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Substitution effects in intramolecular aziridine–allylsilane cyclizations

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ABSTRACT

We report here the synthesis of an aziridine tethered to a substituted allylsilane via a substituted tether. These tether-substituted aziridine–allylsilanes cyclize differently upon treatment with $BF_3{\cdot}OEt_2$ than tether-unsubstituted aziridine–allylsilanes and provide a 6-*endo*-type product. We show that steric interactions between the *N*-substituent of the aziridine and substitution on the tether can control the product distribution.

1. Introduction

The inter-[1] and intramolecular[2–5] cyclization reactions of aziridines with allylsilanes have been shown to be a general method for the synthesis of a variety of nitrogen containing heterocycles and carbocycles including γ-amino olefins (**2**), the silylated azabicycles (**3**), or the desilylated azabicycle (**4**) (Fig. 1). Compounds **2** and **3** have served as valuable precursors to the *Rauwolfia* alkaloid (−)-yohimbane (**5**)[4] and bicyclic proline analogs (**6**).[3]

With goals of studying the intramolecular cyclization of aziridine–allylsilanes containing a substituted tether and a substituted allylsilane, as well as applying this methodology to natural product synthesis, an aziridine–allylsilane (**10**) was envisioned via retrosynthetic analysis of (+)-α-skytanthine (**7**)[6–12] (Scheme 1). This alkaloid features a 3-azabicyclo[4.3.0]nonane that could be formed upon Mitsunobu ring closure of amino alcohol **8**. Alcohol **8** could be derived from a hydroboration/oxidation sequence of olefin **9**, though an appropriate hydroboration protocol would be needed to set the desired stereochemistry of the C-5 methyl group (skytanthine numbering). Finally, it was hypothesized that γ-amino olefin **9** would result from an intramolecular cyclization reaction of aziridine–allylsilane **10**, featuring a methyl group on the tether connecting the two reacting moieties.

2. Results and discussion

The synthesis of aziridine–allylsilane **10** was achieved using a Suzuki cross-coupling between olefinic aziridine **14** and allylsilane **15** (Scheme 2). The starting point for the proposed synthesis was the amino acid derivative **11**, which was prepared via an enantioselective Claisen rearrangment.[13,14] Basic hydrolysis of optically pure amino acid derivative **11** followed by esterification and tosylation provided diprotected amino acid **12a** (82% yield, three steps). Reduction of the methyl ester with $LiAlH_4$ and Mitsunobu ring closure provided aziridine **14a** in good overall yield. The enantiomeric purity of intermediates **12a**, **13a**, and **14a** was determined to be >98% by chiral HPLC analysis. Compounds **12a**, **13a**, and **14a** were compared with the corresponding enantiomers of these intermediates, synthesized in an identical manner starting from the known enantiomer of amino acid derivative **11**. Olefin **14a** was treated with 9-BBN followed by (*E*)-1-iodo-2-methyl-3-trimethylsilylpropene (**15**)[15] and $PdCl_2(dppf){\cdot}CH_2Cl_2$ under Suzuki

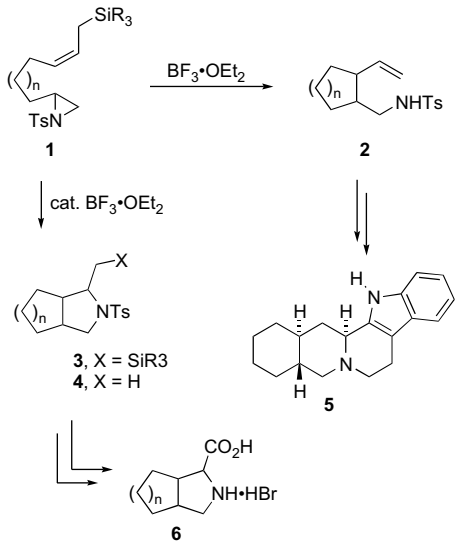

Figure 1. Previous syntheses utilizing intramolecular aziridine–allylsilane cyclizations.

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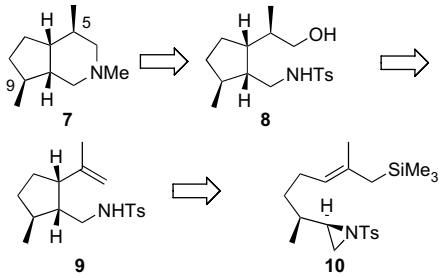
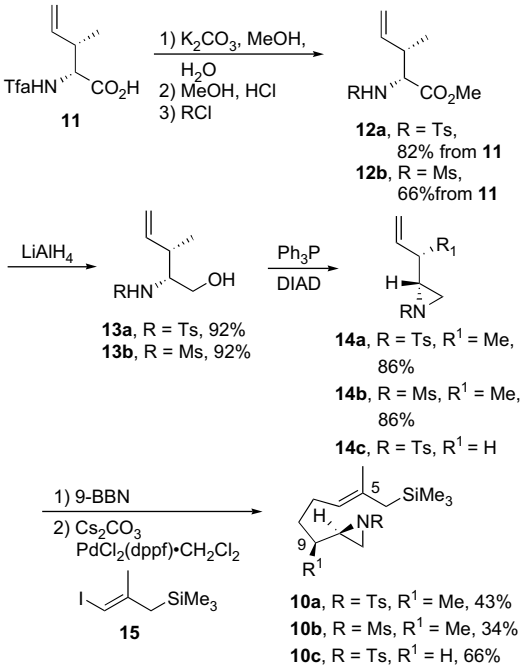


Scheme 1. Retrosynthesis of (+)-α-skytanthine using an intramolecular aziridine–allylsilane cyclization.

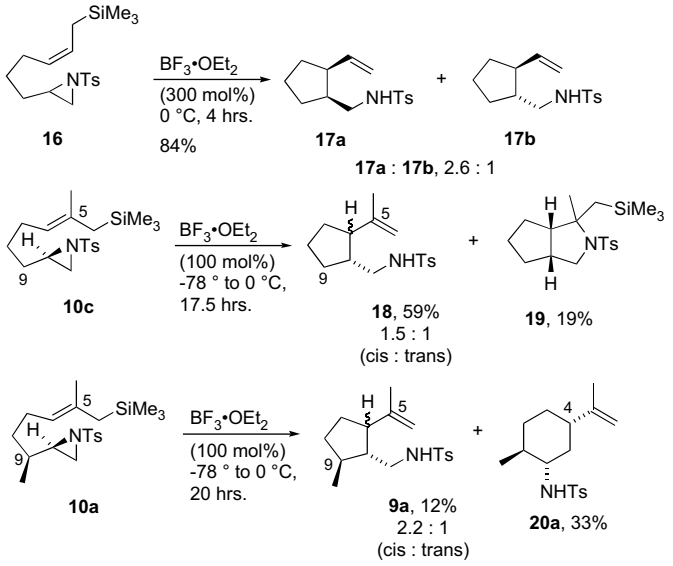
cross-coupling conditions.[16] It was satisfying to find that the coupling provided target aziridine–allylsilane **10a** in 43% yield. In order to study the effect of the C-9 methyl group on the intramolecular cyclization of aziridine–allylsilane **10a**, a control aziridine–allylsilane containing the same allylsilane moiety with no substitution of the tether was needed. Aziridine–olefin **14c**[5] was subsequently cross-coupled in an identical manner to provide control aziridine–allylsilane **10c** containing no C-9 methyl group (skytanthine numbering).



Scheme 2. Synthesis of aziridine–allylsilanes.

With the necessary aziridine–allylsilanes in hand, their cyclization reactions were examined. The cyclization of **16** has previously been shown to provide an inseparable 2.6:1 mixture of *cis* **17a** to *trans* **17b** γ-amino olefins (84% yield) resulting from treatment with 300 mol% of $BF_3{\cdot}OEt_2$ at 0 °C for 4 h.[2] The aziridine–allylsilane **10c** was examined in the cyclization reaction first. This allylsilane differs from previously used allylsilanes by possessing two structural variables yet encountered in these types of cyclizations, an *E*-olefin geometry and methyl substitution of the carbon β to the silyl group. Upon treatment of aziridine–allylsilane **10c** with 100 mol% of $BF_3{\cdot}OEt_2$, the major product of the reaction was the formation of an inseparable mixture of *cis* and *trans* γ-amino olefins **18** (59% yield) whose apparent diastereomeric ratio was 1.5:1 (cis/trans) based on the integration values of the sulfonamide protons. A cis-fused silylated azabicycle (**19**) resulting from a formal [3+2] intramolecular cycloaddition[3] was also isolated (19% yield). While this compound appears to be a single diastereomer, we have not been able to confirm the relative stereochemistry. Based on previous cyclizations we would expect that the methyl group and bridgehead hydrogen should be trans.[3] It should be noted that silylated azabicycle **19** could be converted into an additional amount of *cis* γ-amino olefin **18** by fluoride-induced silicon fragmentation.[1] As a result, the true diastereoselectivity for the cyclization of aziridine–allylsilane **10c** is 2.3:1 (cis/trans). It was important to see that the cyclization of **10c** was comparable to **16** in terms of diastereoselectivity and yield, and that the reaction proceeded in an identical manner with attack of the allylsilane at the more substituted carbon of the aziridine ring.

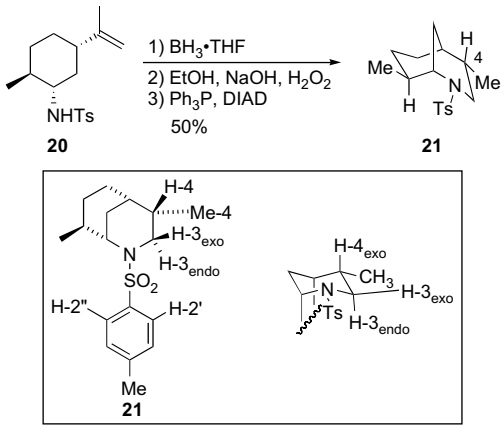
Satisfied that the modifications made to the allylsilane moiety had no deleterious effect on the results of the cyclization reaction, we turned our attention toward the cyclization of aziridine–allylsilane **10a**. This aziridine–allylsilane features a methyl group on the tether connecting the two reacting moieties and the previously examined modifications to the allylsilane moiety (Scheme 3). Aziridine–allylsilane **10a** was cyclized under similar reaction conditions as control aziridine–allylsilane **10c** (i.e., 100 mol% of $BF_3{\cdot}OEt_2$, −78 to 0 °C, 20 h), but the results proved dramatically different. The major product of the reaction was the formation of six-membered carbocycle **20a** (33% yield) as a single diastereomer. This product results from attack of the allylsilane at the less substituted carbon of the aziridine ring and not the more substituted carbon as we have usually seen with our aziridine–allylsilanes.[2–4] The inseparable mixture of five-membered carbocycles **9a** (12% yield, 2.2:1 (cis/trans)) results from cyclization in the traditional mode. From this reaction, it is clearly evident that the substitution of a methyl group on the tether has contributed to an alternative mode of cyclization.



Scheme 3. Initial aziridine–allylsilane cyclizations.

The relative stereochemistry of products such as **9** was previously determined to be primarily *cis*-disubstituted cyclopentanes.[2–4] However, the stereochemistry at C-4 of compound **20a** could not be directly determined in a similar fashion. A chemical proof of the stereochemistry via a cyclization of the olefin with the amine was thus carried out. Six-membered carbocycle **20a**, as a single diastereomer, was hydroborated with 400 mol% of $BH_3{\cdot}THF$ at room temperature for 15 h, then subsequently oxidized to provide a mixture of amino alcohols (Scheme 4). The crude amino alcohol mixture was subjected to Mitsunobu reaction

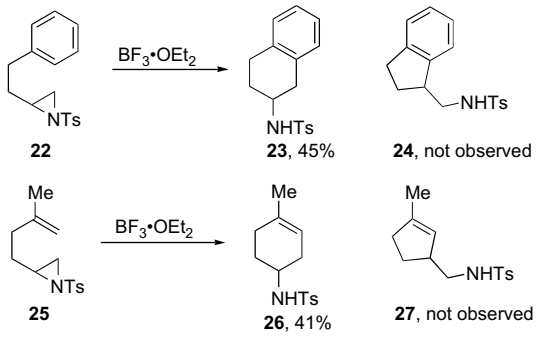
conditions to provide 2-azabicyclo[3.3.1]nonane **21** in 50% yield over two steps. The result of this hydroboration/oxidation/Mitsunobu reaction sequence confirms that the 1,3-substituents of substrate **20a** possess a cis relationship since a trans relationship would not result in ring closure under Mitsunobu conditions. The relative stereochemistry of the 4-methyl group was established based on coupling constants between the C-3 hydrogens and the C-4 methine. The identity of H-4, H-3, and Me-4 was identified based upon 2D spectra. The identity of H-3$_{exo}$ was established through the observation of NOESY cross-peaks with H-2′ and H-2″ of the tosyl group as we have previously observed.[3] As shown in Scheme 4, H-3$_{exo}$ has coupling constants of 11.5 Hz and 6.5 Hz, while H-3$_{endo}$ has coupling constants of 11.5 Hz and 11.0 Hz. Clearly the 11.5 Hz coupling constants are the geminal coupling constants between H-3$_{exo}$ and H-3$_{endo}$. H-3$_{exo}$ has a coupling constant with H-4$_{exo}$ of only 6.5 Hz, consistent with the equatorial/axial relationship between H-3$_{exo}$ and H-4$_{exo}$. The coupling between H-3$_{endo}$ and H-4$_{exo}$ is 11.0 Hz consistent with a diaxial relationship.



Scheme 4. Hydroboration/oxidation/Mitsunobu ring closure.

A priori it is not clear why **10a** provides both **9a** and **20a** upon treatment with $BF_3 \cdot OEt_2$. One is tempted to use Baldwin's rules for ring closure to classify these cyclizations.[17–19] However, the sp^2 hybridization of the nucleophilic carbon precludes this application. A second set of rules for ring closure was developed to address the cyclization reactions of enolates.[20] We have used a modification of the enolate classification system to name these cyclizations. Thus, the cyclization of **16** to **17** would be classified as a 5-(π-*exo*)-*exo*-aziridine, indicating that the π-nucleophile (the allylsilane) is *exo* to the newly formed ring and the aziridine is *exo* in the typical Baldwin's rules nomenclature. The reaction of **10a** thus cyclizes via both a 6-(π-*exo*)-*endo*-aziridine to provide **20a** and the expected 5-(π-*exo*)-*exo*-aziridine cyclization to provide **9a**. *endo*-Aziridine cyclizations have been previously observed in the cyclizations of aziridines with simple π-nucleophiles such as olefins and arenes.[21] In addition this type of 6-(π-*endo*)-*endo*-epoxide cyclization has been reported.[22–25] For example, the cyclizations of **22** and **25** provide only the six-membered ring products **23** and **26**, respectively (Scheme 5), in a 6-(π-*endo*)-*endo*-aziridine cyclization. None of the five-membered cyclization products (**24** or **27**) resulting from a 5-(π-*endo*)-*exo*-aziridine was observed. We have thus identified a previously unobserved type of cyclization the 6-(π-*exo*)-*endo*-aziridine cyclization. A related (but tether-unsubstituted) epoxide–allylsilane has been reported to provide very low yields (1–9%) of this type of 6-(π-*exo*)-*endo*-epoxide cyclization.[26]

In an effort to understand the origins of this change in regioselectivity of the cyclization we modeled two possible cyclization conformations (Fig. 2). The lowest energy conformation (Conformation A) leading to the expected product **9** shows the



Scheme 5. Previously observed aziridine cyclizations with simple π-nucleophiles.

methyl group and the aziridine groups in roughly axial conformations. The lowest energy conformation (Conformation B) leading to product **20** has the tether in a pseudo-boat conformation with both the methyl group and aziridine in equatorial orientations. We hypothesized that having both the aziridine and methyl in a pseudo-axial conformation drives the reaction toward Conformation B where both groups occupy an equatorial conformation. This conformational analysis led us to hypothesize that placing a smaller activating group (R=Ms) on the nitrogen could decrease strain of the unfavorable diaxial conformation in **10a** and potentially generate more five-membered ring product (**9**) upon cyclization.

To test this hypothesis, a mesylated analog (**10b**) of tether-substituted aziridine–allylsilane **10a** was synthesized and cyclized. Mesylated analog **10b** was synthesized in an identical manner to its tosyl analog (**10a**) with the only difference being the substitution of MsCl for TsCl (Scheme 2). As shown in Scheme 6, aziridine–allylsilane **10b** featuring the smaller mesyl activating group was treated under the same cyclization conditions (i.e., 100 mol % of $BF_3 \cdot OEt_2$, −78 to 0 °C, 18 h) as aziridine–allylsilane **10a** containing the larger tosyl group. The major product of the reaction was an inseparable mixture of five-membered carbocycle **9b** and six-membered carbocycle **20b** in 54% yield. The ratio of the carbocycles was determined to be 1.2:1 based on integration values for the sulfonamide protons (two distinct triplets for *cis* and *trans* **9b** (ratio of 1.8:1) and one distinct doublet for **20b**). As a result of using a smaller mesyl group, the cyclization showed a slight improvement in terms of desired five-membered carbocycle formation when compared to its tosyl counterpart (45% yield of 1:3 five-membered/six-membered carbocycles).

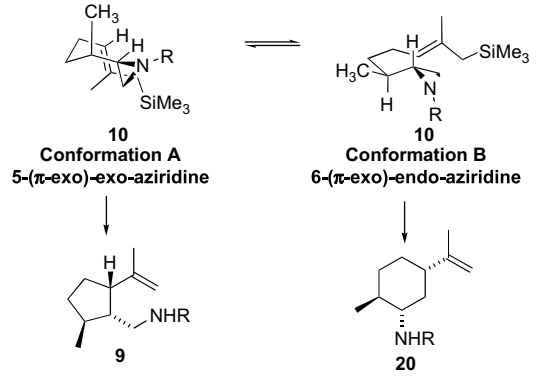
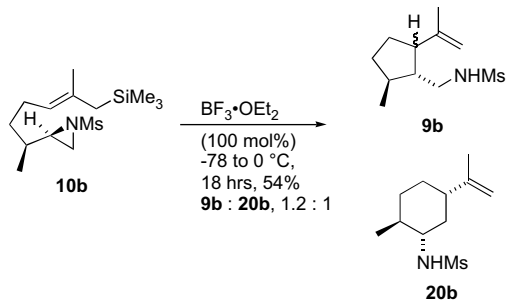


Figure 2. Steric interactions leading to five- or six-membered carbocycles.



Scheme 6. Cyclization of *N*-Ms aziridine–allylsilane **10b**.

While attempts to prepare the alkaloid (+)-α-skytanthine via an aziridine–allylsilane cyclization ultimately proved unsuccessful, an alternative cyclization pathway for tether-substituted C-3 aziridine–allylsilanes has been identified. Furthermore, it is apparent that the ratio of cyclization products is dependent upon the steric environment of the aziridine ring nitrogen substituent. It also appears that the course of the cyclization is not affected by substitution on the allylsilane component. The 6-(π-*exo*)-*endo*-aziridine cyclization of **10a** leading to the six-membered carbocycle appears to be more stereoselective than the corresponding reaction pathway leading to five-membered carbocycles.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a Bruker AG 250 MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian VX 400 MHz spectrometer. Chemical shifts are reported in parts per million relative to $CDCl_3$ (7.27 for ^{1}H, 77.23 for ^{13}C) or C_6D_6 (7.16 for ^{1}H, 128.39 for ^{13}C). Coupling constants (*J*) are reported in hertz. The use of * denotes a signal from minor isomer. Thin layer chromatography (TLC) was performed on EM Science pre-coated silica gel 60 F_{254} aluminum foils. Purification of the reaction products was carried out by flash chromatography using a glass column dry packed with silica gel (ICN SiliTech 32-63D 60 Å) according to the method of Still.[27] Visualization was accomplished with UV light, I_2, and/or phosphomolybdic acid solution followed by heating. HRMS measurements were determined at The Ohio State University Chemical Instrument Center with a Kratos MS-30 mass spectrometer in the electron impact (EI) mode. Optical activity was measured on an Autopol IV automatic polarimeter. Chiral HPLC was performed using an (*R*,*R*)-WHELK-O 1 5/100 HPLC column (250 mm×4.6 mm, particle size 5 μm) purchased from Regis Technologies. HPLC runs were performed using 10% EtOH in hexanes at a flow rate of 1.5 mL/min. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone prior to use. Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) were distilled from CaH_2 before use. Triethylamine (Et_3N) was distilled from CaH_2 and stored over KOH pellets. Methanol (MeOH) was distilled from Mg and I_2 and stored over molecular sieves. All reactions were carried out in flame-dried glassware under an Ar atmosphere unless otherwise specified.

3.2. Methyl (2*R*,3*S*)-3-methyl *N*-[(4-methylphenyl)sulfonyl]-2-aminopent-4-enoate (12a)

The PEA salt of **11**[13,14] was dissolved in satd aq $KHSO_4$ solution and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the free acid **11**, which was used without further purification. A solution of free acid **11** (0.76 g, 3.4 mmol) in MeOH (129 mL) was treated with H_2O (7.7 mL) and K_2CO_3 (2.44 g, 17.7 mmol), then refluxed for 16.5 h. The mixture was cooled to room temperature, acidified to pH 7 using concentrated HCl, and concentrated to provide a crude amino acid salt that was used without further purification. A suspension of the crude salt (assume 3.39 mmol) in dry MeOH (6.8 mL) was cooled to 0 °C and treated carefully with freshly distilled AcCl (1.2 mL, 16.9 mmol). After the addition, the reaction mixture was refluxed for 14.5 h, cooled to room temperature, and concentrated to provide a crude methyl ester hydrochloride salt that was used without further purification. A suspension of the crude ester salt (assume 3.39 mmol) in CH_2Cl_2 (6.8 mL) was cooled to 0 °C and treated with Et_3N (1.2 mL, 8.5 mmol) and TsCl (0.71 g, 3.7 mmol). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 13 h. The mixture was diluted with $CHCl_3$ and washed with 1 M HCl. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were washed with satd aq $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to give 0.83 g of diprotected amino acid **12a** (82% from acid **11**). R_f 0.23 (25% EtOAc in hexanes), $[\alpha]_D^{25}$ −9.0 (*c* 5.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (d, 2H, *J*=8.8 Hz), 7.24 (d, 2H, *J*=8.8 Hz), 5.59 (m, 1H), 5.32 (d, 1H, *J*=10.8 Hz), 5.01 (m, 2H), 3.81 (m, 1H), 3.39 (s, 3H), 2.47 (m, 1H), 2.38 (s, 3H), 0.99 (d, 3H, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 143.5, 137.9, 136.7, 129.5, 127.2, 116.7, 59.9, 51.9, 41.4, 21.4, 15.8. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.83; H, 6.37; N, 4.64. Chiral HPLC t_R=9.609 min (>98% *ee*).

3.3. Methyl (2*R*,3*S*)-3-methyl *N*-[methylsulfonyl]-2-aminopent-4-enoate (15)

The (+)-phenethylamine salt of **11**[13,14] was dissolved in satd aq $KHSO_4$ solution and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the free acid **11**, which used without further purification. A solution of free acid **11** (1.71 g, 7.61 mmol) in MeOH (289 mL) was treated with H_2O (17.4 mL) and K_2CO_3 (5.48 g, 39.6 mmol), then refluxed for 18 h. The mixture was cooled to room temperature, acidified to pH 7 using concentrated HCl, and concentrated to provide a crude amino acid salt that was used without further purification. A suspension of the crude salt (assume 7.61 mmol) in dry MeOH (15.2 mL) was cooled to 0 °C and treated carefully with freshly distilled AcCl (2.7 mL, 38.0 mmol). After the addition, the reaction mixture was refluxed for 19 h, cooled to room temperature, and concentrated to provide a crude methyl ester hydrochloride salt that was used without further purification. A suspension of the crude ester salt (assume 7.61 mmol) in CH_2Cl_2 (15.2 mL) was cooled to 0 °C and treated with Et_3N (2.7 mL, 19.0 mmol) and freshly distilled MsCl (0.7 mL, 8.4 mmol). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 16.5 h. The mixture was diluted with $CHCl_3$ and washed with 1 M HCl. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were washed with satd aq $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (35% EtOAc in hexanes) to give 1.11 g of diprotected amino acid **12b** (66% from acid **11**). R_f 0.34 (40% EtOAc in hexanes), $[\alpha]_D^{34}$ −5.4 (*c* 3.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.74 (m, 1H), 5.14 (m, 3H), 4.07 (m, 1H), 3.76 (s, 3H), 2.93 (s, 3H), 2.66 (m, 1H), 1.04 (d, 3H, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 138.1, 116.8, 59.9, 52.4, 41.3, 40.9, 15.1. HRMS calcd for $C_8H_{15}NO_4S{\cdot}Na^+$ 244.0614, found 244.0607.

3.4. (2*R*,3*S*)-3-Methyl-*N*-[(4-methylphenyl)sulfonyl]-2-amino-4-pentenol (13a)

A solution of ester **12a** (1.00 g, 3.35 mmol) in THF (8.4 mL) was cannulated into a 0 °C suspension of $LiAlH_4$ (0.64 g, 16.7 mmol) in THF (6.7 mL). After the addition, the ice bath was removed and

the reaction mixture was stirred for an additional 20 h. The reaction was quenched by the sequential dropwise addition of H_2O (0.64 mL), 15% aq NaOH (0.64 mL), and H_2O (1.91 mL), stirring for 15 min after each addition. The precipitate was filtered, washed with EtOAc, and concentrated. Chromatography (40% EtOAc in hexanes) provided 0.83 g of alcohol **13a** (92%). R_f 0.36 (50% EtOAc in hexanes), $[\alpha]_D^{24}$ −7.1 (*c* 5.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.76 (d, 2H, *J*=8.8 Hz), 7.28 (d, 2H, *J*=8.8 Hz), 5.54 (m, 1H), 5.38 (d, 1H, *J*=7.8 Hz), 4.97 (m, 2H), 3.55 (m, 2H), 3.12 (m, 1H), 2.60 (br s, 1H), 2.41 (s, 3H), 2.28 (m, 1H), 0.89 (d, 3H, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 139.6, 137.8, 129.6, 127.1, 116.0, 62.4, 59.4, 39.6, 21.5, 16.4. Anal. Calcd for $C_{13}H_{19}SO_3N$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.03; H, 7.09; N, 5.12. Chiral HPLC t_R=8.977 min (>98% ee).

3.5. (2*R*,3*S*)-3-Methyl-*N*-[methylsulfonyl]-2-amino-4-pentenol (13b)

A solution of ester **12b** (1.04 g, 4.69 mmol) in THF (11.7 mL) was cannulated into a 0 °C suspension of $LiAlH_4$ (0.89 g, 23.4 mmol) in THF (9.4 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 16 h. The reaction was quenched by the sequential dropwise addition of H_2O (0.89 mL), 15% aq NaOH (0.89 mL), and H_2O (2.67 mL), stirring for 15 min after each addition. The precipitate was filtered, washed with EtOAc, and concentrated. Chromatography (65% EtOAc in hexanes) provided 0.83 g of alcohol **13b** (92%). R_f 0.18 (65% EtOAc in hexanes), $[\alpha]_D^{27}$ −9.7 (*c* 2.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.73 (m, 1H), 5.11 (m, 3H), 3.73 (dd, 1H, *J*=3.9, 2.9 Hz), 3.59 (dd, 1H, *J*=5.9, 5.9 Hz), 3.33 (m, 1H), 3.03 (s, 3H), 2.64 (br s, 1H), 2.41 (m, 1H), 1.09 (d, 3H, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8, 116.2, 63.2, 59.9, 41.8, 40.2, 16.5. HRMS calcd for $C_7H_{15}SO_3N{\cdot}Na^+$ 216.0665, found 216.0653.

3.6. (2*R*)-2-[(1*S*)-1-Methyl-2-propenyl]-*N*-[(4-methylphenyl)-sulfonyl]aziridine (14a)

Diisopropyl azodicarboxylate (0.2 mL, 1.2 mmol) was added dropwise to a 0 °C solution of alcohol **13a** (0.29 g, 1.1 mmol) and PPh_3 (0.31 g, 1.2 mmol) in THF (5.4 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 16 h. The mixture was concentrated and chromatographed (5–15% EtOAc in hexanes) to give 0.23 g of aziridine **14a** (86%). R_f 0.26 (15% EtOAc in hexanes), $[\alpha]_D^{25}$ −20.5 (*c* 5.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.81 (d, 2H, *J*=8.8 Hz), 7.32 (d, 2H, *J*=7.8 Hz), 5.67 (m, 1H), 5.02 (m, 2H), 2.63 (d, 1H, *J*=6.9 Hz), 2.59 (m, 1H), 2.43 (s, 3H), 2.11 (d, 1H, *J*=4.9 Hz), 1.91 (m, 1H), 0.89 (d, 3H, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.5, 138.6, 134.9, 129.6, 128.0, 115.2, 44.3, 39.3, 32.8, 21.6, 17.1. Anal. Calcd for $C_{13}H_{17}NSO_2$; C, 62.12; H, 6.82; N 5.57. Found: C, 62.36; H, 6.83; N, 5.48. Chiral HPLC t_R=6.007 min (>98% ee).

3.7. (2*R*)-2-[(1*S*)-1-Methyl-2-propenyl]-*N*-[methylsulfonyl]-aziridine (14b)

Diisopropyl azodicarboxylate (0.9 mL, 4.4 mmol) was added dropwise to a 0 °C solution of alcohol **13b** (0.78 g, 4.0 mmol) and PPh_3 (1.16 g, 4.4 mmol) in THF (20.1 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 65 h. The mixture was concentrated and chromatographed (4–30% EtOAc in hexanes) to give 0.64 g of aziridine **14b** (86%). R_f 0.48 (40% EtOAc in hexanes), $[\alpha]_D^{25}$ −74.4 (*c* 5.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.76 (m, 1H), 5.09 (m, 2H), 3.03 (s, 3H), 2.61 (m, 1H), 2.55 (d, 1H, *J*=6.9 Hz), 2.14 (d, 1H, *J*=3.9 Hz), 2.06 (m, 1H), 1.13 (d, 3H, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 115.4, 43.5, 39.4, 38.9, 32.3, 17.0. HRMS calcd for $C_7H_{13}SO_2N{\cdot}Na^+$ 198.0559, found 198.0560.

3.8. (2*R*)-2-[(1*S*)-1-Methyl-5-methyl-5-[(trimethylsilyl)-methyl]-4-pentenyl]-*N*-[(4-methylphenyl)-sulfonyl]aziridine (10a)

9-BBN (9.3 mL, 0.5 M in THF, 4.7 mmol) was added to a 0 °C solution of olefin **14a** (1.06 g, 4.2 mmol) in THF (20 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 4 h. H_2O (4.2 mL) and a solution of iodide **15**[15] (1.19 g, 4.68 mmol) in THF (10 mL) were added to a flask containing Cs_2CO_3 (4.14 g, 12.70 mmol) and $PdCl_2(dppf){\cdot}CH_2Cl_2$ (0.31 g, 0.38 mmol). The organoborane solution was then added via cannula to the iodide flask with an additional THF (3 mL) rinsing. The reaction mixture was stirred in the dark for 17 h, then poured into H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to give 0.69 g of aziridine–allylsilane **10a** (43%). R_f 0.36 (15% EtOAc in hexanes), $[\alpha]_D^{26}$ −11.3 (*c* 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.83 (d, 2H, *J*=7.8 Hz), 7.33 (d, 2H, *J*=7.8 Hz), 4.84 (t, 1H, *J*=6.8 Hz), 2.66 (d, 1H, *J*=6.8 Hz), 2.51 (m, 1H), 2.45 (s, 3H), 2.12 (d, 1H, *J*=4.9 Hz), 1.96 (q, 2H, *J*=7.8 Hz), 1.56 (s, 3H), 1.44 (s, 2H), 1.38–1.21 (m, 3H), 0.77 (d, 3H, *J*=6.9 Hz), −0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 135.1, 133.3, 129.5, 128.1, 121.7, 45.6, 34.9, 34.6, 33.4, 29.8, 25.4, 21.6, 18.5, 17.5, −1.3. HRMS calcd for $C_{20}H_{33}SiNSO_2{\cdot}Na^+$ 402.1893, found 402.1897.

3.9. (2*R*)-2-[5-Methyl-5-[(trimethylsilyl)methyl]-4-pentenyl]-*N*-[(4-methylphenyl)sulfonyl]aziridine (10c)

9-BBN (7.1 mL, 0.5 M in THF, 3.6 mmol) was added to a 0 °C solution of olefin **14c**[5] (0.77 g, 3.2 mmol) in THF (20 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 3 h. H_2O (3.2 mL) and a solution of iodide **15**[15] (0.90 g, 3.6 mmol) in THF (5.2 mL) were added to a flask containing Cs_2CO_3 (3.16 g, 9.68 mmol) and $PdCl_2(dppf){\cdot}CH_2Cl_2$ (0.24 g, 0.29 mmol). The organoborane solution was then added to the iodide flask via cannula. The reaction mixture was stirred in the dark for 14.5 h, then poured into H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to give 0.78 g of aziridine–allylsilane **10c** (66%). R_f 0.35 (15% EtOAc in hexanes), $[\alpha]_D^{26}$ −6.1 (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.82 (d, 2H, *J*=7.8 Hz), 7.33 (d, 2H, *J*=7.8 Hz), 4.82 (t, 1H, *J*=7.8 Hz), 2.72 (m, 1H), 2.63 (d, 1H, *J*=6.9 Hz), 2.45 (s, 3H), 2.05 (d, 1H, *J*=4.9 Hz), 1.92 (q, 2H, *J*=6.8 Hz), 1.55 (s, 3H), 1.44 (s, 2H), 1.60–1.25 (m, 4H), −0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 135.2, 133.3, 129.6, 127.9, 121.6, 40.4, 33.7, 30.8, 29.8, 27.4, 27.1, 21.6, 18.6, −1.3. HRMS calcd for $C_{19}H_{31}SiNSO_2{\cdot}Na^+$ 388.1737, found 388.1747.

3.10. (2*R*)-2-[(1*S*)-1-Methyl-5-[(trimethylsilyl)methyl]-4-hexenyl]-*N*-[methylsulfonyl]aziridine (10b)

9-BBN (3.3 mL, 0.5 M in THF, 1.6 mmol) was added to a 0 °C solution of olefin **14b** (0.26 g, 1.49 mmol) in THF (11.6 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 5 h. H_2O (1.5 mL) and a solution of iodide **15**[15] (0.42 g, 1.6 mmol) in THF (5 mL) were added to a flask containing Cs_2CO_3 (1.46 g, 4.48 mmol) and $PdCl_2(dppf){\cdot}CH_2Cl_2$ (0.11 g, 0.13 mmol). The organoborane solution was then added via cannula to the iodide flask with an additional THF (1.6 mL) rinsing. The reaction mixture was stirred in the dark for 19 h, then poured into H_2O and Et_2O. The layers were separated and the aqueous layer was

extracted with Et_2O. The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to give 0.16 g of aziridine–allylsilane **10b** (34%). R_f 0.41 (25% EtOAc in hexanes). ^1H NMR ($CDCl_3$, 250 MHz) δ 4.89 (t, 1H, J=6.8 Hz), 3.07 (s, 3H), 2.61 (d, 1H, J=6.8 Hz), 2.54 (m, 1H), 2.1 (d, 1H, J=4.9 Hz), 2.04 (q, 2H, J=6.8 Hz), 1.57 (s, 3H), 1.46 (s, 2H), 1.45–1.27 (m, 3H), 1.06 (d, 3H, J=5.9 Hz), 0.0 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.5, 121.6, 45.0, 39.4, 34.8, 34.6, 33.0, 29.8, 25.4, 18.6, 17.7, −1.3. HRMS calcd for $C_{14}H_{29}SiNSO_2 \cdot Na^+$ 326.1586, found 326.1599.

3.11. *cis* and *trans*-(1*R*)-2-(2-Propenyl)-1-[(4-methylphenyl)sulfonyl]aminomethyl-cyclopentane (18) and (3a*R*,6a*S*)-*N*-[(4-methylphenyl)sulfonyl]-1-methyl-1-[(trimethylsilyl)methyl]hexahydrocyclopenta[*c*]pyrrole (19)

A solution of aziridine–allylsilane **10c** (0.30 g, 0.83 mmol) in CH_2Cl_2 (8.3 mL) was cooled to −78 °C and treated with freshly distilled $BF_3 \cdot OEt_2$ (0.1 mL, 0.8 mmol). After the addition, the reaction mixture was warmed to 0 °C and maintained at this temperature for 17.5 h. The mixture was quenched with satd aq $NaHCO_3$ and warmed to room temperature. The mixture was diluted with CH_2Cl_2 and H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to first give 57.3 mg of bicycle **19** (19%) followed by an inseparable mixture of 142.7 mg of olefins **18** (59%, ca. 1.5:1 cis/trans). Data for bicycle **19**: R_f 0.40 (15% EtOAc in hexanes). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.71 (d, 2H, J=7.8 Hz), 7.26 (d, 2H, J=7.8 Hz), 3.62 (t, 1H, J=9.8 Hz), 2.92 (dd, 1H, J=15.6, 5.9 Hz), 2.67–2.50 (m, 1H), 2.41 (s, 3H), 2.32–2.22 (m, 1H), 1.91–1.80 (m, 1H), 1.74–1.12 (m, 5H), 1.49 (s, 3H), 1.45 (s, 2H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.5, 138.6, 129.2, 127.1, 70.7, 56.8, 54.1, 38.8, 31.9, 31.3, 28.2, 26.0, 25.0, 21.4, 0.4. Data for olefins **18**: R_f 0.27 (15% EtOAc in hexanes), $[\alpha]_D^{26}$ −8.8 (c 7.3, $CHCl_3$). (* denotes signal from minor isomer) ^1H NMR (C_6D_6, 250 MHz) δ 7.95–7.91 (two overlapping d, 4.15H), 6.87–6.82 (two overlapping d, 4.20H), 5.63 (t, 1H, J=5.9 Hz), 5.55* (t, 0.68H, J=6.8 Hz), 4.70–4.68 (two overlapping app s, 3.24H), 4.60* (app s, 0.82H), 3.08–3.06 (m, 1.26H), 2.91–2.82* (m, 0.90H), 2.78–2.65 (m, 1.04H), 2.62–2.54* (m, 0.53H), 2.13–2.08 (m, 2.14H), 1.92 (s, 3H), 1.90* (s, 3H), 1.86–1.68 (m, 2.03H), 1.57* (s, 3H), 1.50 (s, 3H), 1.57–1.14 (m, 12.79H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.3, 145.5*, 143.2, 143.1*, 137.1*, 137.0, 129.6, 129.6*, 127.0, 127.0*, 111.0, 110.9*, 52.1*, 49.3, 47.5, 44.1*, 42.4, 40.8*, 31.7, 30.1*, 29.0, 27.6*, 23.8, 23.3, 23.3*, 22.6*, 21.4, 19.1*. HRMS for $C_{16}H_{23}NSO_2 \cdot Na^+$ calcd 316.1342, found 316.1344.

3.12. *cis* and *trans*-(1*R*,5*S*)-2-(2-Propenyl)-5-methyl-1-[(4-methylphenyl)sulfonyl]aminomethyl-cyclopentane (9a) and (1*S*,3*S*,6*S*)-3-(2-propenyl)-6-methyl-1-[(4-methylphenyl)-sulfonyl]amino-cyclohexane (20a)

A solution of aziridine–allylsilane **10a** (0.60 g, 1.6 mmol) in CH_2Cl_2 (15.9 mL) was cooled to −78 °C and treated with freshly distilled $BF_3 \cdot OEt_2$ (0.2 mL, 1.6 mmol). After the addition, the reaction mixture was warmed to 0 °C and maintained at this temperature for 20 h. The mixture was quenched with satd aq $NaHCO_3$ and warmed to room temperature. The mixture was diluted with CH_2Cl_2 and H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to first give an inseparable mixture of 57.4 mg of cyclopentanes **9a** (12%, ca. 2.2:1 cis/trans) followed by 162.5 mg of cyclohexane **20a** (33%). Data for cyclopentanes **9a**: R_f 0.42 (100% benzene), $[\alpha]_D^{24}$ +41.0 (c 3.1, $CHCl_3$). (* denotes signal from minor isomer) ^1H NMR (C_6D_6, 250 MHz) δ 7.88 (two overlapping d, 3.61H), 6.85–6.80 (two overlapping d, 3.62H), 5.29 (t, 1H, J=6.8 Hz), 5.16* (t, 0.46H, J=5.9 Hz), 4.74–4.68 (three overlapping app s, 2.93H), 4.62 (app s, 0.58H), 3.06–2.87 (m, 1.88H), 2.92–2.73 (m, 1.77H), 2.73–2.62 (m, 0.51H), 2.32* (q, 0.54H, J=6.8 Hz), 2.11 (q, 1.16H, J=8.8 Hz), 1.91 (s, 3H), 1.88* (s, 3H), 1.83–1.63 (m, 0.75H), 1.55* (s, 3H), 1.52 (s, 3H), 1.60–1.48 (m, 1.66H), 1.44–1.22 (m, 2.86H), 1.12–0.96 (m, 0.66H), 0.92–0.88 (two overlapping d, 5.76H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 146.1*, 143.2, 143.2*, 137.0*, 136.9, 129.6, 129.6*, 127.1, 127.0*, 111.4*, 111.2, 53.0, 49.4*, 48.3, 48.1*, 46.2, 44.4, 37.7, 37.2*, 33.1, 33.1*, 29.6, 28.6*, 23.1*, 23.1, 21.5*, 21.5, 19.4, 18.8*. HRMS for $C_{17}H_{25}NSO_2 \cdot Na^+$ calcd 330.1498, found 330.1505. Data for cyclohexane **20a**: R_f 0.30 (100% benzene), $[\alpha]_D^{24}$ +81.0 (c 8.3, $CHCl_3$). ^1H NMR (C_6D_6, 250 MHz) δ 7.96 (d, 2H, J=7.8 Hz), 6.84 (d, 2H, J=7.8), 5.54 (d, D_2O-exchangeable, 1H, J=8.8 Hz), 4.66 (app s, 1H), 4.63 (app s, 1H), 2.92 (m, 1H), 2.00–1.90 (m, 1H), 1.90 (s, 3H), 1.73–1.63 (m, 1H), 1.49–1.34 (m, 2H), 1.49 (s, 3H), 1.15–0.75 (m, 4H), 0.91 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 143.0, 138.6, 129.5, 126.9, 108.6, 59.2, 44.3, 39.8, 38.2, 34.1, 30.7, 21.4, 20.8, 18.8. HRMS for $C_{17}H_{25}NSO_2 \cdot Na^+$ calcd 330.1498, found 330.1508.

3.13. (1*S*,5*S*,8*S*)-4,8-Dimethyl-*N*-[(4-methylphenyl)sulfonyl]-2-azabicyclo[3.3.1]nonane (21)

$BH_3 \cdot THF$ (2.1 mL, 1 M in THF, 2.1 mmol) was added to a solution of olefin **20a** (0.16 g, 0.53 mmol) in THF (1.1 mL). After the addition, the reaction mixture was stirred for 15 h, then cooled to 0 °C. EtOH (1.2 mL) was added dropwise and the mixture was stirred for 5 min before adding 6 N NaOH (0.4 mL) and 30% H_2O_2 (0.8 mL). The mixture was refluxed for 1 h, then cooled to room temperature and diluted with H_2O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 165.7 mg of a crude mixture of amino alcohols (96%) that was used without further purification. Diisopropyl azodicarboxylate (0.1 mL, 0.6 mmol) was added dropwise to a 0 °C solution of the crude mixture of amino alcohols (0.17 g, 0.53 mmol) and PPh_3 (0.15 g, 0.58 mmol) in THF (2.6 mL). After the addition, the ice bath was removed and the reaction mixture was stirred for an additional 23.5 h. The mixture was concentrated and chromatographed (100% benzene) to give 80.9 mg of bicycle **21** (50% from olefin **20a**) as a single diastereomer. R_f 0.41 (15% EtOAc in hexanes), $[\alpha]_D^{23}$ −15.9 (c 1.1, $CHCl_3$). ^1H NMR (C_6D_6, 250 MHz) δ 7.77 (d, 2H, J=7.8 Hz), 6.83 (d, 2H, J=7.8 Hz), 3.67–3.60 (m, 2H), 2.49–2.41 (m, 2H), 2.09–1.92 (m, 1H), 1.92 (s, 3H), 1.67–1.61 (m, 1H), 1.39–1.22 (m, 1H), 1.19–0.78 (m, 5H), 0.86 (d, 3H, J=7.8 Hz), 0.59 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.9, 135.3, 129.5, 127.3, 54.7, 47.5, 33.3, 32.5, 32.3, 26.5, 22.6, 21.6, 21.4, 20.3, 16.7. HRMS for $C_{17}H_{25}NSO_2 \cdot Na^+$ calcd 330.1498, found 330.1497.

3.14. *cis* and *trans*-(1*R*,5*S*)-2-(2-Propenyl)-5-methyl-1-[methylsulfonyl]aminomethyl-cyclopentane (9b) and (1*S*,3*S*,6*S*)-3-(2-propenyl)-6-methyl-1-[methylsulfonyl]amino-cyclohexane (20b)

A solution of aziridine–allylsilane **10b** (88 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and treated with freshly distilled $BF_3 \cdot OEt_2$ (0.04 mL, 0.29 mmol). After the addition, the reaction mixture was warmed to 0 °C and maintained at this temperature for 20 h. The mixture was quenched with satd aq $NaHCO_3$ and warmed to room temperature. The mixture was diluted with CH_2Cl_2 and H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (100% benzene) to give an inseparable mixture of 36 mg (54%) of cyclopentane **9b** (2.2:1 cis/trans) and

cyclohexane **20b**. R_f 0.18 (25% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.73 (m, 2H), 4.42 (br t, 0.7H, J=7.5 Hz), 4.28 (br t, 0.4H, J=7.5 Hz), 4.11 (d, 0.9H, J=9.0 Hz), 2.95–2.68 (m, 2.0H), 2.40 (s, 1.3H), 2.30 (s, 1.0H), 2.26 (s, 0.6H), 2.10 (m, 1.4H), 1.69 (m, 0.6H), 1.58 (m, 3H), 1.56–1.20 (m, 0.6H), 1.21 (m, 2H), 0.88 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 148.3, 146.2, 111.7, 111.5, 109.2, 59.5, 56.3, 52.9, 49.9, 48.7, 48.2, 46.0, 44.5, 42.1, 40.6, 39.9, 38.3, 37.6, 37.2, 34.2, 33.1, 30.9, 29.7, 28.7, 23.4, 21.9, 20.8, 19.6, 19.2, 18.9. HRMS for $C_{11}H_{21}NSO_2 \cdot Na^+$ calcd 254.1191, found 254.1205.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.043.

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