Stereoselective Synthesis of Polyhydroxylated Indolizidines from γ-Hydroxy α,β-Unsaturated Sulfones

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The polyhydroxylated indolizidines castanospermine and swainsonine as well as some of their stereoisomers are powerful glycosidase inhibitors. An efficient and stereochemically flexible synthesis of racemic 1,7,8-trihydroxylated and 1,6,7,8-tetrahydroxylated indolizidines (castanospermine stereoisomers) from readily available N-substituted γ-oxygenated α,β-unsaturated sulfones **3** and **4** has been developed. The construction of the bicyclic skeleton of 1-hydroxyindolizidine has been accomplished by intramolecular conjugate addition of the nitrogen moiety of **3** and **4** to the α,β-unsaturated sulfone unit to give the pyrrolidine intermediates **5** and **6**, followed by formation of the C(7)−C(8) bond by intramolecular acylation (or alkylation) of the α-sulfonyl carbanion. The stereoselectivity of the pyrrolidine synthesis was highly dependent on the bulkiness of the γ-oxygenated function; thus, the free alcohols gave predominantly *cis*-pyrrolidines while the OTIPS derivatives led to the *trans* isomers. After straightforward functional group transformations, the removal of the sulfonyl group at C(8) either by Julia reaction or by basic elimination (depending on the substrate used) afforded the key C(7)C(8) unsaturated indolizidines **10**, **22**, **30**, and **31**, whose stereoselective dihydroxylations with OsO_4 gave a variety of *cis* C(1)C(8a) and *trans* C(1)C(8a) trihydroxylated and tetrahydroxylated indolizidines, among which (±)-1,7-di-*epi*-castanospermine and (±)-1,8-di-*epi*-castanospermine have been reported for the first time.

Introduction

A variety of alkaloids having the structure of polyhydroxylated indolizidine have been isolated from natural sources,[1] mainly plants and microorganisms, and some of them are excellent inhibitors of biologically important pathways, including the binding and processing of glycoproteins.[1,2] Among naturally occurring polyhydroxylated indolizidines, castanospermine[3] (a potent α-glucosidase inhibitor), swainsonine[4] (a potent α-mannosidase inhibitor), and lentiginosine[5] (an amyloglucosidase inhibitor) have attracted the greatest attention from both synthetic and biological points of view and represent good examples of tetrahydroxylated, trihydroxylated, and dihydroxylated indolizidines, respectively (Figure 1).

To find structure−activity relationships,[6] this interest has been extended to the synthesis of stereoisomers and analogues.[3−5] Although in some cases there is a close structural resemblance between the biologically active indolizidine and the natural sugar substrate, in many other cases this resemblance does not exist. For instance, swainsonine, which is one of the strongest α-mannosidase inhibitors, lacks any significant resemblance with man-

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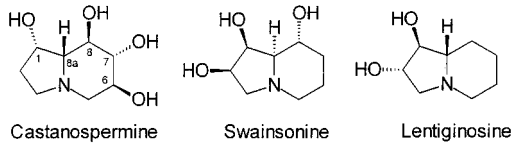
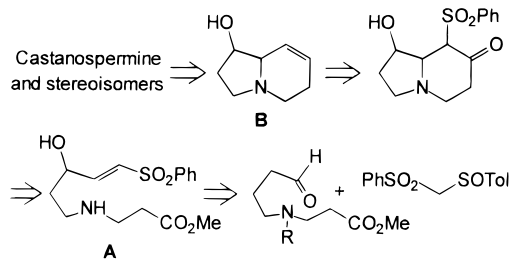


Figure 1. Representative examples of glycosidase inhibitors with the structure of polyhydroxylated indolizidine.

Scheme 1



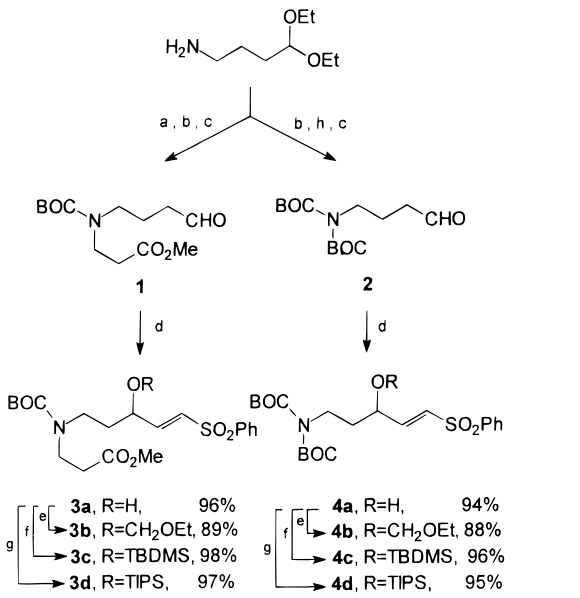
nose. Since the structure−activity relationships in indolizidines are not straightforward, as many stereoisomers and analogues as possible should be synthesized and tested for their biological activity. Due to their vicinal polyhydroxylated structure, most of the reported syntheses of castanospermine, swainsonine, and analogues employ natural sugars as starting materials.[3−5] However, this approach often has the drawback of lacking enough flexibility for the ready preparation of a wide range of stereoisomers from a common intermediate.

As part of our current interest in the use of γ-hydroxy α,β-unsaturated sulfones as versatile intermediates in stereoselective synthesis,[7] here we describe in detail a concise and stereochemically flexible approach to the synthesis of a wide range of polyhydroxylated indolizidines based on these readily available vinyl sulfones.[8] In our retrosynthetic analysis, we envisaged that using the vinyl sulfone moiety as a Michael acceptor the bicyclic skeleton of these alkaloids could be readily prepared by two successive ring closures: intramolecular conjugate addition of the amine moiety to the sulfones **A** followed by intramolecular acylation of the α-sulfonyl carbanion with the ester function (Scheme 1). Further functional group manipulations would allow the preparation of olefins **B**, which would be suitable substrates for the introduction of hydroxyl groups at C(6) (by allylic oxidation) and at C(7)−C(8) (by dihydroxylation). Interestingly, as the stereogenic centers would be incorporated gradually, a stereochemical control could be achieved in each step, allowing the preparation of different stereoisomers from a common intermediate.

Results and Discussion

Synthesis of the γ-Hydroxy α,β-Unsaturated Sulfones and Construction of the Pyrrolidine Ring. We reported that γ-hydroxy α,β-unsaturated sulfones can be prepared from sulfonylsulfinylmethanes and enolizable aldehydes on a multigram scale.[9] The required protected 4-aminobutyraldehyde **1** was readily prepared in three steps from commercially available 4-aminobutyraldehyde diethyl acetal as follows: conjugate addition to methyl acrylate (EtOH, 0 °C, 90%), subsequent protection of the amine as BOC derivative (BOC_2O, CH_2Cl_2, 0 °C, 98%), and acid hydrolysis of the acetal moiety ($AcOH/H_2O$ 2:1, rt, 88%). As expected, the condensation of **1** with (±)-(phenylsulfonyl)(*p*-tolylsulfinyl)methane (piperidine, CH_2Cl_2, 0 °C) afforded the racemic vinyl sulfone **3a** in excellent yield (96%). Similarly, the *N*,*N*-diprotected aminobutyraldehyde **2** was prepared from the same starting material by two successive BOC protections (BOC_2O, CH_2Cl_2, 0 °C, then *n*-BuLi, BOC_2O, THF, 0 °C; 92%) and further hydrolysis of the acetal (Scheme 2). The reaction of **2** with (phenylsulfonyl)(*p*-tolylsulfinyl)methane gave cleanly the corresponding γ-hydroxyvinyl sulfone **4a** (94% yield).

Scheme 2[a]



[a] Reagents: (a) $CH{=}CH_2CO_2Me$, EtOH, 0 °C; (b) BOC_2O, CH_2Cl_2, rt; (c) $AcOH/H_2$ 2:1, rt; (d) $PhSO_2CH_2SO$-*p*-Tol, piperidine, CH_2Cl_2, 0 °C; (e) $ClCH_2OCH_2CH_3$, *i*-Pr_2EtN, CH_2Cl_2, rt; (f) TBDMSCl, imidazole, CH_2Cl_2, rt; (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (h) *n*-BuLi, BOC_2O, THF, 0 °C.

To determine if the size of the oxygenated substitution at the γ-position had a significant effect on the stereoselectivity of the intramolecular conjugate addition, the hydroxyl group of **3a** and **4a** was protected as ethoxymethoxy acetals **3b** and **4b** (chloromethyl ethyl ether, *i*-Pr_2EtN, CH_2Cl_2, rt) and as the silyl ethers OTBDMS **3c** and **4c** (TBSCl, imidazole, CH_2Cl_2, rt) and OTIPS **3d** and **4d** (TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt). Deprotection of carbamates **3** and **4** with TFA at room temperature afforded quantitatively the corresponding ammonium salts, which after isolation were redissolved in THF, cooled at −78 °C, and treated with Et_3N (10 equiv) to liberate in situ the free amines. In all cases, a clean and fast cyclization was observed, being complete

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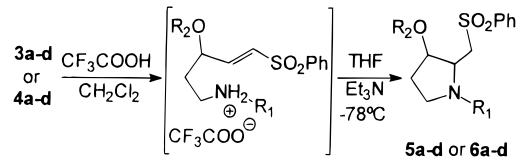
Table 1. Intramolecular Conjugate Addition of the γ-Oxygenated α,β-Unsaturated Sulfones 3 and 4



entry	substrate	product	R_1	OR_2	*cis*/*trans*[a]
1	**3a**	**5a**	$CH_2CH_2CO_2Me$	OH	81/19[b]
2	**3b**	**5b**	$CH_2CH_2CO_2Me$	OCH_2OEt	36/64
3	**3c**	**5c**	$CH_2CH_2CO_2Me$	OTBDMS	19/81
4	**3d**	**5d**	$CH_2CH_2CO_2Me$	OTIPS	10/90
5	**4a**	**6a**	H	OH	80/20
6	**4b**	**6b**	H	OCH_2OEt	44/56
7	**4c**	**6c**	H	OTBDMS	40/60
8	**4d**	**6d**	H	OTIPS	22/78

[a] Determined by ^1H NMR on the crude mixture. [b] Reaction run in toluene.

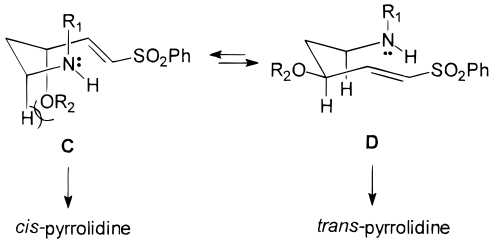
in less than 30 min at −78 °C, to afford *cis*/*trans* mixtures of pyrrolidines **5**−**6** in nearly quantitative yields (Table 1).[8a]

Interestingly, the hydroxyvinyl sulfones (substrates **a**, entries 1 and 5) and their TIPS derivatives (substrates **d**, entries 4 and 8) showed remarkable and opposite stereoselectivities. Thus, whereas the cyclizations of **3a** and **4a** were *cis*-stereoselective (*cis*/*trans* = 81/19 from **3a** and *cis*/*trans* = 80/20 from **4a**), those of **3d** and **4d** were *trans*-stereoselective (*cis*/*trans* = 10/90 from **3d** and *cis*/*trans* = 22/78 from **4d**).[10]

The dependence between stereoselectivity and substitution at the γ-position might be roughly explained taking into account the likely most stable chairlike transition states leading to *cis*- and *trans*-pyrrolidines[8a] (**C** and **D** in Scheme 3, respectively). From a steric point of view, due to the presence of the substituent OR_2 in the axial position, the participation of the transition state **C** should decrease as the bulkiness of OR_2 rises, decreasing consequently the amount of the *cis*-pyrrolidine.[11] In good agreement with this model, the *trans*-stereoselectivity of the cyclization increases in the following order from both substrates **3** and **4**: OTIPS > OTBDMS > OCH_2OEt > OH.

Stereoselective Synthesis of Trihydroxylated Indolizidines. Having developed a stereoselective method for preparing pyrrolidines **5** and **6** with a *trans* or *cis* configuration, their independent use would lead to the stereoselective synthesis of indolizidines with a *trans* or *cis* configuration at C(1)−C(8a),[12] respectively. The overall transformation of *trans*-**5d** into the pair of 1,7,8-trihydroxylated indolizidines with *cis*-stereochemistry at C(7)−C(8) is depicted in Scheme 4.

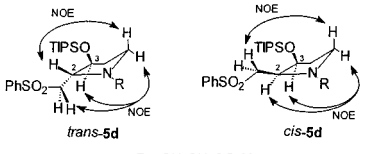
Scheme 3



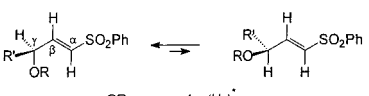
The formation of the indolizidine skeleton was accomplished cleanly by intramolecular acylation of the α-sulfonyl anion obtained by deprotonation of *trans*-**5d** with LHDMS (2 equiv, THF, 0 °C).[13] The resulting crude α-sulfonyl ketones **7** were obtained as a 60:40 mixture of epimers at C(8), being the isomer having the sulfone group in axial position the major one (**7ax**).[14] Reduction of **7** with $NaBH_4$ resulted in a 42:58 mixture of alcohols **8** and **9**, which could be separated by flash chromatography (31% and 48% yields from *trans*-**5d**, respectively). This result showed that the reduction of **7eq** and **7ax** with $NaBH_4$ was in both cases fully stereoselective. Whereas **7eq** furnished the axial alcohol **8**, in the case of **7ax** the presence of the phenylsulfonyl group in the axial position precludes the equatorial approach of the hydride to the carbonyl group, leading exclusively to the formation of the equatorial alcohol **9**. Similar stereochemical results have been reported for the reduction of equatorially and axially conformationally restricted 2-sulfonylcyclohexanones.[15]

A different reaction outcome was observed in the reaction of **8** and **9** with Na−Hg (MeOH, rt). The axial alcohol **8** gave the desired Julia olefination product **10**

(10) The mixtures of *cis* and *trans* isomers **5b**−**d** could be easily separated by flash chromatography but not those of **5a** and **6a**−**d**, which were used in the next step as *cis* + *trans* isomers and then separated. The stereochemical assignment of *cis*- and *trans*-**5a**−**d** and -**6a**−**d** has been firmly established by a combination of chemical correlations and NMR studies. **5a** was transformed into the ketal or silyl derivatives (compounds **5b**−**d**), or vice versa, by straightforward protection or deprotection reactions, whereas compounds **6a**−**d** were transformed into the corresponding N-alkylated compounds **5a**−**d** by reaction with methyl acrylate (as solvent) at room temperature. From a spectroscopic point of view, as it has been reported for related 2,3-disubstituted pyrrolidines (Gallina, C.; Paci, M.; Viglino, P. *Org. Magn. Reson.* **1972**, *4*, 31), the vicinal coupling constant $J_{2,3}$ is significantly higher in the *cis* isomers ($J_{2,3\text{-cis}} \approx 6.5$ H) than in the *trans* ones ($J_{2,3\text{-trans}} \approx 2.5$ Hz). Furthermore, the NOESY spectra of *cis*-**5d** and *trans*-**5d** are in fully agreement with this assignment (see below).



(11) Taking into account the conformational analysis around the C_β−C_γ bond of compounds **3**−**4**, the conformation **E** (OR/H_α in 1,3-parallel arrangement) would be more stable than conformation **F** (H_α/H_γ in 1,3-parallel arrangement) as it is deduced from the low value of $J_{\beta,\gamma}$ (see below), especially significant in the case of the hydroxy derivatives that show the lowest $J_{\beta,\gamma}$ values (**3a** and **4a:** $J_{\beta,\gamma} = 3.0$ Hz). We assume that this conformational preference would act in an opposite sense to the steric effects discussed in Scheme 3, because it would favor the transition state **C** (conformationally similar to **E**) to a larger extent than **D** (conformationally similar to **F**). This conformational effect could explain why in the case of the hydroxy derivatives **3a** and **4a**—the substrates besides with the sterically least demanding OR group—their cyclizations gave predominantly the pyrrolidines of *cis* configuration. For conformational analysis in allylic alcohols and derivatives, see: Gung, B. W.; Melnick, J. P.; Wolf, M. A.; King, A. *J. Org. Chem.* **1995**, *60*, 1947.



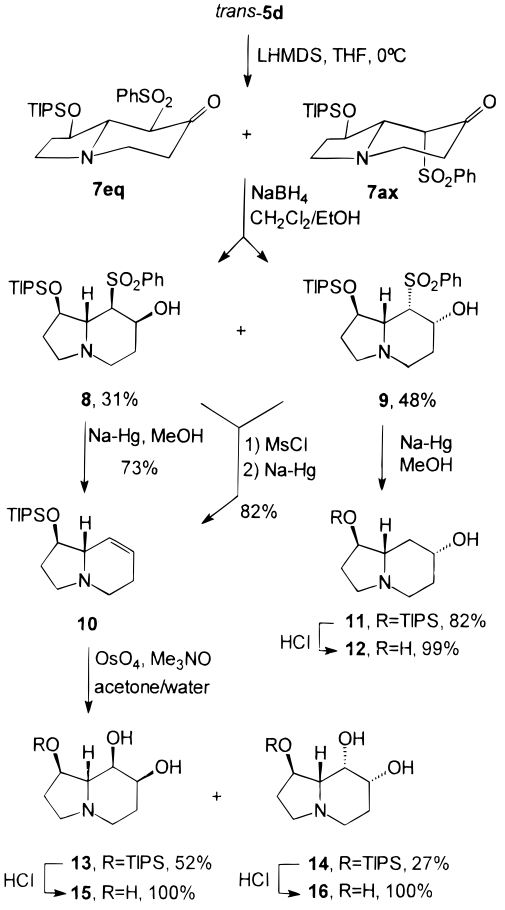
OR	$J_{\beta,\gamma}$ (Hz)*
OH	3.0
OCH_2CH_3	5.0-5.1
OTBDMS	3.9-4.0
OTIPS	4.4-4.5

* in $CDCl_3$

(12) The use of the stereochemical terms *cis* and *trans* refers to the H(1)/H(8a) relationship.

(13) Unexpectedly, the use of other bases such as LDA led to the formation of mixtures of products.

Scheme 4



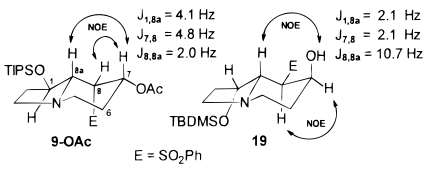
(73% yield), while the equatorial alcohol **9** under otherwise identical conditions yielded predominantly the alcohol **11** (82%) as a result of the reductive elimination of the sulfone. Further hydrolysis of the silyl ether (5 M HCl) and neutralization (Dowex 1-X8 ion-exchange chromatography) provided the 1,7-dihydroxylated indolizidine **12** (99% yield). To improve the overall yield in the preparation of the key unsaturated indolizidine **10**, the crude mixture of alcohols **8** + **9** obtained after reduction of **7** was mesylated (MsCl, Et_3N, CH_2Cl_2, rt), and the resulting mixture was treated with Na−Hg (MeOH, rt). In that case, the excellent ability of the mesylate as leaving group determined that both isomers evolved by Julia reaction, affording olefin **10** in 82% yield after purification.

The *syn*-dihydroxylation of **10** with OsO_4 under standard catalytic conditions (OsO_4 3 mol %, Me_3NO, acetone/water 5:1, rt) was moderately stereoselective, leading to a 2:1 mixture of diols **13** and **14**, which were separated by chromatography (52% and 27%, respectively).[16] As the last step, quantitative desilylation of **13** and **14** (HCl) and neutralization gave the trihydroxylated indolizidines **15** and **16**.[16]

Following a similar reaction sequence, in Scheme 5 is shown the stereoselective transformation of a *cis*-pyrrolidine into hydroxylated indolizidines of *cis*-stereochemistry at C(1)C(8a). Pyrrolidine *cis*-**5c** was prepared in 71% yield by silylation of the 80:20 mixture of *cis*-**5a** + *trans*-**5a** (TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt) and chromatographic separation. Unlike cyclization of *trans*-**5d**, intramolecular acylation of *cis*-**5c** with LHMDS (THF, 0 °C) occurred in a complete stereoselective manner to give the indolizidine bearing the sulfonyl group at the equatorial position (compound **17**).[14] In this case, the absence of the epimer at C(8), which would have the sulfone in axial position, might be due to its higher thermodynamic instability derived from the presence of a 1,3-parallel interaction between the bulky substituents at C(1) and C(8) (silyl ether and sulfone, respectively). According to this hypothesis, **17** was recovered unchanged after treatment with 1 M LiOH in THF/H_2O, proving that it is the thermodynamically most stable epimer at C(8).

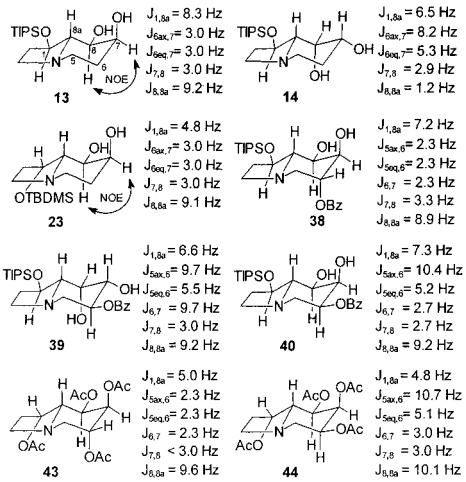
As expected, the stereoselectivity of the carbonyl reduction of **17** was highly dependent on the hydride used. The reaction with DIBALH (CH_2Cl_2, −78 °C) afforded exclusively the equatorial alcohol **18** (75% yield from *cis*-**5c**), while the reduction with a typical hydride of equatorial attack such as $LiEt_3BH$ (THF, −78 °C) was

(14) Interestingly, the treatment of the mixture of sulfonyl ketones **7eq** + **7ax** with Et_3N in $CHCl_3$ at room temperature (or LiOH in THF/H_2O) afforded the isomer **17** as the major product, proving its higher thermodynamic stability and the easiness of the reverse conjugate addition in these compounds. The configuration at C-8 of the α-sulfonyl ketones **7eq**, **7ax**, and **17** was tentatively established from their ^1H NMR data, mainly from the values of δ_1 and $^3J_{8,8a}$. **7eq**: δ_1 = 4.49 ppm, $^3J_{8,8a}$ = 6.3 Hz; **7ax**: δ_1 = 5.41 ppm, $^3J_{8,8a}$ = 3.2 Hz; **17**: δ_1 = 4.69 ppm, $^3J_{8,8a}$ = 7.9 Hz. This stereochemical assignment was further confirmed by analysis of the ^1H NMR and NOESY spectra of their hydroxy derivatives **8**, acetate of **9** (**9-OAc**), and **19** (see below).

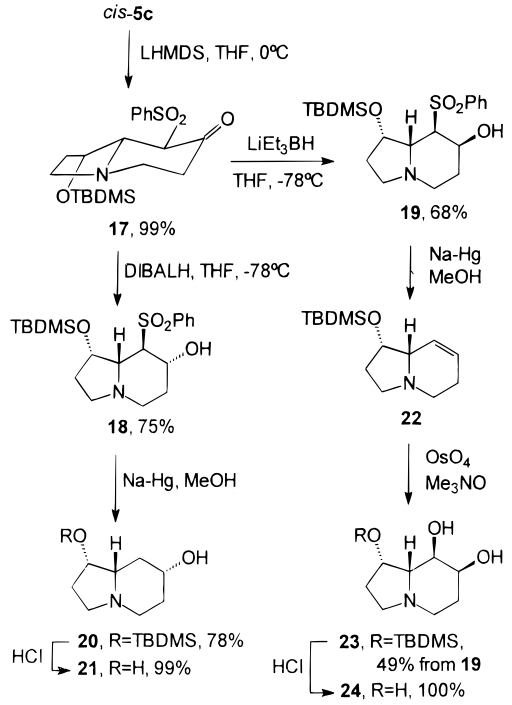


(15) For a general study on the stereoselectivity of the reduction of conformationally restrained 2-sulfonylcyclohexanones, see: Carreño, J. C.; Domínguez, E.; García Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619.

(16) **Configurational assignment of trihydroxylated and tetrahydroxylated indolizidines:** as is usual in this kind of compounds, the stereochemistry of the substitution at the chair conformation of the six-membered ring has been established by ^1H NMR, mainly from the typical *gauche* or *anti* values of $J_{8,8a}$, $J_{8,7}$, $J_{7,6}$, $J_{6,5eq}$, and $J_{6,5ax}$. To assign unequivocally the signals corresponding to H(1), H(8a), H(8), H(7), and H(6) and obtain accurate values of the coupling constants, compounds lacking overlap between these hydrogens were particularly useful (see below). Similarly, with regard to the substitution at the five-membered ring, as expected, it was observed that $J_{1,8a}$ in the *cis* isomers is always significantly lower (4.8−5.0 Hz, H_1 and H_{8a} in *gauche* relationship) than in the *trans* ones (6.5−8.3 Hz, H_1 and H_{8a} in *anti* relationship).



Scheme 5



also fully stereoselective but in favor of the axial alcohol **19**. It is interesting to note that in the subsequent sulfonyl elimination step with Na−Hg the reaction pathways of epimers **18** and **19** were identical to those previously observed for the pair of isomers **8** and **9**. Thus, reductive elimination occurred from the equatorial alcohol **18** to give the hydroxylated indolizidine **20** (78% yield), which was transformed into the dihydroxylated indolizidine **21** after acid hydrolysis, while the axial alcohol **19** evolved by Julia olefination to yield predominantly the unsaturated indolizidine **22**. Due to its moderate stability, crude **22** was immediately dihydroxylated (OsO_4 cat., Me_3NO, acetone/water 5:1, rt) to provide diol **23** as a single isomer (49% yield from **19**). The very high stereoselectivity in the dihydroxylation of **22** contrasts with the poor stereocontrol observed from its epimer **10**, suggesting that in **22** the bulky silyl ether at C(1), presumably in a pseudoaxial position ($J_{1,8a}$ = 2.2 Hz), provokes a significant steric differentiation of both olefin faces, reinforcing the approach of the oxidant *syn* to H_{8a} (Figure 2). Finally, deprotection of **23** (5 M HCl) and neutralization (Dowex-OH) furnished quantitatively the trihydroxylated indolizidine **24**.[16]

Stereoselective Synthesis of 1,6,7,8-Tetrahydroxylated Indolizidines. Next, we focused our attention on the synthesis of 1,6,7,8-tetrahydroxylated indolizidines (castanospermine stereoisomers). Since all trials to achieve the allylic oxidation at C(6) of olefins **10** and **22** were unsuccessful,[17] we slightly modified our initial retrosynthetic approach in order to introduce the functionalization at C(6) in an earlier stage of the reaction sequence. To this end, the enones **30** and **31** were particularly appealing substrates because via stereoselective carbonyl reduction at C(6) and dihydroxylation at C(7)−C(8) (or vice versa) a wide range of tetrahydroxylated isomers could be prepared.

(17) In all attempts of allylic oxidation of **10** or **22** with PCC/tBuOOH (cat.), PDC/*t*-BuOOH (cat.), SeO_2, or SeO_2/*t*-BuOOH (cat.), complex mixtures of products were obtained.

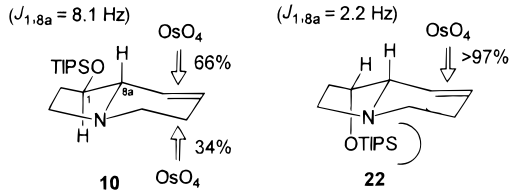
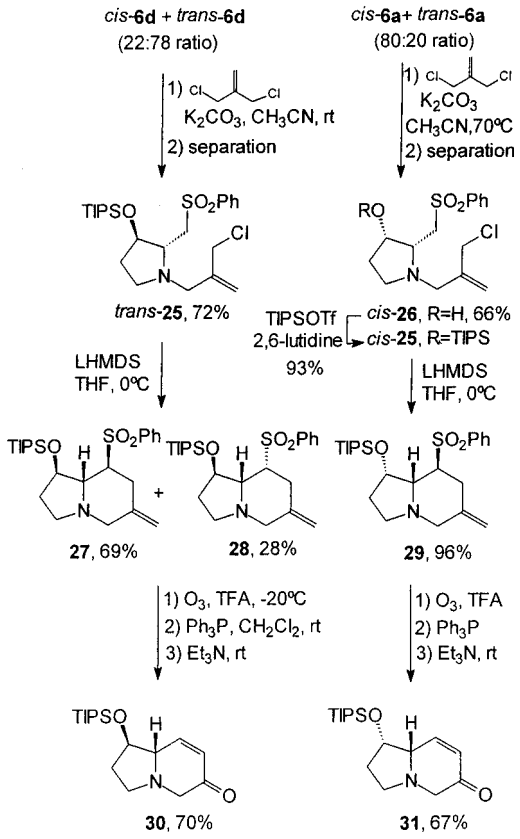


Figure 2. Proposed models for the dihydroxylation of **10** and **22.**

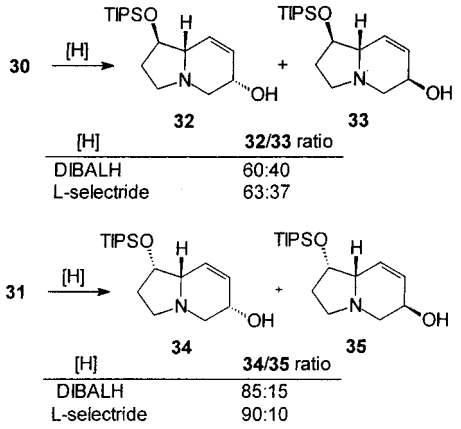
Scheme 6



We found that suitable precursors of such enones were the 6-methyleneindolizidines **27** + **28** and **29** shown in Scheme 6. N-Alkylation of the mixtures of *cis*-**6d** + *trans*-**6d** (22:78) and *cis*-**6a** + *trans*-**6a** (80:20), obtained directly from the cyclization of **4d** and **4a**, respectively, with 3-chloro-2-chloromethylpropene (K_2CO_3, cat. LiI, CH_3CN, rt), followed by silica gel chromatography, afforded separately *trans*-**25**, and *cis*-**25** in good overall yields (72% and 61%, respectively). Further intramolecular C-alkylation of *trans*-**25** and *cis*-**25** took place almost quantitatively using LHMDS as base (THF, 0 °C). In the case of *trans*-**25**, a mixture of both epimers **27** + **28** was obtained, while from *cis*-**25** only the epimer **29**, that avoiding the 1,3-parallel diaxial interaction between substituents at C(1) and C(8), was detected.[18] After extensive experimentation, it was observed that the ozonolysis of **27** + **28** and **29** only occurred cleanly when pure TFA was used as solvent, likely due to the competitive amine oxidation and formation of side products in

(18) The attempts to perform directly the synthesis of **27**−**29** in one step by double alkylation of **6d** with 3-chloro-2-(chloromethyl)propene in the presence of 2 equiv of *n*-BuLi were unfruitful. For direct dialkylation of *β*-nitrogenated sulfones, see: (a) Alonso, D. A.; Costa, A.; Mancheño, B.; Nájera, C. *Tetrahedron* **1997**, *53*, 4791. (b) Caturla, F.; Nájera, C. *Tetrahedron Lett.* **1997**, *38*, 3789.

Scheme 7

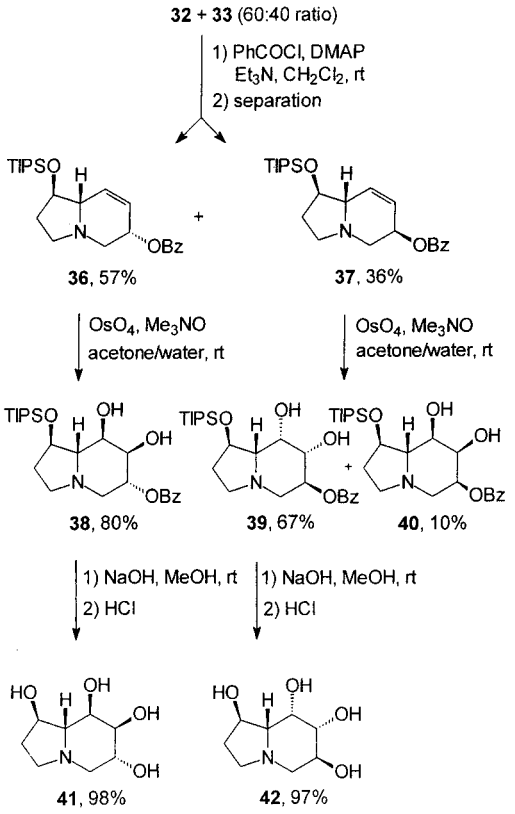


nonacidic solvents.[19] Subsequent reductive workup (PPh_3) and in situ addition of Et_3N to promote the basic elimination of the sulfonyl group led to the enones **30** and **31** in 70% and 67% overall yields, respectively. [20]

Because compounds **30** and **31** proved to be rather unstable at room temperature, they must be immediately used after chromatographic purification. Due at least in part to this instability, all attempts to dihydroxylate them with OsO_4 (a reaction that usually requires long periods of time) were unfruitful, giving complex mixtures of products. In contrast, a quantitative and fast reaction occurred in the reduction of these enones with L-Selectride or DIBALH in THF at −78 °C (Scheme 7). Both hydrides afforded similar stereochemical results, the reductions with L-Selectride being somewhat more stereoselective. However, while the reductions of **30** (*trans*-stereochemistry at C(1)C(8a)) to give the alcohols **32** + **33** was hardly stereoselective in favor of **32** (de = 20−26%), the reaction of its diastereomer **31** (*cis*-stereochemistry at C(1)C(8a)) occurred with much higher stereocontrol, leading predominantly to the alcohol **34** (de = 70−80%) as a result of the approach of the hydride from the face opposite to the OTIPS group at C(1). These results parallel those obtained in the dihydroxylation of the diastereomeric olefins **10** and **22**, where it was also noted that the compound having *cis*-sterochemistry at C(1)C-(8a) (**22**) evolved in a much more stereoselective manner than the isomer of *trans* configuration (**10**). This behavior was ascribed to the presence of the bulky OTIPS unit in a pseudoaxial position in the compounds of *trans* configuration at C(1)C(8a), which would induce an important steric differentiation between both sides of the indolizidine (Figure 2). Interestingly, this effect seems to be effective even at a relatively far position such as C(6).

The preparation of tetrahydroxylated indolizidines by *syn* dihydroxylation of substrates **32**−**35** is depicted in Schemes 8 and 9. As we were unable to separate the mixture of allylic alcohols **32** + **33**, this crude mixture was benzoylated (PhCOCl, Et_3N, DMAP, CH_2Cl_2, rt) and then separated by flash chromatography. Pure benzoates **36** and **37** were obtained in 57% and 36% yields, respectively. Taking into account that the dihydroxylation of the C(6)-unsubstituted indolizidine **10** (Scheme 4) was hardly stereoselective, it could be anticipated that the stereoselectivity in the dihydroxylation of the epimers

Scheme 8



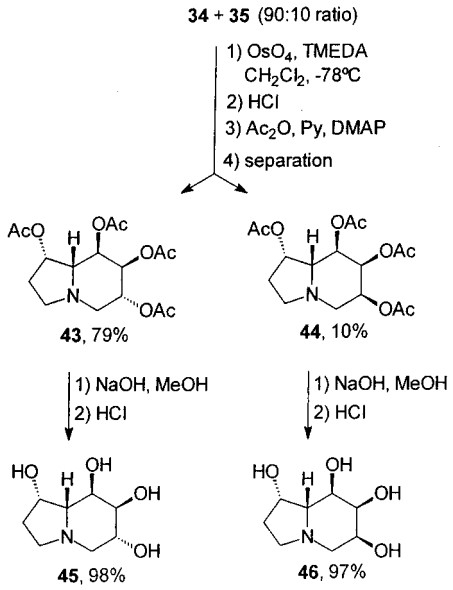
36 and **37** was mainly controlled by the benzoate substituent at C(6). Indeed, the reaction of **36** occurred with very high stereocontrol from the face opposite to the benzoate group to give diol **38** as a single isomer (80% yield). Similarly, the reaction of the epimer **37** also took place preferentially in the *anti* position with regard to the benzoate group, furnishing a 85:15 mixture of diols **39** + **40** that could be separated by flash chromatography (67% and 10% yields, respectively).[16]

Basic hydrolysis (NaOH, MeOH, rt) of the benzoate groups of **38** and **39**, followed by cleavage of the OTIPS (HCl and then neutralization), gave quantitatively (±)-8,8a-di-*epi*-castanospermine(**41**)and(±)-1,8-di-*epi*-castanospermine (**42**), respectively. To the best of our knowledge, these castanospermine stereoisomers had not been previously reported.

Unexpectedly, all attempts to dihydroxylate the allylic alcohols **34** and **35**, both with *cis* stereochemistry at C(1)C(8a), as well as their TIPS, benzoyl, or MOM derivatives under the usual catalytic conditions (OsO_4 3 mol %, Me_3NO, acetone, rt) were completely unsuccessful, recovering the starting olefins after 2 days of reaction. In an attempt to improve the reactivity of this process, we turned to the conditions recently reported by Donohoe et al.[21] for the dihydroxylation of allylic alcohols, which employ stoichiometric amounts of OsO_4 and TMEDA in CH_2Cl_2 at −78 °C. We were pleased to find that under these conditions a 9:1 mixture of alcohols **34** + **35** reacted cleanly and with complete stereocontrol, leading in 15 min to an inseparable 9:1 mixture of the corresponding triols. To separate these compounds, the crude mixture was desilylated (HCl), fully acetylated (CH_3COCl, Et_3N, DMPA, CH_2Cl_2), and then separated by flash chromatography. The tetraacetates **43** and **44** were obtained in

(19) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.

Scheme 9



79% and 10% yields, respectively, from **34** + **35** (Scheme 9). The fact that in both cases, and regardless the stereochemistry at C(6), the acetates at C(7)/C(8) are located in an *anti* relationship with respect to the OTIPS group at C(1) indicates that the stereoselectivity of the dihydroxylation in compounds having the *cis* configuration at C(1)C(8a) is controlled by the steric effects associated with the axially oriented OTIPS group at C(1) and not by the substitution at C(6). As previously discussed, similar steric arguments have been invoked to explain the high stereoselectivity observed in the reaction of other C(1)C(8a) *cis*-indolizidines, such as **22** and **31**.

Quantitative deacetylation of **43** (NaOH, MeOH, rt,) and desilylation (HCl) gave (±)-6,7-di-*epi*-castanospermine (**45**) in 98% yield, whose ^{1}H and ^{13}C NMR data were identical with those reported for enantiomerically pure (+)-6,7-di-*epi*-castanospermine.[22] This natural product has been isolated from the seeds of *Castanospermum australe* and shows a remarkable biological activity as an amyloglucosidase inhibitor. Following the same reaction sequence, the minor tetraacetate **44** was converted into (±)-7-*epi*-castanospermine (**46**). The preparation of enantiopure **44** and **46** from castanospermine has been recently reported.[23]

Conclusions

In conclusion, the approach described in this paper for the preparation of polyhydroxylated indolizidines combines efficiency and stereochemical flexibility, allowing the preparation of a wide variety of both 1,7,8-trihydroxylated and 1,6,7,8-tetrahydroxylated stereoisomers. The γ-oxygenated α,β-unsaturated sulfones **3** and **4** used as starting products were readily prepared in multigram quantities from 4-aminobutyraldehyde diethyl acetal. The two-step construction of the indolizidine skeleton from **3** and **4** takes place in excellent yield, and a remarkable stereochemical control is achieved at the C(1)C(8a) ring junction depending on the bulkiness of the γ-oxygenated substitution. Further stereochemical control at C(6) and at C(7)/C(8) have been attained by carbonyl reduction and dihydroxylation reactions, respectively. The extension of this methodology to the preparation of optically pure indolizidines from enantiopure sulfones is underway.

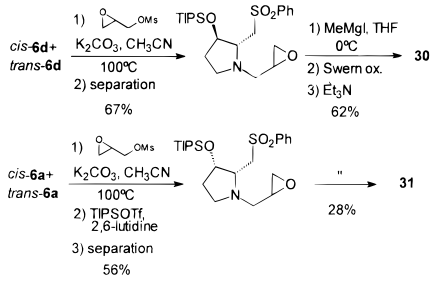
Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were acquired at 200 and 50 MHz, respectively. Chemical shifts (δ) are reported in ppm, relative to the solvent used: $CDCl_3$ (7.26 and 77 ppm), C_6D_6 (7.15 and 128 ppm), CD_3OD (3.4 and 49.9 ppm), and DHO (4.6 ppm). Mass spectra (MS) and high-resolution mass spectra (HRMS) were determined at an ionizing voltage of 70 eV. Reaction were usually carried out under a dry Ar atmosphere in anhydrous solvents. THF was distilled from sodium benzophenone under argon. CH_2Cl_2 was distilled from P_2O_5. MeOH was distilled from CaH_2. Flash column chromatographies were performed using silica gel Merck-60 (230−400 mesh) or with aluminum oxide Merck-90 active (neutral, activity I) where indicated. In the last case, alumina was previously deactivated with H_2O (8 wt %). *"Standard workup" refers to separation of the organic layer, extraction of the aqueous layer with an organic solvent, CH_2Cl_2, or EtOAc, drying over Na_2SO_4 of the combined organic layers, and removal of the solvents under reduced pressure on a rotary evaporator.*

(±)-(Phenylsulfonyl)(*p*-Tolylsulfinyl)methane. To a solution of phenyl methyl sulfone (20 g, 128 mmol) in THF (110 mL), cooled at −78 °C, was slowly added 2.5 M *n*-BuLi in hexane (51 mL, 128 mmol). The solution was stirred at −78 °C for 1 h. Then, a solution of *p*-tolyl disulfide (15.7 g, 64.0 mmol) in THF (40 mL) was slowly added by cannula. After being stirred at −78 °C for 1 h, saturated aqueous NH_4Cl (60 mL) was added. After standard workup, the residue was dissolved in MeOH (80 mL), and the solution was stored overnight at −20 °C to induce the precipitation of (±)-(phenylsulfonyl)(*p*-tolylsulfenyl)methane. After filtration, (±)-(phenylsulfonyl)(*p*-tolylsulfenyl)methane (11.5 g, 70%) was obtained as a white solid: mp 56−58 °C; ^{1}H NMR ($CDCl_3$) 7.95−7.90 (m, 2H), 7.68−7.49 (m, 3H), 7.28 and 7.06 (AA′BB′ system, 4H), 4.31 (s, 2H), 2.30 (s, 3H). The filtrate can be evaporated and the residue purified by flash chromatography (*n*-hexane/EtOAc 4:1) to afford a second crop of (±)-(phenylsulfonyl)(*p*-tolylsulfenyl)methane (5.0 g, 23%), followed by the excess phenyl methyl sulfone (10.5 g).

To a solution of (±)-(phenylsulfonyl)(*p*-tolylsulfenyl)methane (24.6 g, 88.6 mmol) in CH_2Cl_2 (100 mL), cooled at −78 °C, was added dropwise a solution of *m*-CPBA (15.3 g, 88.6 mmol) in CH_2Cl_2 (40 mL). After the mixture was stirred for 15 min at

(20) Alternatively, enones **30** and **31** have been prepared as follows: alkylation of *cis*+*trans*-**6d** with glycidyc mesylate, intramolecular opening of the epoxide using MeMgBr as base, Swern oxidation of the resulting alcohols (DMSO, Cl_2CO), and basic elimination of the sulfone (Et_3N). However, mainly due to an incomplete regioselectivity in the opening of the epoxide, and the rather different reactivity exhibited by each stereoisomer of the resulting mixture of hydroxy sulfones, the overall yields in the preparation of **30** and **31** were much lower than those obtained by applying the reactions of Scheme 6.



(21) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

(22) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Benson, M.; Kaushal, G. P.; Elbein, A. D. *Biochemistry* **1991**, *30*, 9981.

(23) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1997**, *53*, 245.

−78 °C, saturated aqueous Na_2SO_3 (30 mL) was added, the mixture was allowed to reach rt, and saturated aqueous $NaHCO_3$ (150 mL) was added. After standard workup, (±)-(phenylsulfonyl)(*p*-tolylsulfinyl)methane (25.8 g, 99%) was obtained as a white solid.[13a]

Methyl 4-Aza-4-(*tert*-butoxycarbonyl)-8-oxooctanoate (1). To a solution of 4-aminobutyraldehyde diethyl acetal (3.0 g, 18.60 mmol) in EtOH (38 mL), cooled at 0 °C, was added methyl acrylate (1.84 mL, 20.46 mmol). After the mixture was stirred at 0 °C for 2 h, the solvent and the excess of methyl acrylate were removed at reduced pressure. The residue was dissolved in CH_2Cl_2, cooled at 0 °C, and treated with BOC_2O (4.70 mL, 20.46 mmol). The solution was allowed to reach rt and stirred for 30 min. Then solvent was evaporated, and the residue was dissolved in a 2:1 mixture of AcOH/H_2O (50 mL). The solution was stirred at room temperature for 5 h and then neutralized with saturated aqueous $NaHCO_3$. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 3:1) to afford aldehyde **1** (3.7 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 9.73 (bs, 1H), 3.63 (s, 3H), 3.42 (t, J = 7.1 Hz, 2H), 3.20 (t, J = 7.1 Hz, 2H), 2.53 (t, J = 7.1 Hz, 2H), 2.41 (t, J = 7.1 Hz, 2H), 1.80 (quint, J = 7.1 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) 201.4, 172.2, 155.2, 79.8, 51.6, 46.8, 43.3, 40.9, 33.4, 28.3 (3C), 20.9.

4-[*N*,*N*-Bis(*tert*-butoxycarbonyl)]butyraldehyde (2). To a solution of 4-aminobutyraldehyde diethyl acetal (10.0 g, 62.0 mmol) in CH_2Cl_2 (100 mL), cooled at 0 °C, was added BOC_2O (15 mL, 65 mmol). The solution was allowed to reach rt and stirred for 30 min. The solvent was evaporated, and the residue was dissolved in THF (130 mL), cooled at 0 °C, and treated with 2.5 M *n*-BuLi in hexane (26 mL, 65 mmol). After the mixture was stirred at 0 °C for 30 min, saturated aqueous NH_4Cl (30 mL) was added. After standard workup, the residue was dissolved in a 2:1 mixture of AcOH/H_2O (150 mL) and stirred at room temperature for 6 h. Then, the mixture was neutralized with saturated aqueous $NaHCO_3$. After standard workup, the residue was purified by flash chromatography (*n*-hexane/EtOAc 6:1) to afford aldehyde **2** (16 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 9.72 (m, 1H), 3.56 (t, J = 7.0 Hz, 2H), 2.41 (t, J = 7.0 Hz, 2H), 1.84 (quint, J = 7.0 Hz, 2H), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$) 201.0, 152.3, 82.1, 45.1, 40.7, 27.8 (6C), 21.3.

(*E*)-Methyl 4-Aza-4-(*tert*-butoxycarbonyl)-7-hydroxy-9-(phenylsulfonyl)non-8-enoate (3a). To a solution of (±)-(phenylsulfonyl)(*p*-tolylsulfinyl)methane (5.7 g, 19.4 mmol) and piperidine (3.9 mL, 39.5 mmol) in CH_2Cl_2 (45 mL), cooled at 0 °C, was added a solution of aldehyde **1** (7.0 g, 26 mmol) in CH_2Cl_2 (35 mL). After the mixture was stirred at 0 °C for 10 h, saturated aqueous NH_4Cl was added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 2:1) to give **3a** (8.0 g, 96%). Recrystallization from *n*-hexanes−Et_2O gave **3a** as colorless crystals: mp 64−65 °C; IR ($CHCl_3$) 3370, 2960, 1730, 1660, 1480, 1370, 1310, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.91−7.86 (m, 2H), 7.61−7.48 (m, 3H), 6.95 (m, 1H), 6.70 (dd, J = 14.8, 2.0 Hz, 1H), 4.88 (bs, 1H), 4.23 (m, 1H), 3.75 (m, 1H), 3.70 (s, 3H), 3.52 (m, 1H), 3.33 (m, 1H), 3.06 (m, 1H), 2.58 (t, J = 7.1 Hz, 2H), 1.84 (m, 1H), 1.49 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) 171.9, 157.1, 147.4, 140.4, 133.2, 129.4, 129.2 (2C), 127.6 (2C), 81.1, 66.2, 51.8, 43.4, 34.7, 33.4, 28.2 (3C). Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.18; H, 6.84; N, 3.28. Found: C, 55.89; H, 6.90; N, 3.21.

(*E*)-Methyl 4-Aza-4-(*tert*-butoxycarbonyl)-7-(ethoxymethoxy)-9-(phenylsulfonyl)non-8-enoate (3b). To a solution of **3a** (400 mg, 0.94 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (348 mL, 2.0 mmol) and chloromethyl ethyl ether (350 mL, 3.8 mmol) at 0 °C. After the solution was stirred at room temperature for 7.5 h, aqueous $NaHCO_3$ (5 mL) was added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 3:1) to give **3b** (405 mg, 89%) as a colorless oil: IR ($CHCl_3$) 2980, 1730, 1680, 1470, 1440, 1410, 1370, 1310, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.91−7.86 (m, 2H), 7.62−7.49 (m, 3H), 6.89 (dd, 1H, J = 15.1, 5.1 Hz, 1H), 6.55 (dd, 1H, J = 15.1, 1.2 Hz, 1H), 4.63 and 4.60 (AB system, J = 7.1 Hz, 2H), 4.26 (m, 1H), 3.66 (s, 3H), 3.63−3.39 (m, 4H), 3.38−3.25 (m, 2H), 2.53 (m, 2H), 1.82 (m, 2H), 1.44 (s, 9H), 1.13 (t, 3H, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) 171.9, 154.9, 145.4, 140.0, 133.3, 130.7, 129.1 (2C), 127.4 (2C), 93.7, 79.7, 72.8, 63.7, 51.4, 43.9, 43.4, 33.2, 33.1, 28.2 (3C), 14.7. Anal. Calcd for $C_{23}H_{34}NO_8S$: C, 57.01; H, 7.07; N, 2.89. Found: C, 57.02; H, 7.28; N, 2.86.

(*E*)-Methyl 4-Aza-4-(*tert*-butoxycarbonyl)-9-(phenylsulfonyl)-7-[(*tert*-butyldimethylsilyl)oxy]non-8-enoate (3c). To a solution of **3a** (200 mg, 0.47 mmol) in CH_2Cl_2 (2.5 mL) were added imidazole (64 mg, 0.94 mmol) and *tert*-butyldimethylsilyl chloride (142 mg, 0.94 mmol). After the mixture was stirred overnight at room temperature, water (3 mL) was added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 4:1) to give **3c** (253 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.90−7.83 (m, 2H), 7.64−7.47 (m, 3H), 6.94 (dd, 1H, J = 14.7, 4.0 Hz, 1H), 6.50 (dd, 1H, J = 14.7, 1.6 Hz, 1H), 4.37 (m, 1H), 3.65 (s, 3H), 3.39 (m, 2H), 3.32−3.07 (m, 2H), 2.51 (m, 2H), 1.76 (m, 2H), 1.43 (s, 9H), 0.83 (s, 9H), 0.00 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) 171.9, 155.0, 147.8, 140.3, 133.3, 130.1, 129.2 (2C), 127.5 (2C), 79.9, 69.1, 51.6, 44.1, 43.6, 35.4, 33.6, 28.3 (3C), 25.6 (3C), 18.0, −4.0, −3.7; MS 468 (M^+ − Bu^tO, 9) 454 (12), 428 (85), 396 (82), 384 (51), 368 (38), 142 (100).

(*E*)-Methyl 4-Aza-4-(*tert*-butoxycarbonyl)-9-(phenylsulfonyl)-7-[(triisopropylsilyl)oxy]non-8-enoate (3d). To a solution of **3a** (2.23 g, 5.2 mmol) and 2,6-lutidine (0.82 mL, 6.76 mmol) in CH_2Cl_2 (30 mL), cooled at 0 °C, was slowly added triisopropylsilyl trifluoromethanesulfonate (1.36 mL, 6.24 mmol). After the mixture was stirred at 0 °C for 5 min and at room temperature for 2 h, 0.3 M HCl (50 mL) was added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 4:1) to give **3d** (2.92 g, 97%) as a colorless oil: IR ($CHCl_3$) 2950, 2870, 1730, 1680, 1470, 1450, 1420, 1370, 1330, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.92−7.86 (m, 2H), 7.66−7.49 (m, 3H), 6.99 (dd, J = 14.9, 4.4 Hz, 1H), 6.57 (dd, J = 14.9, 1.5 Hz, 1H), 4.56 (m, 1H), 3.67 (s, 3H), 3.39 (m, 2H), 3.21 (m, 2H), 2.53 (m, 2H), 1.85 (m, 2H), 1.45 (s, 9H), 0.97 (m, 21H); ^{13}C NMR ($CDCl_3$) 172.0, 155.0, 147.8, 140.4, 133.3, 130.3, 129.2 (2C), 127.6 (2C), 79.9, 69.3, 51.5, 43.5, 43.3, 35.9, 33.3, 28.3 (3C), 17.8(6C), 12.1(3C). Anal. Calcd for $C_{29}H_{49}NO_7SSi$: C, 59.66; H, 8.47; N, 2.40. Found: C, 59.46; H, 8.72; N, 2.62.

(*E*)-5-[*N*,*N*-Bis(*tert*-butoxycarbonyl)amino]-1-(phenylsulfonyl)pent-1-en-3-ol (4a). Following a procedure identical to that described for the preparation of **3a**, the reaction of (phenylsulfonyl)(*p*-tolylsulfinyl)methane (5.0 g, 17.0 mmol) and piperidine (3.5 mL, 34.0 mmol) in CH_2Cl_2 (40 mL) with aldehyde **2** (6.8 g, 23.8 mmol) in CH_2Cl_2 (30 mL) at 0 °C afforded **4a** (7.0 g, 94%) as a white solid after flash chromatography (*n*-hexanes−EtOAc 3:1): mp 72−73 °C; ^{1}H NMR ($CDCl_3$) 7.88−7.85 (m, 2H), 7.62−7.48 (m, 3H), 6.94 (dd, J = 14.8, 3.0 Hz, 1H), 6.67 (dd, J = 14.8, 2.0 Hz, 1H), 4.32 (m,1H), 4.07 (bs, 1H), 3.78−3.72 (m, 2H), 2.03−1.86 (m, 2H), 1.49 (s, 18H); ^{13}C NMR ($CDCl_3$) 153.5, 147.2, 140.4, 133.3, 129.6, 129.2 (2C), 127.6 (2C), 83.4, 66.6, 42.3, 35.3, 28.0 (6C). Anal. Calcd for $C_{21}H_{31}NO_7S$: C, 57.13; H, 7.08; N, 3.17. Found: C, 57.21; H, 6.95; N, 3.15.

(*E*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-3-(ethoxymethoxy)-5-(phenylsulfonyl)pent-4-en-1-amine (4b). By a procedure identical to that described for **3b**, the reaction of **4a** (350 mg, 0.80 mmol), diisopropylethylamine (210 mL, 1.2 mmol), and chloromethyl ethyl ether (370 mL, 4.0 mmol) in CH_2Cl_2 (2.5 mL) afforded **4b** (351 mg, 88%, colorless oil) after flash chromatography (*n*-hexanes−EtOAc 10:1): ^{1}H NMR ($CDCl_3$) 7.90−7.84 (m, 2H), 7.64−7.46 (m, 3H), 6.89 (dd, J = 15.0, 5.0 Hz, 1H), 6.54 (dd, J = 15.0, 1.3 Hz, 1H), 4.62 and 4.58 (AB system, J = 7.1 Hz, 2H), 4.30 (q, J = 5.7 Hz, 1H), 3.64−3.43 (m, 4H), 1.85 (m, 2H), 1.47 (s, 18H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) 152.2, 145.3, 140.1, 133.2, 130.9, 129.1 (2C), 127.4 (2C), 93.6, 82.2, 72.6, 63.6, 42.4, 33.2, 27.8 (6C), 14.7.

(*E*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-5-(phenylsulfonyl)-pent-4-en-1-amine (4c). By a procedure identical to that described for **3c**, the reaction of **4a** (400 mg, 0.91 mmol), imidazole (75 mg, 1.10 mmol), and *tert*-butyldimethylsilyl chloride (206 mg, 1.3 mmol) in CH_2Cl_2 (3 mL) afforded **4c** (484 mg, 96%, colorless oil) after flash

chromatography (*n*-hexanes−EtOAc 10:1): ^{1}H NMR ($CDCl_3$) 7.89−7.84 (m, 2H), 7.63−7.46 (m, 3H), 6.98 (dd, J = 14.9, 3.9 Hz, 1H), 6.50 (dd, J = 14.9, 1.6 Hz, 1H), 4.39 (m, 1H), 3.55 (m, 2H), 1.81 (m, 2H), 1.47 (s, 18H), 0.83 (s, 9H), 0.00 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) 152.2 (2C), 147.8, 140.2, 133.2, 130.0, 129.1 (2C), 127.4 (2C), 82.2, 69.2, 42.7, 35.7, 27.9 (6C), 25.5, 17.9, −5.0, −5.2. Anal. Calcd for $C_{27}H_{45}NO_7SSi$: C, 58.35; H, 8.17; N, 2.52; S, 5.76. Found: C, 58.82; H, 8.61; N, 2.55; S, 5.40.

(*E*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-5-(phenylsulfonyl)-3-[(triisopropylsilyl)oxy]pent-4-en-1-amine (4d). By a procedure identical to that described for the preparation of **3d**, the reaction of **4a** (2 g, 4.5 mmol), 2,6-lutidine (630 mL, 5.4 mmol), and triisopropylsilyl trifluoromethane sulfonate (1.1 mL, 0.5 mmol) in CH_2Cl_2 (20 mL) afforded **4d** (2.54 g, 95%, colorless oil) after flash chromatography (*n*-hexanes−EtOAc 10:1): ^{1}H NMR ($CDCl_3$) 7.91−7.87 (m, 2H), 7.64−7.48 (m, 3H), 7.03 (dd, J = 14.9, 4.5 Hz, 1H), 6.59 (dd, J = 14.9, 1.6 Hz, 1H), 4.55 (m, 1H), 3.68−3.45 (m, 2H), 1.98−1.81 (m, 2H), 1.50 (s, 18H), 0.96 (bs, 21H); ^{13}C NMR ($CDCl_3$) 152.4 (2C), 148.0, 140.5, 133.2, 130.4, 129.2 (2C), 127.6 (2C), 82.4, 69.4, 42.2, 36.6, 28.0 (6C), 17.9 (6C), 12.1 (3C). Anal. Calcd for $C_{30}H_{51}NO_7SSi$: C, 60.27; H, 8.60; N, 2.34; S, 5.36. Found: C, 60.77; H, 8.63; N, 2.73; S, 5.48.

General Procedure for the Cyclization of γ-Oxygenated α,β-Unsaturated Sulfones 3a-d and 4a-d. To a solution of the corresponding γ-oxygenated α,β-unsaturated sulfone (6.8 mmol) in CH_2Cl_2 (50 mL) was added TFA (9.0 mL). After the mixture was stirred at room temperature for 5 h, the solvent was removed in vacuo. The resulting ammonium salt was dissolved in THF (90 mL), cooled at −78 °C, and treated with Et_3N (2 mL). After being stirred at −78 °C for 20 min, the solvent was removed, and then CH_2Cl_2 (50 mL) and 10% aqueous NaOH (10 mL) were added. After standard workup, mixtures of *cis*- and *trans*-pyrrolidines were obtained.

(2*R,3*S**)- and (2*R**,3*R**)-3-Hydroxy-1-[2-(methoxycarbonyl)ethyl]-2-[(phenylsulfonyl)methyl]pyrrolidine (*cis*-5a) and (*trans*-5a).** Following the general procedure but using toluene as solvent instead of THF, **3a** (3.0 g, 7.03 mmol) was transformed into a 81:19 mixture of *cis*-**5a** and *trans*-**5a** (2.18 g, 96%), which could not be separated by flash chromatography. Alternatively, pure *cis*-**5a** and *trans*-**5a** were obtained by quantitative desilylation (TBAF, THF, 0 °C) of pure *cis*-**5d** and *trans*-**5d**, respectively. ***cis*-5a**: ^{1}H NMR ($CDCl_3$) 7.97−7.92 (m, 2H), 7.73−7.54 (m, 3H), 4.49 (m, 1H), 3.65 (dd, J = 14.0, 10.1 Hz, 1H), 3.63 (s, 3H), 3.23 (dd, J = 14.0, 2.3 Hz, 1H), 3.16 (m, 1H), 3.04−2.81 (m, 3H), 2.45−2.06 (m, 4H), 1.85−1.72 (m, 1H); ^{13}C NMR ($CDCl_3$) 172.6, 139.5, 133.9, 129.4 (2C), 127.8 (2C), 71.3, 62.9, 54.4, 51.6, 50.9, 49.2, 33.1, 32.1. ***trans*-5a**: ^{1}H NMR ($CDCl_3$) 7.98−7.93 (m, 2H), 7.73−7.55 (m, 3H), 4.32 (dt, J = 6.8, 3.1 Hz, 1H), 3.63 (s, 3H), 3.44 (dd, J = 14.3, 2.0 Hz, 1H), 3.08 (dd, J = 14.3, 10.3 Hz, 1H), 3.05−2.71 (m, 4H), 2.50−2.13 (m, 3H), 2.06 (m, 1H), 1.81 (m, 1H), 1.69 (bs, 1H);^{13}C NMR ($CDCl_3$) 172.6, 139.3, 134.0, 129.4 (2C), 127.9 (2C), 77.1, 67.7, 58.9, 51.6, 50.8, 49.1, 33.1, 32.0.

(2*R,3*S**)- and (2*R**,3*R**)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-[2-(methoxycarbonyl)ethyl]-2-[(phenylsulfonyl)methyl]pyrrolidine (*cis*-5c) and (*trans*-5c). Method A.** Following the general procedure, **3c** (2.0 g, 3.70 mmol) was transformed into a 19:81 mixture of *cis*-**5c** and *trans*-**5c** that was separated by flash chromatography (*n*-hexanes−EtOAc 4:1) to afford successively *cis*-**5c** (285 mg, 17%) and *trans*-**5c** (1.22 g, 75%).

Method B. To a solution of a 81:19 mixture of *cis*-**5a** and *trans*-**5a** (2.18 g, 6.67 mmol) in CH_2Cl_2 (80 mL) were successively added imidazole (590 mg, 8.67 mmol), DMAP (817 mg, 6.7 mmol), and *tert*-butyldimethylsilyl chloride (2.0 g, 13.3 mmol). After the solution was stirred at room temperature for 24 h, saturated aqueous NH_4Cl was added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 4:1) to afford successively *cis*-**5c** (2.20 g, 71%) and *trans*-**5c** (540 mg, 17%). ***cis*-5c**: IR ($CHCl_3$) 2940, 2860, 1730, 1440, 1310, 1260, 1150, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.97−7.91 (m, 2H), 7.68−7.51 (m, 3H), 4.36 (m, 1H), 3.78 (m, 1H), 3.64 (s, 3H), 3.11−2.89 (m, 4H), 2.41 (m, 2H), 2.18 (m, 2H), 2.05 (m, 1H), 1.65 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) 172.6, 140.1, 133.4, 129.1 (2C), 127.7 (2C), 71.9, 62.3, 54.3, 51.4, 50.0, 49.3, 33.7, 33.1, 25.7 (3C), 17.9, −3.5, −3.8; HRMS calcd for $C_{21}H_{35}NO_5SSi$ 441.2005, found 441.2003. ***trans*-5c**: ^{1}H NMR ($CDCl_3$) 7.97−7.90 (m, 2H), 7.70−7.51 (m, 3H), 4.39 (m, 1H), 3.63 (s, 3H), 3.18 (dd, J = 13.3, 2.0 Hz, 1H), 3.04−2.85 (m, 4H), 2.74−2.48 (m, 2H), 2.30 (m, 2H), 1.89−1.63 (m, 2H), 0.87 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) 172.7, 140.0, 133.5, 129.1 (2C), 127.8 (2C), 75.8, 67.7, 59.5, 51.4, 50.7, 50.4, 33.5, 33.4, 25.6 (3C), 17.7, −4.8 (2C); HRMS calcd for $C_{21}H_{35}NO_5SSi$ 441.2005, found 441.2003.

(2*R,3*S**)- and (2*R**,3*R**)-1-[2-(Methoxycarbonyl)ethyl]-2-[(phenylsulfonyl)methyl]-3-[(triisopropylsilyl)oxy)]pyrrolidine (*cis*-5d) and (*trans*-5d).** Following the general procedure, **3d** (2.9 g, 5.0 mmol) was transformed into a 10:90 mixture of *cis*-**5d** and *trans*-**5d**, which was separated by flash chromatography (*n*-hexanes−EtOAc 4:1) to give pyrrolidine *cis*-**5d** (220 mg, 9%) followed by the major isomer *trans*-**5d** (2.0 g, 84%), both as colorless oils. ***cis*-5d**: IR ($CHCl_3$) 3050, 2940, 2870, 2720, 1440, 1310, 1210, 1150 cm^{-1}; ^{1}H NMR (C_6D_6) 7.97−7.92 (m, 2H), 6.96−6.91 (m, 3H), 4.39 (q, J = 6.4 Hz, 1H), 3.95 (dd, J = 14.5, 4.9 Hz, 1H), 3.40 (m, 1H), 3.31 (s, 3H), 3.27−3.16 (m, 2H), 2.75 (m, 1H), 2.52 (m, 1H), 2.29 (m, 2H), 1.97 (dt, J = 9.3, 7.9 Hz, 1H), 1.77−1.68 (m, 1H), 1.46 (m, 1H), 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$) 172.7, 140.3, 133.3, 129.1 (2C), 127.7 (2C), 72.1, 61.8, 54.8, 51.4, 49.5, 49.4, 33.4, 33.2, 17.9 (6C), 12.2 (3C); HRMS calcd for $C_{24}H_{41}O_5NSSi$ 483.2475, found 483.2470. ***trans*-5d**: ^{1}H NMR ($CDCl_3$) 7.97−7.91 (m, 2H), 7.69−7.51 (m, 3H), 4.52 (m, 1H), 3.65 (s, 3H), 3.23−2.93 (m, 5H), 2.82−2.56 (m, 2H), 2.31 (m, 2H), 1.87−1.78 (m, 2H), 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$) 172.5, 140.1, 133.3, 129.0 (2C), 127.6 (2C), 76.2, 67.8, 59.7, 51.3, 51.0, 50.5, 33.6, 33.5, 17.9 (6C), 12.2 (3C). Anal. Calcd for $C_{24}H_{41}O_5NSSi$: C, 59.60; H, 8.55; N, 2.90. Found: C, 59.68; H, 8.76; N, 2.92.

(2*R,3*S**)- and (2*R**,3*R**)-3-Hydroxy-2-[(phenylsulfonyl)-methyl]pyrrolidine (*cis*-6a) and (*trans*-6a).** Following the general procedure, **4a** (3.0 g, 6.80 mmol) was transformed into an 80:20 mixture of hydroxypyrrolidines *cis*-**6a** and *trans*-**6a** (1.62 g, 99%). Compound *cis*-**6a** was isolated diastereomerically pure by recrystallization from EtOAc/EtOH/ether. ***cis*-6a**: mp 133−134 °C; ^{1}H NMR ($CDCl_3$): 7.95−7.89 (m, 2H), 7.71−7.52 (m, 3H), 4.32 (m, 1H), 3.48 (dd, J = 15.8, 8.6 Hz, 1H), 3.37−3.24 (m, 2H), 3.12 (ddd, J = 10.5, 8.5, 5.6 Hz, 1H), 2.81 (m, 1H), 2.59 (bs, 2H), 2.10 (m, 1H), 1.85−1.69 (m, 1H); ^{13}C NMR ($CDCl_3$) 139.4, 133.9, 129.4 (2C), 127.8 (2C), 72.4, 57.6, 56.6, 44.0, 34.6. Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.81; S, 13.26. Found: C, 54.59; H, 5.91; N, 5.73; S, 13.51. ***trans*-6a**: ^{1}H NMR ($CDCl_3$) 7.95−7.89 (m, 2H), 7.71−7.52 (m, 3H), 4.05 (dt, J = 9.0, 4.6 Hz, 1H), 3.40−2.88 (m, 5H), 2.02 (m, 1H), 1.72 (m, 1H); ^{13}C NMR ($CDCl_3$) 139.3, 133.8, 129.3 (2C), 127.8 (2C), 76.0, 60.4, 59.9, 43.9, 33.2.

(2*R,3*S**)- and (2*R**,3*R**)-2-[(Phenylsulfonyl)methyl]-3-[(triisopropylsilyl)oxy]pyrrolidine (*cis*-6d) and (*trans*-6d).** Following the general procedure, **4d** (2.3 g, 3.85 mmol) was transformed into an 80:20 mixture of *cis*-**6d** and *trans*-**6d** (1.5 g, 98%), which could be only partially separated by flash cromatography (EtOAc). ***cis*-6d**: ^{1}H NMR ($CDCl_3$) 7.95−7.89 (m, 2H), 7.64−7.50 (m, 3H), 4.41 (q, J = 5.5 Hz, 1H), 3.48−3.30 (m, 3H), 3.16 (dd, J = 14.7, 9.9 Hz, 1H), 3.11 (m, 1H), 2.87 (ddd, J = 10.4, 8.4, 6.5 Hz, 1H), 2.04 (m, 1H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$) 139.6, 133.6, 129.2 (2C), 127.9 (2C), 73.6, 56.8, 56.1, 43.0, 33.9, 17.9 (6C), 12.1 (3C). ***trans*-6d**: ^{1}H NMR ($CDCl_3$) 7.96−7.90 (m, 2H), 7.70−7.22 (m, 3H), 4.08 (dt, J = 6.7, 4.3 Hz, 1H), 3.34 (dd, J = 13.6, 2.2 Hz, 1H), 3.33−2.93 (m, 4H), 2.21 (bs, 1H), 1.99 (m, 1H), 1.71 (m, 1H), 0.98 (m, 21H); ^{13}C NMR ($CDCl_3$) 139.2, 133.6, 129.1 (2C), 127.7 (2C), 76.4, 60.8, 59.8, 43.7, 33.3, 17.7 (6C), 11.8 (3C); MS 397 (M^+, 3), 354 (M^+ − *i*-Pr, 73), 255 (42); HRMS (FAB) calcd for $C_{20}H_{30}NO_3SSi$ ($M + H^+$) 398.2182, found 398.2185.

(1*R,7*S**,8*R**,8a*R**)- and (1*R**,7*R**,8*S**,8a*R**)-7-Hydroxy-8-(phenylsulfonyl)-1-[(triisopropylsilyl)oxy]indolizidine (8) and (9).** To a solution of *trans*-**5d** (2.0 g, 4.14 mmol) in THF (55 mL), cooled at 0 °C, was added 1 M LHMDS in THF (9.5 mL). After the solution was stirred at 0 °C for 2.5

h, saturated aqueous NH_4Cl (100 mL) was added. After standard workup, a 60:40 mixture of keto sulfones **7eq** and **7ax** (1.85 g, 100%) was obtained as a yellow solid. This crude mixture was dissolved in a mixture of CH_2Cl_2 (16 mL) and EtOH (28 mL), cooled at 0 °C, and treated with solid $NaBH_4$ (280 mg, 7.4 mmol). After the mixture was stirred at 0 °C for 30 min, saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (50 mL) were added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 2:1) to give hydroxy sulfone **9** (882 mg, 48%) as a white solid, followed by **8** (570 mg, 31%) as a colorless oil. **8**: ^{1}H NMR ($CDCl_3$) 7.96−7.91 (m, 2H), 7.72−7.54 (m, 3H), 5.03 (m, 1H), 3.72 (m, 2H), 3.17−2.59 (m, 5H), 2.39 (m, 1H), 1.84−1.69 (m, 2H), 1.51 (m, 1H), 1.13 (m, 21H); ^{13}C NMR ($CDCl_3$) 138.2, 134.0, 129.4 (2C), 128.4 (2C), 74.4, 66.3 66.1, 64.2, 51.2, 45.5, 34.5, 31.0, 18.3 (6C), 12.9 (3C); HRMS (FAB) calcd for $C_{23}H_{40}NO_4SSi$ ($M + H^+$) 454.2444, found 454.2447. **9**: mp 143−144 °C; IR ($CHCl_3$) 3500, 3020, 2950, 1510, 1420, 1210, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.97−7.92 (m, 2H), 7.64−7.47 (m, 3H), 4.85 (m, 1H), 3.99 (m, 1H), 3.83 (m, 1H), 3.63 (m, 1H), 3.19 (ddd, J = 10.6, 4.7, 1.9 Hz, 1H), 3.02 (m, 1H), 2.48−2.06 (m, 5H), 1.93 (m, 1H), 1.64 (m, 1H), 0.87 (m, 21H); ^{13}C NMR ($CDCl_3$) 143.4, 133.1, 128.9 (2C), 127.5 (2C), 76.4, 73.2, 72.6, 67.8, 52.0, 50.4, 35.3, 31.2, 17.8 (6C), 11.9 (3C). Anal. Calcd for $C_{23}H_{39}NO_4SSi$: C, 60.90; H, 8.67; N, 3.09. Found: C, 61.22; H, 8.30; N, 3.20.

(1*R,8a*S**)-1,2,3,5,6,8a-Hexahydro-1-[(triisopropylsilyl)oxy]indolizine (10). Method A.** To a solution of hydroxy sulfone **8** (184 mg, 0.41 mmol) in MeOH (7 mL) were added solid Na_2HPO_4 (810 mg, 5.70 mmol) and freshly prepared powdered 6% Na(Hg) (651 mg). The solution was vigorously stirred at room temperature for 4 h. Then, the resulting Hg was decanted, and the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1% aqueous NaOH (25 mL). After standard workup, the residue was purified by flash chromatography (EtOAc) to give **10** (88 mg, 73%) as a colorless oil. **Method B.** To a solution of a 58:42 mixture of alcohols **8** and **9** (250 mg, 0.55 mmol) in CH_2Cl_2 (4 mL), cooled at 0 °C, were added Et_3N (382 mL, 2.75 mmol) and MsCl (49 mL, 0.63 mmol). After the solution was stirred at room temperature for 4 h, aqueous saturated NH_4Cl (1 mL) was added. After standard workup, the residue was dissolved in MeOH (8 mL) and treated with Na_2HPO_4 (1.09 g, 7.51 mmol) and powdered 6% Na(Hg) (873 mg). Following an isolation procedure identical to that described in method A, **10** (133 mg, 82%, colorless oil) was obtained after flash chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) 5.87 (m, 1H), 5.78 (m, 1H), 4.10 (ddd, J = 8.1, 6.4, 4.8 Hz, 1H), 3.00−2.71 (m, 3H), 2.64 (ddd, J = 11.5, 9.3, 4.9, Hz, 1H), 2.39−2.18 (m, 3H), 2.11−1.92 (m, 1H), 1.73 (ddd, J = 13.4, 9.3, 4.8 Hz, 1H), 1.07 (m, 21H); ^{13}C NMR ($CDCl_3$) 127.0, 125.6, 76.0, 67.7, 50.6, 47.3, 33.5, 24.0, 17.8 (6C), 12.0 (3C).

(1*R,7*R**,8a*S**)-7-Hydroxy-1-[(triisopropylsilyl)oxy]indolizidine (11).** By a procedure identical to that described for the preparation of olefin **10** (method A), the reaction of **9** (215 mg, 0.47 mmol) with Na_2HPO_4 (930 mg, 6.5 mmol) and 6% Na(Hg) (750 mg) in MeOH (8 mL) at room temperature, for 4 h, followed by purification by flash chromatography (EtOAc) afforded alcohol **11** (121 mg, 82%) as a white solid: mp 79−80 °C; ^{1}H NMR ($CDCl_3$) 4.06 (m, 1H), 3.67 (m, 1H), 3.04−2.90 (m, 2H), 2.43−1.46 (m, 7H), 1.62 (m, 2H), 1.24 (q, J = 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 76.2, 69.5, 69.3, 51.7, 50.6, 38.5, 34.2, 33.5, 17.9 (6C), 12.1 (3C); MS 313 (M^+, 15), 270.2 ($M^+ - i$-Pr, 19); HRMS (FAB) calcd for $C_{17}H_{36}NO_2Si$ ($M + H^+$) 314.2518, found 314.2515.

(1*R,7*R**,8a*S**)-1,7-Dihydroxyindolizidine (12).** A solution of **11** (65 mg, 0.21 mmol) in 5 M HCl (5 mL) was stirred at room temperature for 10 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the aqueous layer was concentrated to dryness. The resulting chlorohydrate was dissolved in MeOH and chromatographed on a Dowex 1 × 8 200 (OH^- form) ion-exchange column. The ninhydrin-positive fractions were combined and concentrated to dryness to afford diol **12** (32.4 mg, 99%) as a colorless oil: ^{1}H NMR (D_2O) 3.67 (m, 1H), 3.50 (m, 1H), 2.79−2.61 (m, 2H), 2.19−1.62 (m, 6H), 1.43−1.09 (m, 2H), 0.95 (q, J = 11.1 Hz, 1H); ^{13}C NMR (D_2O) 74.2, 68.4, 68.2, 50.5, 49.1, 36.0, 32.5, 31.0; HRMS (FAB) calcd for $C_8H_{16}NO_2$ ($M + H^+$) 158.1177, found 158.1181.

(1*R,7*S**,8*R**,8a*S**)- and (1*R**,7*R**,8*S**,8a*S**)-7,8-Dihydroxy-1-[(triisopropylsilyl)oxy]indolizidines (13) and (14).** To a solution of olefin **10** (83 mg, 0.29 mmol) in acetone/water 5:1 (3.6 mL) were added trimethylamine *N*-oxide (35.6 mg, 0.32 mmol) and catalytic OsO_4 (4 wt % in water, 55 mL, 9×10^{-3} mmol). After the solution was stirred at room temperature for 4 h, solid Na_2SO_3 (40 mg) was added, and the mixture was stirred for a further 30 min. The reaction mixture was concentrated to dryness, and the residue was stirred vigorously in CH_2Cl_2. The suspension was filtered through a short column of Celite and the column washed several times with CH_2Cl_2. The combined filtrates were evaporated, and the residue was purified by flash chromatography on alumina (CH_2Cl_2−0.4% MeOH) to give **13** (37 mg, 52%) as a colorless oil, followed by **14** (19 mg, 27%) as a white solid. **13**: ^{1}H NMR ($CDCl_3$) 4.28 (q, J = 8.3 Hz, 1H), 3.99 (q, J = 3.0 Hz, 1H), 3.64 (dd, J = 9.2, 3.0 Hz, 1H), 3.03 (td, J = 8.9, 3.3 Hz, 1H), 2.64 (ddd, J = 7.1, 5.0, 2.0 Hz, 1H), 5.49−2.10 (m, 5H), 1.94 (dq, J = 14.3, 2.7 Hz, 1H), 1.78−1.53 (m, 2H), 1.07 (m, 21H); ^{13}C NMR ($CDCl_3$) 77.8, 74.8, 66.6, 51.7, 46.3, 31.3, 30.0, 29.7, 18.0 (3C), 17.9 (3C), 12.4 (3C); HRMS calcd for $C_{17}H_{35}NO_3Si$ 329.2386, found 329.2384. **14**: mp 115−116 °C; IR ($CHCl_3$) 2920, 2860, 1460, 1380, 1260, 1120, 1090 cm^{-1}; ^{1}H NMR (C_6D_6) 4.46 (ddd, J = 8.6, 6.5, 3.9 Hz, 1H), 4.07 (m, 1H), 3.34 (ddd, J = 11.1, 5.4, 2.9 Hz, 1H), 2.59 (td, J = 8.3, 2.4 Hz, 1H), 2.42 (ddd, J = 10.7, 4.5, 2.4, 1H), 2.10 (q, J = 8.8 Hz, 1H), 1.91 (m, 2H), 1.66−1.10 (m, 4H), 1.12 (m, 21H); ^{13}C NMR ($CDCl_3$) 74.4, 71.5, 71.0, 68.1, 51.9, 49.7, 34.1, 28.9, 17.9 (6C), 12.1 (3C). Anal. Calcd for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70; N, 4.25. Found: C, 61.95; H, 11.00; N, 4.21.

(1*R,7*S**,8*R**,8a*R**)-1,7,8-Trihydroxyindolizidine (15).** Following a procedure identical to that described for the preparation of **12**, TIPS derivative **13** (113 mg, 0.34 mmol) was deprotected to give **15** (59.3 mg, 100%) as a crystalline solid: mp 145−146 °C; ^{1}H NMR (D_2O) 4.04 (ddd, J = 9.2, 7.0, 3.8 Hz, 1H), 3.91 (q, J = 3.0 Hz, 1H), 3.40 (dd, J = 10.0, 3.0 Hz, 1H), 2.78 (td, J = 8.9, 1.8 Hz, 1H), 2.60 (ddd, J = 11.5, 4.9, 2.3 Hz, 1H), 2.36 (q, J = 9.2 Hz, 1H), 2.26 (qd, J = 11.5, 3.9 Hz, 1H), 2.12 (dd, J = 10.0, 7.0 Hz, 1H), 2.06 (dq, J = 13.7, 9.2 Hz, 1H), 1.77−1.57 (m, 2H), 1.55−1.39 (m, 1H); ^{13}C NMR (D_2O) 74.0, 72.6, 67.8, 67.5, 50.9, 45.3, 31.2, 30.0; MS 173 (M^+, 34), 156 (26), 129 (100); HRMS (FAB) calcd for $C_8H_{16}NO_3$ ($M + H^+$) 174.1132, found 174.1130. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.47; H, 9.11; N, 7.94.

(1*R,7*R**,8*S**,8a*R**)-1,7,8-Trihydroxyindolizidine (16).** By a procedure identical to that described for the preparation of **12**, TIPS derivate **14** (50.2 mg, 0.15 mmol) was desilylated to give **16** (26.2 mg, 100%) as a crystalline solid: mp 155−156 °C dec; ^{1}H NMR (D_2O) 4.04 (m, 1H), 3.77 (m, 1H), 3.47 (m, 1H), 2.68 (m, 2H), 2.11 (q, J = 9.2 Hz), 2.04−1.76 (m, 4H), 1.62−1.30 (m, 3H); ^{13}C NMR (D_2O) 72.3, 70.3, 69.4, 66.3, 51.2, 49.2, 31.3, 26.4; HRMS calcd for $C_8H_{15}NO_3$ 173.1048, found 173.1053. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C. 55.68; H, 8.56; N, 7.89.

(1*S,8*R**,8a*R**)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-oxo-8-(phenylsulfonyl)indolizidine (17).** To a solution of *cis*-**5c** (2.0 g, 4.54 mmol) in THF (400 mL), cooled at 0 °C, was added 1 M LHMDS in THF (10 mL, 10 mmol). After the solution was stirred at 0 °C for 1 h, saturated aqueous NH_4Cl (80 mL) was added. After standard workup, keto sulfone **17** (1.85 g, 100%) was obtained: ^{1}H NMR ($CDCl_3$) 7.85−7.80 (m, 2H), 7.66−7.49 (m, 3H), 4.56 (m, 1H), 4.41 (dd, J = 7.9, 1.4 Hz, 1H), 3.28 (dd, J = 7.9, 5.0 Hz, 1H), 3.31 (m, 1H), 2.85−2.52 (m, 4H), 2.39−2.20 (m, 2H), 1.86 (m, 1H), 0.89 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$) 199.7, 137.9, 133.9, 128.7 (4C), 72.3, 70.2, 65.9, 52.1, 47.4, 37.6, 34.9, 25.7 (3C), 17.7, −4.6, −5.1.

(1*S,7*R**,8*R**,8a*R**)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxy-8-(phenylsulfonyl)indolizidine (18).** To a solution of keto sulfone **17** (500 mg, 1.22 mmol) in CH_2Cl_2 (10 mL), cooled at −78 °C, was added 1 M DIBALH in hexane (2.44 mL, 2.44 mmol). After the mixture was stirred at −78 °C for

3 h, a few drops of MeOH followed by EtOAc (20 mL) and saturated aqueous sodium potassium tartrate (60 mL) were added. The mixture was stirred at room temperature for further 30 min. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 2:1) to give the hydroxy sulfone **18** as a white solid (376 mg, 75%): mp 98−99 °C; ^{1}H NMR ($CDCl_3$) 7.91−7.85 (m, 2H), 7.71−7.50 (m, 3H), 4.54 (m,1H), 4.52 (bs, 1H), 3.71 (m, 2H), 3.09−2.93 (m, 2H) 2.15−1.43 (m, 7H), 0.90 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) 137.7, 133.9, 129.1 (4C), 71.9, 67.4, 65.9, 65.7, 51.6, 47.8, 33.8, 31.5, 26.1 (3C), 18.1, −3.7, −4.7.

(1*S,7*S**,8*R**,8a*R**)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxy-8-(phenylsulfonyl)indolizidine (19).** To a solution of keto sulfone **17** (1.8 g, 4.54 mmol) in THF (20 mL), cooled at −78 °C, was added 1 M lithium triethylborohydride in THF (9.1 mL, 9.1 mmol). After the solution was stirred at −78 °C for 1 h, a few drops of MeOH was added, and the mixture was allowed to reach rt. Then 20% NaOH (50 mL) and CH_2Cl_2 (80 mL) were added. After standard workup, the residue was purified by flash chromatography on alumina (*n*-hexanes−EtOAc 3:1) to give hydroxy sulfone **19** (1.24 g, 68%) as a white solid: mp 121−122 °C; ^{1}H NMR ($CDCl_3$) 7.97−7.92 (m, 2H), 7.74−7.55 (m, 3H), 4.76 (dd, J = 5.4, 3.3 Hz, 1H), 4.19 (d, J = 1.7 Hz, 1H), 3.83 (m, 1H), 3.41 (dd, J = 10.7, 2.1 Hz, 1H), 3.15 (td, J = 9.0, 3.3 Hz, 1H), 2.85−2.68 (m, 2H), 2.55 (td, J = 11.9, 2.7 Hz, 1H), 2.25 (m, 1H), 2.06 (m, 1H), 1.90−1.72 (m, 2H), 1.55 (m, 1H), 0.96 (s, 9H), 0.23 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) 138.1, 134.0, 129.3 (2C), 128.3 (2C), 72.6, 63.6, 63.2, 60.7, 51.2, 44.9, 32.7, 31.9, 26.4 (3C), 18.2, −3.5, −4.2. Anal. Calcd for $C_{20}H_{33}NO_4SSi$: C, 58.36; H, 8.08; N, 3.40; S, 7.79. Found: C, 58.41; H, 8.25; N, 3.47; S, 8.26.

(1*S,7*R**,8a*S**)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxyindolizidine (20).** By a procedure identical to that described for the preparation of olefin **10**, the reaction of hydroxy sulfone **18** (100 mg, 0.24 mmol), Na_2HPO_4 (465 mg, 3.2 mmol), and Na(Hg) (375 mg) in MeOH (4 mL) at room temperature for 4 h afforded **20** (51 mg, 78%, colorless oil) after flash cromatography (EtOAc): ^{1}H NMR ($CDCl_3$) 4.14 (ddd, J = 7.2, 4.8, 2.3 Hz, 1H), 3.62 (m, 1H), 3.12 (m, 2H), 2.45 (bs, 1H), 2.15 (m, 1H), 1.96−1.40 (m, 8H), 0.85 (s, 9H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$) 72.9, 69.9, 67.9, 52.4, 50.4, 35.1, 34.9, 34.4, 25.9 (3C), 18.3, −4.8 (2C); HRMS (FAB) calcd for $C_{14}H_{30}NO_2Si$ (M + H$^+$) 272.2046, found 272.2046.

(1*S,7*R**,8a*S**)-1,7-Dihydroxyindolizidine (21).** By a procedure identical to that described for the preparation of **12**, TIPS derivative **20** (55 mg, 0.20 mmol) was desilylated to give **21** (31.3 mg, 99%): ^{1}H NMR (CD_3OD) 4.21 (ddd, J = 6.9, 4.4, 2.1 Hz, 1H), 3.72 (m, 1H), 3.20−3.08 (m, 2H), 2.42−2.25 (m, 1H), 2.16−1.53 (m, 8H); ^{13}C NMR (D_2O) 71.5, 69.0, 66.8, 51.2, 49.3, 32.8, 32.6 (2C); HRMS (FAB) calcd for $C_8H_{16}NO_2$ (M + H$^+$) 158.1175, found 158.1181.

(1*S,7*S**,8*R**,8a*S**)-1-[(*tert*-Butyldimethylsilyl)oxy]-7,8-dihydroxyindolizidine (23).** To a solution of hydroxy sulfone **19** (475 mg, 1.16 mmol) in MeOH (10 mL) were added solid Na_2HPO_4 (696 mg, 4.9 mmol) and freshly prepared 6% Na(Hg) (1.89 g). After the mixture was stirred at room temperature for 4 h, the resulting Hg was decanted, and the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1% NaOH. After standard workup, the residue was purified by flash chromatography on alumina (*n*-hexanes−EtOAc 1:4), and **22** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) 5.86 (dtd, J = 10.0, 3.5, 2.0 Hz, 1H), 5.71 (dq, J = 10.0, 2.0 Hz, 1H), 4.32 (ddd, J = 6.6, 4.8, 3.3 Hz, 1H), 3.21 (m, 1H), 3.07−2.71 (m, 4H), 2.38−1.98 (m, 3H), 1.81 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

Due to its relative instability, olefin **22** was immediately dihydroxylated. To a solution of **22** (245 mg, 0.97 mmol) in acetone/water 5:1 (3 mL) were added OsO_4 (4 wt % in water, 150 μL, 0.024 mmol) and Me_3NO (129 mg, 1.16 mmol). The solution was stirred at room temperature for 4 days. Following the isolation procedure described for the preparation of **13** and **14**, diol **23** (161 mg, 49%) was obtained after flash chromatography on alumina (EtOAc). **23** (colorless oil): ^{1}H NMR ($CDCl_3$) 4.44 (m, 1H), 4.09 (q, J = 3.0 Hz, 1H), 3.88 (dd, J = 9.5, 3.2 Hz, 1H), 3.13 (m, 1H), 2.81 (m, 1H), 2.75 (bs, 2H), 2.41−2.04 (m, 4H), 1.91−1.63 (m, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) 72.3, 69.0, 68.0, 67.9, 53.0, 46.5, 34.4, 31.1, 26.1 (3C), 18.4, −4.5, −4.9.

(1*S,7*S**,8*R**,8a*R**)-1,7,8-Trihydroxyindolizidine (24).** By a procedure identical to that described for the preparation of **12**, TBDMS derivative **23** (70 mg, 0.24 mmol) was deprotected to afford **24** (42.2 mg, 100%) as a crystalline solid: mp 148−149 °C dec; ^{1}H NMR (D_2O) 4.15 (m, 1H), 3.85 (q, J = 3.0 Hz, 1H), 3.53 (dd, J = 10.2, 3.0 Hz, 1H), 2.83 (td, J = 9.1, 2.0 Hz, 1H), 2.55 (ddd, J = 11.5, 4.4, 2.3 Hz, 1H), 2.11−1.85 (m, 4H), 1.66−1.33 (m, 3H); ^{13}C NMR (D_2O) 70.0, 68.2, 67.6, 66.2, 51.9, 45.5, 31.6, 30.0. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.44; H, 8.50; N, 8.52.

(2*R,3*R**)-1-[2-(Chloromethyl)-2-propenyl]-2-[(phenylsulfonyl)methyl]-3-[(triisopropylsilyl)oxy]pyrrolidine (*trans*-25).** To a solution of a 78:22 mixture of pyrrolidines *trans*-**6d** and *cis*-**6d** (750 mg, 1.89 mmol) in acetonitrile (6 mL) were added K_2CO_3 (260 mg, 1.89 mmol), 3-chloro-2-(chloromethyl)prop-1-ene (245 μL, 2.1 mmol), and LiI (26 mg, 0.189 mmol). After the solution was stirred at room temperature for 16 h, water (10 mL) and CH_2Cl_2 (35 mL) were added. After standard workup, the residue was purified by flash chromatography (*n*-hexanes−EtOAc 20:1) to give *trans*-**25** (660 mg, 72%) followed by *cis*-**25** (177 mg, 19%), both as colorless oils. ***trans*-25**: ^{1}H NMR ($CDCl_3$) 7.93−7.88 (m, 2H), 7.67−7.49 (m, 3H), 5.07 (s, 1H), 5.00 (s, 1H), 4.53 (m, 1H), 4.07 and 3.98 (AB system, J = 11.5 Hz, 2H), 3.48 (d, J = 14.3 Hz, 1H), 3.21−2.95 (m, 3H), 2.85 (m, 1H), 2.58 (m, 1H), 1.82 (m, 1H), 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$) 143.4, 140.1, 133.5, 129.2 (2C), 127.8 (2C), 116.2, 76.6, 68.1, 60.1, 58.3, 50.9, 45.9, 33.8, 18.1 (6C), 12.2 (3C); HRMS (FAB) calcd for $C_{24}H_{41}NO_3ClSSi$ (M + H$^+$) 486.2262, found 486.2265. Anal. Calcd for $C_{24}H_{39}NO_3SSiCl$: C, 59.29; H, 8.29; N, 2.88; S, 6.59. Found: C, 59.59; H, 8.37; N, 2.82; S, 6.66.

(2*R,3*S**)- and (2*R**,3*R**)-1-[2-(Chloromethyl)-2-propenyl]-3-hydroxy-2-[(phenylsulfonyl)methyl]pyrrolidine (*cis*-26) and (*trans*-26).** By a procedure identical to that described for the preparation of *trans*-**25**, a 80:20 mixture of pyrrolidines *cis*-**6a** and *trans*-**6a** (1.0 g, 4.15 mmol) in acetonitrile (12 mL) was treated with K_2CO_3 (572 mg, 4.15 mmol), 3-chloro-2-(chloromethyl)prop-1-ene (532 μL, 4.6 mmol), and LiI (57 mg, 0.42 mmol) at 70 °C for 16 h. After flash chromatography (*n*-hexanes−EtOAc 2:1), *cis*-**26** (895 mg, 66%, colorless oil) followed by the *trans*-**26** (218 mg, 16%, white solid) were obtained. ***cis*-26**: ^{1}H NMR ($CDCl_3$) 7.96−7.91 (m, 2H), 7.72−7.54 (m, 3H), 5.14 (s, 1H), 5.07 (s, 1H), 4.53 (m, 1H), 4.11 and 3.95 (AB system, J = 11.3 Hz, 2H), 3.73 (dd, J = 14.0, 10.0 Hz, 1H), 3.37 and 2.69 (AB system, J = 13.5 Hz, 2H), 3.22 (dd, J = 14.0, 2.3 Hz, 1H) 3.05−2.82 (m, 2H), 2.27−2.01 (m, 2H), 1.75 (m, 1H); ^{13}C NMR ($CDCl_3$) 142.5, 139.1, 133.7, 129.2 (2C), 127.5 (2C), 116.4, 71.2, 62.9, 56.1, 54.3, 51.1, 45.8, 32.0. Anal. Calcd for $C_{15}H_{20}NO_3ClS$: C, 54.52; H, 6.11; N, 4.25; S, 9.72. Found: C, 54.14; H, 5.91; N, 4.19; S, 9.46. ***trans*-26**: mp 82−83 °C; ^{1}H NMR ($CDCl_3$) 7.97−7.92 (m, 2H), 7.73−7.55 (m, 3H), 5.12 (s, 1H), 5.03 (s, 1H), 4.36 (dq, J = 7.2, 3.0 Hz, 1H), 4.07 and 3.94 (AB system, J = 11.2 Hz, 2H), 3.42 (dd, J = 14.4, 2.1 Hz, 1H), 3.30 (d, J = 13.4 Hz, 1H), 3.15 (dd, J = 14.4, 10.3 Hz, 1H), 3.03 (m, 1H), 2.89−2.70 (m, 2H), 2.39 (td, J = 9.7, 7.2 Hz, 1H), 2.16−1.95 (m, 1H), 1.85−1.73 (m, 1H); ^{13}C NMR ($CDCl_3$) 142.8, 139.3, 134.0, 129.5 (2C), 127.9 (2C), 116.8, 77.4, 68.0, 59.2, 56.2, 51.3, 45.9, 32.1. Anal. Calcd for $C_{15}H_{20}NO_3ClS$: C, 54.52; H, 6.11; N, 4.25; S, 9.72. Found: C, 54.72; H, 5.94; N, 4.16; S, 9.42.

(2*R,3*S**)-1-[2-(Chloromethyl)-2-propenyl]-2-[(phenylsulfonyl)methyl]-3-[(triisopropylsilyl)oxy]pyrrolidine (*cis*-25).** To a solution of *cis*-**26** (800 mg, 2.4 mmol) in CH_2Cl_2 (20 mL), cooled at −78 °C, were added 2,6-lutidine (340 μL, 2.9 mmol) and triisopropylsilyl trifluoromethanesulfonate (680 μL, 3.1 mmol). After the solution was stirred at room temperature for 6 h, water (10 mL) was added. After standard workup and purification by flash chromatography (*n*-hexanes−EtOAc 20:1), *cis*-**25** (1.08 g, 93%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.93−7.89 (m, 2H), 7.66−7.49 (m, 3H), 5.16 (s, 1H), 5.08 (s, 1H), 4.48 (q, J = 6.2 Hz, 1H), 4.12 and 4.02 (AB system, J = 11.7 Hz, 2H), 3.87 (dd, J = 14.6, 4.5 Hz,

1H), 3.52 and 2.87 (AB system, J = 13.5 Hz, 2H), 3.22 (m, 1H), 3.10 (dd, J = 14.6, 4.7 Hz, 1H), 2.95−2−83 (m, 1H) 2.22 (m, 1H), 2.07 (m, 1H), 1,66 (m, 1H), 1.04 (m, 21H); ^{13}C NMR ($CDCl_3$) 143.2, 140.4, 133.3, 129.1 (2C), 127.7 (2C), 115.9, 72.4, 62.2, 56.7, 55.3, 49.7, 46.0, 33.5, 18.0 (6C), 12.3 (3C); HRMS (FAB) calcd for $C_{24}H_{41}NO_3ClSi$ (M + H^+) 486.2263, found 486.2265. Anal. Calcd for $C_{24}H_{40}NO_3ClSSi$: C, 59.29; H, 8.29; N, 2.88. Found: C, 59.50; H, 8.61; N, 2.44.

(1*R,8*S**,8a*R**)- and (1*R**,8*R**,8a*R**)-6-Methylene-8-(phenylsulfonyl)-1-[(triisopropylsilyl)oxy]indolizidines (27 and 28).** To a solution of *trans*-**25** (310 mg, 0.64 mmol) in THF (7 mL), cooled at 0 °C, was added a 0.5 M solution of LHMDS in THF (1.6 mL, 0.80 mmol). After the solution was stirred at 0 °C for 15 min, saturated aqueous NH_4Cl (5 mL) was added. After standard workup and purification by flash chromatography (*n*-hexanes−EtOAc 6:1), **28** (81 mg, 28%) followed by **27** (198 mg, 69%) were obtained, both as colorless oils. **27**: ^{1}H NMR ($CDCl_3$) 7.93−7.88 (m, 2H), 7.70−7.52 (m, 3H), 5.08 (dt, J = 7.3, 1.7 Hz, 1H), 4.77 (m, 1H), 4.67 (s, 1H), 3.30 and 3.15 (AB system, J = 14.0 Hz, 2H), 3.09−2.91 (m, 2H), 2.75 (dd, J = 8.1, 6.1 Hz, 2H), 2.35−2.04 (m, 3H), 1.87 (m, 1H), 1.09 (m, 21H); ^{13}C NMR ($CDCl_3$) 139.3, 137.9, 133.7, 129.1 (2C), 129.0 (2C), 112.1, 75.1, 69.2, 61.9, 55.5, 49.4, 34.7, 34.5, 18.3 (6C), 12.7 (3C); HRMS (FAB) calcd for $C_{24}H_{40}NO_3SSi$ (M + H^+) 450.2495, found 450.2498. **28**: ^{1}H NMR ($CDCl_3$) 7.92−7.86 (m, 2H), 7.61−7.42 (m, 3H), 5.36 (m, 1H), 4.68 (m, 1H), 4.60 (m, 1H), 3.61 (m, 1H), 3.44 (d, J = 12.1 Hz, 1H), 2.97 (m, 1H), 2.68 (m, 2H), 2.44 (dd, J = 5.0, 2.8 Hz, 1H), 2.37−2.09 (m, 3H), 1.78−1.61 (m, 1H), 1.09 (m, 21H); ^{13}C NMR ($CDCl_3$) 140.5, 137.9, 133.2, 129.5 (2C), 128.4 (2C), 112.0, 75.6, 72.2, 61.4, 59.6, 52.7, 34.4, 34.2, 18.1 (6C), 12.2 (3C); HRMS (FAB) calcd for $C_{24}H_{40}NO_3SSi$ (M + H^+) 450.2501, found 450.2498.

(1*S,8*S**,8a*R**)-6-Methylene-8-(phenylsulfonyl)-1-[(triisopropylsilyl)oxy]indolizidine (29).** To a solution of *cis*-**25** (500 mg, 1.03 mmol) in THF (10 mL), cooled at 0 °C, was added a 0.5 M solution of LHMDS in THF (2.6 mL, 1.3 mmol). After the solution was stirred at 0 °C for 15 min, saturated aqueous NH_4Cl (7 mL) was added. After standard workup and purification by flash chromatography (*n*-hexanes−EtOAc 10:1), **29** (439 mg, 96%) was obtained as a yellow solid: mp 88−89 °C; ^{1}H NMR ($CDCl_3$) 7.90−7.85 (m, 2H), 7.70−7.52 (m, 3H), 4.84 (m, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.70 (m, 2H), 3.47 (d, J = 12.4 Hz, 1H), 3.16 (m, 1H), 2.61 (d, J = 12.4 Hz, 1H), 2.40 (dd, J = 9.3, 3.6 Hz, 1H), 2.31 (d, J = 7.7 Hz, 2H), 2.23−2.04 (m, 2H), 1.97−1.81 (m, 1H), 1.13 (m, 21H); ^{13}C NMR ($CDCl_3$) 140.2, 137.9, 133.6, 129.1 (2C), 128.9 (2C), 110.7, 72.4, 65.3, 59.3, 57.1, 51.5, 33.4, 32.4, 18.4 (3C), 18.3 (3C), 13.0 (3C). Anal. Calcd for $C_{24}H_{39}NO_3SSi$: C, 64.10; H, 8.74; N, 3.11; S, 7.13. Found: C, 63.8; H, 8.74; N, 3.37; S, 7.15.

(1*R,8a*S**)-1,2,3,5,6,8a-Hexahydro-6-oxo-1-[(triisopropylsilyl)oxy]indolizine (30).** A solution of a 70:30 mixture of **27** and **28** (550 mg, 1.22 mmol) in TFA (5 mL) and CH_2Cl_2 (2 mL) was ozonolyzed at −20 °C for 20 min. Then, Ph_3P (352 mg, 1.34 mmol) was added, and the solution was stirred at room temperature for 1 h. The solvent and TFA were evaporated. The residue was dissolved in CH_2Cl_2 (8 mL), and cooled at 0 °C, and Et_3N (1 mL) was added. The solution was stirred at room temperature for 40 min. The solvents were evaporated, and the residue was purified by flash chromatography (*n*-hexanes−EtOAc 10:1) to give enone **30** (263 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.10 (dd, J = 10.1, 1.6 Hz, 1H), 6.10 (dd, J = 10.1, 2.5 Hz, 1H), 4.27 (ddd, J = 5.0, 6.3, 8.3 Hz, 1H), 3.51 (d, J = 16.7 Hz, 1H), 3.26−3.16 (m, 2H), 2.98 (td, J = 8.9, 4.8, 1H), 2.79 (td, J = 8.9, 6.4 Hz, 1H), 2.29 (m, 1H), 1.77 (ddd, J = 13.8, 9.1, 5.0 Hz, 1H), 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$) 202.5, 148.4, 128.5, 75.3, 68.0, 59.6, 50.9, 33.5, 18.0 (6C), 12.2 (3C); MS (FAB) 296 (M + H^+, 100).

(1*S,8a*S**)-1,2,3,5,6,8a-Hexahydro-6-oxo-1-[(triisopropylsilyl)oxy]indolizine (31).** Following a procedure identical to that described for the preparation of enone **30**, the ozonolysis of **29** (450 mg, 1 mmol) afforded enone **31** (222 mg, 72%) as a pale yellow oil after flash chromatography (*n*-hexanes−EtOAc 4:1): ^{1}H NMR ($CDCl_3$) 7.14 (dd, 1H, J = 10.5, 1.9 Hz, 1H), 6.16 (dd, 1H, J = 10.5, 2.5 Hz, 1H), 4.65 (m, 1H), 3.66 (m, 1H), 3.46 (s, 2H), 3.00−2.76 (m, 2H), 2.22 (m, 1H), 1.76 (m, 1H), 1.14−1.03 (m, 21H); ^{13}C NMR ($CDCl_3$) 197.8, 146.8, 129.0, 73.7, 63.1, 58.3, 49.4, 34.0, 18.0 (6C), 12.0 (3C).

(1*R,6*S**,8a*S**)- and (1*R**,6*R**,8a*S**)-1,2,3,5,6,8a-Hexahydro-6-hydroxy-1-[(triisopropylsilyl)oxy]indolizines (32) and (33) and (1*R**,6*S**,8a*S**)- and (1*R**,6*R**,8a*S**)-6-(Benzoyloxy)-1,2,3,5,6,8a-hexahydro-1-[(triisopropylsilyl)oxy]-indolizines (36) and (37).** To a solution of **30** (350 mg, 1.13 mmol) in THF (6 mL), cooled at −78 °C, was added 1 M DIBALH in hexane (1.36 mL, 1.36 mmol). The solution was stirred at −78 °C for 30 min. Then, a few drops of MeOH followed by EtOAc (30 mL) and saturated aqueous sodium potassium tartrate (60 mL) were added, and the mixture was stirred at room temperature for further 1 h. After standard workup, a 60:40 mixture of **32** and **33** was obtained as a yellow oil. This mixture could not be separated by flash chromatography: ^{1}H NMR ($CDCl_3$) **32** + **33** 6.13 (dd, J = 9.8, 1.7 Hz, 1H, compound **32**), 6.02 (m, 1H, **33**), 5.90 (m, 1H, **33**), 5.84 (dt, J = 9.8, 2.6 Hz, 1H, **32**), 4.32−4.01 (m, **32** and **33**), 3.13 (dd, J = 10.8, 5.1 Hz 1H, **32**), 3.20−2.80 (m, **32** and **33**), 2.68−2.12 (m, **32** and **33**), 1.74−1.57 (m, **32** and **33**), 1.08 (m, **32** and **33**).

A 60:40 mixture of **32** + **33** was dissolved in CH_2Cl_2 (5 mL) and treated with Et_3N (780 μL, 5.6 mmol) and benzoyl chloride (232 μL, 2.0 mmol). After the solution was stirred at room temperature overnight, saturated aqueous $NaHCO_3$ (5 mL) was added. After standard workup and purification by flash chromatography (CH_2Cl_2-EtOAc 33:1), **37** (187 mg, 36%) followed by **36** (280 mg, 57%) were obtained, both as colorless oils. **36**: ^{1}H NMR (C_6D_6) 8.27−8.21 (m, 2H), 7.16−6.99 (m, 3H), 6.31 (m, 1H), 5.99 (m, 1H), 5.56 (m, 1H), 4.18 (ddd, J = 8.3, 6.8, 5.0 Hz, 1H), 3.12 (m, 1H), 2.94−2.84 (m, 2H), 2.66 (dd, J = 13.0, 3.9 Hz, 1H), 2.54 (td, J = 9.0, 7.0 Hz, 1H), 2.11 (m, 1H), 1.64 (m, 1H), 1.10 (m, 21H); ^{13}C NMR ($CDCl_3$) 166.4, 133.0, 132.9, 130.3, 129.7 (2C), 128.2 (2C), 123.9, 75.7, 67.7, 67.3, 52.5, 51.1, 34.3, 18.0 (6C), 12.1 (3C); HRMS (FAB) calcd for $C_{24}H_{38}NO_3Si$ (M + H^+) 416.2630, found 416.2621. **37**: ^{1}H NMR ($CDCl_3$) 8.08−8.02 (m, 2H), 7.59−7.37 (m, 3H), 6.11 (m, 1H), 5.86 (m, 1H), 5.65 (m, 1H), 4.14 (dt, J = 7.7, 5.5 Hz, 1H), 3.45 (dd, J = 11.8, 6.1 Hz, 1H), 3.16 (m, 1H), 3.02−2.86 (m, 2H), 2.95 (m, 2H), 2.77 (dd, J = 11.8, 8.6 Hz, 1H), 2.25 (m, 1H), 1.73 (m, 1H), 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$) 166.2, 132.9, 131.2, 130.2, 129.6 (2C), 128.3 (2C), 125.7, 76.4, 67.2, 66.1, 51.4, 50.4, 33.5, 17.9 (6C), 12.1 (3C); HRMS (FAB) calcd for $C_{24}H_{38}NO_3Si$ (M + H^+) 416.2630, found 416.2621.

(1*S,6*S**,8a*S**)- and (1*S**,6*R**,8a*S**)-1,2,3,5,6,8a-Hexahydro-6-hydroxy-1-[(triisopropylsilyl)oxy]indolizidines (34) and (35) and (1*S**,6*S**,8a*S**)- and (1*S**,6*R**,8a*S**)-6-(Benzoyloxy)-1,2,3,5,6,8a-hexahydro-1-[(triisopropylsilyl)oxy]-indolizidines (34-OBz) and (35-OBz).** Following the experimental procedure mentioned above, the reaction of **31** (250 mg, 0.81 mmol) with 1 M DIBALH in hexane (0.90 mL, 0.90 mmol) afforded a 85:15 mixture of **34** and **35** that could not be separated by flash chromatography. **34**: ^{1}H NMR ($CDCl_3$) 5.96 (ddd, J = 10.2, 3.8, 2.1 Hz, 1H), 5.87 (dd, J = 10.2, 1.6 Hz, 1H), 4.29 (ddd, J = 6.5, 4.3, 2.1 Hz, 1H), 4.08 (m, 1H), 3.12 (m, 2H), 2.95 (bs, 1H), 2.68 (m, 1H), 2.59 (dd, J = 11.8, 3.2 Hz, 1H), 2.43 (q, J = 8.6 Hz, 1H), 2.12 (m, 1H), 1.82 (m, 1H). The benzoylation of this mixture with benzoyl chloride (188 μL, 1.43 mmol) and Et_3N (560 μL, 4.0 mmol) in CH_2Cl_2 (3.5 mL), according to the previous procedure, and purification by flash chromatography (*n*-hexanes−ether 9:1), afforded **34-OBz** (255 mg, 76%), followed by **35-OBz** (45 mg, 13%). **34-OBz**: ^{1}H NMR (C_6D_6) 8.24−8.19 (m, 2H), 7.22−7.05 (m, 3H), 6.17 (dt, J = 10.4, 1.4 Hz, 1H), 6.07 (m, 1H), 5.59 (m, 1H), 4.46 (q, J = 5.6 Hz, 1H), 3.45 (m, 1H), 3.27 (dd, J = 13.7, 2.4 Hz, 1H), 3.24 (m, 1H), 3.14 (dd, J = 13.7, 4.7 Hz, 1H), 2.89 (ddd, J = 9.7, 9.3, 6.5 Hz, 1H), 2.02 (m, 2H), 1.09 (m, 21H); ^{13}C NMR ($CDCl_3$) 166.1, 132.8, 130.7, 129.6 (2C), 128.3 (2C), 126.2, 124.8, 73.7, 66.5, 62.2, 50.9, 49.0, 34.1, 18.0 (6C), 12.1 (3C); HRMS (FAB) calcd for $C_{24}H_{38}NO_3Si$ (M + H^+) 416.2630, found 416.2621. **35-OBz**: ^{1}H NMR (C_6D_6) 8.27−8.22 (m, 2H), 7.16−7.04 (m, 3H), 6.18−6.05 (m, 2H), 5.88 (m, 1H), 4.28 (q, J = 5.5 Hz, 1H), 3.52 (dd, J = 12.4, 5.5 Hz, 1H), 3.39 (m, 1H), 3.00 (dd, J = 12.4, 7.7 Hz, 1H), 2.92−2.66 (m, 2H), 1.86−1.67 (m, 2H), 1.09 (m, 21H); ^{13}C NMR (C_6D_6) 166.1, 132.8, 131.2,

130.4, 130.0 (2C), 128.3 (2C), 126.7, 74.1, 66.0, 63.5, 51.5, 49.7, 34.7, 18.2 (6C), 12.4 (3C); HRMS (FAB) calcd for $C_{24}H_{38}NO_3Si$ ($M + H^+$) 416.2630, found 416.2621.

(1*R,6*R**,7*R**,8*R**,8a*S**)-6-(Benzoyloxy)-7,8-dihydroxy-1-[(triisopropylsilyl)oxy]indolizidine (38).** To a solution of **36** (50 mg, 0.12 mmol) and Me_3NO dihydrate (16 mg, 0.14 mmol) in acetone (0.5 mL) was added a catalytic amount of OsO_4 (4 wt % in water, 50 μL, 0.009 mmol). The solution was stirred at room temperature for 16 h. By an isolation procedure identical to that described for the preparation of **13** and **14**, and further purification by flash chromatography (*n*-hexanes−EtOAc 4:1), **38** (43 mg, 80%) was obtained as a white solid: mp 172−173 °C; ^{1}H NMR (C_6D_6) 8.17−8.11 (m, 2H), 7.05−6.92 (m, 2H), 5.42 (q, J = 2.2 Hz, 1H), 4.33 (ddd, J = 8.4, 7.2, 5.5 Hz, 1H), 4.11−4.03 (m, 2H), 2.95 (dd, J = 12.5, 2.2 Hz, 1H), 2.72−2.62 (m, 2H), 2.39 (dd, J = 7.2, 8.9 Hz, 1H), 2.16 (m, 1H), 1.89 (m, 1H), 1.47−1.32 (m, 1H), 1.05 (m, 21H); ^{13}C NMR ($CDCl_3$) 165.7, 133.1, 130.2, 129.9 (2C), 128.3 (2C), 76.4, 72.6, 72.0, 68.5, 66.4, 51.6, 50.8, 31.6, 18.0 (6C), 12.4 (3C); HRMS (FAB) calcd for $C_{24}H_{40}NO_5Si$ ($M + H^+$) 450.2676, found 450.2676.

(1*R,6*S**,7*S**,8*S**,8a*S**)- and (1*R**,6*S**,7*R**,8*R**,8a*S**)-6-(Benzoyloxy)-7,8-dihydroxy-1-[(triisopropylsilyl)oxy]indolizidines (39 and 40).** To a solution of **37** (60 mg, 0.14 mmol) and Me_3NO dihydrate (18 mg, 0.16 mmol) in acetone (0.5 mL) was added a catalytic amount of OsO_4 (4 wt % in water, 55 μL, 0.009 mmol). The solution was stirred at room temperature for 48 h. By a procedure identical to that described for the isolation of **13** + **14**, and further purification by flash chromatography (*n*-hexanes−EtOAc 5:1), **39** (42 mg, 67%) followed by **40** (6.5 mg, 10%) was obtained. **39**: mp 171−172 °C; ^{1}H NMR ($CDCl_3$) 8.06−8.02 (m, 3H), 7.61−7.39 (m, 3H), 5.19 (td, J = 9.9, 5.5 Hz, 1H), 4.52 (ddd, J = 8.7, 6.5, 3.9 Hz, 1H), 4.12 (m, 1H), 3.70 (dd, J = 9.6, 3.2 Hz, 1H), 3.33 (dd, J = 10.2, 5.5 Hz, 1H), 3.02 (td, J = 8.8, 2.1 Hz, 1H), 2.53 (q, J = 8.8 Hz, 1H), 2.30−2.17 (m, 2H), 1.72 (m, 1H), 1.07 (m, 21H); ^{13}C NMR ($CDCl_3$) 166.8, 133.2, 129.8 (3C), 128.4 (2C), 74.6, 74.0, 72.6, 71.0, 68.0, 53.5, 51.6, 34.4, 17.9 (6C), 12.2 (3C); HRMS calcd for $C_{24}H_{39}NO_5Si$ 449.2598, found 449.2600. **40**: ^{1}H NMR ($CDCl_3$) 8.09−8.05 (m, 2H), 7.61−7.40 (m, 3H), 5.14 (ddd, J = 10.4, 5.2, 2.7 Hz, 1H), 4.37−4.26 (m, 1H), 4.29 (t, J = 2.7 Hz, 1H), 3.73 (dd, J = 9.3, 2.7 Hz, 1H), 3.08−3.75 (m, 1H), 2.99 (dd, J = 10.3, 5.2 Hz, 1H), 2.70 (t, J = 10.3 Hz, 1H), 2.61 (m, 1H), 2.40 (dd, J = 9.3, 7.3 Hz, 1H), 2.34−2.15 (m, 1H), 1.70 (m, 1H), 1.10 (s, 21H); ^{13}C NMR ($CDCl_3$) 165.7, 133.2, 129.7 (3C), 128.4 (2C), 72.9, 71.2, 69.1, 66.7, 50.9, 48.6, 32.4, 17.9 (6C), 12.3 (3C); HRMS (FAB) calcd for $C_{24}H_{40}NO_5Si$ ($M + H^+$) 450.2677, found 2676.

(1*R,6*R**,7*S**,8*R**,8a*R**)-1,6,7,8-Tetrahydroxyindolizidine [(±)-1,7-Di-*epi*-castanospermine] (41).** To a solution of **38** (40 mg, 0.089 mmol) in MeOH (1.5 mL) was added 10% aqueous NaOH (400 μL). The solution was stirred for 1 h at room temperature. Then, the reaction mixture was concentrated, 5 M HCl (3 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the aqueous layer was concentrated to dryness. The residue was dissolved in MeOH and chromatographed on a Dowex 1-X8 200 (OH^- form) ion-exchanged column. The combined ninhidrin-positive fractions were concentrated to afford **41** (16.5 mg, 98%, colorless oil): ^{1}H NMR (D_2O) 4.31 (ddd, J = 8.6, 6.6, 3.9 Hz, 1H), 3.96 (q, J = 2.6 Hz, 1H), 3.90−3.83 (m, 2H), 3.27 (m, 1H), 3.12−2.94 (m, 3H), 2.87 (dd, J = 6.6, 9.6 Hz, 1H), 2.30 (dq, J = 14.2, 9.0 Hz, 1H), 1.71 (m, 1H); ^{13}C NMR (D_2O) 72.0, 69.6, 68.0, 67.1 (2C), 51.7, 51.2, 30.3; HRMS (FAB) calcd for $C_8H_{16}NO_4$ ($M + H^+$) 190.1080, found 190.1079.

(1*R,6*S**,7*R**,8*S**,8a*R**)-1,6,7,8-Tetrahydroxyindolizidine [(±)-1,8-Di-*epi*-castanospermine] (42).** By a procedure identical to that described for the preparation of **41**, deprotection of **39** (40 mg, 0.089 mmol) afforded **42** (16.4 mg, 97%, colorless oil): ^{1}H NMR (D_2O) 4.05 (ddd, J = 9.2, 7.5, 4.2 Hz, 1H), 3.85 (dd, J = 3.3, 1.6 Hz, 1H), 3.55 (td, J = 9.7, 5.2 Hz, 1H), 3.21 (dd, J = 9.7, 3.3 Hz, 1H), 2.87 (dd, J = 10.5, 5.2 Hz, 1H), 2.68 (td, J = 8.9, 2.0 Hz, 1H), 2.20 (q, J = 8.9 Hz, 1H), 2.00 (m, 1H), 1.88 (dd, J = 7.5, 1.6 Hz, 1H), 1.81 (t, J = 10.5 Hz, 1H), 1.41 (dddd, J = 10.4, 8.9, 4.2, 2.0 Hz, 1H); ^{13}C NMR (D_2O) 75.3, 72.4, 69.2, 67.2, 66.4, 55.6, 51.1, 31.7; HRMS calcd for $C_8H_{15}NO_4$ 189.1001, found 189.0998.

(1*S,6*R**,7*S**,8*R**,8a*R**)- and (1*S**,6*S**,7*S**,8*R**,8a*R**)-1,6,7,8-Tetraacetoxyindolizidines (43) and (44)**. To a solution of a 9:1 mixture of **34** + **35** in CH_2Cl_2 (2 mL), cooled at −78 °C, were added TMEDA (147 μL, 0.97 mmol) and a solution of OsO_4 (250 mg, 0.98 mmol) in CH_2Cl_2 (2 mL). After the solution was stirred at −78 °C for 15 min, THF (10 mL) and saturated aqueous sodium sulfite (10 mL) were added. The mixture was heated at reflux for 3 h and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and filtered through Celite. Evaporation under reduced pressure gave a 90:10 mixture of the corresponding dihydroxylated compounds as a brown oil. This mixture was dissolved in pyridine (3 mL) and treated with DMAP (20 mg, 0.16 mmol) and acetic anhydride (610 μL, 6.48 mmol). After the solution was stirred at room temperature overnight, saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) were added. After standard workup and purification of the residue by flash chromatography (*n*-hexanes−EtOAc 2:1), **44** (29 mg, 10%, colorless oil) followed by **43** (227 mg, 79%, colorless oil) were obtained. **43**: ^{1}H NMR (C_6D_6) 5.78−5.71 (m, 2H) 5.54 (m, 1H), 5.04 (q, J = 2.8 Hz, 1H), 3.09 (dd, J = 12.8, 2.0 Hz, 1H), 2.86−2.73 (m, 1H), 2.42 (dd, J = 9.6, 5.0 Hz, 1H), 2.26 (dd, J = 12.8, 2.3 Hz, 1H), 1.87 (s, 3H), 1.80 (s, 3H), 1.73 (s, 3H), 1.82−1.56 (m, 3H), 1.55 (s, 3H); ^{13}C NMR (C_6D_6) 169.8, 169.4 (2C), 168.7, 71.9, 70.0, 68.3, 67.38, 63.9, 52.7, 51.3, 31.0, 20.6, 20.4, 20.3 (2C); HRMS (FAB) calcd for $C_{16}H_{24}NO_{38}$ ($M + H^+$) 358.1510, found 358.1502. **44**: ^{1}H NMR (C_6D_6) 5.97 (t, J = 3.0 Hz, 1H), 5.48 (m, 1H), 5.41 (dd, J = 10.2, 3.0 Hz, 1H), 5.12 (ddd, J = 10.7, 5.1, 3.0 Hz, 1H), 2.97 (dd, J = 5.1, 10.0 Hz, 1H), 2.75 (m, 1H), 2.51 (dd, J = 10.1, 4.8 Hz, 1H), 2.31 (t, J = 10.0 Hz, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.83 (s, 3H), 1.64 (s, 3H), 1.90−1.55 (m, 3H); ^{13}C NMR (C_6D_6) 169.8, 169.4, 169,2, 168.8, 71.2, 69.0, 68.8, 67.4, 63.8, 51.7, 49.5, 31.3, 20.6, 20.3 (3C).

(1*S,6*R**,7*S**,8*R**,8a*R**)-1,6,7,8-Tetrahydroxyindolizidine [(±)-6,7-Di-*epi*-castanospermine] (45).**[22] By a procedure identical to that described for the preparation of **41**, deprotection of **43** (200 mg, 0.56 mmol) afforded **45** (104 mg, 98%) as a colorless oil: ^{1}H NMR (D_2O) 4.37 (m, 1H), 4.02 (dd, J = 10.0, 3.0 Hz 1H), 3.94 (m, 1H), 3.07 (m, 1H), 2.94 (dd, J = 12.7, 2.3 Hz, 1H), 2.41 (dd, J = 12.7, 2.0 Hz, 1H), 2.35−2.08 (m, 4H), 1.74−1.59 (m, 1H); ^{13}C NMR (D_2O) 71.8, 71.5, 70.9, 67.3, 66.7, 53.3, 53.2, 32.8.

(1*S,6*S**,7*S**,8*R**,8a*R**)-1,6,7,8-Tetrahydroxyindolizidine [(±)-7-*epi*-Castanospermine] (46).**[23] By a procedure identical to that described for the preparation of **41**, deprotection of **44** (8 mg, 0.022 mmol) afforded **46** (4.1 mg, 97%) as a colorless oil: ^{1}H NMR (D_2O) 4.37 (m 1H), 4.07 (t, J = 2.9 Hz, 1H), 3.85−3.75 (m, 2H), 3.06 (m, 1H), 2.90 (dd, J = 10.4, 4.9 Hz, 1H), 2.39−2.14 (m, 4H), 1.69 (m, 1H); ^{13}C NMR (D_2O) 72.5, 70.4, 68.8, 67.8, 66.8, 52.4, 52.0, 33.2; HRMS calcd for $C_8H_{15}NO_4$ 189.1001, found 189.0998.

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Supporting Information Available: Copies of proton NMR spectra of new compounds (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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