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The Tetrahydrooxazinone Way to Enantiopure α-Amino Acids: Synthesis of *Cis* and *Trans* 3-Vinyl Pipecolic Acids via an Intramolecular Reaction between an Iminium Ion and an Allylsilane Moieties

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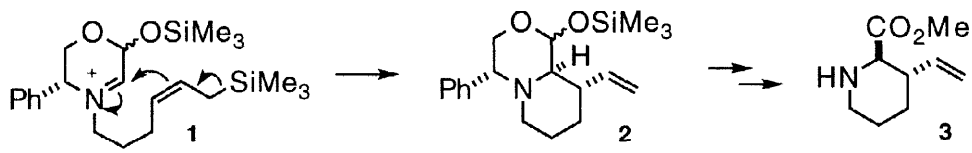
Abstract: Reaction of glyoxal with a derivative of (*R*)-phenylglycinol having an allylsilane side-chain afforded a transient iminium ion. Intramolecular reaction of the iminium ion and the allylsilane moieties occurred in a totally stereoselective way. Straightforward transformations ultimately led to enantiopure either *cis* or *trans* 3-vinyl pipecolic acid methyl ester. The stereochemical course of this reaction was rationalized via AM1 calculations. © 1998 Elsevier Science Ltd. All rights reserved.

Addition of allylsilane reagents onto acyliminium and iminium ions is a well-documented process when it comes to create a homoallylic amine moiety.[1,2] This methodology has culminated in the Overman total synthesis of morphine.[3] We have recently reported a new entry into the chemistry of acyclic α-amino acids; our approach is based on an intermolecular reaction between allylsilanes and an iminium ion which is generated from glyoxal and *N*-methyl (*R*)-phenylglycinol.[4] We wish to present here an extension of this method which allows an easy access to enantiopure vinyl substituted pipecolic acids, i.e. cyclic α-amino acids, via an intramolecular version of the above methodology.[5] Many syntheses of various unsaturated α-amino acids have been reported[6] since they are very promising targets in view of their potential biological interest. However, in spite of the current interest in pipecolic acid derivatives, reports of asymmetric syntheses of their unsaturated analogs are very scarce.[7]



Scheme 1

As shown in Scheme 1, the key-step of this procedure is an intramolecular reaction of a cyclic iminium ion linked to an allylsilane moiety. Thus, compound **1** was transformed into bicyclic derivative **2**. Complete stereocontrol occurred during the reaction of the new stereocenters present in product **2** which was finally transformed to target compound **3** through some conventional functional group manipulations.

RESULTS AND DISCUSSION

Scheme 2 describes the synthesis of the first pipecolic acid derivative. It starts from compound **6** which is a β-amino alcohol attached to an allylsilane moiety; this product was obtained from a substitution reaction between (*R*)-phenylglycinol **4** and the mesyloxyallylsilane **5**.[7] Condensation of compound **6** with glyoxal, in the presence of thiophenol, occurred quantitatively and afforded heterocycle **7** whose hemiacetal function was protected in the next step as the trimethylsilyloxy derivative **8**. The aminothioether function of the latter product was transformed into an iminium ion which reacted with the allylsilane part to yield bicyclic compound **9**. A fluoride ion-mediated desilylation of compound **9** afforded hemiacetal **10** which was oxidized in order to

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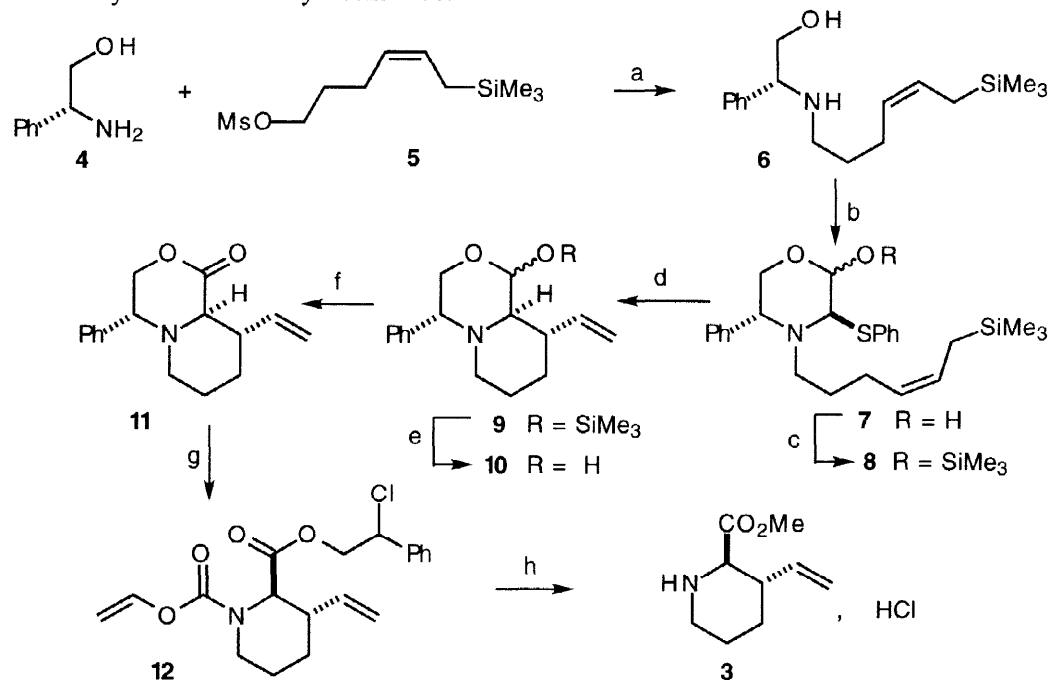
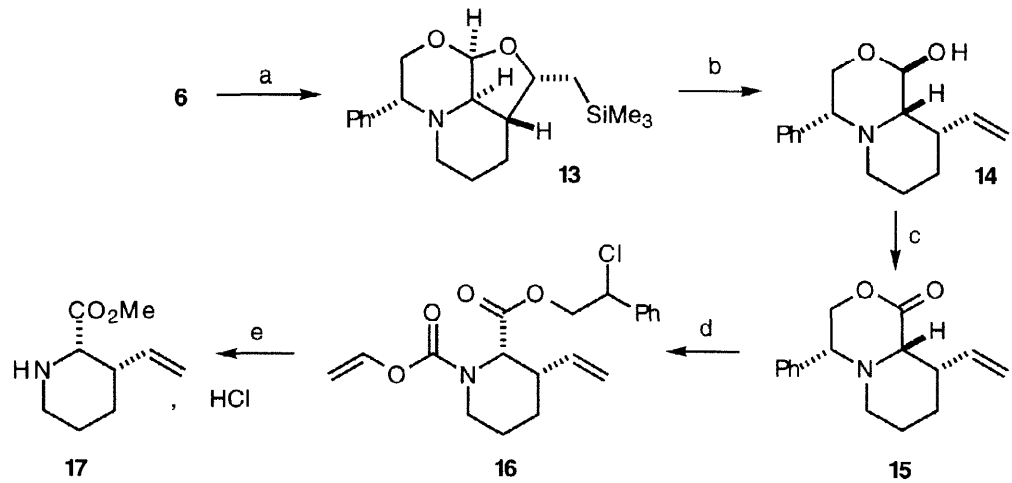
produce lactone **11** (compounds **7** and **10** were obtained as a mixture of epimers at the hemiacetal center). This product was debenzylated (by formation of vinylcarbamate **12**) and final methanolysis gave (2*R*,3*S*)-3-vinyl pipecolic acid methyl ester **3** as its hydrochloride.



Scheme 2

Reagents and conditions: (a) $(i\text{-Pr})_2NH$, MeCN (70%); (b) OHC-CHO, then PhSH (98%); (c) Me_3SiCl, Et_3N (60%); (d) $ZnBr_2$ (60%); (e) $n\text{-Bu}_4NF$, 0°C (80%); (f) Swern oxidation (65%); (g) CH_2=CH-OCOCl (85%); (h) 5N HCl in MeOH (95%).

Unexpectedly, when a similar condensation between compound **6** and glyoxal was performed in the presence of trifluoroacetic acid, tricyclic compound **13** was obtained, in addition to a minor amount of hemiacetal **10** (Scheme 3). Treatment of compound **13** with a refluxing solution of $n\text{-Bu}_4NF$ in THF yielded hemiacetal **14**. This bicyclic product is a diastereomer of hemiacetal **10** whose synthesis was described above.

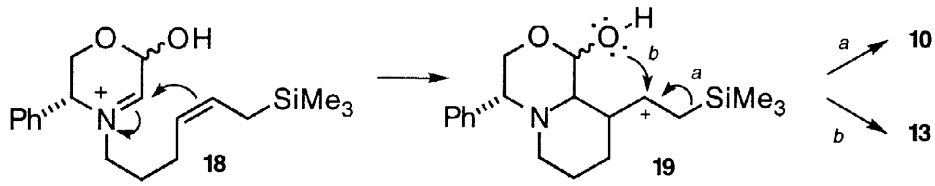


Scheme 3

Reagents and conditions: (a) OHC-CHO, CF_3CO_2H (45%); (b) $n\text{-Bu}_4NF$, THF, reflux (98%); (c) Swern oxidation (70%); (d) CH_2=CH-OCOCl (40%); (h) 5N HCl in MeOH (80%).

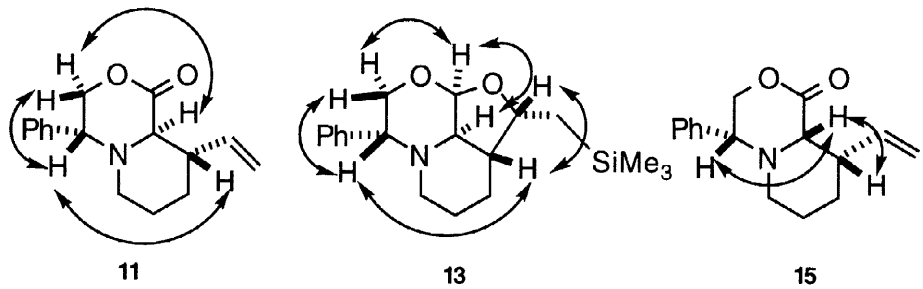
Compound **14** was treated in the same way as **10** and, in the present case, (2*S*,3*S*)-3-vinyl pipecolic acid methyl ester **17** was obtained. It is worth noting that hemiacetal **14** was also obtained quantitatively by treatment of hemiacetal **10** with *n*-Bu_4NF in refluxing THF. These features suggest that formation of compounds **10** and **13** is kinetically controlled whereas **14** results from a thermodynamic control and its formation probably occurs via the ring-opened form of the lactol under the basic TBAF conditions.

Formation of the tricyclic derivative **13** results from an intramolecular attack onto the transient carbocation **19** by the hydroxyl part of the hemiacetal moiety as shown in Scheme 4. The expected intramolecular condensation of the allylsilane and the iminium ion moieties of intermediate **18** leads to **19** which can react either by the departure of the trimethylsilyl group (pathway *a*) affording hemiacetal **10** or by the aforementioned intramolecular attack (pathway *b*) leading to compound **13**.



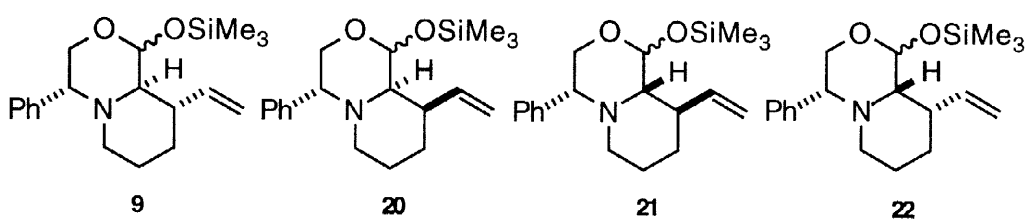
Scheme 4

In both cases (cf. Schemes 2 and 3) the iminium ion/allylsilane reaction was totally stereoselective, yielding only one stereoisomer. Configurations of compounds **11**, **13** and **15** were established from the DIFNOE ^1H NMR observations which are summarized in Scheme 5.



Scheme 5

We have analyzed the stereochemical outcome of the cyclization which occurs within iminium ion **1** resulting from morpholine **8** by using AM1 calculations in order to understand the complete stereoselectivity which was observed during the formation of the two stereocenters included in bicyclic compound **9**. Calculations were performed in order to define the activation energies required to reach the four possible transition states corresponding to the formation of products **9** (effectively produced) and **20**-**22** (not observed).



Reactive conformations leading to the transition states and the respective calculated activation energies are depicted in Scheme 6. The four possible interactions between the diastereofaces of the C=N and C=C double bonds have been taken into account: *Re*/*Si* (**A**), *Re*/*Re* (**B**), *Si*/*Re* (**C**) and *Si*/*Si* (**D**).

The lower energies are related to cyclizations involving conformations **A** and **B** in which the C=N double bond is attacked on its *Re* diastereoface, thus creating a *R* stereocenter at the ring junction. In this stereochemical course, attack of the C=C moiety occurs on the face opposite to the phenyl group and is controlled by a steric factor. This fact is in complete agreement with all our preceding observations about nucleophilic attacks on similar iminium ions.[3,9] The *anti* or *syn* disposition of the interacting double bonds differentiates conformations **A** and **B** respectively. The MO calculations (cf. Scheme 6) show that **A** presents the preferred topology: the creation of the vinyl-bearing center with a *S* configuration can thus be explained. This *anti* relationship between the interacting double bonds is favored because it minimizes the steric hindrance between the heterocycle and the allylsilane moiety which exists in the *syn* conformation **B** (the same trend is also apparent from the relative activation energies of the disfavored reactive conformations **C** and **D**). The calculated transition state resulting from the **A** disposal of the double bonds is displayed in Figure 1.

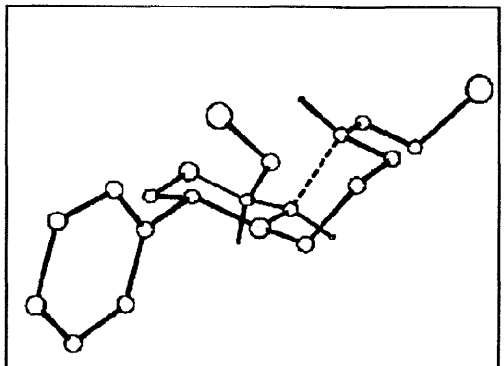
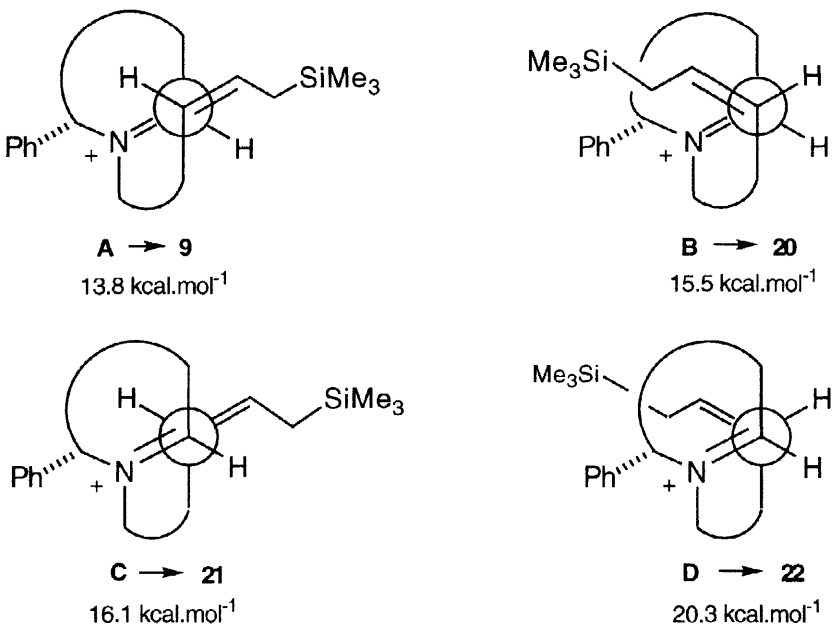


Figure 1. Calculated transition state leading to heterocycle **9**.



Scheme 6

In conclusion, the asymmetric syntheses reported herein are characterized by a high level of stereoselectivity exhibited during the cyclization step. By virtue of its flexibility, the key-reaction between the iminium ion and the allylsilane moieties should be appropriate for the elaboration of other cyclic unsaturated α-amino acids.

EXPERIMENTAL SECTION

General comments

^1H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were respectively recorded on a Bruker AC 250 spectrometer at 250 and 62.9 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were

determined with a Perkin Elmer 141 instrument. MS and HRMS were measured in the EI mode with an ionization potential of 70 eV; the accurate mass measurements were done with a resolving power of 10 000. Melting points are uncorrected. All reactions were carried out under nitrogen except those performed in aqueous solution. Column chromatography was performed on silica gel, 230-400 mesh by using various mixtures of diethyl ether (E) and petroleum ether (PE). THF was distilled from sodium/benzophenone ketyl. Mention of "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

(2R)-2-Phenyl-2-(6-trimethylsilanylhex-4-enylamino)ethanol **6**

Compound **5** (4.35 g, 17.4 mmol) and diisopropylamine (3 mL, 17.4 mmol) were successively added to a solution of (*R*)-phenylglycinol (2.17 g, 15.8 mmol) in acetonitrile (60 mL). The mixture was heated under reflux for 10 days. The reaction mixture was then allowed to reach room temperature and the usual work-up gave a residue which was chromatographed (E/PE: 10/90). Compound **6** was obtained as an oil (3.2 g, 70%); $[\alpha]_D^{20}$: -56 (*c* 1.3, $HCCl_3$). ^1H NMR: 0.00 (s, 9H), 1.33-1.52 (m, 4H), 1.89-1.98 (m, 2H), 2.37-2.56 (m, 2H), 3.41-3.51 (m, 1H), 3.61-3.71 (m, 2H), 5.11-5.22 (m,1H), 5.23-5.38 (m, 1H), 7.18-7.32 (m, 5H). ^{13}C NMR: 0.0, 20.2, 26.6, 32.0, 48.9, 66.4, 68.4, 127.6, 128.4, 129.0, 129.3, 130.3, 142.6. Anal. Calcd for $C_{17}H_{29}NOSi$: C, 70.04; H, 10.03; N,4.80. Found: C, 69.99; H, 10.08; N, 4.76.

(5R)-5-Phenyl-3-phenylsulfanyl-4-(6-trimethylsilanylhex-4-enyl)morpholin-2-ol **7**

Amino-alcohol **6** (1.3 g, 4.46 mmol) was dissolved in THF (1.7 mL). Water (4.2 mL) and an aqueous solution of glyoxal (40% weight, 1 mL, 8.93 mmol) were added and the mixture was stirred for 30 min. Water (12.5 mL) and thiophenol (0.46 mL, 4.46 mmol) were successively added and stirring was maintained for 18 h. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. Evaporation furnished quantitatively compound **7** as a mixture (80/20) of diastereoisomers which was used in the next step without further purification. ^1H NMR (major isomer): 0.15 (s, 9H), 0.88-1.20 (m, 2H), 1.31-1.42 (m, 2H), 1.47-1.89 (m, 2H), 2.27-2.45 (m, 1H), 2.66-2.87 (m, 1H), 3.63 (dd, J=11 and 12 Hz, 1H), 3.76-3.95 (m, 2H), 4.82-4.93 (m, 2H), 5.12 (bs, 1H), 5.21-5.40 (m, 1H), 7.18-7.72 (m, 10H). ^{13}C NMR (major isomer): 0.0, 20.1, 26.2, 27.3, 51.1, 62.8, 73.2, 86.0, 95.1,127.4-139.6.

(3R,5R)-5-Phenyl-3- phenylsulfanyl -4-(6-trimethylsilanylhex-4-enyl)-2-trimethylsilyloxymorpholine **8**

Trimethylsilyl chloride (0.35 mL, 2.80 mmol) and triethylamine (0.4 mL, 2.80 mmol) were successively added at 0 °C to a solution of compound **7** (0.82 g, 1.87 mmol) in THF (10 mL). The reaction mixture was stirred at rt for 24 h. After usual work-up and chromatography (E/PE: 5/95), compound **8** was isolated as a pure isomer (0.55 g, 60%). ^1H NMR: -0.11 (s, 9H), 0.16 (s, 9H), 0.92-1.14 (m, 2H), 1.20-1.32 (m, 2H), 1.52-1.83 (m, 2H), 2.13-2.26 (m, 1H), 2.69-2.84 (m, 1H), 3.39-3.52 (m, 1H), 3.65-3.78 (m, 2H), 4.43 (d, J=2 Hz, 1H), 4.86-4.97 (m, 1H), 5.06 (d, J=2Hz, 1H), 5.14-5.25 (m, 1H), 7.12-7.57 (m, 10H). ^{13}C NMR: -2.1, 0.0, 18.1, 24.2, 25.8, 48.5, 61.0, 71.2, 80.1, 95.9, 125.2-136.1.

(4R)-4-Phenyl-9-vinyloctahydropyrido[2,1-c][1,4] -1-trimethylsilyloxyoxazine **9**

Zinc bromide (0.28 g, 1.25 mmol) was added to a solution of the silylated derivative **8** (0.43 g, 0.83 mmol) in dichloromethane (2 mL) at rt and the mixture was vigorously stirred for 1h. Addition of water was followed by extraction with dichloromethane. Combined organic layers were washed with a saturated solution of ammonium sulfate, then dried over $MgSO_4$. After evaporation, the residue was chromatographed (E/PE: 30/70) and yielded compound **9** (0.16 g, 60%) as a colourless oil. $[\alpha]_D^{20}$: -8 (*c* 0.8, $HCCl_3$). ^1H NMR: 0.23 (s, 9H), 0.74-0.84 (m, 1H), 1.28-1.60 (m, 4H), 2.03-2.12 (m, 1H), 2.53 (dd, J=2 and 10 Hz, 1H), 2.74 (d, J=11Hz, 1H), 3.65 (d, J=4 Hz, 1H), 3.79 (d, J=11 Hz, 1H), 4.66 (dd, J=4 and 11Hz, 1H), 5.03-5.13 (m, 3H), 5.56-5.64 (m,

1H), 7.32-7.57 (m, 5H). ^{13}C NMR: 0.0, 24.5, 31.1, 42.8, 52.7, 60.3, 62.4, 63.1, 91.7, 115.9, 127.4, 127.9, 130.2, 138.3, 139.9. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82. Found: C, 68.38; H, 8.83.

(4R,9S,9aR)-4-Phenyl-9-vinyloctahydropyrido[2,1-c][1,4]oxazin-1-ol ***10***

A 1M solution of tetrabutylammonium fluoride (1.8 mL) was slowly added at 0°C to a solution of compound **9** (0.47 g, 1.22 mmol) in THF (8 mL). After stirring for 30 min at 0°C, usual work-up was followed by chromatography (E/PE: 30/70). Product **10** (0.26 g, 81%) was obtained as an epimeric mixture (60/40) at C-1. ^{1}H and ^{13}C NMR spectra of this complex mixture of diastereoisomers gave the following characteristic peaks for the major isomer. ^{1}H NMR: 1.02-1.83 (m, 5H), 2.38-2.45 (m, 1H), 2.55-2.79 (m, 2H), 3.44-3.51 (m, 1H), 3.77-3.88 (m, 1H), 4.21 (dd, J=4 and 11Hz, 1H), 4.95-5.14 (m, 3H), 5.46-5.56 (m, 1H), 7.21-7.42 (m, 5H). ^{13}C NMR: 17.6, 31.5, 35.1, 48.8, 56.4, 63.9, 64.1, 90.3, 116.0, 127.2, 128.3, 129.7, 136.7, 139.8.

(4R,9S,9aR)-4-Phenyl-9-vinylhexahydropyrido[2,1-c][1,4]oxazin-1-one ***11***

Dimethyl sulfoxide (0.18 mL, 2,52 mmol) was added dropwise to a solution of oxalyl chloride (0.11 mL, 1.26 mmol) in dichloromethane (2.5 mL) at -50 °C. The mixture was stirred for 5 min and a solution of hemiacetal **10** (0.22 g, 0.84 mmol) in dichloromethane (2.5 mL) was introduced. After 1 h at -50 °C, triethylamine (0.59 mL, 4.25 mmol) was added and the mixture was allowed to warm to rt during 1h30. Addition of water and usual work-up gave a residue which was purified by chromatography (E/PE: 20/80) to afford compound **11** (0.14 g, 65%). $[\alpha]_D^{20}$: +37 (*c* 0.7, $HCCl_3$). ^{1}H NMR: 1.39-1.45 (m, 3H), 1.71-1.92 (m, 1H), 2.50-2.68 (m, 2H), 2.73-2.88 (m, 1H), 3.58 (d, J=6Hz, 1H), 3.99 (dd, J=5 and 10 Hz, 1H), 4.13 (dd, J=10 and 11 Hz, 1H), 4.40 (dd, J=5 and 11 Hz, 1H), 5.01-5.10 (m, 2H), 5.93-6.07 (m, 1H), 7.19-7.31 (m, 5H). ^{13}C NMR: 19.5, 27.5, 36.5, 50.3, 59.4, 60.3, 70.3, 113.9, 126.5, 127.2, 127.8, 136.5, 138.8, 169.2. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N,5.44. Found: C,74.23; H, 7.88; N, 5.25.

Urethane derivative ***12***

Vinylchloroformate (0.19 mL, 2.27 mmol) was added to a solution of lactone **11** (0.12 g, 0.45 mmol) in dichloromethane (3 mL). The mixture was refluxed for 7 days. After evaporation, the crude residue was chromatographed (E/PE: 30/70) to give compound (0.14 g, 85%) as a yellow oil. ^{1}H NMR: 1.34-1.53 (m, 2H), 1.59-1.80 (m, 2H),2.89-3.08 (m, 2H), 4.04-4.12 (m, 1H), 4.47-4.58 (m, 3H), 4.74-4.96 (m, 2H), 5.11-5.19 (m, 3H), 5.79-5.98 (m, 1H), 7.12-7.28 (m, 1H), 7.34-7.45 (m, 5H). ^{13}C NMR: 20.9, 26.9, 39.1, 43.2, 58.8, 60.6, 69.7, 97.2, 117.4, 128.9, 130.3, 130.6, 138.6, 139.4, 143.9, 155.4, 171.7.

(2R,3S)-3-vinylpiperidine-2-carboxylic acid methyl ester ***3***

A solution of carbamate **12** (0.10 g, 0.27 mmol) in 5N hydrochloric acid in methanol (6.5 mL) was refluxed for 3 days and then concentrated under reduced pressure to remove excess of HCl. The residue was dissolved in water and the aqueous solution was extracted with ether. Removal of water under reduced pressure afforded compound **3** (0.53 g, 95 %). $[\alpha]_D^{20}$: –10 (*c* 0.5, H_2O). ^{1}H NMR (D_2O): 1.32-1.94 (m, 4H), 2.25-2.50 (m, 1H), 2.87 (dt, J=3 and 12 Hz, 1H), 3.23-3.49 (m, 1H), 3.62 (s, 3H), 3.71 (d, J=11 Hz, 1H), 4.91-5.11 (m, 2H), 5.47-5.70 (m, 1H). ^{13}C NMR (D_2O): 22.3, 29.8, 43.6, 45.0, 54.5, 62.3, 119.2, 137.5, 170.9. HRMS: calcd for $C_9H_{15}NO_2$.HCl (M-HCl) m/z = 169.1102, obsd m/z = 169.1103.

Tricyclic compound ***13***

Trifluoroacetic acid (0.09 mL, 1.2 mmol) was added to a solution of amino alcohol **6** (0.35 g, 1.2 mmol) in THF (0.45 mL) at 0°C. After stirring for 30 min, water (4 mL) and an aqueous solution of glyoxal (40% weight, 0.27 mL, 2.4 mmol) were added. Stirring was maintained at rt for 5 days. The reaction mixture was poured into a 5N aqueous solution of NaOH and the aqueous layer was extracted with ether. Organic layers were washed

with a saturated solution of ammonium chloride and evaporated under reduced pressure. The crude product was chromatographed and the following products were obtained by order of elution:
1. Tricyclic compound **13** (E/PE: 12/88): 0.17 g (45%) white solid, mp 73°C. $[\alpha]_D^{20}$: –22 (c 0.7, $HCCl_3$) ^{1}H NMR: 0.00 (s, 9H), 0.56 (dd, J=3 and 14 Hz, 1H), 0.78 (dd, J = 12 and 14 Hz, 1H), 1.21-1.37 (m, 1H), 1.38-1.47 (m, 1H), 1.60-1.76 (m, 1H), 1.86-1.97 (m, 1H), 2.58-2.87 (m, 3H), 3.06 (dd, J=4 and 12 Hz, 1H), 3.31 (dd, J=10 and 12 Hz, 1H), 3.63 (dd, J=3 and 12 Hz, 1H), 4.03 (dd, J=3 and 10 Hz, 1H), 4.46-4.55 (m, 1H), 4.99 (d, J=4Hz, 1H), 7.16-7.30 (m, 5H). ^{13}C NMR: 0.0, 20.3, 20.6, 26.4, 33.6, 49.3, 57.5, 63.7, 70.5, 80.8, 97.4, 128.6, 128.8, 129.3, 139.7. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82; N, 4.22. Found: C, 68.74; H, 8.94; N, 4.13.
2. Hemiketal product **10** (E/PE: 15/85): 0.04 g (14%).

(4R,9S,9aS)-4-Phenyl-9-vinyloctahydropyrido[2,1-c][1,4]oxazin-1-ol ***14***
A 1M solution of tetrabutylammonium fluoride in THF (4.45 mL) was added to a solution of tricyclic compound **13** (0.29 g, 0.89 mmol) in THF (1 mL), and the mixture was refluxed for 24 h. After the solution was cooled, usual work-up gave quantitatively hemiacetal **14** as a pure isomer. ^{1}H NMR: 1.19-1.38 (m, 2H), 1.65-1.90 (m, 3H), 2.13 (dd, J=3 and 8 Hz, 1H), 2.73-2.79 (m, 2H), 3.24 (dd, j=4 and 11 Hz, 1H), 3.48 (t, J=11 Hz, 1H), 3.74 (dd, J=4 and 12 Hz, 1H), 4.67 (d, J=8 Hz, 1H), 5.13-5.21 (m, 2H), 6.43-6.52 (m, 1H), 7.27-7.39 (m, 5H). ^{13}C NMR: 20.2, 31.2, 38.7, 52.7, 66.4, 67.3, 69.8, 94.8, 115.4, 127.1, 127.4, 127.9, 138.9, 138.1.

(4R,9S,9aS)-4-Phenyl-9-vinylhexahydropyrido[2,1-c][1,4]oxazin-1-one ***15***
Dimethyl sulfoxide (0.26 mL, 3.73 mmol) was added dropwise to a solution of oxalyl chloride (0.16 mL, 1.86 mmol) in dichloromethane (3 mL) at -50 °C. The mixture was stirred for 5 min and a solution of hemiketal **14** (0.32 g, 1.24 mmol) in dichloromethane (3 mL) was introduced. After 1 h at -50 °C, triethylamine (0.83 mL, 6.2 mmol) was added and the mixture was allowed to warm to rt during 1 h 30. Addition of water and usual work-up gave a residue which was washed with petroleum ether to give lactone **15** as a solid (0.22 g, 70%), mp 70°C. $[\alpha]_D^{20}$: –77 (c 0.7, $HCCl_3$). ^{1}H NMR: 1.21-1.87 (m, 5H), 2.72-2.77 (m, 1H), 3.07-3.17 (m, 2H), 3.45 (dd, J=4 and 11 Hz, 1H), 4.07 (dd, J=4 and 11 Hz, 1H), 4.20 (t, J=11 Hz, 1H), 5.08-5.22 (m, 2H), 6.11-6.24 (m, 1H), 7.27-7.34 (m, 5H). ^{1}H NMR (500 MHz, C_6D_6): 0.84-1.72 (m, 5H), 2.05-2.57 (m, 1H), 2.83 (d, J=3Hz, 1H), 2.88 (dd, J=3 and 11 Hz, 1H), 3.32-3.35 (m, 1H), 3.66 (dd, J=3 and 11 Hz, 1H), 3.96 (t, J=11 Hz, 1H), 5.21-5.42 (m, 2H), 6.25-6.39 (m, 1H), 6.97-7.09 (m, 5H). ^{13}C NMR: 19.6, 29.5, 39.3, 51.8, 62.7, 67.6, 71.8, 116.2, 127.3, 127.6, 127.9, 135.4, 136.3, 167.6. HRMS: calcd for $C_{16}H_{19}NO_2$ m/z = 257.1416, obsd m/z = 257.1398.

Urethane derivative ***16***
Vinylchloroformate (0.18 mL, 2.18 mmol)was added to a solution of compound **15** (0.11 g, 0.43 mmol) in dichloromethane (3 mL) and the reaction mixture was refluxed for 10 days. Evaporation of the solvent was followed by a chromatography (E/PE: 15/85) to afford carbamate **16** as an oil (0.06 g, 40%). ^{1}H NMR: 1.26-1.78 (m, 4H), 2.28-2.47 (m, 1H), 2.86-3.14 (m, 1H), 3.82-4.05 (m, 1H), 4.30-4.51 (m, 3H), 4.62-5.11 (m, 5H), 5.67-5.88 (m, 1H), 7.02-7.10 (m, 1H), 7.21-7.35 (m, 5H). ^{13}C NMR: 23.5, 40.0, 41.2, 56.7, 58.0, 66.9, 94.8, 114.7, 126.4, 127.8, 127.9, 136.2, 136.9, 141.4, 152.2, 168.4.

(2S,3S)-3-vinylpiperidine-2-carboxylic acid methyl ester ***17***
A solution of carbamate **16** (0.06 g, 0.16 mmol) in 5N hydrochloric acid in methanol (6.5 mL) was refluxed for 3 days and then concentrated under reduced pressure to remove excess of HCl. The residue was dissolved in water and the aqueous solution was extracted with ether. Removal of water under reduced pressure afforded compound **17** (0.026 g, 80%).$[\alpha]_D^{20}$: –5 (*c* 0.4, H_2O). ^{1}H NMR (D_2O): 1.69-2.04 (m, 4H), 2.97-3.21 (m, 2H), 3.41-3.56 (m, 1H), 3.80 (s, 3H), 4.27 (d, J=4Hz, 1H), 5.19-5.37 (m, 2H), 5.82-5.96 (m, 1H). ^{13}C NMR (D_2O): 17.1, 25.9, 37.9, 43.9, 53.4, 59.8, 120.1, 132.1, 169.4. HRMS: calcd for $C_9H_{15}NO_2$.HCl (M-HCl) m/z = 169.1103, obsd m/z = 169.1110.

Epimerization of compound ***10***

A 1M solution of tetrabutylammonium fluoride in THF (1.15 mL) was added to a solution of compound **10** (0.06 g, 0.23 mmol) in THF (0.5 mL), and the mixture was refluxed for 24 h. Then, the solution was allowed to warm to rt and treated by addition of water. After usual work-up, ^{1}H and ^{13}C NMR spectra of the crude residue (0.04 g, 80%) showed the same physical characteristics as compound **14.**

MO Calculations

The four possible paths for the cyclization of iminium ion **1** were studied by MO calculations using the AM1 hamiltonian[10] as implemented in the AMPAC program version 4.0 QCPE No 527. The energy profiles were determined, the reaction coordinate being the distance between the iminium carbon atom and the olefinic carbon atom distal from the trimethylsilyl moiety. The approximate transition states thus obtained were optimized by minimizing the energy gradient (NLLSQ procedure).

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