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Synthesis of Bicyclic Proline Analogs Using a Formal [3 + 2] Intramolecular Aziridine-Allylsilane Cycloaddition Reaction

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***Abstract*::** Bicyclic proline analogs have a wide range of biological uses. We report here our synthesis of bicyclic proline analogs using a formal [3+2] intramolecular aziridine-allylsilane cycloaddition reaction. This synthesis allows for the preparation of both 5-5 and 6-5 fused ring systems and should be amenable to the preparation of analogs with substitution on the carbocyclic ring.

Keywords: aziridines; bicyclic heterocyclic compounds; nitrogen heterocycles; silicon and compounds.

The biological utility of proline analogs as analgesics, enzyme inhibitors and peptidomimetics is multifold. Proline is a unique dialkylated amino acid. Isomerization of proline has profound effects on peptide and protein structure and function.[1] Bicyclic proline analogs have been investigated as analgesics,[2] Angiotensin Converting Enzyme (ACE) inhibitors,[3] and peptidomimetics.[4] Bicyclic proline analogs can be inserted into peptides in order to create more rigid analogs.[4b] Incorporation of these rigid analogs into a specific peptide sequence can dictate the 3-dimensional shape adopted by that sequence. This is very useful when the spatial requirements for a peptide are well understood. We report here our enantioselective synthesis of bicyclic proline analogs **1-4** (Figure 1). Our synthesis allows for the preparation of proline analogs containing substituents on the carbocyclic ring.

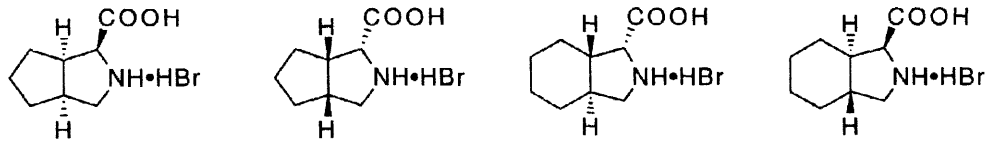

Figure 1

While many possible connectivities for bicyclic proline analogs are possible, only the analogs shown in Figure 2 have been previously reported.[5] All but one of the compounds (**10**) shown were prepared as racemates. Since many of these proline analogs have shown promising activity as ACE inhibitors, analgesics, and peptidomimetics, new methods for the synthesis of enantiomerically pure proline analogs as well as the synthesis of new types of proline analogs should be useful.

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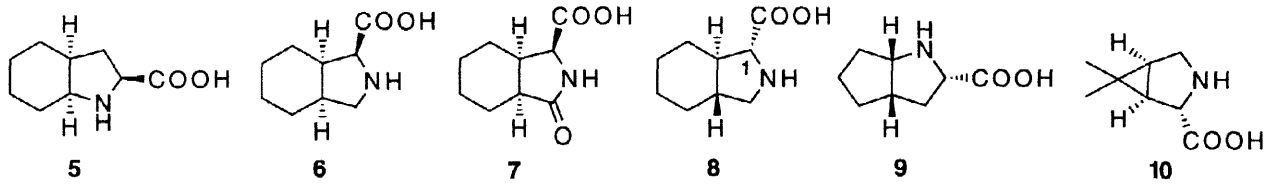
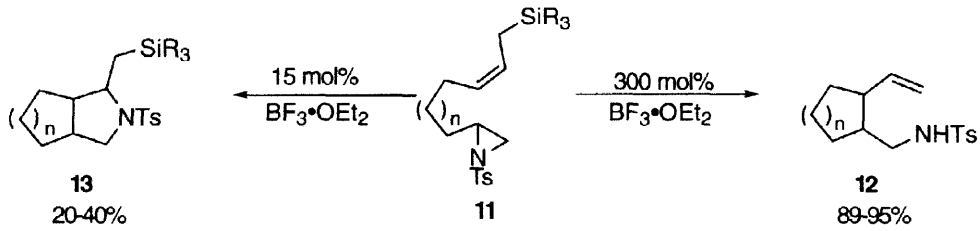


Figure 2

Our synthesis of proline analogs **1**, **2**, **3**, and **4** uses an intramolecular formal [3+2] cycloaddition reaction of an aziridine and allylsilane to form the bicyclic skeleton. There have only been two previous[6] examples of intramolecular formal [3+2] cycloadditions involving allylsilanes and this is the first example of an intramolecular formal [3+2] cycloaddition of an aziridine-allylsilane.

Previously we had reported on the intramolecular reactions of aziridines with allylsilanes.[7,8] In this earlier work we found that treatment of **11** with excess $BF_3{\bullet}OEt_2$ provided carbocycle **12** in excellent yield and moderate diastereoselectivity (Scheme 1). Upon close examination of some of the crude reaction mixtures we noticed the presence of a small quantity (< 5%) of another product that appeared to still contain the trimethylsilyl group and in which the aziridine ring had opened. We believed that this minor component might be a compound such as **13**.[9] This minor component would be the product of an intramolecular formal [3+2] cycloadduct. The formal [3+2] cycloaddition between allylsilanes and other electrophiles has been successfully exploited for the synthesis of a variety of cyclic molecules.[10]



Scheme 1

Upon further investigation, we found that the major product of this reaction (with cat. $BF_3{\bullet}OEt_2$) was the [3+2] product **13** (R=Me), although in poor yield (~ 40%). Such a cyclization could be very useful for the synthesis of our target proline analogs if the $SiMe_3$ group could be changed to a more readily oxidized silane (e.g. $PhMe_2Si$) and if the yield of the bicyclic pyrrolidines could be improved. Compounds such as **13** would thus be excellent starting points for making proline analogs (**1-4**) because the silicon can be easily oxidized to the corresponding alcohol (**14**). Further oxidation to the acid followed by deprotection of the nitrogen, would give the desired proline analogs **15** (Figure 3).

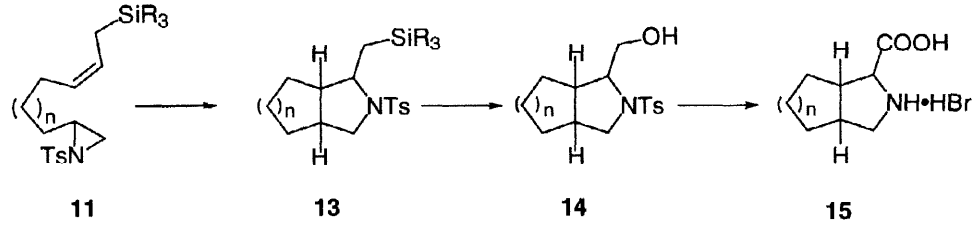
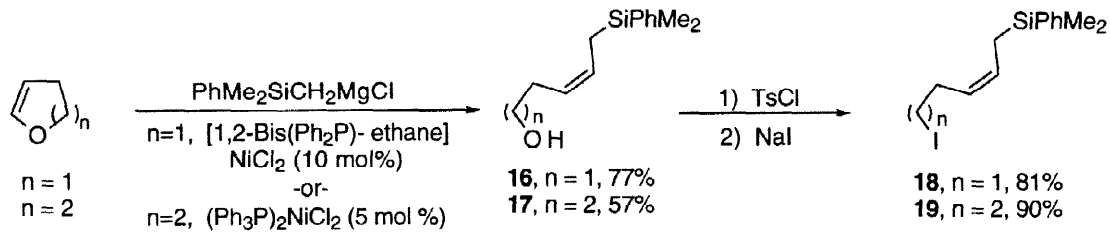


Figure 3

While other silanes (most notably triisopropyl) can be retained in these annulations, (thus improving the yield of the bicycle) we wished to use a silane which could be readily converted to other functionality. We have decided to use the dimethylphenylsilyl group, because it participates well in the [3+2] annulation reaction,[10a] it can be easily oxidized to a hydroxyl group using a variety of conditions,[11] and $PhMe_2SiCH_2Cl$ is commercially available.[12]

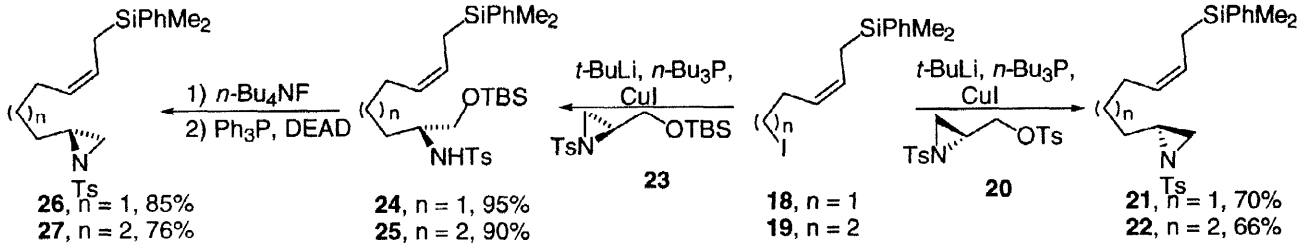
Our synthesis of the requisite aziridine-allylsilane follows from our previously reported method.[13] For this synthesis, iodoallylsilanes **18** and **19** are needed. Ring opening of either dihydrofuran or dihydropyran (Scheme 2), with $PhMe_2SiCH_2MgCl$[14] in the presence of a nickel catalyst gave the corresponding alcohols **16** and **17**.[15] When dihydrofuran was used in this reaction, we found that an optimal yield of **16** was obtained when 10 mol% of [1,2-bis(Ph_2P)ethane] $NiCl_2$ was used as the catalyst. A different catalyst was used (5 mol% of $(Ph_3P)_2NiCl_2$)[15] with dihydropyran which gave a 57% yield of alcohol **17** . Tosylation of the alcohols, followed by treatment with NaI gave the iodides **18** and **19** in 81% and 90% yield over two steps.



Scheme 2

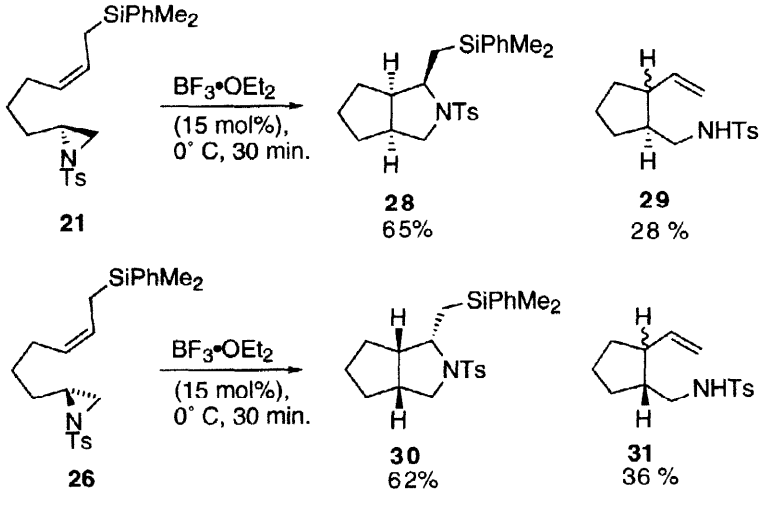
From this point, two different methods were employed for formation of aziridines **21**, **22**, **26** and **27**. First, using our previously reported procedure,[13] iodides **18** and **19** were converted to the corresponding cuprates and then treated with (*R*)-aziridine tosylate **20**[13] (Scheme 3). These reactions occurred in a single step, to provide aziridine-allylsilanes **21** and **22** in 70% and 66% yield respectively on a 1-2 mmole scale. This reaction proceeds via an initial attack at the less substituted carbon of the aziridine followed by aziridine formation. When attempts were made to scale this reaction up (≥4 mmoles), the yields were reduced to 30-50%. For this reason, synthesis of the opposite enantiomers was carried out in a stepwise manner to see if an improvement in the yields was possible. Once again, the cuprate was made from iodides **18** and **19**, but this time they were treated with (*S*)- aziridine **23**,[16] to give the ring opened products **24** and **25**. Deprotection with *n*-Bu_4NF followed by a Mitsunobu reaction[17] formed the aziridine ring to yield aziridine-allylsilanes **26** and **27**

in 85% and 76% yield from **24** and **25** respectively. The overall yield of **26** (81%) was slightly higher than with the one step procedure, whereas, the yield of **27** (68%) was about the same. This stepwise procedure seemed to lend itself much better to larger scale reactions than the one step procedure.



Scheme 3

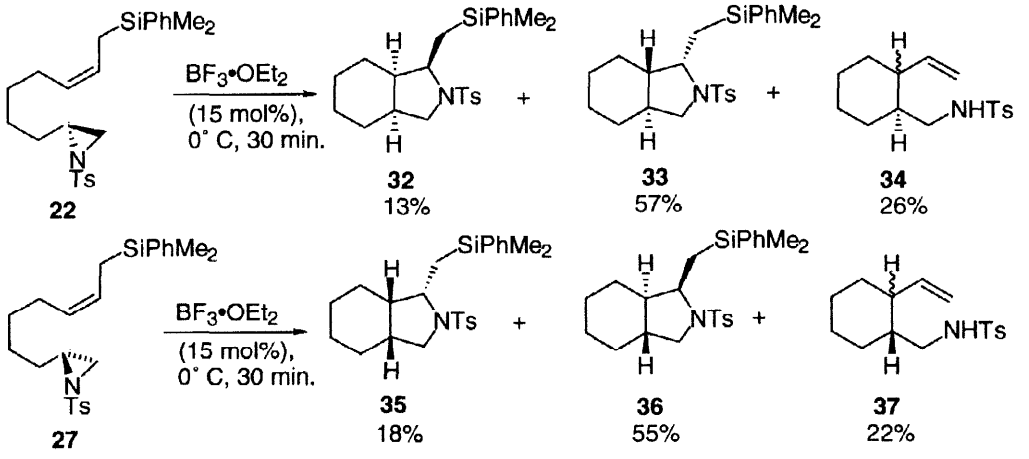
Cyclization of aziridine-allylsilanes **21** and **22** is described in Scheme 4. Cyclization of **21** was carried out using $BF_3{\cdot}OEt_2$ (15 mol %) in CH_2Cl_2. Column chromatography gave diastereomerically pure bicycle **28** in 65% yield. Similar results were obtained when enantiomer **26** was cyclized. This reaction was contaminated with 28% of the corresponding olefin **29** (approximately 1.5:1 trans:cis) which is readily removed by chromatography. The yield of isolated **28** (and **30**) has been substantially improved by changing the silyl group.



Scheme 4

Cyclization of compounds **22** and **27** was also carried out using $BF_3{\cdot}OEt_2$ (15 mol%), but resulted in a different product ratio. As shown in Scheme 5, the more flexible nature of the bicyclic system allows for the formation of either a cis or trans fused bicycle. The trans isomer is the major product in both reactions. Column chromatography again allowed for the ready separation of the trans fused bicycles from the cis. The ratio of **33**:**32** was slightly higher than 4:1, whereas, the ratio of **36**:**35** was 3:1. Each of these reactions was still contaminated with the corresponding olefin (~30% 1.5:1 trans:cis). While the yields of the cyclization are still

not ideal, replacing the Me_3Si with a $PhMe_2Si$ has enabled us to increase the yields sufficiently to continue with the synthesis of proline analogs **1-4**.



Scheme 5

The stereochemistry of bicyclic products was assigned by nOe spectroscopy (Figure 4). The nOes observed agreed with our previous determinations of relative stereochemistry in this type of cyclization.[7,8] We expect that no loss of enantiomeric purity occurs in the initial ring opening of the aziridine (stereochemistry at H_b). It is well established that nucleophilic ring opening reactions of aziridines proceed with very high stereochemical integrity.[8, 18]

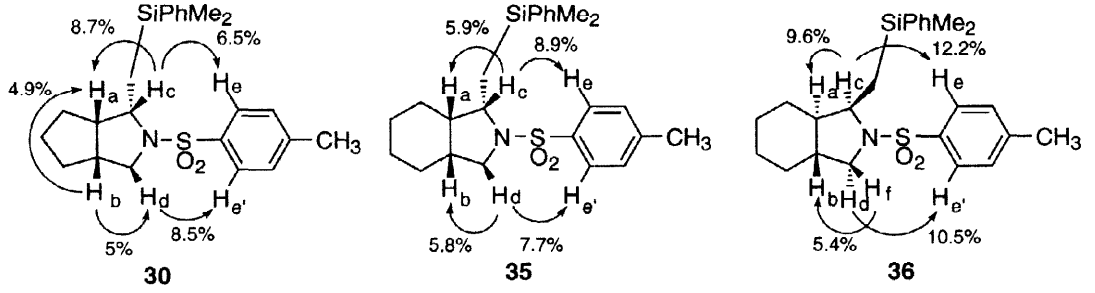
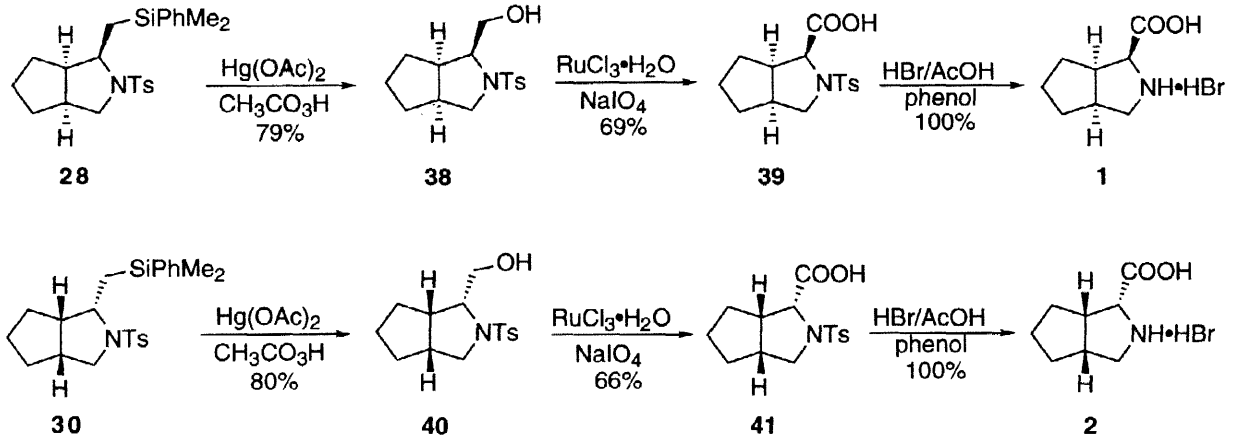


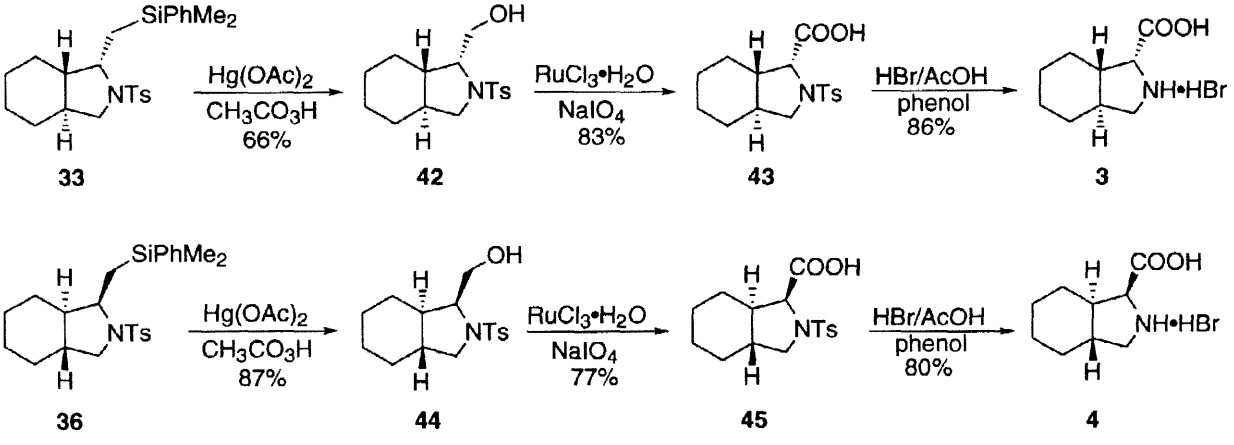
Figure 4

While most of the nOes observed were expected, one interesting nOe deserves note. Protons H_c and H_d in all three bicyclic pyrrolidines (**30**, **35**, **36**) showed a strong nOe to protons $H_e/H_{e'}$ on the aromatic ring of the tosyl group.



Scheme 6

Preparation of proline analogs **1** and **2** from bicycles **28** and **30** is described in Scheme 6. Oxidation of the bicycles to the alcohols was carried out using mercuric acetate with acetic and peracetic acids.[19] This reaction gave alcohols **38** and **40** in excellent yields (79-80%). The alcohols were oxidized to the corresponding carboxylic acids **39** and **41** using $RuCl_3 \cdot H_2O$ and sodium periodate.[20] The final step in formation of compounds **1** and **2** was removal of the tosyl group from the nitrogen. Acids **39** and **41** were treated with 32% HBr/AcOH and phenol[21] to produce amino acid salts **1** and **2** each in quantitative yield. No racemization (i.e. formation of diastereomers) was observed by $^1H/^{13}C$ NMR at C_2 following the $RuCl_3 \cdot H_2O$ oxidation or the deprotection.



Scheme 7

Preparation of proline analogs **3** and **4** was carried out in an analogous fashion to **1** and **2**. The pure trans isomers **33** and **36** were oxidized with mercuric acetate to produce alcohols **42** and **44** respectively. These alcohols were further oxidized to acids **43** and **45**. The yields of the oxidations were comparable to those described earlier with compounds **28** and **30**. A small amount ($\leq$ 5%) of what was believed to be the C_2

diastereomer of acids **43** and **45** was detected in the ^{13}C NMR. Column chromatography allowed for the ready purification of the desired carboxylic acids. Removal of the tosyl group proceeded smoothly to give the target amino acid salts **3** and **4.**

In conclusion, we have described the preparation and characterization of a new group of proline analogs. This synthesis makes use of an intramolecular, formal [3+2] cycloaddition between an aziridine and an allylsilane. This synthesis should be amenable to the preparation of substituted analogs as well. This is the first example of a formal intramolecular [3+2] cycloaddition of an aziridine-allylsilane, and one of only three examples of formal intramolecular [3+2] cycloadditions involving allylsilanes which have been reported to date. Our continuing work to improve the yield of this useful reaction as well as the incorporation of these bicyclic prolines into peptides and the resulting biological activity will be reported at a later date.

Experimental

General. ^1H and ^{13}C spectra were recorded on a Bruker AF 250, Bruker AF 270 or a Bruker DRX 400 model spectrometer. Chemical shifts are reported in ppm relative to trimethylsilane. Coupling constants (J) are reported in Hz. Melting points were taken using a Thomas Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on Whatman pre-coated silica gel F_{254} aluminum foils. Purification of the reaction products was carried out by flash column chromatography using a glass column dry packed with silica gel (230-400 mesh ASTM) according to the method of Still.[22] Visualization was accomplished with UV light and/or Phosphomolybdic acid solution followed by heating. Exact mass measurements recorded in the electron impact (EI) mode were determined at The Ohio State University Chemical Instrument Center with a Kratos MS-30 mass spectrometer. Combustion analyses were performed at Quantitative Technologies, Inc., Whitehouse, New Jersey. THF and Et_2O were distilled from sodium and benzophenone. Benzene and CH_2Cl_2 were distilled from CaH_2 before use. Et_3N was distilled from CaH_2 and stored over KOH pellets. All reactions were carried out under an N_2 atmosphere unless otherwise specified.

5-(Dimethylphenylsilyl)-pent-3-en-1-ol (16). Magnesium (1.1 g, 45 mmol) was flame dried and suspended in Et_2O (45 mL). Ethylene bromide (1.3 mL, 15 mmol) was added and the reaction was allowed to reflux for 20 min followed by a slow addition (over 5 min) of chloromethyldimethylphenylsilane (5.4 mL, 30 mmol). After the addition was complete, the reaction was then allowed to reflux for 3 hours during which all the magnesium dissolved resulting in the formation of a grayish suspension. Benzene (60 mL) was then added to the reaction and the Et_2O was distilled out of the reaction flask (until the distillate coming over had a temperature of 78 °C). 1,2-Bis(Ph_2P)ethane$NiCl_2$ (792 mg, 1.50 mmol) was then added to the reaction as solid and the above mixture was refluxed for 30 min. The reaction was cooled to 0°C for addition of 2,3-dihydrofuran (2.0 mL, 27 mmol) and then heated to reflux for 10 hrs. The reaction was then cooled to rt and quenched by the addition of sat. NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (52 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$) and concentrated. Chromatography (10% EtOAc in hexanes → 15% EtOAc in hexanes) gave 4.6 g (77%) of **16** as a colorless oil. R_f 0.2 (15% EtOAc in hexanes). ^1H NMR ($CDCl_3$, 250 MHz), δ 7.50 (m, 2H), 7.35 (m, 3H), 5.55 (m, 1H), 5.25 (m, 1H), 3.52 (m, 2H), 2.19 (m, 2H), 1.74 (d, 2H, J = 8.7), 1.28 (s, 1H), 0.28 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 138.7, 133.6, 129.0, 128.2, 127.8, 123.5, 62.4, 30.7, 18.0, -3.3. Anal. Calcd for $C_{13}H_{20}OSi$: C, 70.84; H, 9.15. Found: C, 70.42; H, 8.90.

6-(Dimethylphenylsilyl)-hex-4-en-1-ol (17). This alcohol was prepared according to the procedure described for the preparation of **16**, except 2,3-dihydropyran (5.6 mL, 24 mmol) and $(Ph_3P)_2NiCl_2$ (0.98 g, 1.5 mmol)

were used. Chromatography (15% EtOAc in hexanes) gave 3.20 g (57%) of **17** as a colorless oil. R_f 0.21 (15% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.50 (m, 2H), 7.35 (m, 3H), 5.50-5.20 (m, 2H), 3.56 (t, 2H, J = 6.5), 1.99 (m, 2H), 1.70 (d, 2H, J = 8.4), 1.53 (m, 2H), 1.23 (s, 1H), 0.27 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 138.9, 133.6, 129.0, 127.7, 127.4, 125.3, 62.7, 32.7, 23.4, 17.7, -3.3. Anal. Calcd for $C_{14}H_{22}OSi$: C, 71.73; H, 9.46. Found: C, 71.72; H, 9.25.

1-Iodo-5-(dimethylphenylsilyl)-pent-3-ene (18). The alcohol **16** (4.6 g, 21 mmol), triethylamine (4.39 mL, 31.5 mmol) and DMAP (280 mg, 2.29 mmol) were dissolved in CH_2Cl_2 (21 mL) and the reaction was cooled in an ice bath (0 °C). *p*-Toluenesulfonyl chloride (4.4 g, 23 mmol) was added to the reaction over 5 min and the reaction was allowed to stir for another 4 hrs. The reaction was then diluted with $CHCl_3$ (40 mL) and the organic phase was washed with 1M HCl (20 mL), sat. $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to provide the crude tosylate which was used without any further purification. The tosylate obtained above was dissolved in acetone (105 mL) and NaI (12.6 g, 84.0 mmol) was added. The reaction was then refluxed for 2 hrs. after which it was cooled to room temperature and poured into water (170 mL). The aqueous phase was then extracted with hexanes (80 mL) and the organic phase was then washed with sat. $Na_2S_2O_3$ solution, brine, dried ($MgSO_4$) and concentrated. Chromatography (hexanes) provided 5.63 g (81% from **16**) of **18** as a colorless oil. R_f 0.8 (hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.50 (m, 2H), 7.35 (m, 3H), 5.52 (m, 1H), 5.19 (m, 1H), 2.94 (t, 2H, J = 7.5), 2.46 (m, 2H), 1.69 (d, 2H, J = 8.7), 0.28 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 138.4, 133.6, 129.2, 127.8, 127.6, 126.4, 31.5, 18.3, 5.1, -3.3. Anal. Calcd for $C_{13}H_{19}SiI$: C, 47.27; H, 5.79. Found: C, 47.41; H, 5.56.

1-Iodo-6-(dimethylphenylsilyl)-hex-4-ene (19). This iodide was prepared according to the procedure used for the preparation of **18**, except alcohol **17** (2.3 g, 9.6 mmol) was used. Chromatography (hexanes) provided 2.9 g (90% from **17**) of **19** as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.50 (m, 2H), 7.35 (m, 3H), 5.50-5.20 (m, 2H), 3.13 (t, 2H, J = 6.5), 1.99 (m, 2H), 1.70 (m, 4H), 0.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 138.7, 133.6, 129.0, 127.7, 126.5, 125.8, 33.5, 27.9, 17.9, 6.4, -3.3. Anal. Calcd for $C_{14}H_{21}SiI$: C, 48.84; H, 6.15. Found: C, 48.94; H, 6.19.

(*S*)-2-[6-(Dimethylphenylsilyl)-hex-4-en]-*N*-[(4-methylphenyl)sulfonyl]-aziridine (21). *t*-BuLi (4.4 mL of a 0.89 M solution in pentane, 3.9 mmol) was added dropwise to a solution of **18** (686 mg, 1.80 mmol) in Et_2O (5 mL) at -78 °C. The reaction was stirred at -78 °C for 10 min after which it was allowed to warm to rt and stirred an additional 60 min. The reaction was recooled to -78 °C. In a separate flask CuI (119 mg, 0.626 mmol) was dissolved in *n*-Bu_3P (0.75 mL, 3.0 mmol) and Et_2O (2.5 mL). The slightly turbid solution of CuI/*n*-Bu_3P in Et_2O was then transferred to the organolithium prepared above using additional Et_2O (2.5 mL). The yellowish cuprate solution thus formed, was warmed to -40 °C and stirred for 10 min after which it was recooled to -78 °C and allowed to stir for another 40 min. The aziridine **20**[13] (240 mg, 0.630 mmol)was dissolved in THF:Et_2O (1:1, 2 mL) and added to the reaction via cannula. The reaction was stirred for another 60 min at -78 °C after which it was quenched by the addition of sat. NH_4Cl and the organic layer washed with sat. NH_4Cl, brine, dried ($MgSO_4$) and concentrated. Chromatography (8% EtOAc in hexanes) gave 182 mg (70%) of **21** as a colorless oil. R_f 0.25 (8% EtOAc in hexanes), $[\alpha]^{25}_{365}$ = -8.5° (*c* 1.6, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.81 (d, 2H, J = 8.2), 7.50 (m, 2H), 7.35 (m, 5H), 5.35 (m, 1H), 5.10 (m, 1H), 2.65 (m, 1H), 2.60 (d, 1H, J = 7.0), 2.44 (s, 3H), 2.02 (d, 1H, J = 4.5), 1.85 (m, 2H), 1.66 (d, 2H, J = 8.5), 1.65-1.10 (m, 4H), 0.26 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 144.3, 138.8, 135.5, 133.6, 129.6, 129.0, 128.0, 127.7, 127.3, 125.3, 40.2, 33.7, 30.9, 26.6, 26.4, 21.5, 17.7, -3.3. Anal. Calcd for $C_{23}H_{31}NO_2SiS$: C, 66.78; H, 7.55; N, 3.39. Found: C, 66.49; H, 7.51; N, 3.34.

(*S*)-2-[7-(Dimethylphenylsilyl)-hept-5-en]-*N*-[(4-methylphenyl)sulfonyl]-aziridine (22). This aziridine was prepared according to the procedure described for the preparation of **21**, except iodide **19** (1.15 g, 3.36 mmol) was used. Chromatography (8% EtOAc in hexanes) gave 338 mg (66%) of **22** as a colorless oil. R_f 0.24 (8% EtOAc in hexanes), $[\alpha]^{25}_{365}$ = -31.0° (*c* 2.2, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.81 (d, 2H, *J* = 8.3), 7.52 (m, 2H), 7.35 (m, 5H), 5.31 (m, 1H), 5.15 (m, 1H), 2.68 (m, 1H), 2.62 (d, 1H, *J* = 7.0), 2.42 (s, 3H), 2.03 (d, 1H, *J* = 4.5), 1.82 (m, 2H), 1.66 (d, 2H, *J* = 8.4), 1.65-1.1 (m, 6H), 0.27 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 144.2, 138.8, 135.5, 133.5, 129.5, 129.0, 128.0, 127.7, 127.6, 125.0, 40.3, 33.6, 31.1, 29.0, 26.8, 26.4, 21.5, 17.6, -3.3. Anal. Calcd for $C_{24}H_{33}NO_2SiS$: C, 67.40; H, 7.77; N, 3.28. Found: C, 67.78; H, 7.38; N, 3.17.

(7*R*)-1-(Dimethylphenylsilyl)-7-[(4-methylphenyl)sulfonyl]amino-8-[(*t*butyldimethyl)silyl]oxo-oct-2-ene (24). *t*-BuLi (16.7 mL of a 1.49 M solution in pentane, 24.9 mmol) was added dropwise to a solution of **18** (3.72 g, 11.3 mmol) in Et_2O (23 mL) at -78 °C. The reaction was then allowed to stir at -78 °C for 10 min after which it was allowed to warm to rt and stirred for an additional 60 min. The reaction was then recooled to -78 °C. In a separate flask CuI (0.77 g, 4.0 mmol) was dissolved in *n*-Bu_3P (4.7 mL, 19 mmol) and Et_2O (5 mL). The slightly turbid solution of CuI/*n*-Bu_3P in Et_2O was then transferred to the organolithium prepared above using additional Et_2O (5 mL). The yellowish cuprate solution thus formed, was warmed to -40 °C and stirred for 10 min after which it was recooled to -78 °C and allowed to stir for another 40 min. The aziridine **23**[16] (1.7 g, 5.0 mmol) was dissolved in Et_2O (4 mL) and added to the reaction via cannula. The reaction was stirred at -78 °C for 30 min after which it was warmed to rt and stirred for another 30 min. The reaction was quenched by adding sat. NH_4Cl solution and the organic layer washed with sat. NH_4Cl, brine, dried ($MgSO_4$) and concentrated. Chromatography (3% EtOAc in hexanes → 8% EtOAc in hexanes) provided 2.1 g (95%) of **24** as a colorless oil. R_f 0.4 (15% EtOAc in hexanes), $[\alpha]^{25}_D$ = +11.61° (*c* 1.1 EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.66 (d, 2H, *J* = 8.1), 7.39 (m, 2H), 7.25 (m, 3H), 7.17 (d, 2H, *J* = 8.3), 5.31-5.21 (m, 1H), 5.09-5.01 (m, 1H), 4.71 (d, 1H, *J* = 8.27), 3.28 (dd, 1H, *J* = 3.4, 10.2), 3.22 (dd, 1H, *J* = 4.3, 10.1), 3.10-3.03 (m, 1H), 2.29 (s, 3H), 1.79-1.69 (m, 2H), 1.57 (d, 2H, J = 8.50), 1.40-0.09 (m, 4H), 0.75 (s, 9H), 0.17 (s, 6H), -0.12 (s, 3H), -0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ 143.1, 138.8, 138.4, 133.6, 129.58, 128.9, 127.7, 127.6, 127.1, 125.1, 64.1, 54.9, 31.7, 26.7, 25.8, 25.6, 21.4, 18.2, 17.6, -3.3, -5.6. Anal. Calcd for $C_{25}H_{47}NO_3Si_2S$•0.25 H_2O: C, 59.78; H, 9.53; N, 2.78. Found C, 59.69; H, 9.52; N, 2.67.

(8*R*)-1-(Dimethylphenylsilyl)8-[(4-methylphenyl)sulfonyl]amino-9-[(*t*butyldimethyl)silyl]oxo-non-2-ene (25). This reaction was carried out using the same procedure described for the preparation of **24** except iodide **19** (7.55 g, 21.9 mmol) was used. Chromatography (3% EtOAc in hexanes → 8% EtOAc in hexanes) provided 3.93 g (90%) of **25** as a colorless oil. *R*f 0.40 (15% EtOAc in hexanes), $[\alpha]^{25}_D$ = +17.2° (*c* 1.3, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.74 (d, 2H, *J* = 8.0), 7.48 (m, 2H), 7.34 (m, 3H), 7.25 (d, 2H, *J* = 8.1), 5.36-5.25 (m, 1H), 5.22-5.13 (m, 1H), 4.82 (d, 1H, *J* = 8.3), 3.41(dd, 1H, *J* = 2.9, 10.0), 3.31 (dd, 1H, *J* = 4.1, 9.74), 3.21-3.13 (m, 1H), 2.38 (s, 3H), 1.84-1.79 (m, 2H), 1.66 (d, 2H, *J* = 8.48), 1.46-1.36 (m, 2H), 1.20-1.11 (m, 4H), 0.83 (s, 9H), 0.26 (s, 6H), -0.04 (s, 3H), -0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ 143.0, 138.8, 138.4, 133.5, 129.5, 128.9, 127.9, 127.6, 127.0, 124.7, 64.1, 54.9, 32.0, 29.3, 26.6, 25.8, 25.2, 21.4, 18.1, 17.5, -3.3, -5.7. Anal. Calcd for $C_{30}H_{49}NO_3Si_2S$: C, 64.34; H, 8.64; N, 2.50. Found C, 64.66; H, 8.93; N, 2.59.

(*R*)-2-[6-(Dimethylphenylsilyl)-hex-4-en]-*N*-[(4-methylphenyl)sulfonyl]-aziridine (26). *n*-Bu_4NF (1.43 mL of a 1 M solution in THF, 1.43 mmol) was added dropwise over 5 min to a solution of **24** (710 mg, 1.30 mmol) in THF (1.30 mL) at 0 °C. The reaction was stirred for 30 min after which it was diluted with water. The aqueous layer was then extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product thus obtained was dried under vacuum (2 mm Hg) overnight and used without any further purification. The crude alcohol obtained was transferred to a flame dried flask containing triphenylphosphine (380 mg , 1.43 mmol), using THF (6.50 mL) and the resulting solution was

cooled in an ice bath. Diethylazodicarboxylate (0.230 mL, 1.43 mmol) was added to the reaction over 5 min via a syringe and the reaction was then allowed to stir for 3 h after which the solvent was removed in vacuo. The resulting thick oil was triturated with hexanes resulting in precipitation of a white solid (Ph_3PO), which was filtered to provide a solution which was then concentrated. Chromatography (10% EtOAc in hexanes) provided 455 mg (85% from **24**) of aziridine **26** as a colorless oil. Data was the same as that reported for **21** except $[\alpha]^{25}_{365}$ = +8.5° (*c* 1.0, EtOAc).

(*R*)-2-[6-(Dimethylphenyl)-hept-5-en]-*N*-[(4-methylphenyl)sulfonyl]-aziridine(27). This aziridine was prepared using the same general procedure described for **26**, except silyl ether **25** (3.94 g, 7.04 mmol) was used. Chromatography (10% EtOAc in hexanes) provided 2.25 g (76% from **25**) of aziridine **27** as a colorless oil. Data was the same as that reported for **21** except $[\alpha]^{25}_{365}$ = +31.0° (*c* 2.4, EtOAc).

(1*S*, 3a*S*, 6a*R*) -*N*-[(4-Methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl)methyl]hexahydrocyclopenta[*c*] pyrrole (28). The aziridine **21** (580 mg, 1.40 mmol) was dissolved in CH_2Cl_2 (14 mL) and the reaction was cooled to 0 °C. A solution (0.50 mL) of freshly distilled BF_3•OEt_2 (26 μL, 0.21 mmol) in CH_2Cl_2 (0.50 mL), was added to the reaction which was then allowed to stir for 60 min at 0 °C. The reaction was then diluted with $CHCl_3$ (70 mL) and quenched by the addition of sat. $NaHCO_3$ solution (50 mL). The aqueous layer was then extracted with $CHCl_3$ (70 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography (7% EtOAc in hexanes) provided 376 mg (65%) of **28** as a colorless oil. R_f 0.25 (8% EtOAc in hexanes). $[\alpha]^{25}_D$ = -117.7° (*c* 1.7, EtOAc), ^{1}H NMR (C_6D_6, 270 MHz), δ 7.63 (d, 2H, *J* = 8.2), 7.53 (m, 2H), 7.22 (m, 3H), 6.81 (d, 2H, *J* = 8.2), 3.25 (m, 1H), 3.14 (dd, 1H, *J* = 9.0, 11.1), 3.0 (dd, 1H, *J* = 6.8, 11.1), 2.36 (dd, 1H, *J* = 3.0, 14.8), 1.92 (s, 3H), 1.87 (m, 1H), 1.62 (m, 1H), 1.62-0.9 (m, 7H), 0.26 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 143.0, 138.6, 135.7, 129.4, 129.3, 129.1, 127.9, 127.8, 61.5, 55.0, 49.3, 40.3, 30.9, 27.1, 25.7, 21.4, 19.3, -2.1, -2.4. Anal. Calcd for $C_{23}H_{31}NO_2SiS$: C, 66.78; H, 7.55; N, 3.39. Found: C, 67.16; H, 7.65; N, 3.30.

(1*R*, 3a*R*, 6a*S*)-*N*-[(4-Methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl)methyl]hexahydrocyclopenta[*c*] pyrrole (30). This bicycle was prepared using the same general procedure as described for **28**, except, aziridine **26** (1.6 g, 3.8 mmol) was used. Chromatography (7% EtOAc in hexanes) provided 0.97g (62%) of bicycle **30** as a colorless oil. Data was the same as that reported for **28** except $[\alpha]^{25}_D$ = +115.0° (*c* 0.8, EtOAc).

(1*S*, 3a*S*, 7a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl) methyl]octahydro-1*H*-isoindole (32) and (1*R*, 3a*S*, 7a*S*)-*N*-[(4-methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl) methyl]octahydro-1*H*-isoindole (33). This bicycle was prepared using the same general procedure as described for **28** except, aziridine **22** (45 mg, 0.11 mmol) was used. Chromatography (5% EtOAc in hexanes) provided 27 mg (57%) of **33** as a colorless oil. Data for **32**: R_f 0.25 (8% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 270 MHz), δ 7.56 (d, 2H, *J* = 8.9), 7.41 (m, 5H), 7.15 (d, 2H, *J* = 8.2), 3.34-3.23 (m, 3H), 2.37 (s, 3H), 2.04 (dd, 1H, *J* = 3.3, 13.0), 1.65 (m, 2H), 1.55-1.13 (m, 8H), 0.90 (m, 1H), 0.32 (s, 3H), 0.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 142.8, 138.5, 134.5, 133.7, 129.4, 129.0, 127.8, 127.6, 63.7, 49.9, 41.9, 36.1, 24.8, 24.3, 22.7, 21.4, 20.5, 18.1, -2.1, -2.6. Anal. Calcd for $C_{24}H_{33}NO_2SiS$: C, 67.40; H, 7.77; N, 3.27. Found: C, 67.61; H, 7.78; N, 3.14. Data for **33**: R_f 0.27 (8% EtOAc in hexanes). $[\alpha]^{25}_D$ = +39.7° (*c* 0.6, EtOAc), ^{1}H NMR (C_6D_6, 250 MHz), δ 7.72 (d, 2H, *J* = 8.2), 7.66 (d, 2H, *J* = 8.0), 7.28, (m, 3H), 6.80 (d, 2H, *J* = 8.3), 4.0 (m, 1H), 3.46 (dd, 1H, *J* = 6.9, 9.1), 2.53 (dd, 1H, *J* = 9.2, 10.5), 1.86 (s, 3H), 1.45-1.08 (m, 7H), 1.0 (dd, 1H, *J* = 7.4, 15.0), 0.89-0.61 (m, 4H), 0.59 (s, 3H), 0.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 142.8, 139.1, 135.0, 133.7, 129.4, 129.7, 127.7, 127.4, 60.3, 53.3, 49.4, 40.1, 29.3, 26.6, 25.3, 25.1, 21.4, 20.7, -1.9, -2.1.

(1*S*, 3a*R*, 7a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl) methyl]octahydro-1*H*-isoindole (35) and (1*S*, 3a*R*, 7a*R*)-*N*-[(4-methylphenyl)sulfonyl]-1-[(dimethylphenylsilyl) methyl]octahydro-1*H*-isoindole (36). This bicycle was prepared using the same general procedure as described for **28** except, aziridine **27** (0.50 g, 1.2 mmol) was used. Chromatography (5% EtOAc in hexanes) provided 0.27 g (55%) of **36** as a colorless oil. Data for **35** was the same as that reported for **32**. Data for **36** was the same as that reported for **33** except $[\alpha]^{25}_D$ = -40.52° (*c* 0.2, EtOAc).

(1*S*, 3a*S*, 6a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-hydroxymethylhexahydro-cyclopenta[*c*]pyrrole (38). A solution of **28** (290 mg, 0.701 mmol) in peracetic acid (2.78 mL, 19.0 mmol, 32% solution in acetic acid), AcOH (2.78 mL), and of EtOAc (0.5 mL) was cooled to 0 °C and $Hg(OAc)_2$ (290 mg, 0.910 mmol) was added. The reaction was stirred at room temperature for 3 hours. Et_2O (20 mL) was added and the solution was washed with $Na_2S_2O_3$ (10 mL) solution, H_2O (10 mL), $NaHCO_3$ (10 mL), and brine (10 mL), dried, and evaporated in vacuo. Chromatography (30% EtOAc in hexanes) provided 163 mg (79%) of **38** as a colorless oil. R*f* 0.36 (35% EtOAc in hexanes) $[\alpha]^{25}_D$ = -64.6° (*c* 1.0, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.78 (d, 2H, *J* = 8.3), 7.29 (d, 2H, *J* = 8.1), 3.86 (dd, 1H, *J* = 7.1, 12.1), 3.75 (m (br), 1H), 3.45 (m, 2H), 3.29 (dd, 1H, *J* = 9.0, 11.4), 3.05 (dd, 1H, *J* = 7.1, 11.2), 2.40 (s, 3H), 2.18-2.09 (m, 1H), 1.70-1.30 (m, 7H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 143.8, 133.3, 129.7, 127.8, 65.2, 63.4, 55.4, 47.8, 41.0, 30.4, 26.6, 26.2, 21.4. Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.74; H, 7.34; N, 4.61.

(1*S*, 3a*S*, 6a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-carboxylic acid hexahydro-cyclopenta[*c*]pyrrole (39). To a solution of **38** (160 mg, 0.542 mmol) and $NaIO_4$ (350 mg, 1.62 mmol) in CCl_4 (1.10 mL), CH_3CN (1.10 mL) H_2O (1.65 mL), and $RuCl_3 \cdot 3H_2O$ (2.4 mg 0.012 mmol) was added. The reaction was stirred at room temperature for 18 hours, diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3x5 mL). The crude mixture was then extracted with sat. aq. $NaHCO_3$ (3x10 mL). The aqueous layer was acidified with conc. HCl to pH 3, and then extracted with $CHCl_3$ (3x10 mL). The organic phase was dried ($MgSO_4$) and concentrated to give 115 mg (69%) of **39** as a colorless oil. R*f* 0.29 (EtOAc) $[\alpha]^{25}_D$ = -57.6° (*c* 3.6, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 8.78 (s (br), 1H), 7.73 (d, 2H, *J* = 8.1), 7.29 (d, 2H, *J* = 8.0), 4.43 (d, 1H, *J* = 9.1), 3.59 (dd, 1H, *J* = 9.0, 10.9), 3.06 (dd, 1H, *J* = 8.2, 10.6), 2.92-2.79 (m, 1H), 2.40 (s, 3H), 1.78-1.35 (m, 7H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 175.8, 143.8, 135.0, 129.7, 127.6, 63.9, 53.8, 47.5, 43.6, 29.5, 27.9, 26.2, 21.5. Anal. Calcd for $C_{15}H_{19}NO_4S \cdot 0.25\ H_2O$: C, 57.40; H, 6.26; N, 4.46. Found: C, 57.68; H, 6.28; N, 4.25.

(1*S*, 3a*S*, 6a*R*)-1-Carboxylic acid hexahydrocyclopenta[*c*]pyrrole hydrobromide (1). Phenol (0.99 g, 10.5 mmol) was dissolved in 10.0 mL of 32% HBr/AcOH. In a second flask, **39** (109 mg, 0.35 mmol) was dissolved in EtOAc (3 mL). The phenol solution was added to the solution of **39** in 3 parts over 1 hour. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with EtOAc (30 mL) and then extracted with H_2O (3x15 mL). Concentration of the aqueous layer provided 83 mg (100%) of **1** as an orange solid. $[\alpha]^{25}_{578}$ = -38.5° (*c* 0.2, 1M HCl), mp decomposes >175°C. ^{1}H NMR (D_2O, 400 MHz), δ 4.28 (d, 1H, *J* = 8.1), 3.24 (dd, 1H, *J* = 8.9, 11.6), 3.07-2.93 (m, 2H), 2.83 (m, 1H), 1.90 (m, 1H), 1.73 (m, 1H), 1.57 (m, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.12 (m, 1H) ^{13}C NMR (D_2O, 100 MHz) δ 155.9, 35.5, 33.9, 29.2, 26.5, 17.3, 13.5, 11.3. HRMS calculated for $C_8H_{13}NO_2$ was 155.0947, found 155.0977.

(1*R*, 3a*R*, 6a*S*)-*N*-[(4-Methylphenyl)sulfonyl]-1-hydroxymethylhexahydro-cyclopenta[*c*]pyrrole (40). This bicycle was prepared using the same general procedure as described for preparation of **38** except bicycle **30** (140 mg, 0.338 mmol) was used. Chromatography (30% EtOAc in hexanes) provided 80 mg (80%) of **40** as a colorless oil. Data was the same as that reported for **38** except $[\alpha]^{25}_D$ = +64.35° (*c* 0.2, EtOAc).

(1*R*, 3a*R*, 6a*S*)-*N*-[(4-Methylphenyl)sulfonyl]-1-carboxylic acid hexahydro-cyclopenta[*c*]pyrrole (41). This bicycle was prepared using the same general procedure as described for preparation of **39** except bicycle **40** (30 mg, 0.10 mmol) was used. Acid-base extraction (as described for **39**) gave 21 mg (66%) of **41** as a colorless oil. Data was the same as that reported for **39** except $[\alpha]^{25}_{D}$ = +57.8° (*c* 1.0, EtOAc).

(1*R*, 3a*R*, 6a*S*)-1-Carboxylic acid hexahydrocyclopenta[*c*]pyrrole hydrobromide (2). This bicycle was prepared using the same general procedure as described for preparation of **1** except acid **41** (70 mg, 0.23 mmol) was used. Rotary evaporation of the aqueous phase gave 55 mg (100%) of **2** as an orange solid. Data was the same as that reported for **1** except $[\alpha]^{25}_{578}$ = +36.5° (*c* 0.2, 1M HCl).

(1*R*, 3a*S*, 7a*S*)-*N*-[(4-Methylphenyl)sulfonyl]-1-hydroxymethyloctahydro-1*H*-isoindole (42). This bicycle was prepared using the same general procedure as described for **38** except, bicycle **33** (211 mg, 0.493 mmol) was used. Chromatography (30% EtOAc in hexanes) provided 102 mg (66%) of **42** as a colorless oil. R*f* 0.36 (15% EtOAc in hexanes) $[\alpha]^{25}_{D}$ = +4.6° (*c* 0.6, EtOAc), ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.69(d, 2H, *J* = 8.2), 7.29 (d, 2H, *J* = 8.1), 3.71 (m (br), 1H), 3.62-3.55 (m, 3H), 2.94-2.88 (m, 1H), 2.53 (dd, 1H, *J* = 8.8, 11.0), 2.40 (s, 3H), 1.82-1.58 (m, 5H), 1.20-0.71 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 143.5, 133.8, 129.6, 127.6, 63.9, 63.2, 54.2, 46.9, 41.4, 29.1, 25.9, 25.5, 25.1, 21.4. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 62.22; H, 7.45; N, 4.42.

(1*R*, 3a*S*, 7a*S*)-*N*-[(4-Methylphenyl)sulfonyl]-1-carboxylic acid octahydro-1*H*-isoindole (43). This bicycle was prepared using the same general procedure as described for **39** except, alcohol **42** (100 mg, 0.323 mmol) was used. Acid-base extraction (as described for **39**) provided 85.4mg (83%) of **43** as a white solid. R*f* 0.29 (EtOAc) $[\alpha]^{25}_{D}$ = +10.0° (*c* 0.4, EtOAc), mp 189-191°C, ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.73 (d, 2H, *J* = 8.4), 7.31 (d, 2H, *J* = 8.1), 4.25 (d, 2H, *J* = 8.9), 3.63 (dd, 1H, *J* = 6.5, 8.2), 2.69 (dd, 1H, *J* = 8.3, 10.5), 2.42 (s, 3H), 1.89-1.65 (m, 5H), 1.50-1.38 (m, 1H), 1.19-0.85 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 176.0, 143.7, 134.9, 129.7, 127.5, 63.0, 53.0, 47.7, 41.7, 28.6, 26.8, 25.0, 22.6, 21.5. Anal. Calcd for $C_{19}H_{21}NO_4S$•0.50 H_2O: C, 57.81, H, 6.67, N, 4.21. Found C, 57.65, H, 6.32, N, 4.01.

(1*R*, 3a*S*, 7a*S*)-1-Carboxylic acid octahydro-1*H*-isoindole hydrobromide (3). This bicycle was prepared using the same general procedure as described for preparation of **1** except acid **43** (65 mg, 0.20 mmol) was used. Rotary evaporation of the aqueous phase gave 43 mg (86%) of **3** as an orange solid. Data was the same as that reported for **4** except $[\alpha]^{25}_{578}$ = +19.5° (*c* 0.2, 1M HCl).

(1*S*, 3a*R*, 7a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-hydroxymethyloctahydro-1*H*-isoindole (44). This bicycle was prepared using the same general procedure as described for **38** except bicycle **36** (214 mg, 0.500 mmol) was used. Chromatography (30% EtOAc in hexanes) provided 134 mg (87%) of **44** as colorless oil. Data was the same as that reported for **42** except $[\alpha]^{25}_{D}$ = -3.5° (*c* 0.6, EtOAc).

(1*S*, 3a*R*, 7a*R*)-*N*-[(4-Methylphenyl)sulfonyl]-1-carboxylic acid octahydro-1*H*-isoindole (45). This bicycle was prepared using the same general procedure as described for **39** except alcohol **44** (151 mg, 0.487 mmol) was used. Acid-base extraction (as described for **39**) provided 122 mg (77%) of **45** as a white solid. Data was the same as that reported for **43** except $[\alpha]^{25}_{D}$ = -9.0° (*c* 0.3, EtOAc).

(1*S*, 3a*R*, 7a*R*)-1-Carboxylic acid octahydro-1*H*-isoindole hydrobromide (4). This bicycle was prepared using the same general procedure as described for **1** except acid **45** (110 mg, 0.340 mmol) was used. Concentration of the aqueous phase gave 68 mg (80%) of **4** as an orange solid. $[\alpha]^{25}_{578}$ = -16.1° (*c* 0.4, H_2O). mp decomposes >170°C. ^{1}H NMR (D_2O, 400 MHz), δ 4.17 (d, 1H, *J* = 8.8), 3.43 (m, 1H), 2.68 (t, 1H, *J* =

11.5), 1.73-1.65 (m, 3H), 1.65-1.32 (m, 3H), 0.09-0.75 (m, 4H). ^{13}C NMR (D_2O, 100 MHz) δ 158.1, 48.8, 36.7, 32.4, 27.2, 13.9, 13.0, 11.2, 10.7. FABMS (M+H) calculated for $C_9H_{15}NO_2$ was 169.110, found 170.120.

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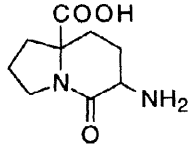

Other proline analogs with various substitution patterns on the pyrrolidine ring have also been reported. For example, see: Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron* **1998**, *54*, 15759-15780. and references cited therein.
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