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SYNTHESIS OF SUBSTITUTED TETRAHYDROPYRIDINES BY CYCLIZATIONS OF SILICON-CONTAINING IMINIUM IONS

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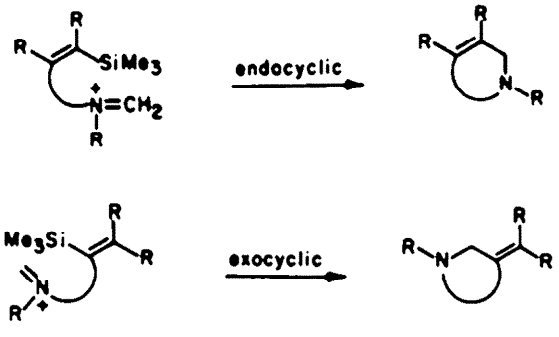
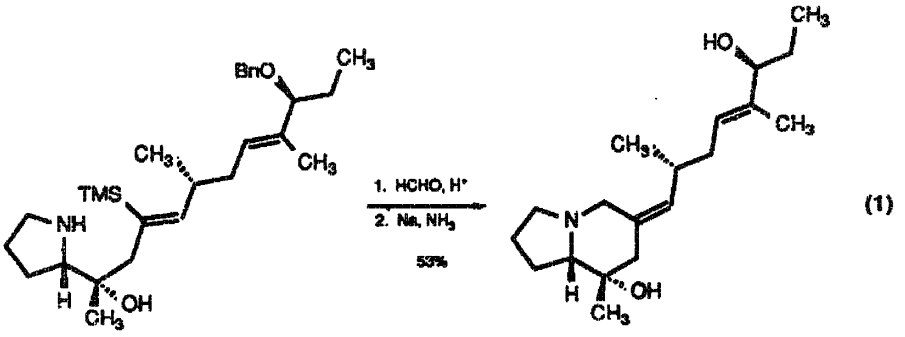
Summary: *Trans-2,6-disubstituted-1,2,5,6-tetrahydropyridines are formed stereoselectively from the cyclization of silicon-containing iminium cations* **5** *if the nitrogen substituent* R^1 *is an alkyl group. In contrast, cyclization of the corresponding NH or N-acyl iminium ions occurs in a stereorandom fashion. Non-racemic tetrahydropyridines cannot be prepared in this way, since both iminium ion and N-acyliminium ion intermediates racemize prior to cyclization.*

Electrophilic cyclization reactions of iminium ions and related intermediates (Mannich cyclizations) are time-honored methods for preparing nitrogen heterocycles.[2] As we have discussed in detail elsewhere,[3] vinylsilanes are particularly attractive nucleophilic reaction components for iminium ion initiated cyclization reactions.[4] The silicon substituent directs the outcome of cyclizations of this type to yield products of electrophilic substitution[3,5] (see Fig 1) and, in many cases,[3] can also be exploited during the synthesis of the cyclization substrate. Two modes of participation of a vinylsilane are possible and these are illustrated in Fig 1.

Figure 1

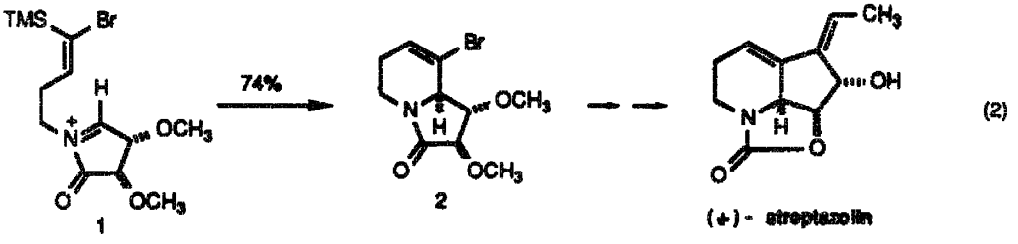


Iminium ion-vinylsilane cyclizations have found considerable application in the area of alkaloid total synthesis.[3,5] Key cyclization steps in recently reported total syntheses of the cardiac stimulant (+)-pumiliotoxin A[6] and the antibiotic (+)-streptazolin[7] are shown in eqns 1 and 2 to illustrate the application of cyclizations that occur in the exocyclic and endocyclic modes, respectively.



(1)

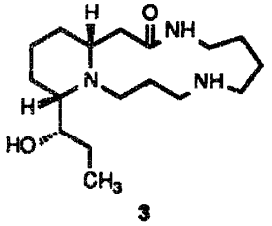
(+)-Pumiliotoxin A



1 2 (+)- streptazolin

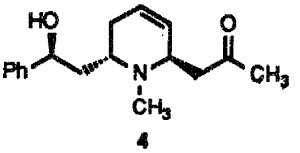
(2)

To date our studies of the preparation of 1,2,5,6-tetrahydropyridines by endocyclic cyclizations of vinylsilane precursors have been limited to cases where the newly-formed tetrahydropyridine ring contains a single stereogenic center (e.g. **1** → **2** in eq 2).[3,8] Since a number of tetrahydropyridine natural products contain 2,6-disubstituted-1,2,5,6-tetrahydropyridine rings[9] (e.g. **3** and **4**) we were interested in exploring the stereochemical outcome of cyclizations of silicon-containing iminium ions such as **5** (see Scheme 1). Two important questions regarding this cyclization arise: (1)



Palustrine

3

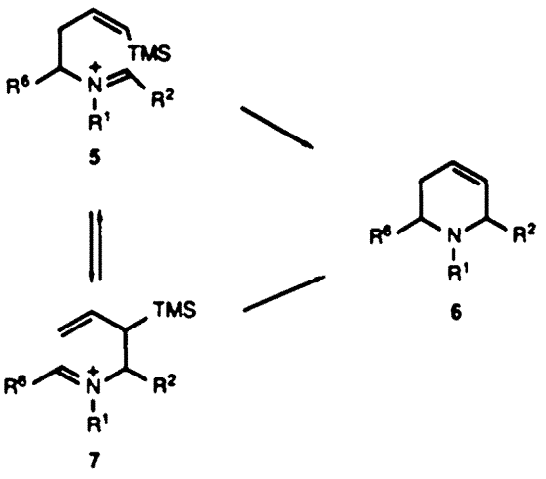


Sedacrine

4

What will be the *cis/trans* diastereoselectivity in forming **6** and can it be controlled by the nature of the R^1 substituent? (2) Can the initial stereogenic center at C-6 in **5** be employed to introduce absolute chirality in the tetrahydropyridine product? Our earlier studies[8] had shown that cationic aza-Cope equilibration of iminium ions **5** and **7** (R^1 = alkyl) occurred more rapidly than cyclization, and, thus, the product tetrahydropyridine was really formed by an allylsilane-iminium ion cyclization (*i.e.* **7** → **6**). Such aza-Cope equilibration could lead to the formation of a racemic product from the cyclization of a non-racemic amine precursor of **5** (*vide infra*), although racemization would not have to occur since the allylsilane sigmatropic isomer contains a newly formed stereogenic center at C-2.

Scheme 1

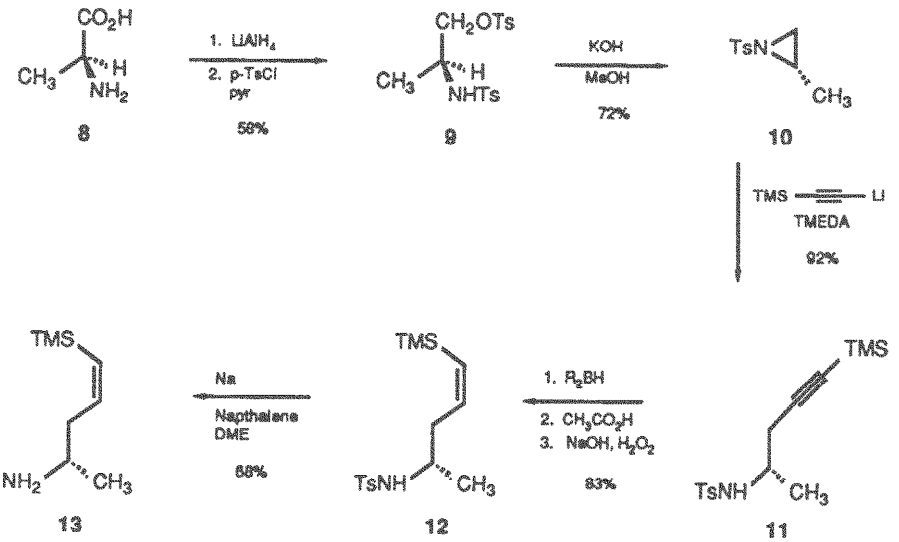


In this paper we describe the results of cyclizations of chiral non-racemic silicon-containing iminium ions (R^1 = H, alkyl) and *N*-acyliminium ions (R^1 = COOEt) **5**. We report that *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridines can be prepared in this fashion with excellent diastereoselectivity if R^1 is an alkyl substituent. We report also that both iminium ion and *N*-acyliminium ion intermediates undergo complete racemization *prior* to cyclization.

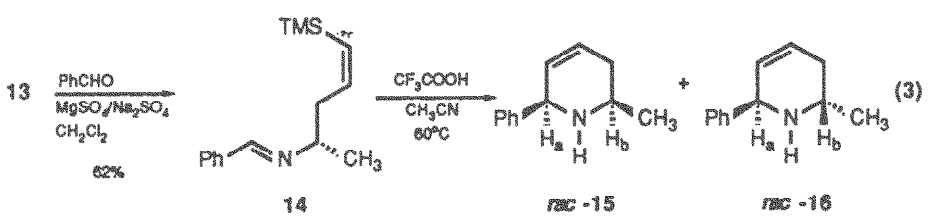
RESULTS AND DISCUSSION

Preparation of Amine 13. We chose to examine cyclizations of iminium ions derived from vinyl silyl amine **13**, which was prepared in high enantiomeric purity as summarized in Scheme 2. Silyl alkynyl amine **11** was obtained by reaction of (trimethylsilyl)alkynyllithium with N-tosylaziridine **10**, which in turn was readily available from *L*-alanine **8**.[10] Reduction of **11** to the stereochemically pure *Z*-vinylsilane **12** was successfully accomplished by treatment with dicyclohexylborane[11] followed by protonolysis. Other methods of semi-hydrogenation (e.g. Pd-$BaSO_4$/H_2 or $HAlBu^i_2$/protonolysis) were less successful. The sulfonamide was successfuly removed by treatment of **12** with sodium naphthalide[12] in 1,2-dimethoxyethane (DME). Attempts to do this deprotection with lithium in ammonia resulted in simultaneous reduction of the vinylsilane, while attempted desulfonylation of **12** with hot ethanolic KOH resulted in extensive decomposition. Amine **13** obtained in this way was >98% pure and was shown to have an enantiomeric excess of >96% by capillary GC analysis of the amide prepared from (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[13]

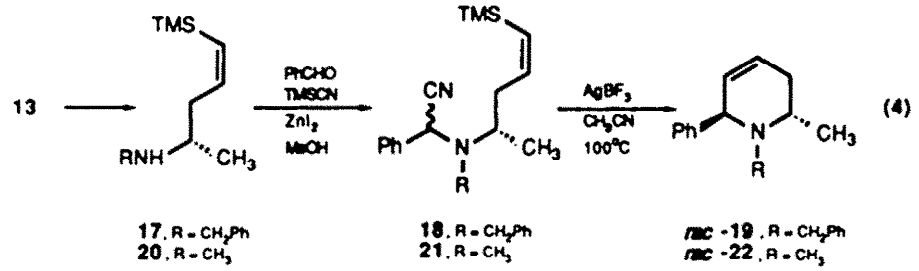
Scheme 2



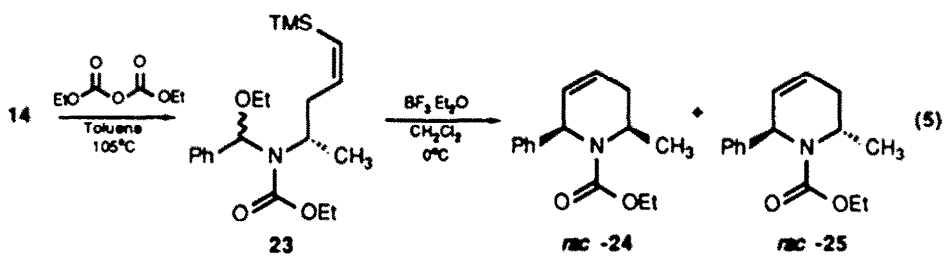
Iminium Ion Cyclizations. We initially examined acid catalyzed cyclization of imine **14**, which was isolated as a single stereoisomer, after vacuum distillation (see eq 3). We assume that **14** is the more stable[14] *E* isomer. Cyclization of **14** at 60°C in acetonitrile in the presence of 3 equiv of CF_3COOH[8,15] afforded, in 85% yield, a 1:1 mixture of racemic[16] tetrahydropyridines *rac*-**15** and *rac*-**16**, which could be separated on silica gel. The strong (10%) NOE between hydrogens H_a and H_b and the absence of NOE between the CH_3 group and H_a of *rac*-**15** support the *cis* stereorelationship for this isomer. Conversely, the strong (20%) NOE between H_b and the Ph group of *rac*-**16** was consistent with a *trans*-stereochemistry for this product.



The corresponding cyclization of *N*-alkyl iminium ions[8] was examined with cyanoalkylamines **18** and **21** which were prepared from silyl amine **13** by standard[17,18] procedures (see eq 4). Exposure of **18** or **21** in refluxing acetonitrile to excess $AgNO_3$ or $AgBF_4$ resulted in clean cyclization to afford a single racemic [16,19] tetrahydropyridine product *rac*-**19** (57% yield) or *rac*-**22** (51% yield), respectively. Both products were shown to be the *trans* stereoisomer by chemical correlation with *rac*-**16** as is detailed in the Experimental Section. Attempted direct cyclization[8] of **17** by treatment with benzaldehyde and 1 equiv of camphorsulfonic acid was not successful.



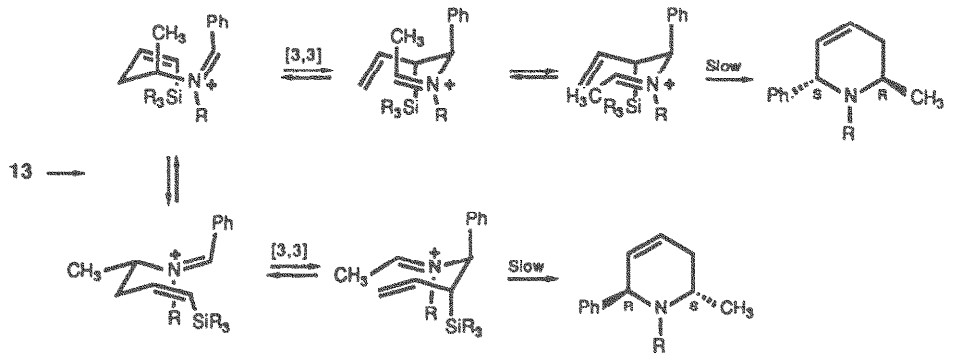
Acyliminium Ion Cyclizations. Imine **14** was converted to the α-ethoxy carbamate **23** by the general procedure of Speckamp and Heimstra.[20] Since diethyl pyrocarbonate slowly decomposes in refluxing toluene, this reagent was added portion-wise to the refluxing toluene solution[20b] until the starting imine was consumed (by capillary GC analysis). Ethoxy carbamate **23** partially decomposed during attempted chromatographic purification, so the crude product was employed directly in cyclization reactions. Treatment of **23** with $BF_3.OEt_2$ at 0°C afforded the racemic[16,21] tetrahydropyridine carbamates, *rac*-**24** and *rac*-**25**, as a 1:1 mixture in 71% yield. These stereoisomers could be separated on silica gel and stereochemical assignments again followed from chemical correlation with *rac*-**15** and *rac*-**16**.



DISCUSSION

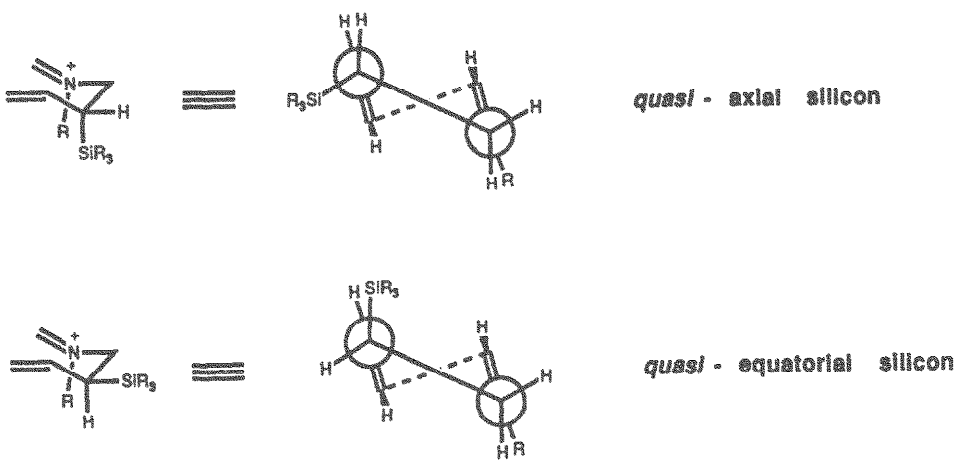
Racemic tetrahydropyridine products were formed from all three (*N*-H, *N*-alkyl, *N*-acyl) iminium ion initiators. This result demonstrates that the iminium ion intermediates involved racemize more rapidly than they undergo cyclization with the silicon-containing alkene terminator. One reasonable process for racemization is shown in Scheme 3 for the illustrative case of forming the *trans*-tetrahydropyridine products. It is reasonable[5,8] that cyclization to afford the tetrahydropyridine would occur most rapidly *via* the allylsilane sigmatropic isomer. A chair topography, similar to that typically preferred for polyene cyclizations of 1,5-dienes, is depicted in Scheme 3 for the allylsilane-iminium ion cyclization.[22] As illustrated in Scheme 4, a *quasi*-axial orientation for the Me_3Si group would be required for proper stereoelectronic participation of the C-Si σ-bond in the cyclization step.[22b] Readily discernable from molecular models and the Newman projections shown in Scheme 4 is the fact that a *quasi*-axial Me_3Si group does not experience any serious non-bonded interactions in a chair cyclization transition state. The more conventional chair conformational drawings shown in

Scheme 3



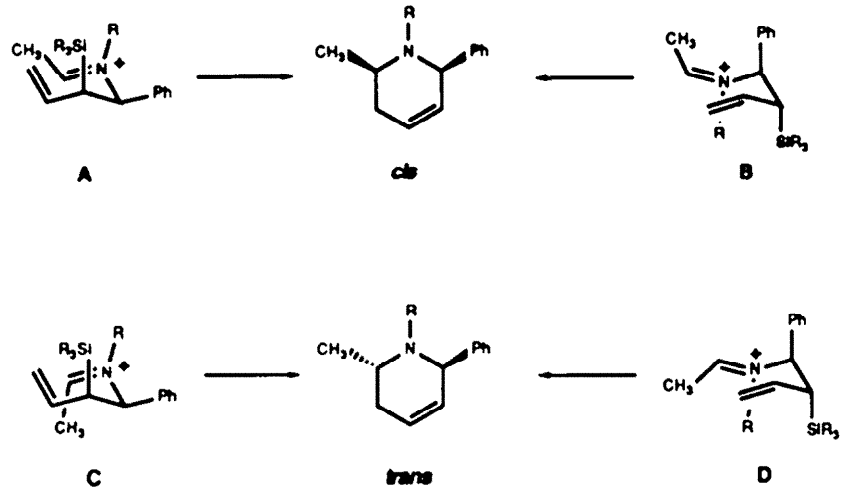
Schemes 3-5 are quite misleading in this regard. Scheme 3 illustrates racemization *via* chair topography aza-Cope rearrangements coupled with equilibration of iminium ion stereochemistry.[23] It should be stressed that [3,3]-sigmatropic rearrangements alone would not result in racemization. Preferences for chair geometries in aza-Cope rearrangements of iminium ions[24] and *N*-acyliminium ions[25] have been reported, while stereomutations of iminium ions are known to be rapid when nucleophiles are present (as is undoubtedly true in the present case) to allow equilibration *via* addition-elimination sequences.[26]

Scheme 4



How does one rationalize the fact that the cyclization of only the *N*-alkyl iminium ions **5** takes place in a stereoselective fashion? Assuming that cyclization ultimately occurs *via* chair allylsilane iminium ion conformers with *quasi* axially-oriented Me_3Si groups, the *cis* diastereomer would derive from the cyclization of intermediate conformers **A** and/or **B** depicted in Scheme 4, while the *trans* isomer would arise from cyclization of **C** and/or **D**. Of these four conformers, **B** is easy to exclude due to severe eclipsing interactions between the CH_3 and Ph groups. With less certainty one can also exclude conformer **D**, since it contains the largest substituent Ph in a *quasi* axial position. The fact that cyclization of the *N*-H iminium ion gives nearly equal amounts of *cis* and *trans* dihydropyridine products suggests that the transition states related to conformers **A** and **C** are of similar energy, a proposition which appears at least reasonable from molecular models. The high *trans* preference observed in cyclizations of *N*-alkyl iminium ions then could be rationalized by destabilizing buttressing interactions between the nearly coplanar CH_3, R, and Ph substituents in transition states

Scheme 5



related to conformer A. Why the *N*-acyl iminium ion also gives a mixture of *cis*- and *trans*- products is less clear. For the time being, we will note only that cyclization *via* conformer A would not be expected to be favored when R = COOR,[26] since this process involves the development of destabilizing $A^{1,3}$ interactions[27] between the *N*-acyl group and both the CH_3 and Ph substituents.

CONCLUSION

Trans-2,6-disubstituted-1,2,5,6-tetrahydropyridines can be prepared with excellent stereocontrol from cyclization of iminium ions derived from secondary 1-substituted-4-(trimethylsilyl)-3-butenyl amines. However, the potential use of this chemistry for the synthesis of tetrahydropyridine natural products is compromised by the fact that racemization occurs more rapidly than cyclization.

EXPERIMENTAL SECTION[28]

(S)-N-(*p*-Toluenesulfonyl)-2-amino-1-propyl *p*-toluenesulfonate (9): A solution of (S)-2-amino-1-propanol (2.19g, 30.0mmol) in pyridine (8mL) was slowly (ca. 10 min.) added to a solution of *p*-toluenesulfonyl chloride (11.4g, 60.0mmol) in pyridine (32mL) at 0°C. After 1h at 0°C, the reaction was allowed to warm to room temperature and was maintained there for 18h. Concentration under reduced pressure (0.5mmHg) afforded a brown oil which was partitioned between ether (75mL) and water (75mL). The aqueous layer was further extracted with ether (2 x 75mL). The combined organic extracts were washed with cold 5% H_2SO_4 (4 x 50mL), sat. $CuSO_4$ (50mL), water (50mL), sat. $NaHCO_3$ (50mL), brine (50mL) and dried over $MgSO_4$. Concentration afforded a yellow solid which was purified by flash chromatography (silica gel, 20% EtOAc/hexane) to give 9.35g (81%) of 9 as a white crystalline solid: mp 104-105°C; $[\alpha]_D^{23}$ -38.2 (c. 1.02, $CHCl_3$); ^1H NMR (250MHz, $CDCl_3$) ∂7.74-7.71 (m, 4H, ArH), 7.37-7.30 (m, 4H, ArH), 4.71 (d, J = 8.8Hz, NH), 3.93 (dd, J = 4.8, 11.4Hz, 1H, CH_2), 3.85 (dd, J = 4.8, 11.4Hz, 1H, CH_2), 3.55 (m, 1H, CH), 2.47 (s, CH_3Ar), 2.42 (s, CH_3Ar), 1.08 (d, J = 7.3Hz, CH_3CH); IR (KBr) 3300, 3100, 2950, 1595, 1350, 1180, cm^{-1}; MS (CI) m/z 384 (MH^+). Anal. Calcd for $C_{17}H_{21}NS_2O_5$: C, 53.25; H, 5.52; N, 3.65; S, 16.72. Found: C, 53.32; H, 5.56; N, 3.62; S, 16.79.

(S)-N-(*p*-Toluenesulfonyl)-2-methylaziridine (10): A solution of KOH (4.10g, 73.2mmol) in MeOH (20mL) was slowly (ca. 15 min.) added to a solution of **9** (9.35g, 24.4mmol) in MeOH (100mL) at room temperature. After 30 min., the reaction was quenched by diluting with water (250mL) and extracting with ether (3 x 150mL). The combined organic extracts were washed with saturated NH_4Cl (100mL), water (100mL), sat. $NaHCO_3$ (100mL), brine (100mL) and dried over $MgSO_4$. Concentration and purification of the residue by flash chromatography (silica gel, 20% EtOAc/hexane) gave a white solid. Recrystallization from hexane gave 3.70g (72%) of analytically pure **10** as white crystals: mp 58-59°C; $[\alpha]_D^{23}$ +29.6 (c. 1.02, $CHCl_3$): ^1H NMR (250MHz, $CDCl_3$) ∂7.80 (app d, 2H, ArH), 7.32 (app d, 2H, ArH), 2.81 (m, CH_3CHN), 2.59 (broad d, J = 7.0Hz, 1H, CH_2), 2.42 (s, CH_3Ar), 2.00 (bd, J = 4.6Hz, 1H, CH_2), 1.23 (d, J = 5.7Hz, CH_3); IR (KBr) 3100, 2960, 1450, 1170, 770cm^{-1}; MS(CI) m/z 212 (MH^+). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.17. Found: C, 56.74; H, 6.22; N, 6.58; S, 15.24.

(S)-N-(*p*-Toluenesulfonyl)-4-amino-1-(trimethylsilyl)-1-pentyne (11): A solution of *n*-BuLi (49mL of a 2.6M solution in hexane, 0.13 mol) was added to a solution of (trimethylsilyl)acetylene (25mL, 0.18 mol) in N,N,N',N'-tetramethylethylenediamine (TMEDA, 100mL) at 0°C. The TMEDA was first refluxed with butyric anhydride (1/6 by weight) for 2h, distilled onto potassium hydroxide and then distilled from potassium hydroxide prior to use.[30] The solution was allowed to warm to room temperature and stirred there for approximately 20 min.. This solution then was cooled to 0°C and added via cannula to a solution of **10** (10.0g, 47.4mmol) in TMEDA (120mL). The resulting solution was allowed to warm to room temperature and stirred for 6h. After cooling to 0°C and the reaction quenched by adding saturated NH_4Cl (20mL). The bulk of the solvent was removed under reduced pressure and the resulting yellow oil was partitioned between water (75mL) and ether (120mL). The aqueous phase was further extracted with ether (2x120mL) and the combined organic extracts were washed with water (50mL), saturated $NaHCO_3$ (2x50mL), brine (2x50mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a yellow solid (13.4g, 92%) that was homogeneous by ^1H NMR analysis and sufficiently pure for use in the next step.

In a seperate experiment, a sample of the crude product was purified by recrystallization from hexane to afford **11** as analytically pure white crystals: mp 106-107°C; $[\alpha]_D^{21.5}$ -74.7 (c. 0.19, $CHCl_3$); ^1H NMR(250MHz, $CDCl_3$) ∂7.78 (app d, 2H, J=8.4Hz), 7.31 (app d, 2H, J=8.4Hz), 4.62 (d, 1H, J=9Hz, NH), 3.50 (m, 1H, NCH), 2.43 (s, 3H, CH_3Ar), 1.18 (d, 3H, J=6.6Hz, CH_3CH), 0.16 (s, 9H, Me_3Si); IR(KBr) 3278, 1339, 1184, 1147, 814cm^{-1}; MS(CI) m/z 310 (MH^+). Anal. Calcd for $C_{15}H_{23}NSSiO_2$: C, 58.21; H, 7.49; N, 4.53; S, 10.36. Found: C, 58.15; H, 7.49; N, 4.50; S, 10.29.

(S)-N-(*p*-Toluenesulfonyl)-4-amino-1-Z-(trimethylsilyl)-1-pentene (12): A suspension of dicyclohexylborane was prepared from a solution of borane (38.8mL of a 1M solution in THF, 38.8mmol) and cyclohexene (7.90mL, 78.0mmol) in THF (78mL) at 0°C.[11] To this was added a solution of **11** (4.01g, 12.9mmol) in THF (25mL). The resulting solution was maintained at 0°C for 1h. Protonolysis was affected by adding glacial acetic acid (10mL) and allowing the reaction to warm to room temperature. Capillary G.C. analysis[31] indicated that protonolysis was complete after 18h. After cooling to 0°C, the reaction was quenched by adding 3N NaOH until the solution was basic (pH≈8). A solution of 30% H_2O_2 (19mL) was added and the resulting solution was maintained at 0°C for 1h and then diluted with water (50mL) and extracted with ether (3x100mL). The combined organic extracts were washed with brine (2x50mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc/hexane) to give a white solid (3.37g, 83%). Capillary G.C. analysis[31] showed the material to be a single olefin isomer.

Recrystallization from pentane gave analytically pure white crystals: mp 49.0 - 50.0°C; $[\alpha]_D^{22.0}$ -44.2 (c. 0.25, $CHCl_3$); ^1H NMR(300MHz, $CDCl_3$) ∂7.77 (app d, 2H, J=8.3Hz, Ar-H), 7.28 (app d, 2H, J=8.3Hz, Ar-H), 6.07 (m, 1H, TMS-CH=C<u>H</u>), 5.60 (d, 1H, J=7.3Hz, TMS-C<u>H</u>=CH),3.60 (m, 1H, NH), 3.33 (m, 1H, CH), 2.42 (s, 3H, CH_3Ar), 2.22 (m, 2H, CH_2), 1.06 (d, 3H, J=6.6Hz, $C\underline{H}_3CH$), 0.07 (s, 9H, Me_3Si); IR(KBr) 3331, 3277, 1337, 1183, 837cm^{-1}; MS(CI) m/z 312 (MH^+); MS(EI) 296(8%), 199(95%), 155(100%), 91(97%). Anal. Calcd for $C_{15}H_{25}NO_2SSi$: C, 57.80; H, 8.10; N, 4.50; S, 10.30. Found: c, 57.95; H, 8.13; N, 4.45; S, 10.21.

(S)-4-Amino-1-Z-(trimethylsilyl)-1-pentene (13): A solution of sodium (0.37g, 16mmol) and naphthalene (2.20g, 17.2mmol) in dry DME (45mL) was added via canula to a solution of 12 (1.01g, 3.25mmol) in dry DME (5mL) at room temperature. The reaction was quenched after 1h by adding DME saturated with HCl gas until the solution was acidic (pH~3). The solvent was removed under reduced pressure to afford a pale yellow solid which was dissolved in water (50mL) and washed with ether (2x30mL). The aqueous phase was made basic with solid NaOH (pH~8). The aqueous phase was then extracted with $CHCl_3$ (3x30mL) and the combined organic extracts were washed with brine (2x20mL) and dried over K_2CO_3. Concentration yielded 0.356g (68%) of amine 13 as a pale yellow oil (>99% pure by capillary G.C. analysis[31]): $[\alpha]_D^{21.0}$ +0.28 (c=1.0, $CHCl_3$); ^1H NMR (250MHz, $CDCl_3$) ∂6.31 (m, 1H, TMSCH=C<u>H</u>), 5.62 (d, 1H, J=14Hz, TMSC<u>H</u>=CH), 3.00 (m, 1H, CH), 2.17 (m, 2H, CH_2), 1.35 (broad s, 2H, NH_2), 1.10 (d, 3H, J=6.3Hz, $C\underline{H}_3CH$), 0.08 (s, 9H, Me_3Si); ^{13}C NMR (75MHz, $CDCl_3$) ∂146.45, 132.15, 47.95, 44.56, 24.39, 0.99; IR ($CHCl_3$) 2988, 1702, 1643, 840cm^{-1}; MS(CI) m/z 158 (MH^+); MS(EI) m/z 157.0083 (157.128 calcd for $C_{14}H_{23}NSi$), 84(58%), 73(100%).

***rac-cis* and *rac-trans* 6-Methyl-2-phenyl-1,2,5,6-tetrahydropyridines (*rac*-15 and *rac*-16):** To a solution of 13 (0.20g, 1.3mmol) in CH_2Cl_2 (2.5mL) at 0°C was added enough $MgSO_4$ and Na_2SO_4 (ca. 1:1 ratio) to make a slurry. Benzaldehyde (0.13g, 1.3mmol) was added and the reaction was allowed to warm to room temperature and stirred for 1h. Filtration and concentration afforded a yellow oil that was purified by bulb-to-bulb distillation (98°C, 0.7mm Hg) to give 0.19g (62%) of imine 14 as a colorless oil. ^1H NMR and capillary G.C. analysis showed that imine 14 exists as a single stereoisomer: $[\alpha]_D^{23}$ +39.7 (c. 1.08, $CHCl_3$); ^1H NMR(250MHz, $CDCl_3$) ∂8.28 (s, PhCH=N), 7.77 (m, 2H, PhH), 7.43 (m, 3H, PhH), 6.28 (m, TMS-CH=C<u>H</u>), 5.58 (d, J = 14Hz, TMS-C<u>H</u>=CH), 3.41 (m, CH), 2.46 (m, CH_2), 1.30 (d, J = 6.3Hz, CH_3), 0.02 (s, 9H, CH_3Si); IR ($CDCL_3$) 2988, 1702, 1643, 858cm^{-1}; MS(CI) m/z 246 (MH^+); MS(EI) m/z 245.1587 (4%, 245.1594 calcd for $C_{14}H_{23}NSi$), 172 (33%), 132 (100%), 77 (6%).

To a solution of imine 14 (0.10g, 0.42mmol) in CH_3CN (2mL) was added trifluoroacetic acid (0.13g, 1.2mmol). The resulting solution was maintained at 60°C for 3h and after cooling to room temperature, the solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (5mL) and 1<u>N</u> NaOH (5mL) and the organic phase was dried over K_2CO_3. Concentration gave 60mg (85%) of racemic tetrahydropyridines 15 and 16 as a pale yellow oil (>95% pure by capillary G.C. analysis[31]). Capillary G.C. analysis[31] showed the product to be a 52:48 ratio of *cis* and *trans* isomers. Separation was achieved by flash chromatography (silica gel, EtOAc): *Cis* isomer *rac*-15: ^1H NMR (300MHz, $CDCl_3$) ∂7.38 (m, 5H, PhH), 5.88 (m, CHCH=C<u>H</u>CH_2), 5.70 (m, CHC<u>H</u>=CHCH_2), 4.55 (broad s, PhCHN), 3.10 (m, $CH_3C\underline{H}N$), 2.10-1.85 (m, CH_2), 1.66 (broad s, NH), 1.15 (d, J = 7Hz, CH_3); IR ($CHCl_3$) 3016, 2968, 1215cm^{-1}; MS(CI) m/z 174 (MH^+). *Trans* isomer *rac*-16: ^1H NMR (300MHz, $CDCl_3$) 7.48 (m, 5H, PhH), 6.02 (m, CHCH=C<u>H</u>CH_2). 5.85 (m, CHC<u>H</u>=CHCH_2), 4.58 (broad s, PhCHN), 3.00 (m, $CH_3C\underline{H}N$), 2.15 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 1.70 (broad s, NH), 1.06 (d, J = 7Hz, CH_3); IR ($CHCl_3$) 3020, 2972, 1215, 732cm^{-1}; MS(CI) m/z 174 (MH^+); MS(EI) m/z 173 (42%0, 158 (73%), 130 (100%).

***rac-trans*-N-Benzyl-6-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (*rac*-19):** To a mixture of benzaldehyde (78mg, 0.74mmol) and (trimethylsilyl)cyanide (78mg, 0.79mmol) was added ZnI_2 (28mg, 0.10mmol). A very exothermic reaction ensued. After 15 min. a solution of amine 13 (0.19g, 0.77mmol) in dry MeOH (3mL) was added and the reaction was heated at 65°C for 21h. After allowing the reaction to cool to room temperature, the solvent was removed *in vacuo* and the residue rapidly passed through basic alumina using 10% EtOAc/hexane as the eluent. Concentration gave 0.12g (43%) of crude cyanoamine 18 as a colorless oil which was used without further purification. ^{1}H NMR showed 18 to be a 2:1 mixture of diastereomers: ^{1}H NMR (300MHz, $CDCl_3$, chemical shifts of minor isomer in italics) ∂7.60-7.25 (m, 10H, ArH), 6.12 (m, TMS-CH=C<u>H</u>), 5.05 (m, TMS-C<u>H</u>=CH), *4.98* and 4.87 (s, PhC<u>H</u>CN), 3.95-3.70 (m, PhCH_2N), 2.95 (m, CH_3C<u>H</u>N), 2.45-2.10 (m, CH_2CH=), 1.28 and *1.15* (d, J = 7Hz, CH_3), and 0.03 (s, 9H, CH_3Si).

To a solution of 18 (0.12g, 0.34mmol) in CH_3CN (3.5mL) was added $AgBF_4$ (0.15g, 0.78mmol) and the resulting mixture was heated at reflux for 20h. After allowing the reaction to cool to room temperature, the silver salts were removed by filtration. The organic phase was washed with 1N NaOH (~2mL), dried over K_2CO_3 and concentrated to give 75mg of a yellow oil. ^{1}H NMR analysis showed this to be a mixture of the desired product 18, benzaldehyde and amine 13. Separation was achieved by flash chromatography (silica gel, 20% EtOAc/hexane) to give 51mg (57%) of *rac*-19 as a clear oil (homogeneous by ^{1}H NMR analysis). In addition, 4mg of benzaldehyde and 3mg (25%) of 13 were isolated: ^{1}H NMR (300MHz, $CDCl_3$) 7.40-7.10 (m, 10H, PhH), 5.72-5.65 (m, CH=C<u>H</u>CH_2), 5.55-5.45 (m,C<u>H</u>=CHCH_2), 4.00 (bs, PhC<u>H</u>N), 3.55 (q_{AB}, $\Delta\nu_{AB}$ = 33.7Hz, J_{AB} = 13.8Hz, PhCH_2), 3.1 (m, CH_3C<u>H</u>), 2.40- 2.30(m, 1H, =CHC<u>H</u>$_2$), 1.80-1.70 (m, 1H, =CHC<u>H</u>$_2$), 0.99 (d, J=6Hz, C<u>H</u>$_3$CH); IR ($CDCl_3$) 3030, 2968, 1493, 1454, 1377cm^{-1}; MS(CI) m/z 264 (MH^+); MS(EI) m/z 263.1658 (20%, 263.1669 calcd for $C_{19}H_{21}N$), 248 (36%), 186 (14%), 130 (90%), 91 (100%).

***rac-trans*-N-Methyl-6-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (*rac*-22):** Following the same general procedure, reaction of benzaldehyde (52mg, 0.50mmol), (trimethylsilyl)cyanide (48mg, 0.50mmol), ZnI_2 (10mg, 0.03mmol)and amine 20 (86mg, 0.50mmol) gave 78mg (55%) of crude cyanoamine 21 as a mixture of diastereomers (ca. 3:2 by ^{1}H NMR analysis). This mixture was used without further purification in the next step: ^{1}H NMR (300MHz, $CDCl_3$, resonances of the minor diastereomer in italics) ∂7.90-7.30 (m, 5H, ArH), 6.40-6.20 (m, TMS-CH=C<u>H</u>), 5.70-5.57 (m, TMS-C<u>H</u>=CH), 5.00 and *4.95* (s, CHCN), 3.10-2.85 (m, CHN), 2.60-2.20 (m, CH_2CH=), *2.30* and 2.20 (s, CH_3N), 1.25-1.17 (m, CH_3CH), *0.80* and 0.75 (s, 9H, CH_3Si).

Following the general procedure described for the preparation of *rac*-19, amine 21 (11.2mg, 39.0μmol) and $AgBF_4$ (10.0mg, 51.0μmol) in CH_3CN (0.3mL) were heated in a sealed tube at 100°C for 24h. After workup, the residue was purified by flash chromatography (silica gel, 20%EtOAc, hexane) to give 3.7mg (51%) of racemic[16] tetrahydropyridine *rac*-22 as a clear oil (homogeneous by TLC analysis). In addition 25% of recovered 20 (1.7mg) was isolated: ^{1}H NMR (250MHz, $CDCl_3$) ∂7.39-7.23 (m, 5H, PhH), 5.81-5.75 (m, =C<u>H</u>CH_2), 5.57-5.54 (m, CHC<u>H</u>=), 3.88 (broad s, PhC<u>H</u>N), 3.18-3.12 (m, CH_3C<u>H</u>N), 2.64-2.54 (m, 1H, =CHC<u>H</u>$_2$), 2.17 (s, CH_3N), 1.97-1.90 (m, 1H, =CHC<u>H</u>$_2$), 1.06 (d, J = 6.6Hz, C<u>H</u>$_3$CH); IR (CCl_4) 3030, 2923, 1452, 1055cm^{-1}; MS(EI) m/z 187.1360 (28%, 187.1357 calcd for $C_{13}H_{17}N$), 172 (46%), 130 (100%), 110 (38%).

***rac-cis* and *trans*-N-(Ethoxycarbonyl)-6-methyl-2-phenyl-1,2,5,6- tetrahydropyridines (*rac*-24 and *rac*-25):** A solution of imine 14 (0.28g, 1.1mmol) and diethyl pyrocarbonate (0.55g, 3.4mmol) in toluene (2mL) was heated at reflux.[20] Additional diethyl pyrocarbonate (2.2g, 13mmol) was added every 5h for 20h. The reaction was then allowed to cool to room temperature and concentrated. The residue was rapidly passed through nuetral alumina using 20%EtOAc/hexane as the elution solvent. Concentration gave 0.26g (71%) of crude 23 (ca. 80% pure by capillary G.C. analysis[31])

which was used without further purification: ^{1}H NMR (250MHz, $CDCl_3$, two diastereomers each doubled due to carbamate conformers) ∂7.55-7.25 (m, ArH), 6.75, 6.60 and 6.45 (broad s, PhCHN), 6.30-6.15, 5.65-5.50 and 5.30-5.17 (m, 2H, CH=CH), 4.30-4.20 (m, 2H), 3.80-3.50 (m, 2H), 3.25-3.10 (m, 1H), 2.80-2.25 (m, 1H), 2.05-1.66 (m, 1H), 1.40 -1.20 (m, 9H), 0.15 and 0.05 (s, 9H, CH_3Si).

To a solution of **23** (30mg, 84μmol) in CH_2Cl_2 (0.3mL) at 0°C was added $BF_3{\cdot}Et_2O$ (36mg, 0.25mmol) and the reaction was maintained at 0°C for 5h. The reaction was quenched by adding 1N NaOH (1mL), allowed to warm to room temperature and the aqueous phase was extracted with $CHCl_3$ (3 x 5mL). The combined organic extracts were washed with brine (5mL) and dried over K_2CO_3. Concentration gave a yellow oil which was found to consist of a 1:1 mixture of *rac*-**24** and *rac*-**25** (as determined by capillary G.C. analysis[31]). Separation by flash chromatography (silica gel, 20% EtOAc/hexane) gave ~7mg(35%) of each isomer (70% combined yield): *Cis* isomer *rac*-**24**: ^{1}H NMR (250MHz, $CDCl_3$, signals broadened by hindered rotation about the carbamate) ∂7.45-7.20 (m, 5H, PhH), 6.04-5.90 (m, 2H, CH=CH), 5.60 (broad s, PhCHN), 4.78-4.71 (m, CH_3CHN), 4.23-4.08 (m, CH_2O), 2.53-2.44 (m, 1H, =CHCH_2), 1.99-1.90 (m, 1H, =CHCH_2), 1.34-0.98 (m, 6H); IR (CCl_4) 2975, 1696, 1304, 1109cm^{-1}; MS(CI) m/z 246 (MH^+); MS(EI) m/z 245.14219 (72%, 245.1411 calcd for $C_{15}H_{19}NO_2$), 230 (14%), 216 (65%), 199 (27%), 172 (43%), 130 (100%), 115 (54%): *Trans* isomer *rac*-**25**: ^{1}H NMR (250MHz, $CDCl_3$, signals broadened by hindered rotation about the carbamate) ∂ 7.34-7.17 (m, 5H, PhH), 5.77 (m, 2H, CH=CH), 5.07 (broad s, PhCHN), 4.19-4.11 (m, CH_2O), 4.08-3.93 (m, CH_3CHN), 2.70-2.61 (m, 1H, CH_2-CH=), 2.14-2.05 (m, 1H, CH_2-CH=), 1.40-1.05 (m, 6H); IR (CCl_4) 2979, 1699, 1311, 1104cm^{-1}; MS(CI) m/z 246 (MH^+); m/z 245.1422 (66%, 245.1411 calcd for $C_{15}H_{19}NO_2$), 230 (20%), 216 (100%), 199 (45%), 172 (77%), 130 (85%), 115 (31%).

Chemical Correlation Studies: Reaction of *rac*-**16** (7.9mg, 0.05mmol) at room temperature with benzylbromide (7.9mg, 0.05mmol), THF (0.3mL) and sat. aqueous K_2CO_3 (0.1mL) gave, after workup, a product (5.6mg, 46%) that was identical in all respects with *rac*-**19**. Likewise, reaction of *rac*-**15** with benzylbromide gave a product that was not identical with *rac*-**19**.

Reaction of *rac*-**16** (9.2mg, 0.05mmol) with ethyl chloroformate (17mg, 16mmol) in THF (0.4mL) gave a product (8.8mg, 68%) that was identical with *rac*-**25**. Likewise, *rac*-**15** gave a product that was identical with *rac*-**24**.

Reduction of *rac*-**25** (10mg, 0.04mmol) with $LiAlH_4$ (3.5mg, 0.09mmol) in THF (0.2mL) gave a product that was identical to *rac*-**22**. Likewise, *rac*-**24** gave a product that was not identical to *rac*-**22**.

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(15) The reaction could also be carried out in neat formic acid at reflux. Nearly identical results were obtained.

(16) Optical rotations were typically measured at 365, 435, 546, 578 and 589 nm.

(17) Amine **17** was obtained by reduction of imine **14** with $LiAlH_4$ or by reaction of amine **13** with benzoyl chloride followed by reduction with $LiAlH_4$. Amine **20** was prepared by acylation of amine **13** with ethyl chloroformate followed by reduction with $LiAlH_4$.

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(19) *Trans*-6-methyl-2-phenylpiperidine, prepared from *rac*-**19** by treatment with 10% Pd-C and H_2, also showed no optical rotation.[16]

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(21) The corresponding *N*-methyl tetrahydropyridines, prepared by $LiAlH_4$ reduction of *rac*-**24** and *rac*-**25**, also showed no optical rotation.[16]

(22) (a) To the best of our knowledge there is no experimental evidence concerning the topography (chair or boat) of endocyclic cyclizations of allylsilanes to afford unsaturated six-membered rings. For a recent discussion of polyene cyclizations, see Bartlett, P.A. in *Asymmetric Synthesis*, Morrison, J.D., ed.; Academic Press: New York, **1984**, Vol. 3, Chap. 5. (b) Decent stereoelectronics are also possible in a cyclization occurring *via* a boat topography.

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(31) A 15-m x 0.25 mm SE-30 column was employed with temperature programming from 70-250°C.