further functionalization of the double bond (step 2) followed by subsequent ring closure (step 3) results in the formation of the indolizidine structure. We also envisioned that the ring annulation reaction could be carried out by using different leaving groups and thus allowing for greater flexibility.

We have previously demonstrated the efficacy of the above methodology in the synthesis of δ-coniceine and 1-hydroxyindolizidine.[14] In addition, we have extended the methodology to the synthesis of 6-aminoindolizidines such as slaframine, through a method that utilizes a novel thermolytic ring closure of an oxazolidinone.[15] Herein, we expound on our previous studies and further extend our methodology to the synthesis of the new indolizidine alkaloid 2-hydroxy-6-aminoindolizidine derived from 4-hydroxyproline. Furthermore, we also provide mechanistic information on both the Wittig condensation with the three-carbon synthon derived from serine and on the thermolytic annulation procedure.

Synthesis of δ-Coniceine

We began our study on the simplest indolizidine δ-coniceine, since its synthesis provides a foundation for the extension of the methodology to more functionalized systems. Starting with commercially available *N*-BOC-L-proline, the methyl ester **7** was prepared under basic conditions in the presence of methyl iodide (Scheme 2). The ester **7** was converted to the aldehyde **8** by direct DIBAL reduction at low temperature. The reduction was somewhat tricky since small amounts of the starting material or the overreduced products accompanied the desired product. These problems were overcome using a two-step route. Reduction of the ester using lithium borohydride/trimethylborate led to the formation of *N*-BOC-prolinol cleanly. Swern oxidation of this material to aldehyde proceeded in high overall yield. A drawback to this route was that residual sulfur impurities complicated later steps.

Generally the aldehyde was used without further purification in the Wittig reaction.[16] The three-carbon synthon required for the chain extension was readily prepared by refluxing 3-chloropropanol with triphenylphosphine in acetonitrile according to literature procedure.[17] Formation of the oxido ylide[18] by treatment of the known phosphorane with 2 equiv of LiHMDS followed by addition of freshly prepared aldehyde **8** furnished compound **9** as a mixture of cis and trans isomers. We have found that longer reaction times at −78 °C and higher dilution favor the formation of the cis isomer. Catalytic hydrogenation of the olefin provided **10** along with as much as 20% of the corresponding aldehyde as a result of irreversible oxidation of the alcohol at the metal surface. We were able to increase the yield of **10** by pretreating the catalyst with hydrogen before introducing the olefin. Conversion of the primary alcohol to the mesylate **11** set up the system for cyclization. Thus, deprotection of the *t*-BOC protecting group with 3 M HCl in THF, followed by neutralization of the resulting residue, produced δ-coniceine (**12**) having properties identical to those reported in the literature.[19] The optical purity of the final product also establishes that there was

(12) Racemic slaframine synthesis: (a) Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1994**, *35*, 9779. (b) Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695. (c) Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 20, 3681. (d) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.

(13) Enantioselective slaframine synthesis: (a) Knight, D. W.; Sibley, A. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2179. (b) Szeto, P.; Lathbury, D. C.; Gallagher, T. *Tetrahedron Lett.* **1995**, *36*, 6957. (c) Gmeiner, P.; Junge, D.; Kaertner, A. *J. Org. Chem.* **1994**, *59*, 6766. (d) Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144. (e) Knight, D. W.; Sibley, W. A. *Tetrahedron Lett.* **1993**, *34*, 6607. (f) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802. (g) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977. (h) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. (i) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469. (j) Kang, S. H.; Kim, J. S.; Youn, J.-H. *Tetrahedron Lett.* **1998**, *39*, 9047. (k) Carretero, J. C.; Arrayás, R. G. *Synlett* **1999**, 49.

(14) For preliminary work in this area see: Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1990**, *31*, 5689.

(15) Sibi, M. P.; Christensen, J. W.; Li, B.; Renhowe, P. *J. Org. Chem.* **1992**, *57*, 4329.

(16) The prolinal is stable to fast flash column chromatographic purification and is optically stable to freezer storage for up to a week. Generally it was used without purification.

(17) Kunz, H. *Justus Liebig Ann. Chem.* **1973**, 2001.

(18) For a general discussion on oxido ylides see: Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

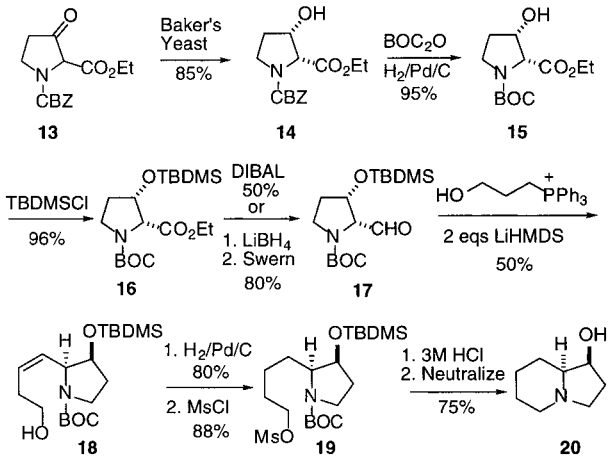
(19) Ringdahl, B.; Pinder, A. R.; Periera, W. E.; Oppenheimer, N. J., Jr.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1.

no racemization of the prolinal during the Wittig condensation. The overall yield from our sequence is 42%, which compares favorably with those in the literature.

Synthesis of 1-Hydroxyindolizidine

To access molecules containing a hydroxyl group in the 1-position of the indolizidine skeleton, as in slaframine, we required optically pure *cis*-3-hydroxyproline. This less abundant hydroxyproline isomer is found in collagen.[20] A relatively straightforward route to this proline involves the stereoselective reduction of 3-ketoproline. The synthesis of the required 3-ketoproline has been achieved through an unsymmetrical Dieckmann condensation by Rapoport and co-workers.[21] Thus, condensation of glycine methyl ester with ethyl bromopropionate provided the required amine, which was subsequently protected as its CBZ derivative.[22] Dieckmann condensation under the conditions established by Rapoport provided 3-ketoproline ethyl ester in 35% yield.[23] The bakers' yeast mediated reduction of *N*-BOC-3-ketoproline ethyl ester had been reported in the literature to provide the cis-*N*-BOC-3-hydroxyproline ethyl ester in 64% chemical yield as a single isomer (Scheme 3).[24] The configuration of the

Scheme 3



reduction product was also established in this study and shown to be 2*R*,3*S*. We have found that the bakers' yeast reduction of the corresponding *N*-CBZ compound provided the product with the same absolute stereochemistry[25] but in higher enantiomeric purity. Furthermore, we were able to improve chemical yields (85%) by immobilizing the yeast in a calcium alginate matrix following the procedure of Nakamura.[26] The next step involved the preparation of the aldehyde precursor for the Wittig condensation. The hydroxyl group in **15** was protected as its *tert*-butyldimethylsilyl (TBDMS) ether. Initially, we attempted the selective reduction of the ethyl ester **16** to the prolinal **17** using DIBAL. This reduction proceeded in very poor yields (average yields of 50%). The preparation of **17** from **16** could also be achieved by a two-step sequence involving the complete reduction of the ester to the alcohol followed by Swern oxidation. The lithium borohydride reduction on alcohol was quite slow, taking as long as 3 days in refluxing ether, but good yields (80%) were generally obtained. Changing to a higher boiling solvent like THF led to considerable decomposition. These difficulties in reduction were attributed to steric hindrance.

Now with access to the desired aldehyde, the next step was the Wittig condensation with the three-carbon synthon. Condensation of crude aldehyde **17** with the three-carbon synthon under the previously established conditions provided a mixture of *cis*- and *trans*-olefins **18** in 50% yield.[27] Completion of the synthesis followed the same reaction sequence as described earlier for *δ*-coinceine. Hydrogenation followed by mesylation of the primary hydroxyl group furnished **19**. Treatment of **19** with 3 M HCl, followed by careful neutralization of the reaction mixture, resulted in deprotection of both the BOC and the silyl protecting group. Neutralization resulted in cyclization of the six-membered ring to provide compound **20** which exhibited properties identical to those reported in the literature.[28] The overall yield for the sequence is 10.2%, starting from **13** (using the DIBAL sequence) or 16.3% (using the $LiBH_4$/oxidation sequence).

Synthesis of 6-Aminoindolizidine

Having established the synthesis of the 1-hydroxyindolizidine, we embarked on the total synthesis of 6-aminoindolizidine alkaloids. To realize this goal, we required a three-carbon synthon, and we envisaged that this could be derived from an amino acid precursor. We had several goals in mind for this choice: (1) to derive the primary amino group in the final target from the amino functional group in the precursor amino acid, (2) to possess a nucleophilic center for the Wittig condensation reaction, (3) to incorporate an electrophilic center for the final ring construction, and (4) the availability of either antipode of the starting amino acid for analogue synthesis.

We have previously reported the synthesis of a nucleophilic alaninol synthon prepared in five steps from serine and have illustrated its chemistry in a number of Wittig

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(21) Prepared in three steps with 25% overall yield following the procedure of Blake, J.; Wilson, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293.

(22) Feil, P. D.; Vercellotti, J. R. *Carbohydr. Res.* **1973**, *31*, 311.

(23) For an alternative regioselective Dieckmann condensation proceeding in higher overall yields see: Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209.

(24) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 509. This procedure utilizes BOC-3-ketoproline ethyl ester as the substrate. For a detailed experimental account and characterization data see ref 13a. For selected and recent syntheses of *syn*-3-hydroxyprolines see: (a) Sundram, H.; Golebiowski, A.; Johnson, C. R. *Tetrahedron Lett.* **1993**, *35*, 6975. (b) Knight, D. W.; Sibley, A. W. *Tetrahedron Lett.* **1993**, *34*, 6607. (c) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1313. (d) Jurczak, J.; Prokopowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107. (e) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 6213. (f) Gotschi, E.; Jenny, C.-J.; Reindl, P.; Ricklin, F. *Helv. Chim. Acta* **1996**, *79*, 2219. (g) Mulzer, J.; Meier, A.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566. (i) Dell'Uomo, N.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Monache, G. D. *Tetrahedron: Asymmetry* **1996**, *7*, 181.

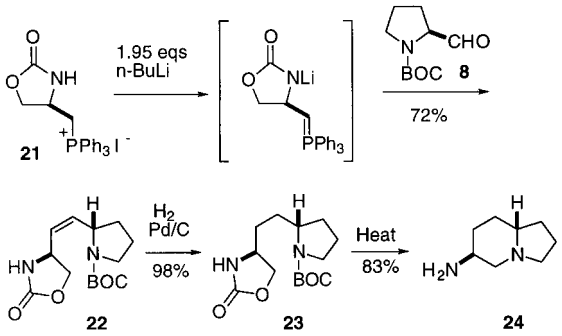
(25) The optical purity and stereochemistry were established by conversion to the known *N*−BOC-protected proline and by comparison of spectral data and rotation values. Additionally, the optical purity was established by HPLC analysis of the 3,5-dinitrobenzoates on a Pirkle column and by MPTA derivatives.

(26) Nakamura, K.; Kawai, Y.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1989**, *30*, 2245 and references therein.

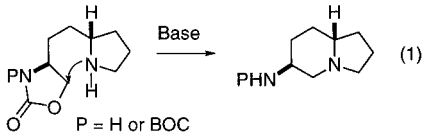
(27) One explanation for the low yield is the observed migration of the TBDMS protecting group to the alkoxide oxygen during the Wittig reaction.

(28) (a) Harris, C. M.; Harris, T. M. *Tetrahedron Lett.* **1987**, *28*, 2559. (b) Takahata, H.; Tajima, M.; Banba, Y.; Mosome, T. *Chem. Pharm. Bull. Jpn.* **1989**, *37*, 2550 and references therein.

Scheme 4



condensations.[29] Utilizing the synthon **21** derived from D-serine, we prepared the condensation product with the prolinal **8**, resulting in alkene **22** exclusively as the cis isomer (Scheme 4).[30] Catalytic hydrogenation of **22** provided the saturated precursor **23** for testing our new annulation strategy. Initially, our plan was to develop an anionic ring closure reaction in which the proline nitrogen was deprotected and attack of the ionic nitrogen at the 5-position of the oxazolidinone would result in the desired product (eq 1). All attempts to carry out such a sequence were unsuccessful.



(1)

In the course of routine GC−mass spectral characterization of **23** we noticed that the base peak had a *m/e* 140, a mass which correlates for compound **24**. This suggested that **23** had undergone loss of two molecules of carbon dioxide and a molecule of isobutylene to furnish **24**. Control experiments indicated that **23** was indeed undergoing thermolysis at the injection port of the GC to provide **24**. In addition, literature precedence suggested that the BOC group could be thermally deprotected in solution, or as a neat melt, to give the free amine.[31] On the basis of these observations, thermolysis of **23** as a neat compound in a sealed tube at 250 °C gave the cyclized product **24** in high chemical yield. This mode of nucleophilic ring opening of an oxazolidinone at the 5-position is rare.[32] There are several advantages to the thermolytic cyclization. These are neutral reaction conditions, gaseous byproducts, high yields, fast and clean reactions, and easy isolation of air-sensitive amine products. This novel bond construction methodology thus opens new avenues for the versatile oxazolidinones. The product **24** corresponded exactly (by carbon and proton NMR, GC/MS, and IR) to the known spectra of desacetoxyslaframine, supplied by Dr. William Pearson.[33] Thus, the cyclization could be accomplished thermolytically. The synthesis of desacetoxyepislaframine proceeded in 47% overall yield (starting from *N*-BOC proline **6**) and could be prepared in gram quantities through the use of a flow pyrolysis apparatus (see the Experimental Section).

Table 1. Effect of Additives on Thermal Cyclization of 23

entry	atmosphere	yield[a] (%)
1	argon	82
2	ammonia	71
3	carbon dioxide	88
4	vacuum	77
5	argon + NH_4OH	65
6	argon + water	68
7	HCl	83

[a] Yields are from GC analysis with benzylamine (added after thermolysis) as an internal reference.

To evaluate the proper temperature at which to perform the pyrolysis, we first took a small amount of the precursor and observed the temperature at which gas began to evolve when placed on a Fischer−Johns melting point apparatus. Gas evolution began at about 220 °C and persisted until completion at about 250 °C. This qualitative experiment was further verified by a thermal gravimetric analysis (TGA) which showed a maximum rate of mass change at 248 °C. We were unable to see any evidence of an intermediate product being formed in the TGA experiment.[34] This lends support that both deprotection and cyclization are occurring nearly simultaneously. We also evaluated the effect of additives on the thermolytic annulation reaction, and the results from these experiments are tabulated in Table 1. Additives, regardless of their nature, did not affect the cyclization to a large extent (entries 1, 2, 3, 5, and 6). On the basis of work by Poindexter et al.,[35] on acid-catalyzed preparation of ureas from oxazolidinones, the effect of acid on the cyclization was investigated. The chemical yield for the cyclization in the presence of HCl was similar to the control reaction (compare entry 7 with entry 1).

Synthesis of (−)-Slaframine

Having established the cyclization methodology for the 6-aminoindolizidine structure, the synthesis of slaframine required the condensation of protected 3-hydroxyprolinal with the Wittig synthon derived from **21**. Reaction of the aldehyde **17** with the ylide derived from **21** gave very low yields of the alkene (average of 25%). Even flash chromatography of the sensitive aldehyde immediately before the reaction did not improve yields. In an attempt to evaluate the factors which contribute to the unexpectedly

(29) Sibi, M. P.; Renhowe, P. *Tetrahedron Lett.* **1990**, *31*, 7407.

(30) In a previous communication (ref 15) we reported that the stereochemistry was trans based on the apparent coupling of the overlapping olefin protons in $CDCl_3$. Further decoupling studies of the resolved olefinic protons in benzene-d_6 indicate that it is instead the cis isomer that is formed. See the Experimental Section for coupling constants indicative of the cis geometry.

(31) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

(32) For reports on intermolecular β-functionalization of cyclic sulfamidates see: (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 881. (b) Alker, D.; Doyle, K. J.; Harwood: L. M.; McGregor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 877. (c) Zubovics, Z.; Tody, L.; Varro, A.; Rabloczky, G.; Kurthy, P.; Duortsak, P.; Jerkovich, G.; Tomori, E. *J. Med. Chem.* **1986**, *21*, 370. (d) White, G. J.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 3177. (e) Gautun, H. S. H.; Carlsen, P. H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1667.

(33) Reference 13h. We thank Professor Pearson, University of Michigan, for providing the spectra and an authentic sample of slaframine.

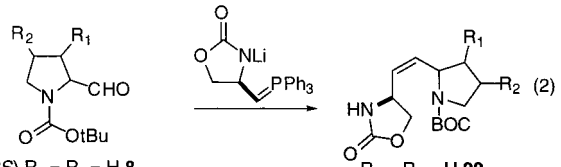
(34) Arguably, the observed change in mass could have only been from evaporation of substrate. To disprove this argument, a thermogravimetric analysis (TGA) was run on the *tert*-butyldimethylsilyloxy (OTBDMS) derivative **35**. If evaporation were the phenomenon being observed, this compound should exhibit a higher value for the first derivative of mass change because of its higher boiling point. When a TGA was run on this derivative, it was found that the temperature of the first-derivative maximum is similar to that of the parent, so the observed mass change must be a result of cyclization and subsequent evaporation of product.

(35) Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257.

low yields of the Wittig reaction, we undertook a systematic study of the reaction of a series of aldehydes under controlled conditions. The results are shown in Table 2. Four different aldehydes were chosen for the study. Where steric hindrance is at its minimum as is the case for aldehyde **8**, the reaction is slow at low temperatures and yields increase as temperature is increased (compare entry 1 with entry 2). Introduction of a 3-(OTBDMS) substituent on the proline ring (**17**) led to low yield of the alkene regardless of the reaction conditions (entries 3−5). We attributed the low yield to the bulky BOC and noncoordinating as well as bulky TBDMS protecting groups flanking the reaction center. As a possible answer to these concerns we switched the hydroxyl protecting group to the less sterically encumbering (trimethylsilyl)ethoxymethyl (SEM) group. The ability of the SEM protecting group to coordinate to lithium counterions was another factor in our selection. The yield of the alkene using the SEM-protected aldehyde **25** was higher and the reactions more reproducible than with the TBDMS-protected prolinal (entries 6 and 7). The effect of the protecting group on chemical yields using the 4-hydroxyprolinals was opposite to that observed for the 3-OH series. The highest chemical yields in the Wittig reaction were obtained using the 4-OTBDMS aldehyde **26** (entries 8 and 9).[36] The double bond stereochemistry was cis in every experiment conducted between the oxazolidinone ylide and the prolinals. This stereoselectivity parallels the exclusive cis-selectivity observed with glyceraldehyde acetonide.[37] Detailed analyses of the stereochemical issues with the ylide derived from **21** are discussed in a recent paper.[38]

Catalytic hydrogenation of the alkene (**27** or **28**) using H_2/Pd/C gave the saturated compounds **30** and **31**, respectively, in excellent yields (Scheme 5). Removal of the silicon protecting groups was carried out using fluoride ion conditions. The OSEM deprotection was more difficult than for the TBDMS compound. TBAF-mediated deprotection could only be realized by heating the substrate to 80 °C in HMPA for several hours.[39] Residual solvent removal had to be done carefully since the polar product had nontrivial water solubility, resulting in losses during copper sulfate washings. A 90% yield was eventually achieved after several trials, providing the identical product as in the TBDMS sequence. Having synthesized the cyclization precursor for slaframine, what remained to complete the synthesis was application of the new cyclization methodology. Since slaframine itself

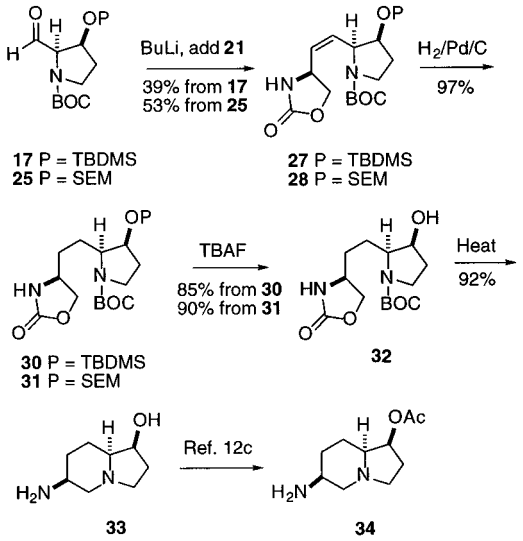
Table 2. Effect of the *O*-Protecting Group on Yields in Wittig Condensation



entry	aldehyde	rxn conditions	yield[a] (%)
1	**8**	−78 °C, 2.5 h	43
2	**8**	−78 °C, 2.5 h to rt	75
3	**17**	−78 °C, 2.5 h	32
4	**17**	−78 °C, 2.5 h to rt	32
5	**17**	−78 °C, 10 h	39
6	**25**	−78 °C, 2.5 h	40
7	**25**	−78 °C, 2.5 h to rt	53
8	**26**	−78 °C, 2.5 h	80
9	**26**	−78 °C, 2.5 h to rt	85

[a] Isolated yield after chromatography.

Scheme 5



is an unstable compound, cyclization should be made the last step in the sequence because of the ease in working up the thermolysis product. Initial experiments were performed on the *O*-acetylated precursor. The elevated temperatures required for the cyclization resulted in approximately 30% of elimination product. Therefore, the convenience of a final step cyclization had to be sacrificed to get a clean product. Cyclization of the alcohol precursor **32**, however, led to deacetoxyslaframine in very good yield. By using the selective acetylation procedure of Harris,[12c] the thermolysis product **33** was converted to (−)-slaframine **34**. The compound was identical in all respects to the properties reported for slaframine in the literature ($[\alpha]_D^{24}$ − 33.1°, c = 0.718, $CHCl_3$).[13h] The synthetic slaframine was further characterized by the preparation of the diacetate. The overall yield of slaframine is 10.4% for the **13** → **17** → **34** sequence and 18.4% for the **13** → **25** → **34**.

Synthesis of 2-Hydroxy-6-aminoindolizidine

To further demonstrate the generality of our methodology, we undertook the synthesis of the slaframine

(36) The corresponding 4-OSEM [2-(trimethylsilyl)ethoxymethyl] aldehyde gave only a 19% yield of the olefin [the (*Z*)-isomer only].

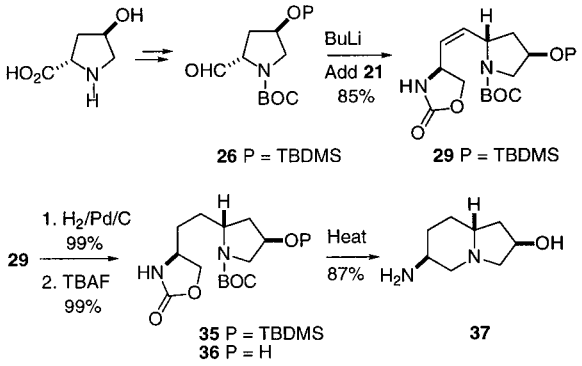
(37) A working hypothesis for the variation in chemical yield with changes in the protecting group is as follows. Chelation of a lithium counterion with the aldehyde oxygen and the BOC group or the 3-oxygen substituent could account for the differences in reactivity. Of the two different protecting groups, the bulky TBDMS group precludes lithium complexation with its oxygen whereas the smaller OSEM forms stable lithium complexes. Although the BOC group is sterically demanding, the carbonyl oxygen is still quite open for intramolecular complexation. Lithium complexation holds the aldehyde in various conformations that either open the carbonyl for nucleophilic attack by the ylide or block the incoming ylide, resulting in lowered chemical yields when the approach is disfavored. For comprehensive reviews on oxido and semistabilized ylides see:: Vedejs, E.; Peterson. M. J. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; Vol. 21, Chapter 1. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863; ref 18.

(38) For details and a discussion on the origins of the selectivity see: Sibi, M. P.; Rutherford, D. R.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.*, in press.

(39) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.

analogue that contained the hydroxyl group at the 2-position. The starting material required for this synthesis was the readily available, naturally occurring 4-hydroxyproline. Attempts to first protect the nitrogen function followed by methyl esterification with methyl iodide and DBU as in the proline case failed in that a large amount of *O*-methylation occurred (Scheme 6). We

Scheme 6



therefore first protected the acid functionality by heating a methanol solution of 4-hydroxyproline while bubbling in HCl gas, thus resulting in the quantitative formation of the HCl salt. The nitrogen was then protected with BOC in excellent yield. Hydroxyl protection with either the SEM or TBDMS proceeded smoothly. Treatment of the protected esters with 3 equiv of DIBAL provided the requisite aldehyde (**26**) as a stable solid following flash chromatographic purification over silica gel. The *O*-TBDMS-protected aldehyde **26** underwent the Wittig reaction with ylide derived from **21** in exceptionally good yield, forming exclusively the cis isomer **29** under a variety of conditions. Reduction and silyl deprotection provided the cyclization precursor **36** in very high yield. Flash vacuum pyrolysis provided compound **37** in 87% yield for a combined overall yield. This compound was characterized as its dihydrochloride. The overall yield for **37** starting from 4-hydroxyproline is 33%.

Conclusions

We have shown that several indolizidine alkaloids and analogues can be readily obtained through a convergent sequence starting from compounds derived from proline and serine using a novel annulation sequence. The overall yields for the target molecules are high and compare favorably with those in the literature. Additionally, our modular approach provides a convenient handle for the preparation of diastereomeric compounds of the natural products as well other analogues.

Experimental Section

General Methods. Serine and proline were purchased from Chemical Dynamics Corp. and were used without purification. Many of the compounds exhibited complex NMR spectra due to hindered rotation, and wherever possible the resonances due to the minor rotamer are indicated with (min) notation.

(+)-*N*-*tert*-Butyloxycarbonyl-2-(1-(*Z*)-buten-4-hydroxy)-pyrrolidine 9 (cis). Into a 25 mL round-bottom flask, under N_2, was placed 5.36 mL (25.4 mmol) hexamethyldisilazane. The flask was cooled to 0 °C, and 17.91 mL of 1.42 M *n*-BuLi in hexane was added dropwise, forming a white precipitate which dissolved when the reagent was warmed to room temperature. The resulting solution was added dropwise over 5 min to a suspension of 5.92 g (12.1 mmol) of phosphonium salt (prepared from 3-chloropropanol and triphenylphosphine) in 50 mL of THF. The clear orange solution was stirred for 1 h, and cooled to −78 °C in a dry ice/2-propanol bath, and a solution of **8** (12.1 mmol in 20 mL of THF) was added dropwise over 5 min. The dry ice bath was removed, and the reaction mixture was allowed to warm to room temperature while being stirred for 1 h. A solution of 0.65 g of NH_4Cl in 2 mL of H_2O was added at once, and THF was stripped in vacuo. The residue was taken up in equal volumes of H_2O and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvent gave 5.25 g of a yellow oil. The crude product was purified by flash chromatography over silica gel (eluted with 3:1 hexane/EtOAc), giving 2.16 g (76%) of pure alkene **9** as a mixture of 2:1 *E*/*Z* isomers. A second chromatographic purification of the mixture provided pure cis and trans isomers. Cis isomer **9**: R_f 0.42 (50:50 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.61 (m, 1H), 1.80 (m, 1H), 1.89, (m, 1H), 2.07 (m, 2H), 2.75 (m, 1H), 3.35 (br, 2H), 3.60 (m, 1H), 3.77 (br, 1H), 4.58 (br, 1H), 5.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 28.5, 30.6, 32.3, 46.5, 53.9, 61.5, 79.6, 127.6, 130.0, 154.7; IR (neat) 3442, 2973, 1696 cm^{-1}; MS (70 eV) *m*/*e* 196 (2, $M^+ - C_2H_5O$), 140 (82), 57 (100); $[\alpha]^{26}_D$ +34.0 (*c* 1.10, EtOH). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found: C, 64.67; H, 9.81; N, 5.88.

(−)-*N*-*tert*-Butyloxycarbonyl-2-(1-(*E*)-buten-4-hydroxyl)-pyrrolidine 9 (trans): R_f 0.37 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.56−1.68 (m, 1H), 1.69−1.86 (m, 2H), 1.87−2.20 (m, 1H), 2.13−2.28 (br, 2H), 2.77 and 2.90 (br, 1H), 3.20−3.39 (br, 2H), 3.47−3.62 (m, 2H), 4.09−4.22 (br, 1H), 5.30−5.47 (m, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 23.1, 28.3, 32.0, 35.4, 46.2, 58.6, 61.3, 79.0, 126.8, 133.5, 154.4; IR (film) 3434, 2976, 1697 cm^{-1}; MS (70 eV) *m*/*e* 211 (1, $M^+ - CH_2O$), 155 (58), 57 (100); $[\alpha]^{26}_D$ −34.9 (*c* 1.12, EtOH). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found: C, 64.62; H, 9.54; N, 5.77.

(−)-*N*-*tert*-Butyloxycarbonyl-2-(4-hydroxybutyl)pyrrolidine (10). A 50 mL round-bottom flask containing a 10 mL EtOAc suspension of 200 mg of 10% Pd on carbon was evacuated and flushed three times with hydrogen. A solution of 1.35 g of alkene **9** in 5 mL of EtOAc was added, and the solution was allowed to stir overnight under a hydrogen atmosphere, at which time TLC indicated complete consumption of starting material. The mixture was filtered through a bed of Celite and evaporated to provide 1.36 g of crude product. Purification by flash chromatography (eluted with 1:1 EtOAc−hexane) provided 1.29 g (95%) pure alkane **10** as a clear oil: R_f 0.28 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27−1.50 (m, 4H), 1.44 (s, 9H), 1.53−1.71 (m, 2H), 1.72−1.98 (m, 4H), 3.24−3.49 (m, 2H), 3.57−4.86 (m, 3H); extra resonances due to hindered rotation; ^{13}C NMR (65 MHz, $CDCl_3$) δ 22.5, 23.0 and 23.6, 28.5, 29.9 and 30.5, 32.3 and 32.4, 33.6 and 34.3, 46.0 and 46.4, 57.1, 62.4, 78.9, 154.7; IR (film) 3437, 2972, 1678 cm^{-1}; MS (50 eV) *m*/*e* 243 (0.02, M^+), 114 (72), 70 (100); $[\alpha]^{26}_D$ −50.3 (*c* 1.36, EtOH); Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.17; H, 10.36; N, 5.76; found: C, 64.11; H, 10.34; N, 5.85.

***N*-*tert*-Butyloxycarbonyl-2-(4-methanesulfonylbutyl)-pyrrolidine (11).** To a 25 mL round-bottom flask was added 436 mg (1.8 mmol) of alcohol **10** followed by 10 mL of CH_2Cl_2. The mixture was cooled to 0 °C, and 0.15 mL (2.0 mmol) of methanesulfonyl chloride was added, followed by 0.28 mL (2.0 mmol) of Et_3N. The mixture was allowed to stir for 30 min, when 10 mL of H_2O was added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and evaporated. The crude mesylate was purified by flash chromatography through silica gel (eluted with 90:10 hexane/EtOAc), providing 552 mg (96%) of pure mesylate **11**: R_f 0.50 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.3−1.48 (m, 4H), 1.42 (s, 9H), 1.55−1.70 (m, 2H), 1.70−2.00 (m, 4H), 2.97 (s, 3H), 3.20−3.42 (m, 2H), 3.63−3.80 (m, 1H), 4.19 (t, J = 6.5 Hz, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 154.5, 78.9, 69.9, 56.8, 46.2, 37.2, 33.6, 30.1, 29.0, 28.5, 23.3, 22.2; IR (film) 2972, 2942, 1689 cm^{-1}; MS (70 eV) *m*/*e* 250 (1.5); $[\alpha]^{26}_D$ −38.0 (*c* 1.46,

EtOH). Anal. Calcd for $C_{14}H_{27}NO_5S$: C, 52.31; H, 8.46; N, 4.35. Found: C, 51.87; H, 8.37; N, 4.33.

(−)-*δ*-Coniceine (12). A solution of 4.92 g of mesylate **11** in 20 mL of dioxane and 20 mL of 3 M HCl was stirred overnight at room temperature under a nitrogen atmosphere. The solvent was stripped, leaving an oily yellow residue, which was taken up in water and washed with an equal amount of CH_2Cl_2. The aqueous portion was adjusted to pH 14 with 1 M NaOH and stirred for 3 h to ensure complete neutralization. The mixture was extracted into CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. Vacuum distillation provided 1.46 g (74%) of pure **12**: bp 70 °C, 38 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.25 (m, 2H), 1.38−1.43 (m, 1H), 1.56−1.59 (m, 1H), 1.60−1.64 (m, 2H), 1.65−1.66 (m, 1H), 1.72−1.85 (m, 3H), 1.94 (dt, J = 11.29, 3.22 Hz, 1H), 2.04 (app q, J = 8.96 Hz, 1H), 3.02 (td, J = 8.86, 2.15 Hz, 1H), 3.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 24.6, 25.6, 30.6, 31.2, 53.1, 54.4, 64.4; $[\alpha]^{26}_D$ −10.8 (*c* 1.76, EtOH).

(+)-*N*-*tert*-Butyloxycarbonyl-2-(1-(*Z*)-buten-4-hydroxyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine (18 cis). To a 25 mL round-bottom flask was added 0.57 g (1.59 mmol) of phosphonium salt derived from 3-chloropropanaol, followed by 5 mL of dry THF. A solution of 2.51 M LiHMDS (3.19 mmol) in hexane was added dropwise over a 5-min period, and the reaction was allowed to stir for 1 h, resulting in a deep yellow-orange solution of ylide. An additional 5 mL of THF was added, and the ylide solution was cooled to −78 °C. A solution of 0.48 g of aldehyde **17** in 2 mL of THF was added dropwise, stirred for 10 min, and allowed to warm to room temperature. A 5 mL saturated NH_4Cl solution was added, and THF was removed under vacuum. The residue was partitioned between CH_2Cl_2 and water and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and evaporated, leaving 0.95 g of crude product. Purification by flash chromatography over silica gel (eluted with 90:10 hexane/EtOAc) provided 0.27 g of pure alkene as a 2:1 mixture of cis and trans isomers. Cis isomer: R_f 0.55 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.40 (s, 9H), 1.75−2.02 (m, 2H), 2.03−2.18 (m, 1H), 3.13−3.52 (m, 3H), 4.27 (app q, J = 6.0 Hz, 1H), 4.48−4.60 (m, 1H), 5.46 (app t, J = 10.5 Hz, 1H), 5.57 (dd, J = 4.5, 10.5 Hz, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −4.9, 18.0, 25.6, 28.4, 30.8, 32.8, 43.8, 57.6, 61.5, 72.8, 79.7, 129.3, 154.7; IR (film) 3453, 2956, 1693 cm^{-1}; $[\alpha]^{26}_D$ +14.4 (*c* 1.85, EtOH). Anal. Calcd for $C_{19}H_{37}NO_4Si$: C, 61.41; H, 10.03; N, 3.76. Found: C, 61.27; H, 9.95; N, 3.72.

(−)-*N*-*tert*-Butyloxycarbonyl-2-(1-(*E*)-buten-4-hydroxyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine (18 trans). R_f 0.52 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.42 (s, 9H), 1.73−1.86 (m, 1H), 1.86−2.01 (m, 1H), 2.13−2.37 (m, 2H), 3.27−3.51 (m, 2H), 3.61 (dd, J = 6.0, 6.0 Hz, 2H), 4.09−4.21 (br s, 1H), 5.40−5.55 (m, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −4.9, 18.1, 25.7, 28.4, 32.0, 35.7, 43.6, 61.2, 62.6, 73.1, 79.4, 130.5, 154.6; IR (film) 3436, 2955, 1693 cm^{-1}; $[\alpha]^{26}_D$ −3.9 (*c* 1.73, EtOH). Anal. Calcd for $C_{19}H_{37}NO_4Si$: C, 61.41; H, 10.03; N, 3.76. Found: C, 61.30; H, 9.96; N, 3.76.

(+)-*N*-*tert*-Butyloxycarbonyl-2-(4-methanesulfonylbutyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine (19). (+)-*N*-*tert*-Butyloxycarbonyl-2-(4-hydroxybutyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine. A 50 mL round-bottom flask containing a 10 mL ethyl acetate suspension of 200 mg of 10% Pd on carbon was evacuated and flushed three times with hydrogen. A solution of 0.83 g of alkene **18** in 3 mL of ethyl acetate was added, and the solution was allowed to stir overnight under a hydrogen atmosphere, at which time TLC indicated complete consumption of starting material. The mixture was filtered through a bed of Celite and evaporated to provide 1.00 g of crude product. Purification by flash chromatography over silica gel (eluted with 10:40 EtOAc/hexane) provided 0.66 g (80%) of pure saturated alcohol as a clear oil: R_f 0.47 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.44 (s, 9H), 1.35−1.98 (m, 8H), 1.97 (s, 1H), 3.30−3.38 (m, 2H), 3.60−3.67 (m, 2H), 3.60−3.75 (m, 1H), 4.23−4.32 (m, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 155.1, 79.2, 72.0, 62.8, 59.7, 43.0, 32.9, 31.8, 28.5, 25.7, 22.6, 18.0, −4.7, −5.0; IR (film) 3450, 2954, 1694 cm^{-1}; $[\alpha]^{26}_D$ +20.9 (*c* 0.94, EtOH). Anal. Calcd for $C_{19}H_{39}NO_4Si$: C, 61.08; H, 10.52; N, 3.74. Found: C, 60.84; H, 10.22; N, 3.61.

To a 25 mL round-bottom flask was added 610 mg (1.8 mmol) of the alcohol prepared above, followed by 10 mL of CH_2Cl_2. The mixture was cooled to 0 °C, and 0.15 mL (2.0 mmol) of methanesulfonyl chloride was added, followed by 0.28 mL (2.0 mmol) of Et_3N. The mixture was warmed to room temperature and allowed to stir for 30 min, at which time water was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered, and evaporated to give 0.70 g of crude product which was purified by flash chromatography through silica gel (eluted with 4:1 hexane/EtOAc), providing 659 mg (88%) of pure mesylate **19**: R_f 0.60 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.90 (s, 9H), 1.46 (s, 9H), 1.40−1.54 (m, 3H), 1.65−1.88 (m, 4H), 1.90−2.03 (m, 1H), 3.00 (s, 3H), 3.28−3.41 (m, 2H), 3.65−3.80 (m, 1H), 4.20−4.33 (m, 3H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −5.0, −4.7, 18.0, 22.5, 25.7, 28.4, 29.4, 32.0, 37.3, 42.9, 59.5, 70.0, 71.9, 79.2, 154.9; IR (film) 2957, 2932, 1699 cm^{-1}; $[\alpha]^{26}_D$ +14.6 (*c* 1.90, EtOH). Anal. Calcd for $C_{20}H_{41}NO_6SSi$: C, 53.18; H, 9.14; N, 3.10. Found: C, 53.34; H, 8.53; N, 3.12.

(+)-1-Hydroxyindolizidine (20). To a 25 mL round-bottom flask containing mesylate **19** was added 5 mL of dioxane followed by 5 mL of 3 M HCl. The mixture was stirred for 12 h, and the solvent was stripped. The residue was taken up in 10 mL of water and washed three times with 5 mL portions of CH_2Cl_2. The combined organics were back-extracted with 5 mL of water, and the combined aqueous fractions were adjusted to pH 13 with 1 M NaOH, allowed to stir 30 min, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to provide 0.1396 g (75%) of **20** as a clear oil which was found to be 98% pure by GC analysis: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.47−1.70 (m, 6H), 1.85 (m, 1H), 1.92 (m, 1H), 2.14 (m, 1H), 3.07 (m, 2H), 3.38 (s, 1H), 4.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 25.0, 25.1, 33.2, 52.8, 53.5, 68.9, 72.6; IR (film) 3361, 2937, 1442 cm^{-1}; $[\alpha]^{26}_D$ +20.2 (*c* 1.03, EtOH).

Alkene 22. To a 100 mL, flame-dried, three-neck, round-bottom flask was added 3.69 g (7.55 mmol) of phosphonium salt **21** derived from D-serine. The flask was flushed with argon and charged with 30 mL of THF. The resulting suspension was cooled to −78 °C, and 5.89 mL (14.72 mmol) of *n*-BuLi (2.50 M in hexane) was added dropwise over a 5-min period. The mixture was allowed to stir at −78 °C for 1 h, generating a deep orange colored slurry of ylide. A solution of 1.50 g (7.55 mmol) of aldehyde **8** in 5 mL of THF was added dropwise to the ylide, and the resulting mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred an additional 30 min. A solution of saturated NH_4Cl was added to the reaction, and THF was removed via rotoevaporator. The residue was partitioned between ethyl acetate and water, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine and dried over $MgSO_4$. Filtration and evaporation of solvent afforded 2.99 g of crude product. Purification via flash chromatography over silica gel (eluted with 70:30 EtOAc/hexane) provided 1.46 g (72%) of **22** which may be recrystallized from CH_2Cl_2/hexane: mp 72−74 °C; R_f 0.67 (20:80 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.58−1.67 (m, 1H), 1.85−1.98 (m, 2H), 2.02−2.11 (m, 1H), 3.32−3.39 (m, 2H), 4.05 (dd, J = 8.3, 6.7 Hz, 1H), 4.49−4.56 (m, 1), 4.92 (dd, J = 14.5, 7.5 Hz, 1H), 5.44 (app ddd, J = 10, 20, 10 Hz, 2H (trans)), 5.57 (t, J = 9 Hz, 1H (cis)), 5.71 (dd, J = 5, 9 Hz, 1H (cis)), 6.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 28.4, 31.5, 46.4, 48.8, 53.0, 69.8, 79.8, 128.4, 134.3, 154.3, 158.8; IR (neat) 3306, 1764, 1679 cm^{-1}. Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 52.31; H, 8.47; N, 4.36. Found: C, 51.50; H, 8.51; N, 4.40.

Alkane 23. To a 25 mL, round-bottom flask, containing 535.9 mg (1.900 mmol) of alkene **22**, was added 10 mL of methanol followed by 50 mg of 10% Pd on activated carbon.

The flask was equipped with a three-way stopcock connected to a vacuum takeoff and a hydrogen balloon. The flask was purged under aspirator vacuum and flushed three times with hydrogen. The catalyst was activated by placement in an ultrasonic bath for 5 min. The bath was removed, and the reaction was allowed to stir at room temperature for 4 h, at which time TLC indicated total consumption of **22**. The reaction mixture was filtered through Celite and evaporated to give 528.3 mg (98%) of alkane **23**. The crude product may be recrystallized from CH_2Cl_2/hexane. *Note*: It has been observed that olefin hydrogenation sometimes occurs at slower rates than indicated here. This is presumably due to phosphorus impurities from the Wittig reaction poisoning the catalyst. Rates may be increased by adding more catalyst, and/or by hydrogenation under higher H_2 pressure (∼3 atm): mp 133−133.5 °C; R_f 0.42 (20:80 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.30−2.00 (m, 8H), 3.20−3.50 (m, 2H), 3.70−3.80 (m, 1H), 3.90−4.10 (m, 2H), 4.45−4.55 (m, 1H), 6.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.7, 28.5, 30.1, 32.0, 46.4, 51.8, 55.9, 70.3, 79.3, 154.7, 159.6; IR (KBr) 3301, 1750, 1709 cm^{-1}; $[\alpha]^{26}_D$ −61.8 (*c* 1.02, EtOH). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.45; H, 8.63; N, 9.82.

(−)-8-*epi*-1-Desacetoxyslaframine (24). To a 5 mL round-bottom flask was added 250 mg of **23**. The flask was placed onto the apparatus shown (see the Supporting Information) which was evacuated to ∼1 Torr for 10 min. Argon flow was begun to the capillary inlet which resulted in an internal pressure measured at ∼3 Torr. Heating of the bottom of the flask was begun with a heat gun which first melted the solid precursor, followed by rapid boiling and gas evolution. The heat gun was used until a majority of the precursor had been driven through the pyrolysis tube and into the receiving end of the apparatus. Further heating of the reactant end of the apparatus with a Bunsen burner ensured both complete pyrolysis of precursor and quantitative transfer of product to the receiving end of the apparatus. Condensed product in the arm of the receiving end was driven down into the liquid N_2 cooled 10 mL trap with the aid of a heat gun.

The vacuum was shut off, and the apparatus was allowed to reach 1 atm of argon pressure before the nitrogen Dewar was removed. When the cold trap had reached room temperature, the product was washed down into the 10 mL flask with ∼5 mL of CH_2Cl_2 and fitted with a septum adapter possessing a sidearm vent. Dry HCl gas was bubbled into the solution via a 6-in. 18-gauge needle for 15 min, resulting in the formation of a white precipitate. Solvent was removed, leaving 180.9 mg of crude **24·HCl** which was dissolved in 3 mL of methanol; 3 mL of EtOAc was added, and the solution was placed in a freezer for 4 h, resulting in precipitation of 135.2 mg of white crystals. An additional 20.0 mg was obtained from concentration and precipitation of the mother liquor for a total yield of 155.2 mg (83%). The titration curve of 100 mg of the product with 0.1 M NaOH showed it to be the dihydrochloride salt of **24**. All data are of the free amine obtained by CH_2Cl_2 extraction of the neutralized product: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (dq, J = 12.1, 3.8 Hz, 1H), 1.14−1.40 (m, 4H), 1.56−1.87 (m, 7H), 2.08 (q, J = 8.8 Hz, 1H), 2.83−2.97 (m, 1H), 3.00 (dt, J = 8.6, 2.0 Hz, 1H), 3.16 (ddd, J = 10.3, 4.3, 1.6 Hz, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 21.4, 29.6, 29.8, 35.2, 48.6, 53.8, 61.8, 63.7; IR (film) 3339, 1619, 1581 cm^{-1}; MS (EI/70 eV) *m/e* 140 M^+ (5.5), 97 (87), 84 (100); $[\alpha]^{26}_D$ 4.7 (*c* 1.41 (free amine), 3M HCl); pK_{a1} = 6.7 (1+), pK_{a2} = 9.7 (2+).

OTBDMS Alkene 27. Prepared according to the Wittig reaction conditions established for the prolinal-derived compound: R_f 0.53 (50:50 hexane/EtOAc); ^{1}H NMR (400 MHz, C_6D_6) δ −0.07 (s, 6H), 0.9 (s, 9H), 1.37 (s, 9H), 1.50−1.54 (m, 2H), 3.00−3.03 (m, 1H), 3.11−3.19 (m, 1H), 3.74−3.80 (m, 2H), 4.33−4.37 (m, 1H), 4.44−4.48 (app t, J = 8.46, 1H), 4.55−4.61 (m, 1H), 5.10−5.14 (m, 1H), 5.33−5.38 (dt, J = 10.7, 0.8 Hz, 1H), 5.90 (s, 1H); from decoupling experiment, alkene coupling J = 11.3 Hz; ^{13}C NMR (100 MHz, C_6D_6) δ −4.9, 17.9, 25.6, 28.2, 30.0, 30.2, 43.4, 50.3, 56.4, 79.3, 128.3, 131.0, 153.8, 159.4. ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, 17.8, 25.5, 28.3, 32.4, 43.4, 49.9, 56.2, 70.9, 72.1, 79.3, 129.9, 130.3, 154.1, 159.8; IR (neat) 3278, 1759, 1693 cm^{-1}. Anal. Calcd for $C_{20}H_{36}N_2O_5Si$: C, 58.22; H, 8.79; N, 6.79. Found: C, 58.04; H, 8.96; N, 6.75.

OSEM Alkene 28. To a flame-dried, 50 mL, three-neck, round-bottom flask was added 1.35 g (2.77 mmol) of phosphonium salt **21**. The flask was flushed with argon and charged with 20 mL of THF. The resulting suspension was cooled to −78 °C, and 2.40 mL (14.72 mmol) of *n*-BuLi (2.24 M in hexane) was added dropwise over a 5-min period. The mixture was allowed to stir at −78 °C for 1 h, generating a deep orange-colored slurry of ylide. A solution of 0.95 g (2.77 mmol) of aldehyde **25**, in 3 mL of THF, was added dropwise to the ylide, and the resulting mixture was stirred at −43 °C (CO_2/acetonitrile) for 90 min, allowed to warm to room temperature, and stirred for an additional 30 min. A solution of saturated NH_4Cl solution was added to the reaction, and THF was removed via rotoevaporator. The residue was partitioned between ethyl acetate and water, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine and dried over $MgSO_4$. Filtration and evaporation of solvent afforded 1.78 g of crude product. Purification by flash chromatography over silica gel (eluted with 50:50 EtOAc/hexane) provided 0.58 g (52%) of alkene **28**: R_f 0.52 (20:80 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.88−0.99 (m, 2H), 1.42 (s, 9H), 1.85−2.02 (m, 1H), 2.10−2.22 (m, 1H), 3.24−3.52 (m, 2H), 3.55−3.63 (m, 2H), 4.00−4.08 (m, 1H), 4.18−4.27 (m, 1H), 4.60−4.72 (m, 5H), 4.81−4.95 (m, 1H), 5.55−5.65 (m, 2H); ^{1}H NMR (400 MHz, C_6D_6) δ 0.02 (s, 9H), 0.94−1.04 (m, 2H), 1.36 (s, 9H), 1.64−1.67 (m, 2H), 3.00−3.06 (m, 1H), 3.14−3.19 (m, 1H), 3.53−3.60 (m, 1H), 3.63−3.70 (m, 1H), 3.75−3.79 (app t, J = 7.5 Hz, 1H), 3.96−4.00 (m, 1H), 4.45−4.52 (m, 2H), 4.57 (s, 2H), 4.76−4.79 (m, 1H), 5.24−5.34 (m, 1H), 5.36−5.45 (m, 1H), 6.11 (s, 1H); from decoupling experiment, alkene coupling was found to be J = 11.3 Hz; ^{13}C NMR (65 MHz, $CDCl_3$) δ −1.5, 17.9, 28.4, 29.5, 43.3, 49.7, 55.1, 65.7, 70.1, 70.7, 79.8, 94.3, 130.2, 130.6, 154.1, 159.3. Anal. Calcd for $C_{20}H_{36}N_2O_6Si$: C, 56.04; H, 8.47; N, 6.54. Found: C, 56.37; H, 8.31; N, 6.45.

OTBDMS Alkane 30. Prepared according to the reaction conditions established for the prolinal-derived alkane in 97% yield: R_f 0.46 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10 (d, 6H), 0.91 (s, 9H), 1.47 (s, 9H), 1.56−1.75 (m, 2H), 1.75−1.90 (m, 2H), 1.90−2.05 (m, 2H), 3.24−3.40 (m, 2H), 3.65−3.95 (m, 2H), 3.95−4.05 (m, 1H), 4.27−4.34 (m, 1H), 4.44−4.52 (m, 1H,), 6.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.6, 25.7, 28.4, 31.9, 32.0, 43.3, 53.4, 59.2, 70.1, 71.6, 79.6, 155.3, 159.4; IR (neat) 3297, 1759, 1692 cm^{-1}; $[\alpha]^{20}_D$ 13.3 (*c* 1.41, EtOH). Anal. Calcd for $C_{20}H_{38}N_2O_5Si$: C, 57.94; H, 9.24; N, 6.76. Found: C, 58.48; H, 9.39; N, 6.75.

OSEM Alkane 31. To a 25 mL round-bottom flask, containing 519.7 mg (1.214 mmol) of alkene **28**, was added 10 mL of ethyl acetate, followed by 100 mg of 10% $Pd(OH)_2$ on activated carbon. The flask was fitted with a three-way stopcock connected to a vacuum takeoff and a hydrogen balloon. The flask was purged under aspirator vacuum and flushed three times with hydrogen. The catalyst was activated by placement in an ultrasonic bath for 5 min. The bath was removed, and the reaction was allowed to stir at room temperature for 24 h (or until TLC indicated total consumption of starting material). The reaction mixture was filtered through Celite, chromatographed over silica gel (eluted with 50:50 EtOAc/hexane), and evaporated to give 507.9 mg (97%) of alkane **31**: R_f 0.36 (20:80 hexane/EtOAc): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.90−0.97 (m, 2H), 1.40−1.46 (m, 2H), 1.43 (s, 9H), 1.60−1.68 (m, 2H), 1.82−1.93 (m, 1H), 2.03−2.14 (m, 1H), 3.30−3.40 (m, 2H), 3.53−3.70 (m, 2H), 3.80−3.96 (m, 2H), 3.97−4.03 (m, 1H), 4.15−4.22 (m, 1H), 4.44−4.52 (m, 1H), 4.66−4.73 (m, 2H), 6.20 (s, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −1.4, 18.1, 25.1, 28.4, 29.3, 31.8, 42.9, 43.3, 52.9, 57.8, 65.5, 70.2, 79.6, 94.3, 154.9, 159.4; IR (film) 3299, 1756, 1693 cm^{-1}; $[\alpha]^{26}_D$ +5.3 (*c* 1.26, EtOH). Anal. Calcd for $C_{20}H_{38}N_2O_6Si$: C, 55.78; H, 8.90; N, 6.51. Found: C, 56.03; H, 8.50; N, 6.58.

Alcohol 32 from OTBDMS Precursor. To a 25 mL round-bottom flask, containing 0.50 g of alkane **30** (1.21 mmol) in 10 mL of dry THF, was added 1.51 mL of TBAF solution (1 M in THF). The reaction was allowed to stir for 30 min when TLC

indicated complete consumption of starting material. The THF was evaporated and replaced with ethyl acetate. The organics were washed with water, followed by saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. Purification by flash chromatography gave 0.31 g (85%) of pure alcohol **32**.

Alcohol 32 from OSEM Precursor. To a 10 mL round-bottom flask, containing 0.2951 g (0.686 mmol) of alkane **31**, was added 2.7 mL of TBAF solution (1 M in THF). THF was stripped and replaced with 3 mL of HMPA. The mixture was stirred at 80 °C for 3 h, transferred to a separatory funnel, diluted with EtOAc, washed with saturated $CuSO_4$ solution, dried over $MgSO_4$, filtered, and evaporated. The crude product was chromatographed over silica gel, giving 0.1854 g (90%) of pure alcohol **31**: mp 118−120 °C; R_f 0.21 (100% EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.53−1.94 (m, 5H), 1.97−2.10 (m, 1H), 2.50 (br s, 1H), 3.30−3.46 (m, 2H), 3.65−3.84 (m, 2H), 3.86−4.08 (m, 2H), 4.29−4.41 (m, 1H), 4.42−4.53 (m, 1H), 6.90 (s br, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 14.4, 24.2, 28.4, 31.4, 43.4, 52.5, 59.1, 70.4, 71.1, 79.6, 155.0, 160.3; IR (film) 3305, 1745, 1672 cm^{-1}; $[\alpha]^{26}_D$ 28.3 (*c* 1.0, EtOH). Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.97; H, 8.06; N, 9.33. Found: C, 55.83; H, 7.87; N, 9.16.

Deacetylslaframine (33). To a 2 mL glass ampule was added 42 mg of alcohol **32**. The ampule was evacuated, flushed with argon three times, and sealed. It was immersed in a 270 °C sand bath for 5 min, providing crude **35** as a yellow oil. Purification by flash chromatography over silica gel (eluted with 10:8:1 $CHCl_3/CH_3OH/NH_4OH$) gave 20 mg of pure alcohol **33** (92%): R_f 0.32 (8:10:1 $CHCl_3/CH_3OH/NH_4OH$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.52−2.20 (m, 9H), 3.00−3.10 (m, 2H), 3.17−3.23 (m, 1H), 3.60−3.70 (br s, 3H), 4.02−4.09 (m, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 19.5, 30.2, 33.1, 45.9, 52.4, 58.4, 68.4, 72.9; MS (70 eV) *m/e* 156 (M^+, 1.7), 100 (83), 70 (100); $[\alpha]^{24}_D$ +2.7 (c 1.76, CH_2Cl_2).

(−)-Slaframine (34). To a 10 mL round-bottom flask was added 20.1 mg of alcohol **33**, followed by ∼5 mL of CH_2Cl_2. Dry HCl gas was bubbled through the solution resulting in the formation of a yellow sticky precipitate. The solvent was stripped, replaced by 5 mL of dry acetic acid, and heated to 75 °C for 4 h. Dry HCl was bubbled in at 30-min intervals throughout the reaction time. The acetic acid was removed in vacuo, and the residue was taken up in saturated $NaHCO_3$ solution. The pH was adjusted to 10 by the addition of Na_2CO_3, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. Purification by flash chromatography over silica gel (eluted with 120:20:1 $CHCl_3/CH_3OH/NH_4OH$) provided 14.37 mg of pure slaframine (57%): R_f 0.21 (120:20:1 $CHCl_3/CH_3OH/NH_4OH$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50−1.67 (m, 2H), 1.68−1.86 (m, 2H), 1.87−1.98 (m, 2H), 1.99−2.07 (m, 1H), 2.08 (s, 3H), 2.18 (dd, J = 11.4, 2.2 Hz, 1H), 2.22−2.33 (m, 1H), 3.08 (dd, J = 9.0, 1.6 Hz, 1H), 3.12−3.20 (m, 1H), 3.27−3.33 (m, 1H), 3.88 (br s, 2H), 5.23 (ddd, J = 7.7, 5.1 Hz, 2.6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 19.7, 21.1, 29.8, 30.5, 46.0, 52.8, 58.3, 67.3, 74.8, 170.9; MS (70 eV) *m/e* 198 (M+, 6), 142 (73), 138 (100); $[\alpha]^{26}_D$ −33 (*c* 0.72, $CHCl_3$).

***N*-Acetylslaframine.** Crude alcohol **33** (0.116 mmol) was transferred to a 5 mL round-bottom flask, to which was added 1 mL of acetic anhydride followed by 3 drops of pyridine. The mixture was allowed to stir for 30 min, and the solvent was stripped. The residue was taken up in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Purification by flash chromatography over silica gel (eluted with 19:1:1 $CHCl_3/CH_3OH/NH_4OH$) provided 15.30 mg (84%) of pure diacetate: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21−2.35 (m, 9H), 2.00 (s, 3H), 2.09 (s, 3H), 2.97−3.15 (m, 2H), 4.13−4.23 (m, 1H), 5.20−5.29 (m, 1H), 6.32 (br s, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 20.5, 21.0, 23.4, 28.1, 30.5, 43.8, 53.0, 57.4, 67.4, 74.7, 169.1, 170.6; MS (70 eV) *m/e* 181 (M^+ − OAc), 153, 138; $[\alpha]^{26}_D$ −12.9 (*c* 1.0, EtOH).

***cis*-4-OTBDMS Alkene 29.** To a 25 mL round-bottom flask, containing a 10 mL THF solution of 1 mmol of ylide derived from **21** at −78 °C, was added 0.33 g of aldehyde **26**. The mixture was allowed to stir for 2.5 h and warmed to room temperature. Saturated NH_4Cl solution was added, and THF was stripped. The residue was extracted into ethyl acetate. The combined organics were washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvent gave 0.70 g of crude which was chromatographed over silica gel (eluted with 30:20 EtOAc/hexane) to provide 0.35 g (85%) of pure *cis*-alkene **29**: mp 76.5−78.0 °C; R_f 0.44 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.43 (s, 9H), 1.64−1.75 (m, 1H), 1.97−2.08 (m, 1H), 3.37 (d, J = 3.5 Hz, 2H), 4.05 (dd, J = 6.6, 8.4 Hz, 1H), 4.32 (m, 1H), 4.52 (app t, J = 8.4 Hz, 1H), 4.58−4.71 (m, 1H), 4.86−4.98 (m, 1H), 5.36 (app t, J = 10.0 Hz, 1H), 5.51 (app t, J = 10.0 Hz, 1H), 6.34 (br s, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −4.8, 25.6, 28.4, 41.3, 48.9, 52.1, 55.1, 69.7, 70.1, 80.0, 129.1, 134.9, 154.8, 158.8; IR (film) 3312, 1766, 1687 cm^{-1}; $[\alpha]^{26}_D$ −23.5 (*c* 1.07, CH_2Cl_2). Anal. Calcd for $C_{20}H_{36}N_2O_5Si$: C, 58.22; H, 8.79; N, 6.78. Found: C, 58.10; H, 8.94; N, 6.73.

4-OTBDMS Alkane 35. To a 25 mL round-bottom flask, containing a 10 mL ethyl acetate solution of 0.58 g (1.41 mmol) of alkene **29**, was added 0.25 g of 10% Pd on carbon. The mixture was stirred under hydrogen for 4 h, at which time TLC indicated complete consumption of starting material. The mixture was filtered through Celite and evaporated to provide 0.58 g (quantitative) of alkane **37**: mp 114−115 °C; R_f 0.20 (50:50 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.84 (s, 9H), 1.43 (s, 9H), 1.30−1.70 (m, 4H), 1.75−2.15 (m, 2H), 3.25−3.45 (m, 2H), 3.78−3.93 (m, 2H), 3.98 (dd, J = 6.0, 8.4 Hz, 1H), 4.29 (app dd, J = 4.2, 4.2 Hz, 1H), 4.47 (dd, J = 8.4, 8.4 Hz, 1H), 6.57 (s, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ −4.8, 17.8, 25.6, 28.4, 30.6, 31.6, 40.4, 52.1, 54.8, 55.2, 70.0, 70.2, 79.4, 155.2, 159.7; IR (film) 3313, 1755, 1693 cm^{-1}; $[\alpha]^{26}_D$ −46.7 (*c* 1.05, CH_2Cl_2). Anal. Calcd for $C_{20}H_{38}N_2O_5Si$: C, 57.93; H, 9.23; N, 6.75. Found: C, 58.14; H, 9.20; N, 6.88.

4-OH Compound 36. To a 25 mL round-bottom flask, containing a 10 mL of THF solution of 1.16 g (2.80 mmol) of silylester **35**, was added 3.5 mL of TBAF solution (1 M in THF). The solution was stirred under argon for 3 h, at which time TLC indicated complete consumption of starting material. The solvent was stripped, and the residue was chromatographed over silica gel (eluted with 95:5 EtOAc/hexane) and evaporated to give 0.83 g (99%) of pure alcohol **36**: mp 140−141 °C; R_f 0.27 (95:5 EtOAc/MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.38−1.60 (m, 2H), 1.65−1.80 (m, 2H), 1.85−2.00 (m, 1H), 2.00−2.13 (m, 1H), 3.25−3.62 (m, 3H), 3.78−3.95 (m, 2H), 3.97 (dd, J = 6.1, 8.2 Hz, 1H), 4.35 (m, 1H), 4.45 (app t, J = 8.2 Hz, 1H), 6.78 (br s, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 28.4, 29.9, 31.4, 39.6, 52.1, 54.6, 55.0, 69.3, 70.2, 79.7, 155.0, 159.9; IR (film) 3302, 1749, 1412 cm^{-1}; $[\alpha]^{29}_D$ −71.9 (*c* 1.08, EtOH). Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05; N, 9.32. Found: C, 55.72; H, 8.16; N, 9.20.

2-Hydroxy-6-aminoindolizidine·2HCl (37). Prepared according to the procedure of desacetoxyslaframine·2HCl on 250 mg of alcohol **35**. Purified by recrystallization from MeOH/EtOAc to give 0.165 g of pure **37**. All data given are for the hydrochloride salt: mp 205 °C; ^{1}H NMR (270 MHz, D_2O) δ 1.60−1.88 (m, 2H), 1.97−2.13 (m, 1H), 2.20 (dd, J = 14.2, 5.5 Hz, 1H), 2.25−2.40 (m, 2H), 3.07 (dd, J = 11.7, 3.7 Hz, 1H), 3.19 (dd, J = 11.7, 11.7 Hz, 1H), 3.45−3.58 (m, 1H), 3.60−3.75 (m, 1H), 3.86−3.95 (m, 1H), 3.97 (dd, J = 12.5, 6.8 Hz, 1H), 4.63−4.72 (m, 1H); ^{13}C NMR (65 MHz, D_2O) δ 27.5, 29.3, 40.9, 47.9, 53.9, 62.8, 66.3, 69.8; $[\alpha]^{28}_D$ −11.2 (*c* 1.23, MeOH). Anal. Calcd for $C_8H_{18}N_2OCl_2$: C, 41.93; H, 7.92; N, 12.22. Found: C, 41.87; H, 8.05; N, 12.14.

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Supporting Information Available: Characterization data for compounds **7**, **8**, **13**−**17**, **21**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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