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Regioselective Synthesis of Nitrones by Decarboxylative Oxidation of *N*-Alkyl-α-amino Acids and Application to the Synthesis of 1-Azabicyclic Alkaloids

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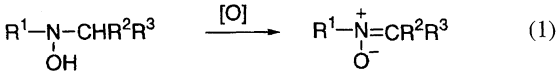
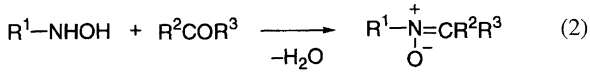
Tungstate-catalyzed oxidation of *N*-alkyl-α-amino acids with 30% H_2O_2 solution under phase-transfer conditions gives nitrones regioselectively in good yields. Using this method, stereodivergent synthesis of (*R*)- and (*S*)-4-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**17a** and (*S*)-**17a**) was achieved. In addition, (*R*)- and (*S*)-3-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**45** and (*S*)-**45**) were prepared by catalytic oxidation of the corresponding chiral pyrrolidines in a regioselective manner. These chiral cyclic nitrones, **17** and **45** are versatile intermediates for the synthesis of optically active nitrogen heterocycles, since stereoselective additions of carbon nucleophiles to these chiral nitrones can be readily performed. Typically, ZnI_2-mediated addition of ketene *t*-butyldimethylsilyl methyl acetal (**29a**) to (*R*)-**17a** gave the *cis*-adduct, methyl (2*R*,4*R*)-[1,4-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-**30**). In contrast, the addition of lithium acetylides **34** to the nitrone (*R*)-**17a** gave the *trans*-adducts, (2*S*,4*R*)-2-(1-alkynyl)-4-(*t*-butyldimethylsilyloxy)-1-hydroxypyrrolidines *trans*-**35**. These adducts are useful intermediates for syntheses of the nitrogen heterocycles (3*R*,5*R*)-1-aza-3-hydroxybicyclo[3.3.0]octane (**37**) and (6*R*,8*R*)-1-aza-8-hydroxybicyclo[4.3.0]nonane (**38**), respectively. The ZnI_2-mediated addition of ketene silyl acetal **29a** to the nitrone (*R*)-**45** gave methyl (2*S*,3*R*)-[1,3-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*trans*-**50a**), which was used for asymmetric synthesis of the Geissman–Waiss lactone ((−)-**49**).

Nitrones[1] are highly versatile synthetic intermediates and excellent spin trapping reagents.[2] For example, 1,3-dipolar cycloadditions[3,4] and asymmetric nucleophilic additions[5,6] have been extensively employed for the construction of nitrogen heterocycles which constitute the backbone of various biologically active compounds.[7] Regio- and stereoselective preparation of nitrones is an important objective in organic synthesis, since there is an increasing demand for highly functionalized nitrones as key intermediates for the synthesis of complex nitrogen-containing compounds.

Generally, nitrones have been prepared by oxidation reactions of *N*,*N*-disubstituted hydroxylamines by treatment with stoichiometric amounts of oxidants such as HgO (Eq. 1).[8] Since the palladium-catalyzed reaction of *N*-substituted hydroxylamines has been discovered,[9] some catalytic reactions have been reported.[10] Condensation of carbonyl compounds with monosubstituted hydroxylamines has been used as an alternative method (Eq. 2)[11] in addition to several other specific methods.[12] These reactions have very weak points, because the preparation of the starting hydroxylamines is generally very tedious.[13] Furthermore, alkylation of oximes usually affords a mixture of oxime *O*-ethers and nitrones.[12c]

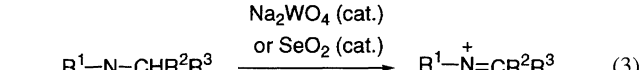


(1)



(2)

To overcome this difficulty associated with the nontrivial task of synthesizing hydroxylamines, we have already developed simple and efficient methods for the preparation of nitrones from secondary amines by oxidation with hydrogen peroxide catalyzed by sodium tungstate[14] or selenium(IV) oxide[15] (Eq. 3). Recently, other catalytic systems were also reported.[16] However, the main disadvantage of these methods is the observation that regioisomeric mixtures of nitrones are obtained from non-symmetric secondary amines in some cases. For example, tungstate-catalyzed oxidation of *N*-ethylbenzylamine gave a mixture of *N*-benzylideneethylamine *N*-oxide (**1**) (41%) and *N*-ethylidenebenzylamine *N*-oxide (**2**) (39%) (Eq. 4).



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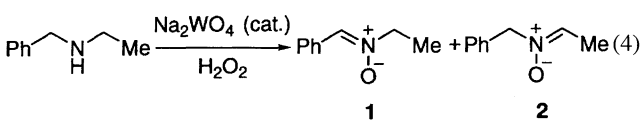
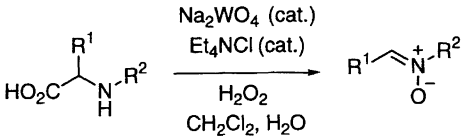


(4)

A new preparative method for regiochemically defined nitrones has now been explored, involving catalytic decarboxylative oxidation of *N*-alkyl-α-amino acids (Eq. 5). The present reaction is particularly important for the synthesis of highly functionalized cyclic nitrones, since only few examples have been reported.[17] Chiral hydroxylated five-membered cyclic nitrones are versatile intermediates for the synthesis of various hydroxylated nitrogen heterocycles such as indolizidines and pyrrolizidines, which have a wide variety of physiological properties including anti-HIV and anticancer activities.[17,18]



(5)

In this paper, we disclose the regioselective synthesis of nitrones by tungstate-catalyzed oxidation of *N*-alkyl-α-amino acids with hydrogen peroxide, and its application to the stereodivergent synthesis of (*R*)- and (*S*)-isomers of 4-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**17a** and (*S*)-**17a**).[19] (*R*)- and (*S*)-Isomers of 3-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**45** and (*S*)-**45**) were also prepared by tungstate-catalyzed oxidation of the corresponding chiral pyrrolidines, (*R*)- and (*S*)-3-(*t*-butyldimethylsilyloxy)-pyrrolidines ((*R*)-**41** and (*S*)-**41**) in a regioselective manner. Application of these chiral nitrones to the synthesis of pyrrolidine-based alkaloids is also described.

Results and Discussion

Decarboxylative Oxidation of α-Amino Acids to Nitrones. *N*-Alkyl-α-amino acids are readily available by either *N*-alkylation of α-amino acids[20] or Strecker synthesis.[21] Initially, we examined the oxidation of 2-(ethylamino)phenylacetic acid (**3**) using our previously reported method for the oxidation of secondary amines.[14,15] The results of these catalytic oxidations are summarized in Table 1. Oxidation of **3** with 30% aqueous H_2O_2 solution in the presence of either Na_2WO_4 catalyst in MeOH (Entry 1) or SeO_2 catalyst in acetone (Entry 2) did not afford the corresponding nitrone. However, when equimolar amounts of 1 M NaOH solution (1 M = 1 mol dm^{-3}) and Na_2WO_4 catalyst were used in MeOH, the expected nitrone **1** was obtained in 50% isolated yield as a single regioisomer (Entry 3). Furthermore, reaction under phase-transfer conditions in 5 : 1 (v/v) CH_2Cl_2–H_2O containing Et_4NCl as the catalyst, gave **1** in 69% yield (Entry 4). The best result was obtained by using K_2CO_3 as base, to afford **1** in 78% yield (Entry 5). The use of other inorganic bases such as $NaHCO_3$ (72%, Entry 6) and K_3PO_4 (71%, Entry 7) gave nitrone **1** in comparable yields.

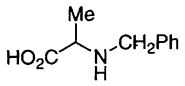
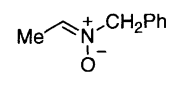
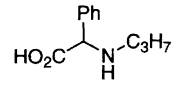
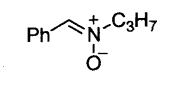
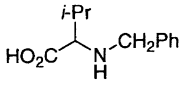
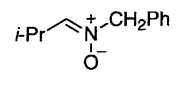
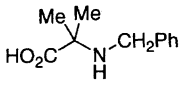
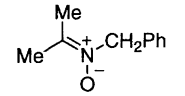
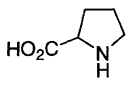
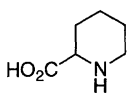
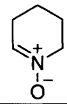
Table 1. Decarboxylative Oxidation of 2-(Ethylamino)-phenylacetic Acid (**3**)[a]

Entry	Catalyst	Base	Solvent	Yield of **1**/%[b]
1	Na_2WO_4	—	MeOH	0
2	SeO_2	—	Acetone	0
3	Na_2WO_4	NaOH	MeOH	50
4	Na_2WO_4	NaOH	CH_2Cl_2/H_2O[c]	69
5	Na_2WO_4	K_2CO_3	CH_2Cl_2/H_2O[c]	78
6	Na_2WO_4	$NaHCO_3$	CH_2Cl_2/H_2O[c]	72
7	Na_2WO_4	K_3PO_4	CH_2Cl_2/H_2O[c]	71

a) The reaction was carried out by addition of 30% H_2O_2 solution (15.0 mmol) to a solution of a catalyst (0.25 mmol), **3** (5.0 mmol), and a base (6.0 mmol) in a solvent. b) Isolated yield. c) Et_4NCl (0.25 mmol) was used.

Next, we investigated the scope of the catalytic decarboxylative oxidation of *N*-alkyl-α-amino acids. Representative results are shown in Table 2. *N*-Ethylidenebenzylamine *N*-oxide (**2**), which is a regioisomer of nitrone **1**, was obtained from the oxidation of *N*-benzylalanine (**4**) in 70% isolated yield as a single isomer (Entry 1). Acyclic amino acids **5** and **7** were regioselectively converted to the corresponding nitrones **6** and **8**, respectively (Entries 2 and 3). Oxidation of the α,α-disubstituted amino acid **9** also proceeded to give keto nitrone **10** in 65% yield (Entry 4). The cyclic nitrones, 1-pyrroline *N*-oxide (**12**) and 2,3,4,5-tetrahydropyridine *N*-oxide (**14**) were prepared from proline (**11**) and pipecolic acid (2-piperidinecarboxylic acid) (**13**), respectively, in moderate yields (Entries 5 and 6). These results show that the tungstate-catalyzed decarboxylative oxidation of *N*-alkyl-α-amino acids under phase-transfer conditions is an efficient method for the regioselective synthesis of ni-

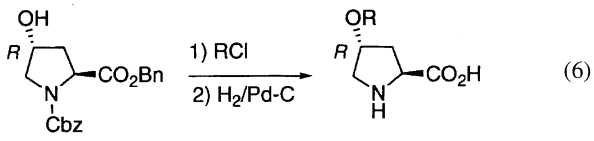
Table 2. Catalytic Oxidation of *N*-Alkyl-α-amino Acids[a]

Entry	Amino acid		Nitrone[b]		Yield/%[c]
1		**4**		**2**	70
2		**5**		**6**	69
3		**7**		**8**	66[d]
4		**9**		**10**	65
5		**11**		**12**	55
6		**13**		**14**	52

a) The reaction was carried out by addition of 30% H_2O_2 solution (15.0 mmol) to a solution of Na_2WO_4 (0.25 mmol), Et_4NCl (0.25 mmol), an amino acid (5.0 mmol), and K_2CO_3 (6.0 mmol) in CH_2Cl_2/H_2O (5/1, 18 mL). b) Satisfactory IR, NMR spectral data, and analyses have been obtained. c) Isolated yield. d) A solution of NaOH (1 M) was used as a base.

trones.

Synthesis of Enantiomerically Pure *O*-Protected 4-Hydroxy-1-pyrroline *N*-Oxides. Enantiomerically pure five-membered cyclic nitrones have been used as chiral building blocks for the synthesis of natural and non-natural pyrrolidine-, pyrrolizidine-, and indolizidine-alkaloids, which exhibit very diverse and important physiological properties.[22,23] The present oxidation of *N*-alkyl-α-amino acids has proved to be especially useful for the preparation of enantiomerically pure *O*-protected 4-hydroxy-1-pyrroline *N*-oxides. *O*-Protected 4-hydroxy-L-prolines **16** can be prepared in two steps from benzyl 1-benzyloxycarbonyl-4-hydroxy-L-prolinate (**15**) (Eq. 6).[24] Typically, 4-benzoyloxy-L-proline (**16c**) was obtained upon treatment of **15** with benzoyl chloride in pyridine and subsequent hydrogenation in 81% isolated yield.

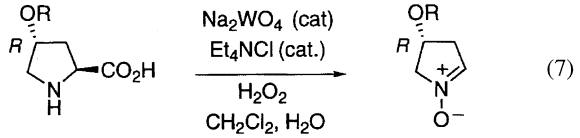


(6)

15

16a: R = $SiMe_2t$-Bu
16b: R = $SiPh_2t$-Bu
16c: R = PhCO
16d: R = *t*-BuCO

Treatment of the proline derivatives **16a—d** thus obtained with a 30% aqueous H_2O_2 solution in the presence of Na_2WO_4 (0.10 mol amt.) and K_2CO_3 (1.2 mol amt.) under phase-transfer conditions gave the corresponding nitrones **17a—d**, completely regioselectively (Eq. 7).

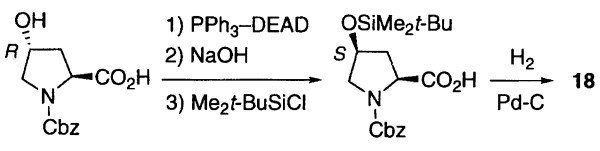


(7)

16a: R = $SiMe_2t$-Bu
16b: R = $SiPh_2t$-Bu
16c: R = PhCO
16d: R = *t*-BuCO

(*R*)-**17a**
(*R*)-**17b**
(*R*)-**17c**
(*R*)-**17d**

Thus, (4*R*)-4-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**17a**) was obtained in 70% isolated yield. In a similar manner, (4*R*)-4-(*t*-butyldiphenylsilyloxy)-1-pyrroline *N*-oxide (**17b**) was obtained in a lower yield (21%), presumably due to the steric bulk of the *t*-butyldiphenylsilyloxy group. The acylated nitrones (4*R*)-4-(benzoyloxy)-1-pyrroline *N*-oxide (**17c**) and (4*R*)-4-(2,2-dimethylpropanoyloxy)-1-pyrroline *N*-oxide (**17d**) were also isolated in 47 and 51% yields, respectively. The molecular structure of **17b** was established by



19 **20**

Scheme 1.

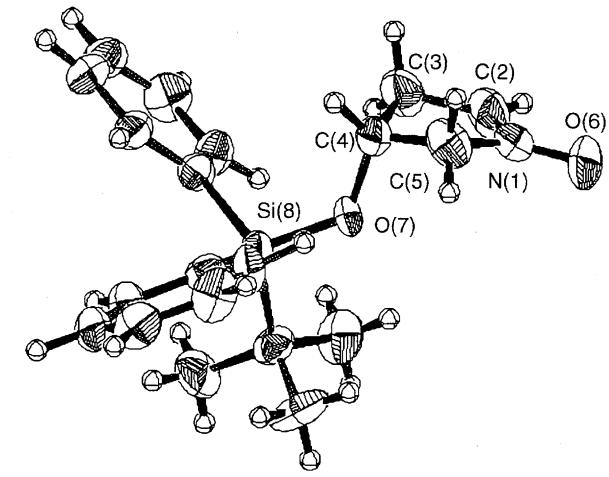
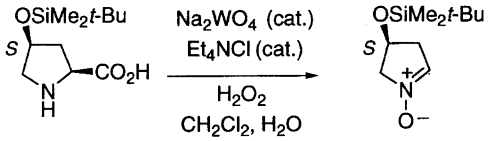


Fig. 1. ORTEP view of chiral nitrone **17b** obtained by X-ray crystallography.

X-ray analysis. An ORTEP view of nitrone **17b** is shown in Fig. 1.

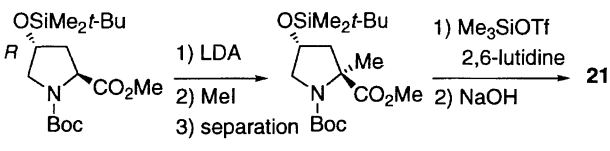
The antipode (*S*)-**17a** at the C-4 position can be prepared as shown in Eq. 8 by the oxidation of (4*S*)-*cis*-4-(*t*-butyldimethylsilyloxy)-L-proline (**18**), which was prepared from (4*R*)-*trans*-1-benzyloxycarbonyl-4-hydroxy-L-proline (**19**)[25] via (4*S*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-proline (**20**) in four steps, as shown in Scheme 1. The tungstate-catalyzed oxidation of **18** under phase-transfer conditions gave (*S*)-**17a** in 68% isolated yield.



(8)

18 (*S*)-**17a**

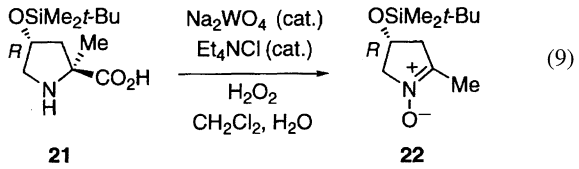
The oxidation of (2*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2-methylproline (**21**), which has no hydrogen at the α-position, proceeded smoothly to give (4*R*)-4-(*t*-butyldimethylsilyloxy)-2-methyl-1-pyrroline *N*-oxide (**22**) in 99% yield (Eq. 9). The starting amino acid **21** was obtained from methyl (2*S*,4*R*)-1-(*t*-butoxycarbonyl)-4-(*t*-butyldimethylsilyloxy)-L-prolinate (**23**)[26] via stereoselective alkylation as shown in Scheme 2. Thus, treatment of **23** with lithium diisopropylamide (LDA) at −78 °C followed by methylation with methyl iodide afforded a 4 : 1 diastereomeric mixture of **24** in 99% yield. The major isomer, methyl (2*S*,4*R*)-1-(*t*-butoxycarbonyl)-4-(*t*-butyldimethylsilyloxy)-2-methylprolinate (**24**) was obtained by column chromatography on SiO_2 in 67% yield from **23** as a single isomer. Deprotection of Boc group on nitrogen of **24**, followed by treatment with a NaOH



23 **24**

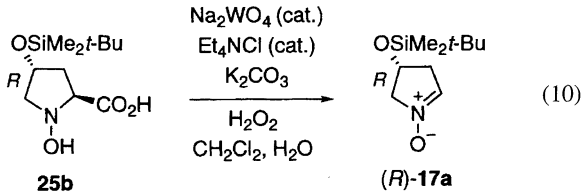
Scheme 2.

solution, gave crystalline **21** in 76% yield.



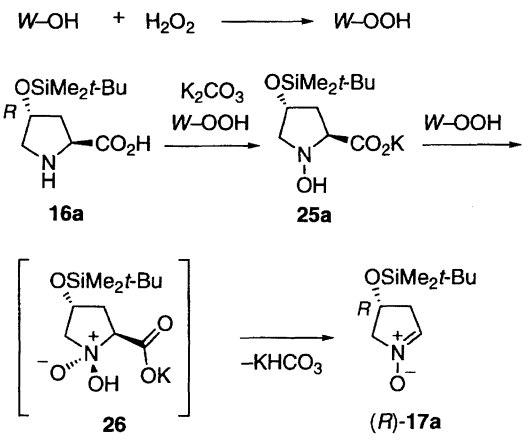
(9)

Mechanism of the Decarboxylative Oxidation of *N*-Alkyl-α-amino Acids. The oxidation is accompanied by decarboxylation, and nitrones are formed regioselectively in the direction of the carbon attached to the carboxyl group. The mechanism of the catalytic oxidation of *N*-alkyl-α-amino acids can be explained by assuming Scheme 3. Initially, peroxytungstate (*W*–OOH) (*W* = WO_3^- or WO_6^-) would be generated from Na_2WO_4 and H_2O_2.[27] Oxidation of potassium salt of α-amino acid (**16a**) gives potassium (4*R*)-4-(*t*-butyldimethylsilyloxy)-1-hydroxy-L-prolinate (**25a**). Sequential oxidation of **25a** with peroxytungstate (*W*–OOH) would give the *N*-hydroxy-*N*-oxido intermediate **26**. The exclusive formation of the regioisomer (*R*)-**17a** can be explained by the elimination of $KHCO_3$ from the intermediate **26**. Intermediacy of the potassium salt of the *N*-hydroxyamino acid **25a** was confirmed by the fact that the catalytic oxidation of **25b** under the same reaction conditions gave **17a** in 69% yield (Eq. 10). The *N*-hydroxy-α-amino acid **25b** was prepared by hydrogenation of methyl (4*R*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-prolinate (**27**),[28] subsequent SeO_2-catalyzed oxidation, and then saponification (Scheme 4).

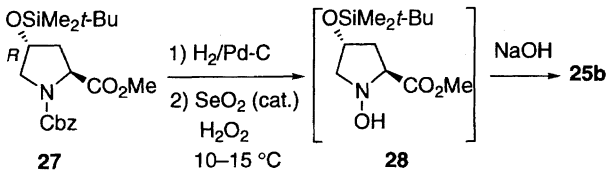


(10)

The possibility of a step-wise process, which includes initial dehydration of **25a** and subsequent decarboxylation, can be ruled out by the fact that the oxidation of the amino acid **21**, which bears no hydrogen at the α-position, also undergoes the oxidation smoothly to give the keto nitrone **22**



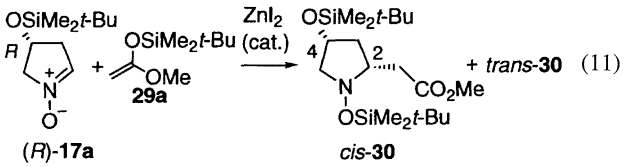
Scheme 3. Mechanism of decarboxylative oxidation.



Scheme 4.

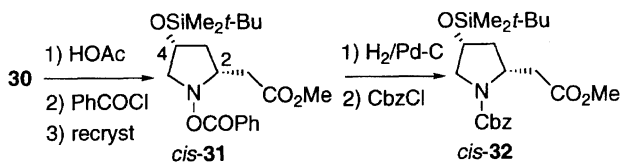
in quantitative yield (Eq. 9).

Stereoselective Nucleophilic Additions to Enantiomerically Pure *O*-Protected 4-Hydroxy-1-pyrroline *N*-Oxides. The stereoselective introduction of a substituent at the α-position of a pyrrolidine ring is of current interest in the synthesis of pyrrolidine-based alkaloids. Therefore, we examined asymmetric introduction of carboxymethyl moiety to chiral nitrones such as (*R*)-**17a**.[29] Typically, the reaction was carried out by adding ketene silyl acetal **29a**, prepared from methyl acetate, to the nitrone (*R*)-**17a** in the presence of a catalytic amount of ZnI_2 at −90 °C (Eq. 11). A mixture of methyl (2*R*,4*R*)-[1,4-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-**30**) and (2*S*,4*R*)-isomer (*trans*-**30**) was obtained in 85% yield. The diastereomeric mixture of **30** was converted to (2*R*,4*R*)-[1-benzoyloxy-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-**31**) and *trans*-**31** upon treatment with acetic acid at room temperature, followed by protection with benzoyl chloride (Scheme 5). The isomeric ratio of **31** was determined to be 81/19 by HPLC analysis.



(11)

Diastereomerically pure *cis* isomer of **31** was obtained by a single recrystallization from hexane in 48% yield. Furthermore, conversion of *cis*-**31** into (2*R*,4*R*)-[1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-**32**) was conducted by catalytic hydrogenation followed by protection with CbzCl in 90% yield. The configuration of *cis*-**32** was confirmed by comparison with *trans*-**32**, prepared from (4*R*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-proline (**33**)[30] via a Wolff rearrangement (Eq. 12). The *cis* selectivity observed for the ZnI_2-catalyzed addition of ketene silyl acetal **29a** can be explained by assuming Fig. 2. Ketene silyl acetal **29a** may attack from the *si* face, preferably due to steric repulsion between incoming **29a** and the coordinated zinc iodide moiety.



Scheme 5.

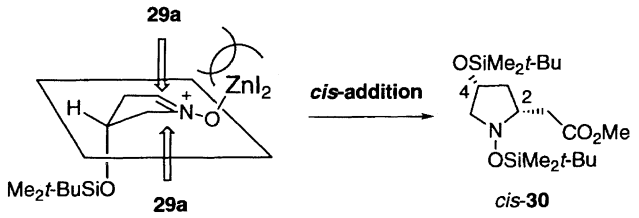
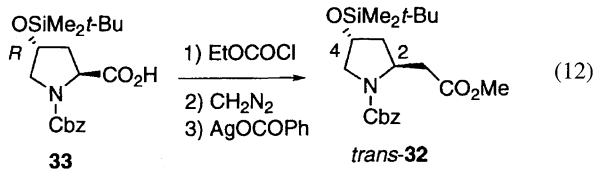
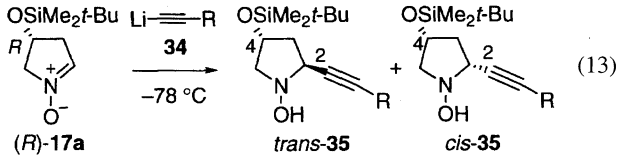


Fig. 2. Model for *cis*-addition of ketene silyl acetal to nitrone (*R*)-**17a**.

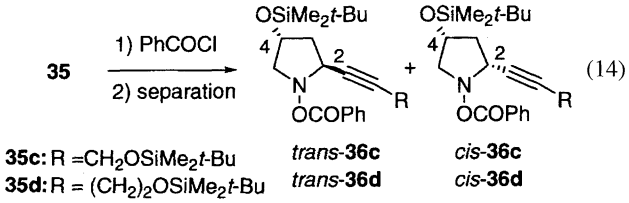


Next, we examined the reaction of chiral nitrone (*R*)-**17a** with lithium acetylides **34**, as shown in Eq. 13,[31] because synthesis of 2-propynylamines is of interest in view of synthetic and biological aspects.[32] The diastereoselective alkynylation of chiral nitrone (*R*)-**17a** was carried out by addition of (*R*)-**17a** to lithium acetylides **34**. Representative results are summarized in Table 3.



34a: R = $SiMe_3$
34b: R = CH_2OLi
34c: R = CH_2OSiMe_2t-Bu
34d: R = $(CH_2)_2OSiMe_2t$-Bu

The acetylide **34a** was allowed to react with nitrone (*R*)-**17a** at −78 °C. A 93 : 7 mixture of (2*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-1-hydroxy-2-(2-trimethylsilylethynyl)-pyrrolidine (*trans*-**35a**) and the (2*R*,4*R*)-isomer (*cis*-**35a**) was obtained in 88% yield (Entry 1). Diastereomerically pure *trans*-**35a** was obtained by single recrystallization of the crude product from hexane in 63% yield. The reaction of *O*-protected lithium acetylide **34c** with nitrone (*R*)-**17a** proceeded smoothly at −78 °C to give a 94 : 6 mixture of (2*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2-[3-(*t*-butyldimethylsilyloxy)-1-propynyl]-1-hydroxypyrrolidine (*trans*-**35c**) and the (2*R*,4*R*)-isomer (*cis*-**35c**) in 91% yield (Entry 3). In a similar manner, a mixture of (2*S*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2-[4-(*t*-butyldimethylsilyloxy)-1-butynyl]-1-hydroxypyrrolidine (*trans*-**35d**) and the (2*R*,4*R*)-isomer (*cis*-**35d**) was obtained in 86% yield in a 92 : 8 ratio (Entry 4). The separation of the diastereomeric mixture **35c** was performed by benzoylation, followed by column chromatography, to give enantiomerically pure *trans*-**36c** (83%) and *cis*-**36c** (7%), as shown in Eq. 14.



The stereochemistry of *trans*- and *cis*-**36** was unambiguously determined from 2D-NOESY spectra of *trans*- and *cis*-**36**, as shown in Fig. 3. NOESY spectrum of *trans*-**36** showed cross-peaks between H^2 and $H^{5\alpha}$, between H^2 and $H^{3\alpha}$, between $H^{3\beta}$ and H^4, and between H^4 and $H^{5\beta}$. On the other hand, cross-peaks between H^2 and H^4 as well as between H^4 and $H^{3\beta}$ were observed in *cis*-**36**. These 2D cross-peaks are consistent with the structures shown in Fig. 3.

The *trans* selectivity for the addition of lithium acetylides **34** to the chiral nitrone (*R*)-**17a** can be explained by using Fig. 4. The *t*-butyldimethylsilyl group is located in a quasi-axial position, as supported by X-ray crystallography of nitrone **17b**, as depicted in Fig. 1. Lithium acetylides may then attack preferably from the less hindered *re*-face of the nitrone.

The adducts **35** obtained can be utilized for the construction of (3*R*,5*R*)-1-aza-3-hydroxybicyclo[3.3.0]octane (**37**) and (6*R*,8*R*)-1-aza-8-hydroxybicyclo[4.3.0]nonane (**38**). Stereoselective transformation of **35c** to the pyrrolizidine **37** can be performed according to the procedure shown in Scheme 6. Chemoselective desilylation of a mixture of

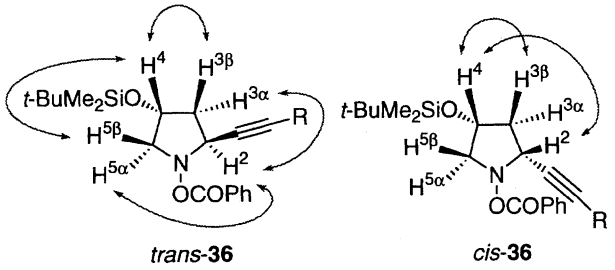


Fig. 3. NOE correlations of *trans*- and *cis*-**36**.

Table 3. Reaction of Nitrone (*R*)-**17a** with Lithium Acetylide **34**[a)]

Entry		Acetylide	Product	Yield/%[b)]	*trans*/*cis* Ratio[c)]
1	**34a:**	R=$SiMe_3$	**35a**	88 (63)[d)]	93/7
2	**34b:**	R=CH_2OLi	**35b**	52[e)]	87/13
3	**34c:**	R=CH_2OSiMe_2t-Bu	**35c**	91	94/6
4	**34d:**	R=$(CH_2)_2OSiMe_2t$-Bu	**35d**	86	92/8

a) The reaction was carried out by treating (*R*)-**17a** (5.00 mmol) with lithium acetylide **34** (7.50 mmol) at −78 °C for 30 min. b) Isolated yield. c) Determined by ^1H NMR spectra. d) Yield of pure *trans*-**35a**. e) The reaction was carried out at 0 °C for 30 min.

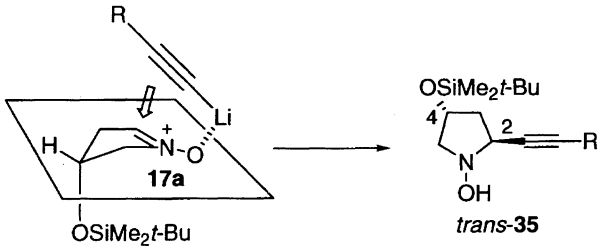
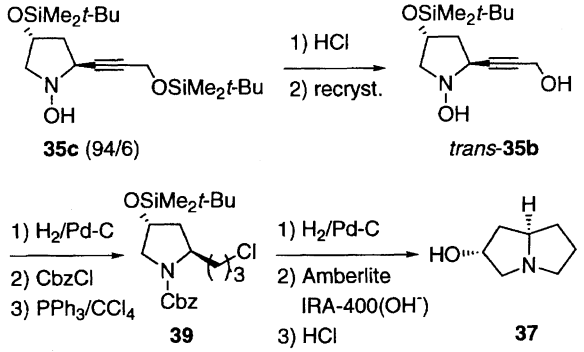


Fig. 4. Model for *trans* selective addition of lithium acetylides to nitrone (*R*)-**17a**.

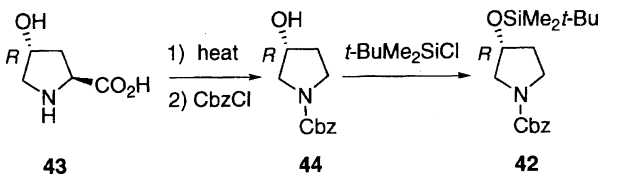


Scheme 6. Synthesis of chiral pyrrolizidine **37**.

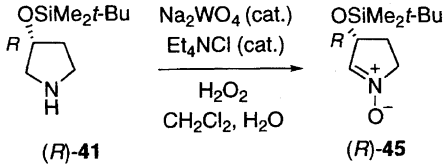
trans-**35c** and *cis*-**35c** upon treatment with a diluted HCl solution, followed by crystallization, gave diastereomerically pure *trans*-**35b** in 85% yield. Catalytic hydrogenation, followed by protection of the amino group with CbzCl and chlorination of the primary hydroxyl group, gave (2*R*,4*R*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-2-(3-chloropropyl)pyrrolidine (**39**) from *trans*-**35b** in 63% yield. Cyclization to the pyrrolizidine **37** was carried out by deprotection, basification, and desilylation in 73% yield.

Chiral indolizidine **38** was also prepared from *trans*-**36d** according to Scheme 7. Catalytic hydrogenation of *trans*-**36d** and desilylation afforded (2*R*,4*R*)-4-(*t*-butyldimethylsilyloxy)-2-(4-hydroxybutyl)pyrrolidine (**40**) in 69% yield. Bromination of **40** by treatment with PPh_3 and CBr_4, followed by treating with K_2CO_3 and desilylation, gave the indolizidine **38** in 50% yield.

Synthesis of Enantiomerically Pure *O*-Protected 3-Hydroxy-1-pyrroline *N*-Oxides and Stereoselective Addition of Carbon Nucleophiles. In contrast to the formation of (4*R*)- and (4*S*)-4-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide ((*R*)-**17a** and (*S*)-**17a**) prepared by tungstate-catalyzed oxidation of the corresponding proline derivatives **16a** and **18**, respectively, the regio isomer of (*R*)-**17a** was obtained by tungstate-catalyzed oxidation of (*R*)-3-(*t*-butyldimethylsilyloxy)pyrrolidine ((*R*)-**41**), prepared by hydrogenation of (*R*)-1-benzyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)pyrrolidine (**42**) (Eq. 15). The starting **42** was obtained by decarboxylation of *trans*-4-hydroxy-L-proline (**43**), protection with CbzCl and silylation, as shown in Scheme 8.[33,34] Hydrogenation of (*R*)-**42**, followed by treatment of (*R*)-**41** with a 30% H_2O_2 solution in the presence of Na_2WO_4 catalyst and Et_4NCl catalyst under phase-transfer conditions, gave (3*R*)-3-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide ((*R*)-**45**)[35] (61%) along with 9% of (*R*)-**17a**.

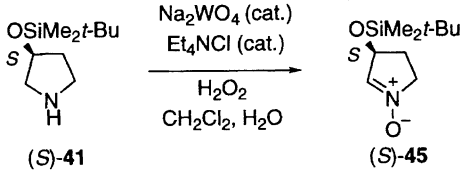


Scheme 8.

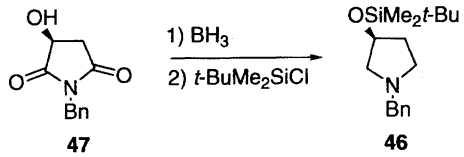


(15)

The enantiomer (*S*)-**45** was obtained in 59% isolated yield by similar treatment of (*S*)-**41**, prepared by hydrogenation of (*S*)-1-benzyl-3-(*t*-butyldimethylsilyloxy)pyrrolidine (**46**) (Eq. 16). The precursor of the optically active pyrrolidine **46** was prepared from (*S*)-*N*-benzyl-3-hydroxysuccinimide (**47**)[36] in two steps in 77% overall yield (Eq. 17).

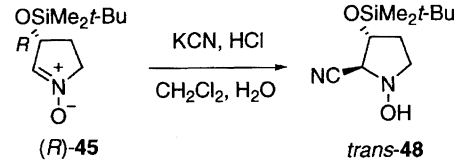


(16)

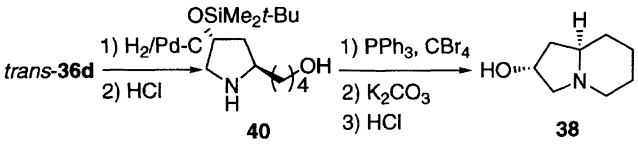


(17)

Next, we examined the asymmetric synthesis of 2-cyano-*N*-hydroxy amines, which are useful precursors of α-amino acid derivatives.[37] Typically, the cyanation of (*R*)-**45** was performed upon treatment with KCN and 4 M HCl solution in a mixture of CH_2Cl_2 and water. (2*S*,3*R*)-3-(*t*-Butyldimethylsilyloxy)-2-cyano-1-hydroxypyrrolidine (*trans*-**48**) (99%) was obtained as a single isomer (Eq. 18). It is noteworthy that Me_3SiOTf-catalyzed addition of Me_3SiCN, followed by acid treatment, gave a mixture of *trans*-**48** (49%) and *cis*-**48** (32%).



(18)



Scheme 7. Synthesis of chiral indolizidine **38**.

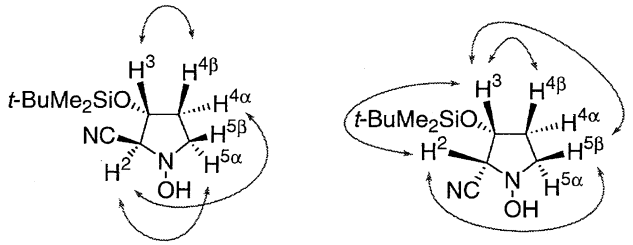
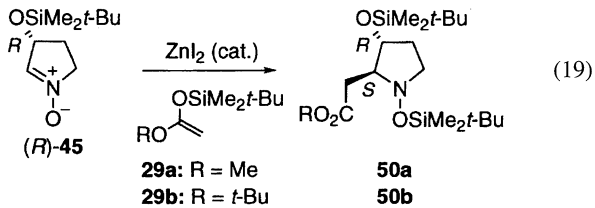


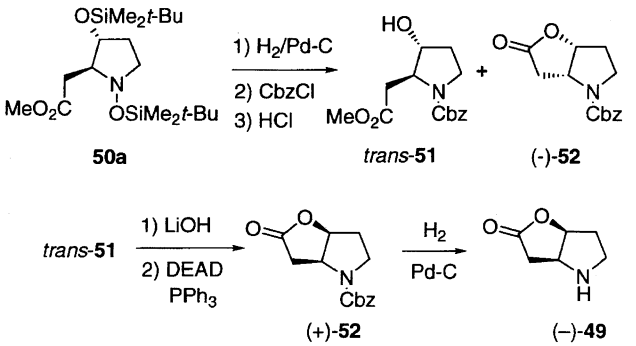
Fig. 5. NOE correlations of *trans*- and *cis*-**48**.

The stereochemistry of *trans*- and *cis*-**48** was unambiguously determined from the results of NOE experiments (Fig. 5). In *trans*-**48**, NOE enhancements were detected between H^2 and $H^{5\alpha}$, H^2, and $H^{4\alpha}$ as well as H^3 and $H^{4\beta}$. In contrast, significant enhancement between H^2 and H^3 was observed in *cis*-**48**.

Asymmetric introduction of a carboxymethyl moiety at the carbon α to the nitrogen of the nitrone (*R*)-**45** can be performed highly stereoselectively, and hence this method can be used for synthesis of the (−)-Geissman–Waiss lactone ((−)-**49**),[38,39] which is a key intermediate for biologically active pyrrolizidine alkaloids such as retronecine and platynecine. The ZnI_2-promoted reaction of the nitrone (*R*)-**45** with ketene *t*-butyldimethylsilyl methyl acetal (**29a**) proceeded smoothly at −70 °C to give a diastereomeric mixture of methyl (2*S*,3*R*)-[1,3-bis(*t*-butyldimethylsilyloxy)-pyrrolidin-2-yl]acetate (*trans*-**50a**) and the (2*R*,3*R*)-isomer (*cis*-**50a**) in quantitative yield in a 90 : 10 *trans*/*cis* ratio (Eq. 19). Enhanced *trans* selectively was achieved by the use of ketene *t*-butyl silyl acetal **29b**, affording *t*-butyl (2*S*, 3*R*)-[1,3-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*trans*-**50b**) and the (2*R*,3*R*)-isomer (*cis*-**50b**) in a 96 : 4 *trans*/*cis* ratio. Hydrogenolysis of the mixture of *trans*- and *cis*-**50a**, protection with CbzCl, and treatment with HCl solution gave methyl (2*S*,3*R*)-(1-benzyloxycarbonyl-3-hydroxy-pyrrolidin-2-yl)acetate (*trans*-**51**) (91%) and (1*R*,5*R*)-(−)-6-aza-6-benzyloxycarbonyl-2-oxabicyclo[3.3.0]octan-3-one ((−)-**52**) (6%), which was formed by acid-catalyzed lactonization of *cis*-**51** (Scheme 9). Saponification of *trans*-**51** and lactonization with PPh_3 and DEAD (diethyl azodicarboxylate) afforded (+)-**52** in 96% yield. Catalytic hydrogenation of (+)-**52** gave the Geissman–Waiss lactone (**49**) in 91% isolated yield. Its crystalline hydrochloride (mp 185—187 °C, $[\alpha]_D^{28}$ −46.4° (*c* 1.43, MeOH); lit, mp 182—184 °C, $[\alpha]_D$ +45.6° (*c* 0.3, MeOH)) had physical properties identical with those reported, except for the sign of $[\alpha]_D$.[39a]



(19)



Scheme 9. Synthesis of Geissman–Waiss lactone (**49**).

Conclusion

We have demonstrated that tungstate-catalyzed decarboxylative oxidation of *N*-alkyl-α-amino acids is a versatile synthetic method for the preparation of regiochemically defined nitrones. By use of this method and tungstate-catalyzed oxidation of secondary amines, four stereo and regio isomers of *O*-protected 3- and 4-hydroxy-1-pyrroline *N*-oxides (**17** and **45**) can be prepared in an enantiomerically pure form. The diastereoselective reactions of chiral cyclic nitrones **17** and **45** thus obtained with carbon-nucleophiles provide a new approach for synthesis of potential precursors of monohydroxylated pyrrolidine-based alkaloids such as (3*R*,5*R*)-1-aza-3-hydroxybicyclo[3.3.0]octane (**37**), (6*R*,8*R*)-1-aza-8-hydroxybicyclo[4.3.0]nonane (**38**), and the Geissman–Waiss lactone ((−)-**49**).

Experimental

Materials and General Methods. All reagents were used as supplied commercially unless otherwise noted. *N*-Alkyl-α-amino acids were prepared by reductive alkylation with sodium cyanoborohydride (sodium cyanotrihydroborate)[20a] (for compounds **3**, **5**, and **7**) or sodium borohydride (sodium tetrahydroborate)[20b] (for compounds **4** and **9**). Compounds **15**,[24] **19**,[25] **23**,[26] **27**,[28] **33**,[30] and **47**[36] were obtained by literature procedures. IR spectra were recorded on a Shimadzu FT IR 4100 spectrometer. NMR spectra were obtained on a JEOL JNM-GSX-270 (^{1}H, 270 MHz; ^{13}C, 68 MHz) or a Bruker AC-200P (^{1}H, 200 MHz) spectrometer. Elemental analyses were carried out on a Yanagimoto Model MT-3 CHN corder. High resolution mass spectra (HRMS) were recorded on a JEOL Model JMS-DX-303 mass spectrometer. Low resolution mass spectra (LRMS) were recorded on a Hitachi M1000H mass spectrometer with a Hitachi LC-APCI interface. Ionization methods (EI: electron impact; CI: chemical ionization; FAB: fast atom bombardment; APCI: atmospheric pressure chemical ionization) are indicated in parentheses. Capillary GC analyses (FID) were carried out using helium as carrier gas on a Shimadzu Model GC-17A equipped with a C-R6A data processor. J & W Scientic GC columns DB-1 (dimethylpolysiloxane, 30 m×0.25 mm i.d.), DB-5 ((5% phenyl)methylpolysiloxane, 30 m×0.25 mm i.d.), or DB-17 ((50% phenyl)methylpolysiloxane, 30 m×0.25 mm i.d.) were used. HPLC analyses were performed on a JASCO TRI ROTAR-4 system with a JASCO MULTI-340 UV detector by use of a 4.6 mm×250 mm analytical column packed with CHIRALCEL OD, CHIRALCEL OD-H, CHIRALPAK AD, or SUMICHIRAL OA-2000. The X-ray analysis was performed on a Rigaku AFC7R

diffractometer with graphite monochromated Cu $K\alpha$ radiation and a 18 kW rotating anode generator. Analytical TLC was performed on E. Merck silica gel 60 F254 (Art. 5714). Flash chromatography was carried out on E. Merck silica gel 60 (230—400 mesh).

Oxidation of *N*-Ethylbenzylamine. To a mixture of *N*-ethylbenzylamine (1.35 g, 10.0 mmol), $Na_2WO_4 \cdot 2H_2O$ (164 mg, 0.5 mmol), and Et_4NCl (83 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) and water (5 mL) was added 30% H_2O_2 solution (3.0 mL, 30.0 mmol) at 0 °C with vigorous stirring. The reaction mixture was gradually warmed up to room temperature and stirred for 12 h. Excess H_2O_2 was decomposed by adding $NaHSO_3$ with ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography on SiO_2 (50% EtOAc in hexane and then 10% MeOH in CH_2Cl_2) gave *N*-benzylideneethylamine *N*-oxide (**1**) (615 mg, 41%) and *N*-ethylidenebenzylamine *N*-oxide (**2**) (586 mg, 39%).

1:[40] IR (neat) 1582 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.58 (t, J = 7.3 Hz, 3 H, CH_3CH_2N), 3.99 (q, J = 7.3 Hz, 2 H, CH_3CH_2N), 7.30—7.50 (m, 4 H, N=CH and 3 H of Ph), 8.10—8.30 (m, 2 H of Ph).

2:[41] Mp 79.0—82.5 °C; IR (Nujol®) 1609 (C=N), 1171 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 270 MHz) δ = 2.00 (d, J = 5.9 Hz, 3 H, CH_3CH), 4.90 (s, 2 H, CH_2N), 6.73 (q, J = 5.9 Hz, 1 H, CH_3CH), 7.35—7.44 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = 12.7 (CH_3CH), 69.0 (CH_2N), 128.9, 129.3, 132.7, 134.6. Found: C, 72.24; H, 7.41; N, 9.31%. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39%.

Typical Procedure for Decarboxylative Oxidation of *N*-Alkyl-α-amino Acids. Preparation of *N*-Benzylideneethylamine *N*-Oxide (1). To a mixture of (ethylamino)phenylacetic acid (**3**) (966 mg, 5.00 mmol), $Na_2WO_4 \cdot 2H_2O$ (82.5 mg, 0.25 mmol), and Et_4NCl (41.1 mg, 0.25 mmol) in CH_2Cl_2 (15 mL) and water (3 mL) were added 30% H_2O_2 solution (1.5 mL, 15.0 mmol) and K_2CO_3 (828 mg, 6.00 mmol) at 0 °C with vigorous stirring. The reaction mixture was gradually warmed up to room temperature and stirred for 8 h. Excess H_2O_2 was decomposed by adding $NaHSO_3$ with ice cooling. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography on SiO_2 (10—20% EtOAc in hexane and then 10% MeOH in CH_2Cl_2) gave nitrone **1** (581 mg, 78%) as an oil.

The isolated yields when bases other than K_2CO_3 were used are as follows: 69% (NaOH); 72% ($NaHCO_3$); 71% (K_3PO_4).

***N*-Benzylidenepropylamine *N*-Oxide (6):** K_2CO_3 was used as a base. 69% yield; IR (neat) 1585 (C=N), 1155 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 270 MHz) δ = 1.00 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 2.04 (tq, J = 6.9 and 7.4 Hz, 2 H, CH_3CH_2), 3.90 (t, J = 6.9 Hz, 2 H, CH_2N), 7.38—7.50 (m, 4 H, N=CH and 3 H of Ph), 8.20—8.30 (m, 2 H of Ph); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = 11.1 (CH_3CH_2), 21.2 (CH_3CH_2), 68.9 (CH_2N), 128.49, 128.52, 130.27, 130.59, 134.2 (C=NH). Found: C, 73.28; H, 8.23; N, 8.74%. Calcd for $C_{10}H_{13}NO$: C, 73.58; H, 8.02; N, 8.58%.

***N*-(2-Methylpropylidene)benzylamine *N*-Oxide (8):**[42] NaOH was used as a base. 66% yield; mp 61.0—61.5 °C; IR (Nujol®) 1595 (C=N), 1115 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 270 MHz) δ = 1.08 (d, J = 6.8 Hz, 6 H, $CH(CH_3)_2$), 3.16 (dq, J = 6.8 and 7.1 Hz, 1 H, $CH(CH_3)_2$), 4.85 (s, 2 H, CH_2N), 6.50 (d, J = 7.1 Hz, 1 H, N=CH), 7.34—7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = 18.7 ($CH(CH_3)_2$), 25.8 ($CH(CH_3)_2$), 69.2 (CH_2N), 128.6, 128.7, 128.9, 133.1, 144.3.

***N*-(1-Methylethylidene)benzylamine *N*-Oxide (10):** K_2CO_3 was used as a base. 65% yield; IR (neat) 1604 (C=N), 1153 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 2.14 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 5.08 (s, 2 H, CH_2N), 7.30—7.50 (m, 5 H, Ph). Found: C, 73.41; H, 7.99; N, 8.45%. Calcd for $C_{10}H_{13}NO$: C, 73.58; H, 8.02; N, 8.58%.

1-Pyrroline *N*-Oxide (12):[14] K_2CO_3 was used as a base. 55% yield; IR (neat) 1590 (C=N), 1170 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.93—2.55 (m, 2 H, $-CH_2-$), 2.55—3.04 (m, 2 H, $-CH_2C=$), 3.94 (tt, J = 8.0 and 2.0 Hz, 2 H, $-CH_2N-$), 6.86 (t, J = 2.0 Hz, 1 H, $-CH=N-$).

2,3,4,5-Tetrahydropyridine *N*-Oxide (14):[14] K_2CO_3 was used as a base. 52% yield; IR (neat) 1448, 1165 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.10—2.20 (m, 4 H, $-CH_2-$), 2.20—2.78 (m, 2 H, $-CH_2C=$), 3.78 (t, J = 5.0 Hz, 2 H, $-CH_2N-$), 7.14 (t, J = 4.0 Hz, 1 H, $-CH=N-$).

Typical Procedure for Preparation of *O*-Protected 4-Hydroxy-L-prolines. (4*R*)-4-(Benzoyloxy)-L-proline (16c). To a mixture of benzyl (4*R*)-1-benzyloxycarbonyl-4-hydroxy-L-prolinate (**15**)[24] (18.4 g, 51.7 mmol) and 4-(dimethylamino)pyridine (315 mg, 2.56 mmol) in pyridine (100 mL) was added benzoyl chloride (7.20 mL, 62.0 mmol) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was concentrated. The residue was diluted with EtOAc and water, and the solution was acidified (pH 2—3) with 6 M HCl. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation gave benzyl (4*R*)-4-benzoyloxy-1-benzyloxycarbonyl-L-prolinate as an oil. The crude oil was dissolved in MeOH (100 mL). To this solution were added HOAc (0.31 mL, 5.17 mmol) and 5% Pd on carbon (5.38 g) and the mixture was stirred under a balloon of hydrogen at room temperature for 2 h. The precipitated white solid was dissolved by adding water. The solution was filtered, and the filtrate was concentrated to afford a crude crystalline solid. After washing with a solvent mixture of MeOH and EtOAc and drying in vacuo, pure **16c** was obtained (9.74 g, 81%): Mp 218.0—218.8 °C; $[\alpha]_D^{21}$ −6.66° (*c* 0.21, MeOH); IR (Nujol®) 3050 (OH), 1715 cm^{-1} (OCO); ^1H NMR (CD_3OD, 200 MHz) δ = 2.42 (ddd, J = 4.8, 10.3, and 14.6 Hz, 1 H of CH_2CHN), 2.73 (dd, J = 7.9 and 14.6 Hz, 1 H of CH_2CHN), 3.65 (d, J = 13.3 Hz, 1 H of CH_2N), 3.80 (dd, J = 4.2 and 13.3 Hz, 1 H of CH_2N), 4.37 (dd, J = 7.8 and 10.3 Hz, 1 H, CHN), 5.65—5.75 (m, 1 H, CHOCOPh), 7.50—7.80 (m, 3 H, Ar), 8.00—8.20 (m, 2 H, Ar); LRMS (APCI) *m/z* 236 (M^++H). Found: C, 61.27; H, 5.33; N, 6.12%. Calcd for $C_{12}H_{13}NO_4$: C, 61.23; H, 5.57; N, 5.95%.

(4*R*)-4-(2,2-Dimethylpropanoyloxy)-L-proline (16d). Treatment of **15** (13.2 g, 37.2 mmol) with 2,2-dimethylpropanoyl chloride (6.87 mL, 55.8 mmol) in pyridine (130 mL) at 60 °C for 5 h, followed by hydrogenation, gave **16d** (6.80 g, 85%): Mp 210.5—211.2 °C; $[\alpha]_D^{23}$ −32.1° (*c* 1.06, MeOH); IR (Nujol®) 1720 cm^{-1} (OCO); ^1H NMR (CD_3OD, 200 MHz) δ = 1.31 (s, 9 H, $C(CH_3)_3$), 2.38 (ddd, J = 4.8, 10.6, and 14.5 Hz, 1 H of CH_2CHN), 2.56 (dd, J = 7.7 and 14.5 Hz, 1 H of CH_2CHN), 3.30—3.40 (m, 1 H of CH_2N), 3.78 (dd, J = 4.7 and 13.4 Hz, 1 H of CH_2N), 4.26 (dd, J = 7.7 and 10.6 Hz, 1 H, CHN), 5.49 (t, J = 4.7 Hz, 1 H, CHOCOBu); LRMS (APCI) *m/z* 216 (M^++H). Found: C, 55.65; H, 7.65; N, 6.43%. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.50%.

(4*R*)-4-(*t*-Butyldimethylsilyloxy)-L-proline (16a).[43] Treatment of **15** (17.8 g, 50 mmol) with *t*-butylchlorodimethylsilane (8.29 g, 55.0 mmol) and NEt_3 (9.10 mL, 65.0 mmol) in DMF (50 mL) at room temperature for 30 min, followed by hydrogenation, gave **16a** (9.45 g, 77%): Mp 160—162 °C (decomp); $[\alpha]_D^{30}$ −34.0° (*c* 1.01,

MeOH); IR (Nujol®) 3400 (COOH), 1634 cm^{-1} (COO); ^1H NMR (CD_3OD, 270 MHz) δ = 0.13 (s, 3 H of $Si(CH_3)_2$), 0.14 (s, 3 H of $Si(CH_3)_2$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 2.11 (ddd, J = 3.9, 10.0, and 13.7 Hz, 1 H of $CHCH_2CH$), 2.34 (ddt, J = 2.0, 7.6, and 13.4 Hz, 1 H of $CHCH_2CH$), 3.18 (dt, J = 1.7 and 12.2 Hz, 1 H of CH_2N), 3.45 (dd, J = 3.8 and 12.2 Hz, 1 H of CH_2N), 4.18 (dd, J = 7.6 and 10.3 Hz, $CHCOOH$), 4.60—4.70 (m, 1 H, CHOSi); ^{13}C NMR (CD_3OD, 68 MHz) δ = −6.9 and −6.8 ($Si(CH_3)_2$), 16.7 ($SiC(CH_3)_3$), 24.1 ($SiC(CH_3)_3$), 37.9, 52.8, 59.4, 70.9 (CHOSi), 171.6 (COOH). HRMS (FAB) Found: m/z 246.1514. Calcd for $C_{11}H_{24}NO_3Si$: (M^++H), 246.1525.

(4*R*)-4-(*t*-Butyldiphenylsilyloxy)-L-proline (16b). Treatment of **15** (35.5 g, 100 mmol) with *t*-butylchlorodiphenylsilane (28.6 mL, 110 mmol) and NEt_3 (18.1 mL, 130 mmol) in DMF (100 mL) at 50 °C for 48 h, followed by hydrogenation, gave **16b** (29.5 g, 80%): Mp 214.6—215.0 °C ; $[\alpha]_D^{23}$ −33.3° (c 1.08, MeOH); IR (Nujol®) 3050 (OH), 1635 cm^{-1} (COOH); ^1H NMR (CD_3OD, 200 MHz) δ = 1.09 (s, 9 H, $C(CH_3)_3$), 1.94 (ddd, J = 4.2, 10.8, and 13.8 Hz, 1 H of CH_2CHN), 2.36 (dd, J = 7.7 and 13.8 Hz, 1 H of CH_2CHN), 3.05—3.40 (m, 2 H, CH_2N), 4.27 (dd, J = 7.6 and 10.4 Hz, NCHCOO), 4.55—4.70 (m, 1 H, CHOSi), 7.35—7.60 (m, 6 H, Ar), 7.60—7.75 (m, 4 H, Ar); LRMS (APCI) m/z 370 (M^++H). Found: C, 68.07; H, 7.35; N, 4.02%. Calcd for $C_{21}H_{27}NO_3Si$: C, 68.26; H, 7.36; N, 3.79%.

Typical Procedure for Decarboxylative Oxidation of *O*-Protected 4-Hydroxy-L-proline. (4*R*)-4-(Benzoyloxy)-1-pyrroline *N*-Oxide ((*R*)-17c). To a solution of **16c** (706 mg, 3.00 mmol) in CH_2Cl_2 (15 mL) was added a solution of $Na_2WO_4 \cdot 2H_2O$ (99 mg, 0.30 mmol) and Et_4NCl (50 mg, 0.30 mmol) in water (4 mL). To the stirred mixture was added 30% H_2O_2 solution (0.75 mL, 7.50 mmol) at 0 °C. Potassium carbonate (497 mg, 3.60 mmol) was added portionwise at 0 °C with vigorous stirring and the solution was stirred at room temperature for 12 h. Excess H_2O_2 was decomposed by adding $NaHSO_3$ with ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography on SiO_2 (2.5—5.0% MeOH in CH_2Cl_2) gave nitrone (*R*)-**17c** (290 mg, 47%). For analytical purposes, the product was recrystallized from hexane: Mp 87.9—89.0 °C; $[\alpha]_D^{22}$ −101.5° (c 1.08, $CHCl_3$); IR (Nujol®) 1715 (COO), 1595 (C=N), 1260 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 2.94 (br d, J = 19.8 Hz, 1 H of CH_2CH=N), 3.32 (ddd, J = 2.2, 6.9, and 19.8 Hz, 1 H of CH_2CH=N), 4.10 (br d, J = 15.4 Hz, 1 H of CH_2N), 4.44 (ddd, J = 1.7, 6.4, and 15.5 Hz, 1 H of CH_2N), 5.65—5.80 (m, 1 H, CHOCO), 6.95 (br s, 1 H, N=CH), 7.40—7.70 (m, 3 H, Ar), 8.00—8.15 (m, 2 H, Ar); LRMS (APCI) m/z 206 (M^++H), 411 ($2M^+$+H). Found: C, 64.30; H, 5.44; N, 6.70%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82%.

(4*R*)-4-(*t*-Butyldimethylsilyloxy)-1-pyrroline *N*-Oxide ((*R*)-17a): 70% yield; mp 70.5—72.5 °C; $[\alpha]_D^{28}$ −50.9° (c 1.14, MeOH); IR (Nujol®) 1599 (C=N), 1223 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 270 MHz) δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 2.54—2.66 (m, 1 H of N=CHCH_2), 2.92—3.08 (m, 1 H of N=CHCH_2), 3.72—3.82 (m, 1 H of CH_2N), 4.08 (dddd, J = 1.5, 3.7, 6.1, and 14.4 Hz, 1 H of CH_2N), 4.57—4.66 (m, 1 H, CHOSi), 6.78—6.84 (m, 1 H, N=CH); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −4.9 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 39.9 ($CHCH_3CH$), 66.4, 70.5, 132.9 (N=CH). HRMS (EI) Found: m/z 215.1342. Calcd for $C_{10}H_{21}NO_2Si$: (M^++H), 215.1339. Found: C, 55.64; H, 9.78; N, 6.50%. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50%.

(4*R*)-4-(*t*-Butyldiphenylsilyloxy)-1-pyrroline *N*-Oxide ((*R*)-17b): 21% yield; mp 114.8—116.0 °C; $[\alpha]_D^{25}$ +2.84° (c 1.05, $CHCl_3$); IR (Nujol®) 1590 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.06 (s, 9 H, $SiC(CH_3)_3$), 2.60—2.95 (m, 2 H, CH_2CH_2N), 3.8—4.1 (m, 2 H, CH_2N), 4.55—4.70 (m, 1 H, CHO), 6.80—6.90 (m, 1 H, CH=N), 7.3—7.8 (m, 10 H, Ar); LRMS (APCI) m/z 340 (M^++H), 679 ($2M^+$+H). Found: C, 70.35; H, 7.59; N, 4.05%. Calcd for $C_{20}H_{25}NO_2Si$: C, 70.75; H, 7.42; N, 4.12%.

(4*R*)-4-(2,2-Dimethylpropanoyloxy)-1-pyrroline *N*-Oxide ((*R*)-17d): 51% yield; mp 93.6—95.1 °C; $[\alpha]_D^{24}$ −41.0° (c 1.05, $CHCl_3$); IR (Nujol®) 1725 (COO), 1592 (C=N), 1150 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.20 (s, 9 H, $C(CH_3)_3$), 2.75 (ddd, J = 1.0, 2.6, and 19.9 Hz, 1 H of CH_2CH=N), 3.20 (dddt, J = 1.7, 2.5, 7.1, and 19.9 Hz, 1 H of CH_2CH=N), 3.92 (br d, J = 15.5 Hz, 1 H of CH_2N), 4.34 (dddd, J = 1.7, 3.7, 6.5, and 15.5 Hz, 1 H of CH_2N), 5.42 (tt, J = 1.9 and 6.8 Hz, 1 H, CHO), 6.95 (dt, J = 2.5 and 3.8 Hz, 1 H, CH=N). Found: C, 58.33; H, 8.33; N, 7.62%. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56%.

(4*S*)-1-Benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-proline (20). To a mixture of (4*R*)-1-benzyloxycarbonyl-4-hydroxy-L-proline (**19**)[25] (23.6 g, 88.8 mmol) and PPh_3 (25.6 g, 97.7 mmol) in CH_2Cl_2 (180 mL) was added diethyl azodicarboxylate (DEAD) (15.4 mL, 97.7 mmol) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was concentrated. The obtained solid was suspended in EtOAc and filtered, and the filtrate was concentrated to give a crude product. To a solution of the crude product in MeOH (90 mL) was added 1 M NaOH (90 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and concentrated. The oily residue was dissolved in water, and the aqueous layer was washed with CH_2Cl_2 and acidified with 1 M HCl (90 mL) to pH 2. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give (4*S*)-*cis*-1-benzyloxycarbonyl-4-hydroxy-L-proline as a foam. The *cis*-proline derivative thus obtained was dissolved in DMF (180 mL). To the solution were successively added NEt_3 (37.1 mL, 266 mmol) and *t*-butylchlorodimethylsilane (29.4 g, 195 mmol) at 0 °C. After stirring at room temperature for 10 h, the reaction mixture was diluted with EtOAc/hexane (1/2). The organic layer was washed with water and brine, and concentrated. After a solution of the crude oil in MeOH (200 mL) was treated with K_2CO_3 (13.8 g, 100 mmol) at room temperature for 2 h, the solution was concentrated. The crude oil was taken up in EtOAc and water. The solution was acidified with 6 M HCl (30 mL) to pH 2. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (5—20% EtOAc in hexane) gave a crude crystalline solid. Recrystallization from hexane gave pure **20** (12.4 g, 37%): Mp 78.5—80.6 °C; $[\alpha]_D^{21}$ −13.0° (c 1.03, MeOH); IR (Nujol®) 3200 (OH), 1755 cm^{-1} (COOH); ^1H NMR (DMSO-d_6, 200 MHz, 1 : 1 of mixture of conformational isomers) δ = 0.00 (s, 0.5×6 H, $Si(CH_3)_2$), 0.01 (s, 0.5×6 H, $Si(CH_3)_2$), 0.79 (s, 0.5×9 H, $SiC(CH_3)_3$), 0.80 (s, 0.5×9 H, $SiC(CH_3)_3$), 1.80—2.02 (m, 1 H of CH_2CHN), 2.24—2.46 (m, 1 H of CH_2CHN), 3.16 (br d, J = 11.0 Hz, 0.5 H of CH_2N), 3.37 (dd, J = 5.1 and 11.0 Hz, 0.5 H of CH_2N), 3.62 (dd, J = 5.2 and 10.8 Hz, 0.5 H of CH_2N), 4.24 (dd, J = 3.3 and 9.2 Hz, 0.5 H, CHN), 4.31 (dd, J = 3.2 and 9.2 Hz, 0.5 H, CHN), 4.30—4.47 (m, 1 H, CHOSi), 5.00 (d, J = 13.0 Hz, 0.5 H of CH_2Ph), 5.02 (d, J = 12.7 Hz, 0.5 H of CH_2Ph), 5.07 (d, J = 13.0 Hz, 0.5 H of CH_2Ph), 5.09 (d, J = 12.8 Hz, 0.5 H of CH_2Ph), 7.25—7.45 (m, 5 H, Ar), 12.2—12.8 (br, 1 H, COOH); LRMS (FAB) m/z (rel intensity) 380.4 (M^++H; 25), 336.4 (−CO_2; 100), 246.2 (20). Found: C, 59.75; H, 7.85; N, 3.85%. Calcd for $C_{19}H_{29}NO_5Si$: C, 60.13; H, 7.70; N, 3.69%.

(4*S*)-4-(*t*-Butyldimethylsilyloxy)-L-proline (18). A mixture of **20** (1.90 g, 5.00 mmol) and 5% Pd on carbon (520 mg) in MeOH (20 mL) was stirred under a balloon of hydrogen at room temperature for 30 min. The catalyst was filtered off, and the filtrate was evaporated to give a crystalline solid **18** (1.23 g, 99%). For analytical purposes, the product was recrystallized from water (652 mg, 53%): Mp 203.8—206.8 °C; $[\alpha]_D^{18}$ −24.9° (*c* 1.06, MeOH); IR (Nujol®) 3400 (COOH), 1620 (COO), 1250 cm^{-1} (N–O); ^1H NMR (CD_3OD, 200 MHz) δ = −0.05 (s, 6 H of $Si(CH_3)_2$), 0.79 (s, 9 H, $SiC(CH_3)_3$), 2.07—2.22 (m, 1 H of NCHCH_2), 2.30 (ddd, *J* = 4.4, 10.1, and 13.6 Hz, 1 H of NCHCH_2), 3.09—3.27 (m, 2 H, CH_2N), 3.92 (dd, *J* = 4.2 and 10.1 Hz, 1 H, C*H*COOH), 4.40—4.50 (m, 1 H, CHOSi); ^{13}C NMR (CD_3OD, 68 MHz) δ = −5.0 and −4.9 ($Si(CH_3)_2$), 18.7 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 39.3, 54.8, 60.9, 72.0, 173.9 (COOH); LRMS (FAB) *m/z* (rel intensity) 246.2 (M^++H; 100), 200.1 (11). Found: C, 54.13; H, 9.80; N, 5.65%. Calcd for $C_{11}H_{23}NO_3Si$: C, 53.84; H, 9.45; N, 5.71%.

(4*S*)-4-(*t*-Butyldimethylsilyloxy)-1-pyrroline *N*-Oxide ((*S*)-17a): 68% yield; mp 69.0—70.1 °C (decomp); $[\alpha]_D^{18}$ +52.7° (*c* 1.02, MeOH); IR (CH_2Cl_2) 1585 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 2.54—2.66 (m, 1 H of NCHCH_2), 2.92—3.08 (m, 1 H of NCHCH_2), 3.72—3.82 (m, 1 H of CH_2N), 4.02—4.14 (m, 1 H of CH_2N), 4.57—4.66 (m, 1 H, CHOSi), 6.78—6.84 (m, 1 H, N=CH); LRMS (FAB) *m/z* (rel intensity) 216.2 (M^++H; 100), 200.1 (M^+−16; 11). Found: C, 55.58; H, 10.02; N, 6.47%. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50%.

Methyl (2*S*,4*R*)-1-(*t*-Butoxycarbonyl)-4-(*t*-butyldimethylsilyloxy)-2-methylprolinate (24). To a solution of methyl (2*S*, 4*R*)-1-(*t*-butoxycarbonyl)-4-(*t*-butyldimethylsilyloxy)-L-prolinate (**23**)[26] (3.29 g, 9.17 mmol) in THF (30 mL) was added 1.50 M lithium diisopropylamide in hexane (6.50 mL, 9.75 mmol) at −78 °C. After stirring for 30 min at −78 °C, the solution was treated with HMPA (7.98 mL) and methyl iodide (0.685 mL, 11.0 mmol) at −78 °C and gradually warmed up to room temperature over 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with a solvent mixture of hexane and EtOAc (2/1). The organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (5—10% EtOAc in hexane) gave **24** (major isomer, 2.29 g, 67%), its diastereomer (273 mg, 8%), and a mixture of diastereomers (847 mg, 25%): $[\alpha]_D^{20}$ −18.0° (*c* 1.10, MeOH); IR (CH_2Cl_2) 1740 (COO), 1690 cm^{-1} (NCO); ^1H NMR ($CDCl_3$, 200 MHz, a 1 : 3 of conformational isomers) δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.82 (s, 9 H, $SiC(CH_3)_3$), 1.35 (s, 3/4×9 H, $OC(CH_3)_3$), 1.39 (s, 1/4×9 H, $OC(CH_3)_3$), 1.58 (s, 3/4×3 H, $NCCH_3$), 1.61 (s, 1/4×3 H, $NCCH_3$), 1.75—1.93 (m, 1 H of CHCH_2C), 2.12—2.30 (m, 1 H of CHCH_2C), 3.20—3.40 (m, 1 H of CH_2N), 3.65 (s, 3 H, OCH_3), 3.55—3.75 (m, 1 H of CH_2N), 4.26—4.37 (m, 1 H, CHOSi); LRMS (FAB) *m/z* (rel intensity) 374.2 (M^++H; 9), 274.1 (100).

(2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-2-methylproline (21). To a mixture of **24** (9.38 g, 26.1 mmol) and 2,6-lutidine (3.64 mL, 31.3 mmol) in CH_2Cl_2 (80 mL) was added trimethylsilyl trifluoromethanesulfonate (5.54 mL, 28.7 mmol) at −78 °C. The reaction mixture was gradually warmed up to room temperature over 1 h. The reaction mixture was diluted with hexane, and the solution was washed with water and brine, and then evaporated. The residue was dissolved in MeOH (30 mL), and treated with 1 M NaOH (31.3 mL) at room temperature for 3 h. The reaction mixture was then concentrated, and the oily residue was dissolved in water. The aqueous layer was washed with EtOAc/hexane (1/2) and acidified with 1 M HCl (31 mL) to pH 4. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give crude **21** as a solid. Recrystallization from 5% MeOH in EtOAc gave pure **21** (3.97 g, 59%). Further purification of mother liquor by column chromatography and recrystallization gave additional **21** (1.15 g, 17%): 76% total yield; mp 185.0—185.2 °C; $[\alpha]_D^{19}$ −39.1° (*c* 1.02, MeOH); IR (CH_2Cl_2) 1610 cm^{-1} (COO); ^1H NMR (CD_3OD, 200 MHz) δ = −0.01 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 1.56 (s, 3 H, $NCCH_3$), 1.85 (ddd, *J* = 1.7, 3.0, and 13.9 Hz, 1 H of CH_2CHN), 2.38 (dd, *J* = 5.2 and 13.9 Hz, 1 H of CH_2CHN), 3.06 (dt, *J* = 2.2 and 12.1 Hz, 1 H of CH_2N), 3.30 (dd, *J* = 4.5 and 12.1 Hz, 1 H of CH_2N), 4.43—4.53 (m, 1 H, CHOSi); ^{13}C NMR (CD_3OD, 68 MHz) δ = −5.0 and −4.8 ($Si(CH_3)_2$), 18.8 ($SiC(CH_3)_3$), 24.4 ($NCCH_3$), 26.2 ($SiC(CH_3)_3$), 46.3, 55.0, 71.2, 73.1, 176.7 (COOH); LRMS (FAB) *m/z* (rel intensity) 260.3 (M^++H; 100), 214.1 (–HCO_2H; 8). Found: C, 55.26; H, 10.01; N, 5.18%. Calcd for $C_{12}H_{25}NO_3Si$: C, 55.56; H, 9.71; N, 5.40%.

The stereochemistry of **21** was determined by the 2D-NOESY analysis. The NOESY spectrum showed cross-peaks between H^4 and $H^{3\beta}$, and between Me and $H^{3\alpha}$. These 2D NOESY cross-peaks are consistent with the structure shown in Fig. 6 where the *t*-butyldimethylsilyl and Me groups are *cis*.

(4*R*)-4-(*t*-Butyldimethylsilyloxy)-2-methyl-1-pyrroline *N*-Oxide (22). The oxidation of **21** (518.8 mg, 2.00 mmol) was carried out according to the typical procedure to give (*R*)-**22** (465 mg, 99%). For analytical purposes, the product was recrystallized from hexane (350 mg, 76%): Mp 71.4—74.4 °C (decomp); $[\alpha]_D^{20}$ −36.8° (*c* 1.09, MeOH); IR (CH_2Cl_2) 1615 (C=N), 1225 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 200 MHz) δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 1.97—2.03 (m, 3 H of N=CCH_3), 2.45—2.63 (m, 1 H of N=CCH_2), 2.97 (ddq, *J* = 1.5, 6.7, and 18.5 Hz, 1 H of N=CCH_2), 3.70—3.85 (m, 1 H of CH_2N), 4.00—4.18 (m, 1 H of CH_2N), 4.38—4.50 (m, 1 H, CHOSi); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −4.8 ($Si(CH_3)_2$), 12.6 (=CCH_3), 17.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 44.1, 63.9, 70.5, 143.1 (N=C); MS (FAB) *m/z* (rel intensity) 459 ($2M^+$+H; 70), 230 (M^++H; 100). Found: C, 57.29; H, 10.37; N, 5.97%. Calcd for $C_{11}H_{23}NO_2Si$: C, 57.59; H, 10.10; N, 6.10%.

(4*R*)-4-(*t*-Butyldimethylsilyloxy)-1-hydroxy-L-proline (25b). A mixture of methyl (4*R*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-prolinate (**27**)[25] (5.39 g, 13.7 mmol) and 5% Pd on carbon (1.42 g) in MeOH (40 mL) was stirred under a balloon of hydrogen at room temperature for 1 h. The catalyst was filtered off, and the filtrate was evaporated. The residue was dissolved in EtOAc, and the solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. To a solution of the residue and SeO_2 (121 mg, 1.09 mmol) in acetone (40 mL) was added a 30% H_2O_2 solution (4.1 mL, 41.0 mmol) at 0 °C. The reaction temperature was then maintained between 10—15 °C, and the mixture was stirred for 40 min. The temperature is important, since a higher temperature may cause further oxidation to nitrones. After reductive work up with Na_2SO_3 (6.9 g), the solution was evaporated. The residue was dissolved in EtOAc,

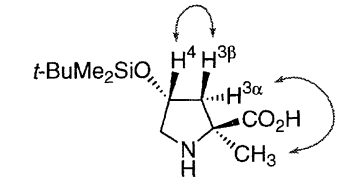


Fig. 6. The NOE correlations of **21**.

and the solution was washed with brine, dried over $MgSO_4$, and evaporated to give methyl (4*R*)-4-(*t*-butyldimethylsilyloxy)-1-hydroxy-L-prolinate (**28**). Ester **28** was dissolved in MeOH (50 mL) and saponified with 1 M NaOH (15.1 mL) at room temperature for 1 h. After treatment with 1 M HCl (15 mL), the solution was concentrated. The residue was taken up in CH_2Cl_2 and water. The organic phase was separated, washed with brine, dried over $MgSO_4$, and evaporated. The precipitated solid was filtered and recrystallized from MeOH to give **25b** (960 mg, 27%): Mp 140.6—140.8 °C (decomp); $[\alpha]_D^{21}$ −49.83° (*c* 0.62, MeOH); IR (Nujol®) 1600 cm^{-1} (COO); ^{1}H NMR (CD_3OD, 200 MHz) δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.81 (s, 9 H, $SiC(CH_3)_3$), 1.93—2.20 (m, 2 H, CH_2CHN), 2.83 (dd, *J* = 4.5 and 11.3 Hz, 1 H of CH_2N), 3.59 (dd, *J* = 5.9 and 11.3 Hz, 1 H of CH_2N), 3.80 (dd, *J* = 8.6 and 9.6 Hz, 1 H, CHN), 4.30—4.42 (m, 1 H, CHOSi); ^{13}C NMR (CD_3OD, 68 MHz) δ = −4.8 and −4.7 ($Si(CH_3)_2$), 18.8 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 38.5, 67.5, 70.4, 70.7, 174.6 (COOH). Found: C, 50.24; H, 9.12; N, 5.20%. Calcd for $C_{11}H_{23}NO_4Si$: C, 50.54; H, 8.87; N, 5.36%.

Oxidation of Hydroxylamine 25b. According to the typical procedure except for the amount of H_2O_2 (1.5 mol amt., 0.15 mL, 1.50 mmol), the oxidation of **25b** (261 mg, 1.00 mmol) was carried out to give (*R*)-**17a** (148 mg, 69%).

ZnI_2-Catalyzed Reaction of Nitrone (*R*)-17a with Ketene *t*-Butyldimethylsilyl Methyl Acetal (29a). To a stirred solution of molecular sieves 4A (1.00 g), ZnI_2(255 mg, 0.80 mmol), and nitrone (*R*)-**17a** (862 mg, 4.00 mmol) in CH_2Cl_2 (20 mL) was added dropwise ketene *t*-butyldimethylsilyl methyl acetal (**29a**) (1.06 mL, 4.80 mmol) at −90 °C; this solution was stirred at −90 °C for 1 h. The crude reaction mixture was poured into a mixture of hexane and saturated aqueous $NaHCO_3$. The organic solution was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent and column chromatography on SiO_2 (5—20% EtOAc in hexane) afforded methyl (2*R*,4*R*)-[1,4-bis(t-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-**30**) and the (2*S*,4*R*)-isomer (*trans*-**30**) (1.54 g, 95%) as a *cis* and *trans* mixture: IR (neat) 1735 cm^{-1} (COOMe); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.02 (s, 6 H, $Si(CH_3)_2$), 0.03 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.35—1.55 (m, 2 H of $NCHCH_2$), 2.25—2.60 (m, 1 H of NCH_2), 2.65—2.85 (m, 1 H of NCH_2), 2.85—3.05 (m, 2 H of CH_2COOMe), 3.15—3.35 (m, 1 H of NC*H*), 3.67 (s, 3 H, $COOCH_3$), 4.35—4.50 (m, 1 H, CHOSi); LRMS (APCI) *m*/*z* 404 (M^++H).

Methyl (2*R*,4*R*)-[1-Benzoyloxy-4-(*t*-butyldimethylsilyloxy)-pyrrolidin-2-yl]acetate (*cis*-31). The diastereomixture of **30** was treated with HOAc (10 mL) at room temperature for 14 h. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The hydroxylamine thus obtained was dissolved in CH_2Cl_2 (30 mL), and treated with NEt_3 (0.627 mL, 4.5 mmol) and benzoyl chloride (0.44 mL, 3.80 mmol) at 0 °C for 30 min. The reaction mixture was diluted with hexane, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on SiO_2 (5% acetone in CH_2Cl_2) gave **31** (1.16 g, 85%) as a solid. The ratio of *cis*-**31**/*trans*-**31** was determined by HPLC analysis (column: OA-2000; eluent: 10% *i*-PrOH in hexane; flow rate: 1.0 mL min^{-1}; detect: UV (229 nm)) to be 81 : 19. Diastereomerically pure *cis*-**31** was obtained by recrystallization from hexane in 48% yield: Mp 66.2—66.7 °C; $[\alpha]_D^{28}$ +31.7° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 1733 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.07 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.70 (ddd, *J* = 5.1, 9.4, and 13.1 Hz, 1 H of $NCHCH_2$), 2.56 (dt, *J* = 7.4 and 13.1 Hz, 1 H of $NCHCH_2$), 2.60 (dd, *J* = 8.5 and 15.9 Hz, 1 H of CH_2COOMe), 2.93 (dd, *J* = 5.5 and 15.9 Hz, 1 H of CH_2COOMe), 3.28 (dd, *J* = 7.3 and 12.5 Hz, 1 H of NCH_2), 3.54 (dd, *J* = 3.2 and 12.5 Hz, 1 H of NCH_2), 3.62 (s, 3 H, $COOCH_3$), 3.60—3.82 (m, 1 H, NCH), 4.50—4.65 (m, 1 H, CHOSi), 7.38—7.60 (m, 3 H, Ar), 7.90—8.10 (m, 2 H, Ar). Found: C, 61.08; H, 8.24; N, 3.56%. Calcd for $C_{20}H_{31}NO_5Si$: C, 61.04; H, 7.94; N, 3.56%.

Methyl (2*R*,4*R*)-[1-Benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*cis*-32). A mixture of *cis*-**31** (210 mg, 0.533 mmol), HOAc (0.15 mL, 2.66 mmol), and 10% Pd on carbon (55 mg) in MeOH (5 mL) was stirred under a balloon of hydrogen at room temperature for 2 h. The catalyst was filtered off and the filtrate was evaporated. The residue was diluted with EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (5 mL), and treated with benzyl chloroformate (0.076 mL, 0.533 mmol) at room temperature for 30 min. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Concentration and preparative TLC (10% EtOAc in hexane) afforded *cis*-**32** (196 mg, 90%): $[\alpha]_D^{28}$ +10.5° (*c* 1.03, $CHCl_3$); IR (neat) 1733 (COO), 1700 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$, 200 MHz, 55 °C) δ = 0.07 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.80—1.93 (m, 1 H of $NCHCH_2$), 2.18 (ddd, *J* = 5.1, 8.2 and 13.5 Hz, 1 H of $NCHCH_2$), 2.75 (dd, *J* = 9.8 and 15.4 Hz, 1 H of CH_2COOMe), 2.85—3.15 (m, 1 H of CH_2COOMe), 3.35 (ddd, *J* = 1.2, 2.4, and 11.6 Hz, 1 H of NCH_2), 3.60 (dd, *J* = 5.2 and 11.6 Hz, 1 H of NCH_2), 3.62 (s, 3 H, $COOCH_3$), 4.23—4.42 (m, 2 H, NCH and CHOSi), 7.3—7.5 (m, 5 H, Ar). Found: C, 61.77; H, 8.35; N, 3.43%. Calcd for $C_{21}H_{33}NO_5Si$: C, 61.88; H, 8.16; N, 3.43%.

Methyl (2*S*,4*R*)-[1-Benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*trans*-32).[39b] To a solution of 1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-L-proline (**33**) (759 mg, 2.00 mmol) and NEt_3 (0.28 mL, 2.00 mmol) in THF (10 mL) was added ethyl chloroformate (0.19 mL, 2.00 mmol) at 0 °C. After the solution was stirred at the same temperature for 30 min, a solution of diazomethane in ether was added until the intense yellow color persisted. The mixture was allowed to warm to room temperature and then stirred for 3 h. Excess diazomethane was destroyed by adding of a small amount of HOAc. The reaction mixture was diluted with EtOAc and the solution was washed with brine, dried over $MgSO_4$, and evaporated. The diazo ketone thus obtained was dissolved in MeOH (10 mL). After the addition of silver benzoate (46 mg, 0.20 mmol) in NEt_3 (0.84 mL, 6.00 mmol) at −25 °C with the exclusion of light, the mixture was allowed to warm to room temperature within 3 h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and preparative TLC (20% EtOAc in hexane) afforded *trans*-**32** (611 mg, 75%): IR (neat) 1725 (COO), 1690 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$, 200 MHz, 2 : 1 mixture of conformers) δ = 0.07 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 1.75—1.85 (m, 1 H of $NCHCH_2$), 2.00—2.20 (m, 1 H of $NCHCH_2$), 2.30—2.55 (m, 1 H), 2.75—3.10 (m, 1 H), 3.35—3.50 (m, 2 H), 3.57 (br s, 1/3×3 H, COOMe), 3.60 (br s, 2/3×3 H, COOMe), 4.20—4.40 (m, 2 H), 5.00—5.20 (m, 2 H, OCH_2Ph), 7.20—7.40 (m, 5 H, Ar); LRMS (APCI) *m*/*z* 408 (M^++H).

Typical Procedure for Addition of Lithium Acetylides 34 to Nitrone (*R*)-17a. (2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-1-hydroxy-2-(2-trimethylsilylethynyl)pyrrolidine (*trans*-35a). To a THF solution (20 mL) of lithium acetylide **34a**, prepared by treating ethynyltrimethylsilane (1.06 mL, 7.50 mmol) with a 1.68 M hexane

solution of butyllithium (4.91 mL, 8.25 mmol) in THF at 0 °C for 30 min, was added a solution of nitrone **17a** (1.08 g, 5.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring at −78 °C for 1 h, the reaction mixture was poured into saturated aqueous NH_4Cl and hexane. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (2.5—7.5% EtOAc in hexane) gave **35a** (1.379 g, 88%) as a *trans/cis* mixture in a ratio of 93/7 (^{1}H NMR analysis). Recrystallization from cold hexane gave pure *trans*-**35a** (790 mg, 63%).

***trans*-35a**: Mp 56—57 °C; $[\alpha]_D^{30}$ −29.40° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 2150 cm^{-1} (acetylene); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = −0.13 (s, 6 H, $Si(CH_3)_2$), 0.2 (s, 9 H, $Si(CH_3)_3$), 0.70 (s, 9 H, $SiC(CH_3)_3$), 1.85 (ddd, *J* = 2.6, 7.6, and 13.2 Hz, 1 H of CH_2CHN), 1.88—2.15 (m, 1 H of CH_2CHN), 2.67 (dd, *J* = 4.7 and 11.3 Hz, 1 H of CH_2N), 3.35 (dd, *J* = 6.3 and 11.3 Hz, 1 H of CH_2N), 3.77 (t, *J* = 8.3 Hz, 1 H, NCH), 4.15—4.35 (m, 1 H, CHOSi), 8.58 (br s, 1 H, NOH).

***cis*-35a (selected)**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.68 (ddd, *J* = 4.3, 8.8, and 13.3 Hz, 1 H of CH_2CHN), 2.35 (dt, *J* = 7.8 and 13.3 Hz, 1 H of CH_2CHN), 2.86 (dd, *J* = 6.8 and 11.0 Hz, 1 H of CH_2N), 3.03 (dd, *J* = 3.2 and 11.0 Hz, 1 H of CH_2N), 3.43 (t, *J* = 8.2 Hz, 1 H, NCH). Found: C, 57.55; H, 9.64; N, 4.61%. Calcd for $C_{15}H_{31}NO_2Si_2$: C, 57.45; H, 9.96; N, 4.47%.

(2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-1-hydroxy-2-(3-hydroxy-1-propynyl)pyrrolidine (*trans*-35b). The reaction of nitrone (*R*)-**17a** (861 mg, 4.00 mmol) and dilithium acetylide **34b**, prepared from 2-propyn-1-ol (336 mg, 6.00 mmol) and 1.68 M butyllithium in hexane (7.14 mL, 12.0 mmol) at 0 °C for 30 min, gave *trans*-**35b** (487 mg, 45%) and *cis*-**35b** (73 mg, 7%) after column chromatographic separation.

***trans*-35b**: Mp 90—91 °C; $[\alpha]_D^{29}$ −28.99° (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.02 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.94 (ddd, *J* = 2.3, 7.4, and 13.2 Hz, 1 H of CH_2CHN), 2.00—2.25 (m, 1 H of CH_2CHN), 2.80 (dd, *J* = 4.7 and 11.4 Hz, 1 H of CH_2N), 3.50 (dd, *J* = 6.4 and 11.4 Hz, 1 H of CH_2N), 3.92 (t, *J* = 8.4 Hz, 1 H, NCH), 4.24 (s, 2 H, CH_2OH), 4.25—4.50 (m, 1 H, CHOSi). Found: C, 57.35; H, 9.22; N, 5.31%. Calcd for $C_{13}H_{25}NO_3Si_2$: C, 57.53; H, 9.28; N, 5.16%.

***cis*-35b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.02 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.80 (ddd, *J* = 4.2, 9.1, and 13.3 Hz, 1 H of CH_2CHN), 2.50 (dt, *J* = 7.9 and 13.4 Hz, 1 H of CH_2CHN), 2.96 (dd, *J* = 6.6 and 11.1 Hz, 1 H of CH_2N), 3.15 (dd, *J* = 3.0 and 11.1 Hz, 1 H of CH_2N), 3.59 (dd, *J* = 7.9 and 9.1 Hz, 1 H, NCH), 4.25 (s, 2 H, CH_2OH), 4.26—4.42 (m, 1 H, CHOSi).

(2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-2-[3-(*t*-butyldimethylsilyloxy)-1-propynyl]-1-hydroxypyrrolidine (*trans*-35c). The reaction (−78 °C, 30 min) of nitrone (*R*)-**17a** (861 mg, 4.00 mmol) and lithium acetylide **34c**, prepared from 3-(*t*-butyldimethylsilyloxy)-1-propyne (1.02 g, 6.00 mmol) and 1.68 M butyllithium in hexane (3.57 mL, 6.00 mmol) at 0 °C for 30 min, gave a mixture of *trans*- and *cis*-**35c** (1.41 g, 91%) in a ratio of 94/6 (^{1}H NMR analysis).

***trans*-35c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$), 0.75 (s, 9 H, $SiC(CH_3)_3$), 0.78 (s, 9 H, $SiC(CH_3)_3$), 1.88 (ddd, *J* = 2.8, 7.5, and 13.2 Hz, 1 H of CH_2CHN), 2.06 (dt, *J* = 8.2 and 13.2 Hz, 1 H of CH_2CHN), 2.75 (dd, *J* = 4.5 and 11.4 Hz, 1 H of CH_2N), 3.39 (dd, *J* = 6.4 and 11.4 Hz, 1 H of CH_2N), 3.85 (t, *J* = 7.7 Hz, 1 H, NCH), 4.23 (s, 2 H, CH_2OH), 4.18—4.40 (m, 1 H, CHOSi), 5.91 (br s, 1 H, NOH).

***cis*-35c (selected)**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.40 (dt, *J* = 6.7 and 13.4 Hz, 1 H of CH_2CHN), 2.86 (dd, *J* = 5.6 and 9.5 Hz, 1 H of CH_2N), 3.08 (dd, *J* = 2.6 and 9.5 Hz, 1 H of CH_2N), 3.50 (t, *J* = 7.0 Hz, 1 H, NCH).

(2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-2-[4-(*t*-butyldimethylsilyloxy)-1-butynyl]-1-hydroxypyrrolidine (*trans*-35d). The reaction (−78 °C, 60 min) of nitrone (*R*)-**17a** (861 mg, 4.00 mmol) and lithium acetylide **34d**, prepared from 4-(*t*-butyldimethylsilyloxy)-1-butyne (1.106 g, 6.00 mmol) and a 1.60 M hexane solution of butyllithium (3.57 mL, 5.71 mmol) at 0 °C for 30 min, gave **35d** (1.368 g, 86%) in a *trans/cis* ratio of 92/8 (^{1}H NMR analysis): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = −0.29 (s, 6 H, $Si(CH_3)_2$), 0.15 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.92 (ddd, *J* = 2.7, 7.4, and 13.2 Hz, 1 H of CH_2CHN), 2.00—2.20 (m, 1 H of CH_2CHN), 2.37 (dt, *J* = 2.0 and 7.2 Hz, 2 H, CH_2CH_2OSi), 2.78 (dd, *J* = 4.6 and 11.3 Hz, 1 H of CH_2N), 3.42 (dd, *J* = 6.4 and 11.3 Hz, 1 H of CH_2N), 3.65 (t, *J* = 7.2 Hz, 2 H, CH_2OSi), 3.78—3.90 (m, 1 H, CHN), 4.27—4.40 (m, 1 H, CHOSi).

(2*S*,4*R*)-1-Benzoyloxy-4-(*t*-butyldimethylsilyloxy)-2-[3-(*t*-butyldimethylsilyloxy)-1-propynyl]pyrrolidine (*trans*-36c). A mixture of **35c** (*trans/cis* = 94 : 6) (3.70 g, 9.59 mmol) and NEt_3 (1.6 mL, 11.5 mmol) in CH_2Cl_2 (30 mL) was treated with benzoyl chloride (1.22 mL, 10.5 mmol) at 0 °C for 30 min and then diluted with hexane/EtOAc (1/1). The mixture was washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (2.5—7.5% EtOAc in hexane) gave *trans*-**36c** (3.90 g, 83%) and *cis*-**36c** (329 mg, 7%).

***trans*-36c**: $[\alpha]_D^{28}$ −31.33° (*c* 1.05, $CHCl_3$); IR (Neat) 1745 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.07 (s, 6 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.93 (s, 9 H, $SiC(CH_3)_3$), 2.14 (ddd, *J* = 2.8, 7.2, and 13.2 Hz, $H^{3\alpha}$), 2.33 (ddd, *J* = 7.2, 8.8, and 13.2 Hz, $H^{3\beta}$), 3.08 (dd, *J* = 3.9 and 12.1 Hz, $H^{5\alpha}$), 3.84 (dd, *J* = 6.6 and 12.1 Hz, $H^{5\beta}$), 4.26 (d, *J* = 1.8 Hz, 2 H, CH_2OSi), 4.30—4.45 (m, 1 H, H^2), 4.45—4.60 (m, 1 H, H^4), 7.38—7.60 (m, 3 H, Ar), 7.95—8.05 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −5.2 and −4.8 ($Si(CH_3)_2$), 18.0 and 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 40.3, 51.8, 57.7, 65.2, 69.5, 81.6, 83.5, 128.4 (Ar), 129.2 (Ar), 129.6 (Ar), 133.0 (Ar), 164.9 (COO). Found: C, 63.59; H, 9.02; N, 2.61%. Calcd for $C_{26}H_{43}NO_4Si_2$: C, 63.76; H, 8.85; N, 2.86%.

***cis*-36c**: $[\alpha]_D^{28}$ +38.11° (*c* 1.01, $CHCl_3$); IR (Neat) 1740 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 2.07 (ddd, *J* = 4.6, 7.8, and 12.8 Hz, $H^{3\alpha}$), 2.59 (dt, *J* = 7.8 and 13.3 Hz, $H^{3\beta}$), 3.37 (dd, *J* = 6.9 and 11.9 Hz, $H^{5\beta}$), 3.49 (dd, *J* = 4.3 and 11.9 Hz, $H^{5\alpha}$), 4.05—4.20 (m, 1 H, H^2), 4.29 (d, *J* = 1.8 Hz, 2 H, CH_2OSi), 4.45—4.60 (m, 1 H, H^4), 7.35—7.60 (m, 3 H, Ar), 7.95—8.05 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −5.1 and −4.8 ($Si(CH_3)_2$), 18.0 and 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 40.3, 51.8, 58.0, 64.1, 69.4, 81.6, 83.8, 128.3 (Ar), 129.2 (Ar), 129.6 (Ar), 133.0 (Ar), 164.8 (COO).

(2*S*,4*R*)-1-Benzoyloxy-4-(*t*-butyldimethylsilyloxy)-2-[4-(*t*-butyldimethylsilyloxy)-1-butynyl]pyrrolidine (*trans*-36d). A mixture of **35d** (367 mg, 0.918 mmol) and NEt_3 (0.153 mL, 1.10 mmol) in CH_2Cl_2 (10 mL) was treated with benzoyl chloride (0.117 mL, 1.01 mmol) at 0 °C for 30 min and then diluted with hexane/EtOAc (1/1). The mixture was washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (2.5—7.5% EtOAc in hexane) gave *trans*-**36d** (400 mg, 87%) and *cis*-**36d** (40 mg, 9%).

***trans*-36d**: $[\alpha]_D^{21}$ −28.6° (*c* 1.11, MeOH); IR (Neat) 1725 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.15 (s, 6 H, $Si(CH_3)_2$), 0.48 (s, 3 H, $Si(CH_3)_2$), 0.65 (s, 3 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 2.11 (ddd, *J* = 2.6, 7.3,

and 13.2 Hz, $H^{3\alpha}$), 2.30 (ddd, J = 7.3, 9.1, and 13.2 Hz, $H^{3\beta}$), 2.33 (dt, J = 2.0 and 7.4 Hz, 2 H, CH_2CH_2OSi), 3.08 (dd, J = 3.8 and 12.4 Hz, $H^{5\alpha}$), 3.60 (t, J = 7.6 Hz, 2 H, CH_2OSi), 3.83 (dd, J = 6.5 and 12.4 Hz, $H^{5\beta}$), 4.23—4.36 (m, 1 H, H^2), 4.48—4.62 (m, 1 H, H^4), 7.38—7.60 (m, 3 H, Ar), 7.95—8.05 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −5.3 and −4.8 ($Si(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 23.1, 25.8 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 40.7, 58.0, 61.8, 65.3, 69.8, 78.1, 82.1, 128.3 (Ar), 129.3 (Ar), 129.6 (Ar), 133.0 (Ar), 165.0 (COO). Found: C, 64.57; H, 9.26; N, 2.69%. Calcd for $C_{27}H_{45}NO_4Si_2$: C, 64.37; H, 9.00; N, 2.78%.

***cis*-36d**: $[\alpha]_D^{26}$ +30.99° (*c* 1.01, MeOH); IR (Neat) 1720 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = −0.01 (s, 3 H, $Si(CH_3)_2$), 0.00 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 2.03 (ddd, J = 4.6, 8.0, and 12.9 Hz, $H^{3\alpha}$), 2.37 (dt, J = 2.0 and 7.6 Hz, 2 H, CH_2CH_2OSi), 2.56 (dt, J = 7.7 and 13.2 Hz, $H^{3\beta}$), 3.37 (dd, J = 6.8 and 12.2 Hz, $H^{5\beta}$), 3.48 (dd, J = 4.3 and 12.3 Hz, $H^{5\alpha}$), 3.62 (t, J = 7.4 Hz, 2 H, CH_2OSi), 3.98—4.10 (m, 1 H, H^2), 4.45—4.60 (m, 1 H, H^4), 7.37—7.60 (m, 3 H, Ar), 7.90—8.11 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −5.3 and −4.8 ($Si(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 23.1, 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 40.8, 58.4, 61.9, 64.3, 69.8, 78.0, 82.4, 128.4, 129.6, 130.2, 133.0, 164.8 (COO).

Synthesis of (3*R*,5*R*)-1-Aza-3-hydroxybicyclo[3.3.0]octane (37). (2*S*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-1-hydroxy-2-(3-hydroxy-1-propynyl)pyrrolidine (*trans*-35b). A solution of **35c** (1.05 g, 2.63 mmol) and 1 M HCl (2.9 mL) in MeOH (10 mL) was stirred at 0 °C for 5 h. The solution was neutralized with 1 M NaOH (3 mL) and the solution was evaporated. The residue was taken up in EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. The precipitated crystalline solid was washed with hexane to give *trans*-**35b** (607 mg, 85%). The spectral data were in good agreement with those mentioned above.

(2*R*,4*R*)-1-Benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-2-(3-chloropropyl)pyrrolidine (39). A mixture of **35b** (1.43 g, 5.28 mmol), HOAc (0.45 mL, 7.93 mmol), and 5% Pd on carbon (550 mg) in MeOH (30 mL) was stirred under a balloon of hydrogen at 0 °C for 1 h and then at room temperature for 10 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in a solvent mixture of EtOAc (20 mL) and THF (3 mL). To the solution were added CbzCl (0.83 mL, 5.80 mmol) and saturated $NaHCO_3$ solution (10 mL). After stirring at room temperature for 30 min, the organic layer was separated, washed with brine, and dried over $MgSO_4$. Purification by column chromatography on SiO_2 (10—40% EtOAc in hexane) gave (2*R*,4*R*)-1-benzyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)-2-(3-hydroxypropyl)pyrrolidine (1.43 g, 69%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.04 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.30—2.20 (m, 6 H), 3.30—3.80 (m, 4 H), 3.90—4.20 (m, 1 H), 4.30—4.42 (m, 1 H, CHO), 5.02 (d, J = 12.4 Hz, 1 H of $PhCH_2O$), 5.12 (d, J = 12.4 Hz, 1 H of $PhCH_2O$), 7.20—7.40 (m, 5 H); LRMS (APCI) 394 (M^++H).

To a solution of the pyrrolidine thus obtained (1.43 g, 3.63 mmol) and PPh_3 (1.05 g, 3.99 mmol) in 1,2-dichloroethane (20 mL) was added carbon tetrachloride (0.45 mL, 4.71 mmol) at room temperature. After the solution was stirred at 50 °C for 4 h, the reaction mixture was concentrated. The residue was purified by column chromatography on SiO_2 (5% EtOAc in hexane) to give **39** (1.36 g, 63% from **35b**). **39**: $[\alpha]_D^{28}$ −42.9° (*c* 1.34, MeOH); IR (CH_2Cl_2) 1700 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.04 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.40—2.10 (m, 6 H), 3.35—3.65 (m, 4 H), 3.90—4.10 (m, 1 H), 4.30—4.42 (m, 1 H, CHO), 5.05 (d, J = 12.4 Hz, 1 H of $PhCH_2O$), 5.15 (d, J = 12.4 Hz, 1 H of $PhCH_2O$), 7.20—7.40 (m, 5 H); LRMS (APCI) 412 (M^++H), 368 (−CO_2). Found: C, 61.33; H, 8.11; N, 3.33%. Calcd for $C_{21}H_{34}ClNO_3Si$: C, 61.21; H, 8.32; N, 3.40%.

(3*R*,5*R*)-1-Aza-3-hydroxybicyclo[3.3.0]octane (37). A mixture of **39** (1.93 g, 4.68 mmol) and 5% Pd on carbon (500 mg) in MeOH (30 mL) was stirred under a balloon of hydrogen at room temperature for 1 h. The catalyst was filtered off, and the filtrate was treated with Amberlite® IRA-400 (OH type) (2.12 g, 9.4 mmol) at room temperature for 30 min. The gel resin was filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on SiO_2 (10—15% MeOH in CH_2Cl_2) to give (3*R*,5*R*)-1-aza-3-(*t*-butyldimethylsilyloxy)bicyclo[3.3.0]octane (944 mg, 84%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.15 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.32—1.62 (m, 2 H), 1.73—2.08 (m, 4 H), 2.40—2.55 (m, 1 H), 2.73 (dd, J = 4.7 and 11.0 Hz, 1 H of CH_2N), 3.00 (dd, J = 2.9 and 10.9 Hz, 1 H of CH_2N), 3.05—3.15 (m, 1 H of CH_2N), 3.65—3.83 (m, 1 H, CHN), 4.40—4.50 (m, 1 H, CHO); LRMS (APCI) 242 (M^++H).

The pyrrolizidine thus obtained (944 mg, 3.91 mmol) was treated with 4 M HCl in 1,4-dioxane (2.0 mL, 8.0 mmol) at room temperature for 30 min. The mixture was concentrated and the precipitated crystalline solid was washed with THF to give **37** (563 mg, 73% from **39**). For analytical purposes **37** was transformed into its hydrochloride by treating with 4 M HCl in EtOAc: Mp 183—185 °C (decomp); $[\alpha]_D^{26}$ −10.6° (*c* 1.19, MeOH); ^{1}H NMR (CD_3OD, 200 MHz) δ = 1.80—2.40 (m, 6 H), 3.08—3.52 (m, 4 H), 3.55—3.67 (m, 1 H), 4.36—4.54 (m, 1 H), 4.55—4.62 (m, 1 H); LRMS (APCI) 128 (M^++H), 108 (M−H_2O). Found: C, 51.29; H, 8.66; N, 8.50%. Calcd for $C_7H_{14}ClNO$: C, 51.38; H, 8.62; N, 8.56%.

Synthesis of (6*R*,8*R*)-1-Aza-8-hydroxybicyclo[4.3.0]nonane (38). (2*R*,4*R*)-4-(*t*-Butyldimethylsilyloxy)-2-(4-hydroxybutyl)-pyrrolidine (40). A mixture of *trans*-**36d** (869 mg, 1.72 mmol), HOAc (0.19 mL), and 5% Pd on carbon (500 mg) in MeOH (10 mL) was stirred under a balloon of hydrogen at 0 °C for 1 h and then at room temperature for 10 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with MeOH and the solution was treated with 1 M HCl (1.7 mL) at 0 °C for 30 min. Purification by column chromatography on SiO_2 (5—10% MeOH in CH_2Cl_2) gave **40** (322 mg, 69%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.40—2.00 (m, 8 H), 2.75—2.90 (m, 1 H of NCH_2), 3.15 (dd, J = 4.6 and 11.8 Hz, 1 H of NCH_2), 3.30—3.50 (m, 1 H), 3.62 (t, J = 5.2 Hz, 2 H, CH_2OH), 4.30—4.50 (m, 3 H); LRMS (APCI) 274 (M^++H).

(6*R*,8*R*)-1-Aza-8-hydroxybicyclo[4.3.0]nonane (38). To a solution of **40** (761 mg, 2.78 mmol) in 1,2-dichloroethane were added PPh_3 (1.09 g, 4.16 mmol) and CBr_4 (1.20 g, 3.61 mmol) at 0 °C. The solution was stirred at room temperature for 30 min. The crude mixture was passed through a SiO_2 column and rinsed with 2.5—5.0% MeOH in CH_2Cl_2. The filtrate was concentrated under reduced pressure. The residue was treated with K_2CO_3 (575 mg, 4.17 mmol) and MeOH (20 mL) at room temperature for 12 h. The reaction mixture was concentrated and the residue was treated with 12 M HCl (0.5 mL) at room temperature for 3 h. The mixture was concentrated and purified by column chromatography on SiO_2 (5—10% MeOH in CH_2Cl_2) to give **38** (195 mg, 50%). For analytical purposes **38** was transformed into its hydrochloride by treatment with 4 M HCl in EtOAc: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.00—2.00 (m, 8 H), 2.05—2.45 (m, 3 H), 2.95—3.10 (m, 1

H), 3.49 (dd, J = 6.8 and 9.8 Hz, 1 H, NCH), 4.35—4.60 (m, 1 H, CHOH); LRMS (APCI) 142 (M^++H).

38·HCl: Mp 155.4—156.6 °C; $[\alpha]_D^{26}$ −19.5° (c 1.31, MeOH); ^{1}H NMR (CD_3OD, 200 MHz) δ = 1.50—2.40 (m, 8 H), 2.70—3.80 (m, 4 H), 3.92 (dd, J = 6.6 and 12.1 Hz, 1 H, NCH), 4.40—4.70 (m, 1 H, CHOH). Found: C, 54.27; H, 9.26; N, 7.69%. Calcd for $C_8H_{16}ClNO$: C, 54.08; H, 9.07; N, 7.88%.

(*R*)-1-Benzyloxycarbonyl-3-hydroxypyrrolidine (44).[33,34] A mixture of *trans*-4-hydroxy-L-proline (**43**) (60.0 g, 0.521 mol), 2-cyclohexen-1-one (3.00 mL, 30.9 mmol), and cyclohexanol (300 mL) was heated at reflux for 3 h. The reaction mixture was taken up in EtOAc and water. To the solution were added K_2CO_3 (64 g) and benzyl chloroformate (74.0 mL, 0.521 mol), while maintaining the temperature below 15 °C, and the solution was stirred at room temperature for 30 min. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. After most of the cyclohexanol was distilled off (ca. 80 °C (0.5 mmHg, 1 mmHg = 133.322 Pa)), the precipitated crystals were recrystallized from solvent mixture of EtOAc and hexane to give **44** (77.7 g, 67%). Column chromatography of the mother liquor afforded more **44** (6.28 g, 5%): Total yield 72%; mp 75—77 °C; $[\alpha]_D^{22}$ −21.2° (c 1.00, $CHCl_3$); IR (Nujol®) 3400 (OH), 1680 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 1.86—1.98 (m, 2 H, NCH_2CH_2), 2.92 (br s, 1 H, OH), 3.37—3.62 (m, 4 H, CH_2NCH_2), 4.36—4.44 (m, 1 H, C*H*OH), 5.11 (s, 2 H, OCH_2Ph), 7.26—7.38 (m, 5 H, Ph).

(*R*)-1-Benzyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)pyrrolidine (42). To a stirred solution of **44** (44.3 g, 200 mmol) and *t*-butylchlorodimethylsilane (33.2 g, 220 mmol) in DMF (500 mL) was added dropwise NEt_3 (33.4 mL, 240 mmol) at 5—10 °C, and the solution was stirred at room temperature for 5 h. The reaction mixture was poured into a stirred mixture of hexane and water. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were washed successively with water and brine, and dried over $MgSO_4$. Concentration followed by distillation gave **42** (65.1 g, 97%) as an oil: Bp 175—176 °C (0.5 mmHg); $[\alpha]_D^{27}$ −21.1° (c 1.20, MeOH); IR (Neat) 1709 cm^{-1} (NCOO); ^{1}H NMR ($CDCl_3$, 270 MHz, 55 °C) δ = 0.06 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.75—1.98 (m, 2 H, NCH_2CH_2), 3.23—3.60 (m, 4 H, CH_2NCH_2), 4.33—4.42 (m, 1 H, CHOSi), 5.13 (s, 2 H, OCH_2Ph), 7.22—7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C, 1 : 1 of mixture of rotomers) δ = −4.9 and −4.8 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 34.1 and 34.8 (NCH_2CH), 43.9 and 44.1 (CH_2N), 54.2 and 54.5 (CH_2N), 66.6 (OCH_2Ph), 70.6 and 70.7 (CHOSi), 127.7, 128.3, and 137.2 (Ph), 154.9 (NCOO). HRMS (CI) Found: m/z 336.2005. Calcd for $C_{18}H_{30}NO_3Si$: (M^++H), 336.1995. LRMS (APCI) m/z 336 (M^++H), 292 (–CO_2), 202 (–Cbz). Found: C, 64.33; H, 8.63; N, 4.22%. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.43; H, 8.71; N, 4.17%.

Tungstate-Catalyzed Oxidation of (*R*)-3-(*t*-Butyldimethylsilyloxy)pyrrolidine ((*R*)-41) Prepared from 42. A mixture of **42** (3.35 g, 10.0 mmol) and 10% Pd on carbon (1.04 g) in MeOH (30 mL) was stirred under a balloon of hydrogen at room temperature for 2 h. The catalyst was filtered off, and the filtrate was evaporated to give a crystalline solid. The product was taken up in EtOAc, and the solution was washed with a K_2CO_3 solution and concentrated to give (*R*)-**41**, which was used for the next step without further purification. To a solution of (*R*)-**41** in CH_2Cl_2 (50 mL) were added at 0 °C a solution of $Na_2WO_4{\cdot}2H_2O$ (165 mg, 0.50 mmol) and Et_4NCl (83 mg, 1.0 mmol) in water (3 mL) and a 30% H_2O_2 solution (1.76 mL). After the mixture was stirred at 0 °C for 4 h, the excess of H_2O_2 was decomposed by adding $NaHSO_3$ with ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography on SiO_2 (1—5% MeOH in CH_2Cl_2) gave nitrone (*R*)-**45** (1.30 g, 61%) and its regioisomer (*R*)-**17a** (192 mg, 9%). (*R*)-**45**:[34] Mp 73.8—75.5 °C; $[\alpha]_D^{28}$ +55.9° (c 1.14, MeOH); IR (Nujol®) 1584 (C=N), 1258 cm^{-1} (N–O); ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 0.10 and 0.11 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 2.05 (dddd, J = 3.3, 5.5, 8.9, and 13.4 Hz, 1 H of CH_2CH_2N), 2.53 (dddd, J = 6.0, 7.5, 9.0, and 13.4 Hz, 1 H of CH_2CH_2N), 3.82 (ddddd, J = 0.7, 1.6, 5.5, 9.0, and 13.9 Hz, 1 H of CH_2N), 4.10 (dddt, J = 1.8, 6.0, 9.1, and 13.9 Hz, 1 H of CH_2N), 4.90—5.06 (m, 1 H, C*H*OSi), 6.85 (dd, J = 1.7 and 3.7 Hz, 1 H, CH=N); LRMS (EI) m/z (rel intensity) 215 (M^++H; 71), 158 (42), 75 (100). Found: C, 55.38; H, 9.56; N, 6.53%. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50%.

(*S*)-1-Benzyl-3-(*t*-butyldimethylsilyloxy)pyrrolidine (46). To a stirred mixture of (*S*)-*N*-benzyl-3-hydroxysuccinimide (**47**) (20.5 g, 100 mmol) in THF (200 mL) was added 10 M dimethyl sulfide–borane (1/1) (35.0 mL, 350 mmol) at 0 °C, and the solution was heated at reflux for 2 h. The excess borane reagent was quenched by slow addition of a solution of THF/water (1/1). To the reaction mixture was added NaOH (46 g), and the solution was heated at reflux for 40 h. The solution was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. To a solution of the crude oil in DMF (50 mL) were added *t*-butylchlorodimethylsilane (15.1 g, 100 mmol) and imidazole (8.85 g, 130 mmol). After stirring at room temperature for 2 h, the solution was diluted with hexane, and the solution was washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. Distillation of the residue gave **46** (22.4 g, 77%): Bp 153—154 °C (0.5 mmHg); ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 0.029 and 0.036 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.64—1.78 (m, 1 H of CH_2CH_2N), 2.31 (ddd, J = 7.8, 13.2, and 15.6 Hz, 1 H of CH_2CH_2N), 2.36 (dd, J = 4.6 and 10.0 Hz, 1 H of $CHCH_2N$), 2.56—2.76 (m, 2 H of CH_2CH_2N), 2.95 (dd, J = 6.1 and 10.0 Hz, 1 H of $CHCH_2N$), 3.63 (d, J = 12.9 Hz, 1 H of CH_2Ph), 3.68 (d, J = 12.9 Hz, 1 H of CH_2Ph), 4.35—4.46 (m, 1 H, C*H*OSi), 7.22—7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz) δ = −4.8 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 34.9, 52.7, 60.6, 62.7, 71.6, 127.0, 128.2, 128.9, 138.5; LRMS (APCI) m/z 292 (M^++H). Found: C, 70.33; H, 9.98; N, 4.82%. Calcd for $C_{17}H_{29}NOSi$: C, 70.04; H, 10.02; N, 4.80%.

Tungstate-Catalyzed Oxidation of (*S*)-3-(*t*-Butyldimethylsilyloxy)pyrrolidine ((*S*)-41). A mixture of **46** (5.32 g, 18.2 mmol), HOAc (2.6 mL), and 5% Pd on carbon (3.12 g) in MeOH (90 mL) was stirred under a balloon of hydrogen at room temperature for 2 h. The catalyst was filtered off, and the filtrate was evaporated to give (*S*)-**41** as a crystalline solid. The crude amine (*S*)-**41** was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed twice with saturated aqueous $NaHCO_3$. To the CH_2Cl_2 solution (150 mL) was added an aqueous solution (9 mL) of $Na_2WO_4{\cdot}2H_2O$ (495 mg, 0.91 mmol) and Et_4NCl (249 mg, 1.81 mmol). To the solution was added dropwise 30% aqueous H_2O_2 solution (6.9 mL, 69.0 mmol) at 0 °C with vigorous stirring, and the solution was stirred at 0 °C for 5 h and at room temperature for 2 h. Excess H_2O_2 was decomposed by adding $NaHSO_3$ with ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography on SiO_2 (1—2% MeOH in CH_2Cl_2) gave nitrone (*S*)-**45** (2.31 g, 59%) and its regioisomer (*S*)-**17a** (310 mg, 8%). (*S*)-**45**: Mp 74.2—75.3 °C; $[\alpha]_D^{27}$ −55.7° (c 1.10, MeOH); IR (Nujol®) 1584 (C=N),

1258 cm^{-1} (N–O); ^1H NMR ($CDCl_3$, 270 MHz) δ = 0.10 and 0.11 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 2.05 (dddd, J = 3.3, 5.5, 8.9, and 13.4 Hz, 1 H of CH_2CH_2N), 2.53 (dddd, J = 6.0, 7.5, 9.0, and 13.4 Hz, 1 H of CH_2CH_2N), 3.82 (ddddd, J = 0.7, 1.6, 5.5, 9.0, and 13.9 Hz, 1 H of CH_2N), 4.10 (dddt, J = 1.8, 6.0, 9.1, and 13.9 Hz, 1 H of CH_2N), 4.90—5.06 (m, 1 H, CHOSi), 6.85 (dd, J = 1.7 and 3.7 Hz, 1 H, CH=N); LRMS (APCI) m/z 431 ($2M^+$+H), 216 (M^++H). Found: C, 55.42; H, 9.53; N, 6.59%. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50%.

Addition of Potassium Cyanide to Nitrone (*R*)-45. To a mixture of nitrone (*R*)-**45** (430 mg, 2.00 mmol), Bu_4NHSO_4 (34 mg, 0.10 mmol), and KCN (156 mg, 2.40 mmol) in CH_2Cl_2 (10 mL) was added 6 M HCl (0.40 mL) at 0 °C. After stirring at room temperature for 50 min, the reaction mixture was diluted with EtOAc/hexane (1/1). The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (20% EtOAc in hexane) gave (2*S*,3*R*)-3-(*t*-butyldimethylsilyloxy)-2-cyano-1-hydroxypyrrolidine (*trans*-**48**) (480 mg, 99%) as a solid. For analytical purposes, recrystallization from hexane gave pure *trans*-**48** (320 mg, 67%): Mp 58.0—59.2 °C; $[\alpha]_D^{26}$ −21.3° (*c* 1.10, $CHCl_3$); IR (Nujol®) 2280 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.11 (s, 3 H, $Si(CH_3)_2$), 0.13 (s, 3 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $Si(CH_3)_3$), 1.75—1.80 (m, 1 H of CH_2CHN), 2.23—2.33 (m, 1 H of CH_2CHN), 3.18 (dt, J = 8.7 and 10.3 Hz, 1 H of CH_2N), 3.28 (ddd, J = 3.9, 8.0, and 10.5 Hz, 1 H of CH_2N), 3.65 (d, J = 5.3 Hz, 1 H, NCH), 4.55 (ddd, J = 3.4, 5.3, and 8.3 Hz, 1 H, CHOSi), 8.58 (br s, 1 H, NOH); ^{13}C NMR (CD_3OD, 68 MHz) δ = −5.0 and −4.9 ($Si(CH_3)_2$), 17.8 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 32.1 (C-4), 55.9 (C-5), 66.7 (C-2), 74.1 (C-3), 117.7 (CN). HRMS (FAB) Found: m/z 243.1521. Calcd for $C_{11}H_{23}N_2O_2Si$: (M^++H), 243.1529.

(2*S*, 3*R*)-3-(*t*-Butyldimethylsilyloxy)-2-cyano-1-hydroxypyrrolidine (*trans*-48) and (2*R*,3*R*)-Isomer (*cis*-48). To a solution of nitrone (*R*)-**45** (215 mg, 1.00 mmol), Me_3SiCN (0.16 mL, 1.20 mmol), and powdered molecular sieves 4A (100 mg) in CH_2Cl_2 (2 mL) was added Me_3SiOTf (0.02 mL, 0.1 mmol) at −65 °C. After stirring at −20 °C for 30 min, the reaction mixture was diluted with MeOH, and then stirred at room temperature for 30 min. The mixture was poured into a mixture of EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography on SiO_2 (5—15% EtOAc in hexane) gave *trans*-**48** (119 mg, 49%) and *cis*-**48** (78 mg, 32%). *cis*-**48**: $[\alpha]_D^{28}$ −42.78° (*c* 1.08, $CHCl_3$); IR (neat) 3400 (OH), 2260 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.11 (s, 3 H, $Si(CH_3)_2$), 0.13 (s, 3 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $Si(CH_3)_3$), 1.83—1.90 (m, 1 H of CH_2CHN), 2.30—2.43 (m, 1 H of CH_2CHN), 2.93 (dt, J = 8.2 and 10.3 Hz, 1 H of CH_2N), 3.43 (ddd, J = 4.8, 8.2, and 10.3 Hz, 1 H of CH_2N), 3.88 (d, J = 6.2 Hz, 1 H, NCH), 4.49 (ddd, J = 4.4, 6.2, and 7.6 Hz, 1 H, CHOSi), 8.58 (br s, 1 H, NOH); ^{13}C NMR (CD_3OD, 68 MHz) δ = −5.0 and −4.9 ($Si(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 32.5 (C-4), 55.7 (C-5), 65.8 (C-2), 70.1 (C-3), 115.9 (CN). HRMS (FAB) Found: m/z 243.1536. Calcd for $C_{11}H_{23}N_2O_2Si$: (M^++H), 243.1529.

ZnI_2-Catalyzed Reaction of Nitrone (*R*)-45a with Ketene *t*-Butyldimethylsilyl Methyl Acetal (29a). To a stirred solution of ZnI_2 (127 mg, 0.40 mmol), molecular sieves 4A (750 mg), and nitrone (*R*)-**45** (430 mg, 2.00 mmol) in CH_2Cl_2 (15 mL) was added dropwise ketene *t*-butyldimethylsilyl methyl acetal (**29a**) (0.532 mL, 2.40 mmol) at −90 °C. After the solution was stirred at −90 °C for 30 min, the mixture was diluted with hexane. The organic solution was washed with brine and dried over $MgSO_4$. Evaporation of the solvent and column chromatography on SiO_2 (0—5% EtOAc in hexane) afforded an unseparable mixture of methyl (2*S*,3*R*)-[1,3-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*trans*-**50a**) and the (2*R*,3*R*)-isomer (*cis*-**50a**) (421 mg, 99%). The *trans*-**50a** (t_R 11.7 min) to *cis*-**50a** (t_R 11.9 min) ratio was determined to be 90 : 10 on the basis of GLC analysis using a capillary column DB-1 (column oven temperature: 210 °C; velocity: 20 cm s^{-1}): IR (neat) 1746 cm^{-1} (COO); ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ = 0.014 (s, 3 H, $Si(CH_3)_2$), 0.019 (s, 3 H, $Si(CH_3)_2$), 0.038 (s, 3 H, $Si(CH_3)_2$), 0.060 (s, 3 H, $Si(CH_3)_2$), 0.85 (s, 18 H, 2×$SiC(CH_3)_3$), 1.55—1.70 (m, 1 H of NCH_2CH_2), 2.00—2.25 (m, 1 H of NCH_2CH_2), 2.39 (dd, J = 5.9 and 15.6 Hz, 1 H of CH_2COO), 2.62 (dd, J = 6.6 and 15.6 Hz, 1 H of CH_2COO), 2.94—3.25 (m, 3 H, $CHNCH_2$), 3.65 (s, 3 H, $COOCH_3$), 4.05—4.14 (m, 1 H, CHOSi). HRMS (EI) Found: m/z 403.2585. Calcd for $C_{19}H_{41}NO_4Si_2$: (M^+), 403.2574.

ZnI_2-Catalyzed Reaction of Nitrone (*R*)-45a with Ketene *t*-Butyl *t*-Butyldimethylsilyl Acetal (29b). According to the above procedure, a mixture of *t*-butyl (2*S*,3*R*)-[1,3-bis(*t*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate (*trans*-**50b**) and the (2*R*, 3*R*)-isomer (*cis*-**50b**) (909 mg, 88%) was obtained by treatment of nitrone (*R*)-**45** (502 mg, 2.33 mmol) with ketene *t*-butyl *t*-butyldimethylsilyl acetal (**29b**) (0.860 mL, 4.67 mmol). The *trans*-**50b** (t_R 8.3 min) to *cis*-**50b** (t_R 8.6 min) ratio was determined by GLC (column: DB-1; column temp : 210 °C; velocity: 20 cm s^{-1}) to be 96 : 4: IR (neat) 1730 cm^{-1} (COO); ^1H NMR ($CDCl_3$, 200 MHz) δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.11 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 2×9 H, 2×$SiC(CH_3)_3$), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.50—1.80 (m, 2 H of NCH_2CH_2), 1.98—2.70 (m, 3 H), 2.95—3.25 (m, 2 H, NCH_2), 4.18 (ddd, J = 3.9, 7.2, and 8.3 Hz, 1 H, CHOSi); LRMS (APCI) m/z 446 (M^++H). Found: C, 58.99; H, 10.45; N, 3.23%. Calcd for $C_{22}H_{47}NO_4Si_2$: C, 59.27; H, 10.63; N, 3.14%.

Synthesis of the Antipode of Geissman–Waiss Lactone (49). Methyl (2*S*,3*R*)-(1-Benzyloxycarbonyl-3-hydroxypyrrolidin-2-yl)acetate (*trans*-51). A mixture of **50a** (*trans*/*cis* 90/10, 721 mg, 1.78 mmol), HOAc (7 mL), and 5% Pd on carbon (700 mg) was stirred under a balloon of hydrogen at room temperature for 12 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was taken up with EtOAc (5 mL) and water (3 mL). To the solution were added K_2CO_3 (276 mg, 2.00 mmol) and benzyl chloroformate (0.305 mL, 2.14 mmol) at room temperature. After stirring for 30 min, the solution was diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was used without further purification. The obtained residue was dissolved in MeOH (5 mL) and the solution was treated with 6 M HCl (0.43 mL) at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, and concentrated under reduced pressure. The residue was diluted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography on SiO_2 gave *trans*-**51** (457 mg, 91%) and (1*R*,5*R*)-(−)-6-aza-6-benzyloxycarbonyl-2-oxabicyclo[3.3.0]octan-3-one ((−)-**52**) (28 mg, 6%) as oils.

***trans*-51**: $[\alpha]_D^{26}$ +2.0° (*c* 1.21, MeOH); IR (Neat) 1736 (COO), 1705 cm^{-1} (NCOO); ^1H NMR ($CDCl_3$, 270 MHz) δ = 1.85—2.15 (m, 2 H, NCH_2CH_2), 2.25 (dd, J = 10.6 and 16.4 Hz, 1 H of CH_2COO), 2.65—3.15 (m, 2 H, 1 H of CH_2COO and OH), 3.46 (ddd, J = 3.9, 8.3, and 11.0 Hz, 1 H of NCH_2), 3.58—3.74 (m, 1 H of NCH_2), 3.68 (s, 3 H, $COOCH_3$), 4.02—4.11 (m, 1 H, NCH), 4.20—4.27 (m, 1 H, CHOH), 5.12 (s, 2 H, OCH_2Ph), 7.28—7.38 (m, 5 H, Ar). HRMS (FAB) Found: m/z 294.1318. Calcd for $C_{15}H_{20}NO_5$: (M^++H), 294.1342.

(−)-52: $[\alpha]_D^{26}$ −128.9° (*c* 0.218, MeOH); IR (Neat) 1786 (COO), 1705 cm^{-1} (NCOO); ^1H NMR ($CDCl_3$, 270 MHz) δ = 1.95—2.15

(m, 1 H of NCH_2CH_2), 2.16—2.38 (m, 1 H of NCH_2CH_2), 2.65—2.96 (m, 2 H, CH_2COO), 3.36—3.51 (m, 1 H of NCH_2), 3.74—3.94 (m, 1 H of NCH_2), 5.03—5.22 (m, 3 H, OCH_2Ph and CHO), 7.25—7.45 (m, 5 H, Ar). HRMS (FAB) Found: *m/z* 262.1106. Calcd for $C_{14}H_{16}NO_4$: (M^++H), 262.1079.

(1*S*,5*S*)-(+)-6-Aza-6-benzyloxycarbonyl-2-oxabicyclo[3.3.0]-octan-3-one ((+)-52).[39a] To a stirred solution of *trans*-**51** (404 mg, 1.38 mmol) in MeOH (8 mL) was added 1 M LiOH (1.51 mL) at 0 °C. The solution was stirred at room temperature for 5 h, and acidified with 6 M HCl to pH 2—3. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude oil was used without further purification. To a solution of the crude oil in THF (15 mL) were successively added PPh_3 (398 mg, 1.52 mmol) and DEAD (0.239 mL, 1.52 mmol) at 0 °C. After stirring at room temperature for 30 min, the solution was concentrated under reduced pressure. Column chromatography of the crude oil on SiO_2 (25—40% EtOAc in hexane) gave (+)-**52** (346 mg, 96%) as an oil: $[\alpha]_D^{28}$ +109.2° (*c* 1.10, MeOH); IR (Neat) 1786 (COO), 1705 cm^{-1} (NCOO); ^1H NMR ($CDCl_3$, 270 MHz) δ = 2.05 (dddd, *J* = 5.0, 8.8, 11.0, and 14.4 Hz, 1 H of NCH_2CH_2), 2.28 (ddd, *J* = 4.0, 6.1, and 14.4 Hz, 1 H of NCH_2CH_2), 2.65—2.96 (m, 2 H, CH_2COO), 3.44 (dt, *J* = 6.1 and 11.0 Hz, 1 H of NCH_2), 3.74—3.94 (m, 1 H of NCH_2), 4.45—4.55 (m, 1 H, CHN), 5.05 (dt, *J* = 4.0 and 5.0 Hz, 1 H, CHO), 5.13 (d, *J* = 12.0 Hz, 1 H of CH_2Ph), 5.17 (d, *J* = 12.0 Hz, 1 H of CH_2Ph), 7.25—7.45 (m, 5 H, Ar). HRMS (FAB) Found: *m/z* 262.1106. Calcd for $C_{14}H_{16}NO_4$: (M^++H), 262.1079.

(1*S*,5*S*)-(−)-6-Aza-2-oxabicyclo[3.3.0]octan-3-one·hydrochloride ((−)-49). A mixture of (+)-**52** (204 mg, 0.780 mmol), 6 M HCl (0.20 mL), and 10% Pd on carbon (53 mg) in MeOH (5.0 mL) was stirred under a balloon of hydrogen at room temperature for 30 min. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The precipitated crystals were filtered and washed with EtOH to give (−)-**49** (116 mg, 81%): Mp 185.0—187.0 °C (lit,[39] mp 185—188 °C); $[\alpha]_D^{28}$ −46.4° (*c* 1.43, MeOH) (lit,[39e] $[\alpha]_D^{28}$ +47.9° (*c* 1.5, MeOH)); ^1H NMR (D_2O, 270 MHz, 45 °C) δ = 2.30—2.55 (m, 2 H, NCH_2CH_2), 3.03 (dd, *J* = 1.7 and 19.5 Hz, 1 H of CH_2COO), 3.32 (dd, *J* = 8.8 and 19.5 Hz, 1 H of CH_2COO), 3.47 (ddd, *J* = 6.8, 10.7, and 12.0 Hz, 1 H of NCH_2), 3.58 (ddd, *J* = 3.9, 7.8, and 12.0 Hz, 1 H of NCH_2), 4.70 (ddd, *J* = 1.7, 5.9, and 8.8 Hz, 1 H, CHN), 5.43 (dt, *J* = 1.7 and 5.4 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 68 MHz, 45 °C) δ = 24.4, 26.7, 39.2, 53.0, 77.6, 170.9 (COO).

Table 4. Crystal Data, Collection Parameters, and Refinement Parameters for **17b**

Formula	$C_{20}H_{25}NO_2Si$
Formula weight	339.51
Crystal size/mm	0.25×0.10×0.05
Cryatal system	Trigonal
Space group	$P3_1$ (#144)
a=*b*, *c*/Å	12.076(5), 11.153(6)
V/Å^3	1408(1)
Z	3
D_{calcd}/g cm^{-3}	1.201
μ/mm^{-1}	11.86
No. of reflections	1716
No. of reflections used	1125 ($F_o \geq 1.5\sigma(F_o)$)
No. of atoms and variables	49, 217
Final *R*, R_w	0.048, 0.042
Goodness to fit	2.14

X-Ray Structure Analysis of Nitrone 17b. A colorless prismatic crystal of **17b** grown in a solvent mixture of EtOAc and hexane was mounted on a glass fiber, and all measurements were made on a Rigaku AFC7R diffractometor with graphite monochromated Cu $K\alpha$ radiation and a 18 kW rotating anode generator. The data were collected at 20 °C using the ω–2θ scan technique to a maximum 2θ value of 130.1°. The structure was solved by direct methods using SIR92 and refined by full-matrix least-squares procedures in the teXsan crystallographic software package of Molecular Structure Corporation. Hydrogen atoms were idealized with C–H = 0.95 Å. Crystal data, data collection parameters, and refinement parameters are summarized in Table 4. Atomic coordinates and anisotropic thermal parameters of non-hydrogen atoms are shown in Table 5. Selected bond lengths and selected bond angles are shown in Table 6. Crystallograhic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained

Table 5. Atomic Coordinates and B_{eq} of **17b**[a)]

Atom	*x*	*y*	*z*	B_{eq}
Si(8)	0.0101(1)	0.6710(2)	−0.002(1)	2.69(3)
O(6)	−0.1856(5)	0.9955(4)	0.141(1)	7.3(2)
O(7)	−0.0428(3)	0.7621(3)	0.053(1)	3.39(9)
N(1)	−0.1848(5)	0.8908(5)	0.152(1)	4.3(1)
C(2)	−0.2768(6)	0.7768(7)	0.136(1)	5.2(2)
C(3)	−0.2396(6)	0.6788(6)	0.164(1)	5.7(2)
C(4)	−0.0942(6)	0.7573(6)	0.170(1)	4.0(1)
C(5)	−0.0699(6)	0.8900(6)	0.199(1)	4.7(2)
C(9)	−0.0887(5)	0.4998(5)	0.050(1)	3.2(1)
C(10)	−0.2135(5)	0.4212(5)	0.010(1)	3.9(1)
C(11)	−0.2850(6)	0.2936(6)	0.046(1)	4.7(1)
C(12)	−0.2333(6)	0.2445(5)	0.125(1)	4.6(1)
C(13)	−0.1100(6)	0.3218(6)	0.168(1)	4.6(2)
C(14)	−0.0382(5)	0.4489(5)	0.132(1)	3.7(1)
C(15)	0.1807(5)	0.7380(5)	0.046(1)	3.2(1)
C(16)	0.2528(6)	0.6826(5)	0.012(1)	3.5(1)
C(17)	0.3839(6)	0.7432(6)	0.035(1)	4.3(1)
C(18)	0.4454(5)	0.8599(6)	0.095(1)	4.7(2)
C(19)	0.3753(6)	0.9145(6)	0.131(1)	4.9(2)
C(20)	0.2432(6)	0.8550(5)	0.107(1)	4.0(1)
C(21)	0.0049(6)	0.6915(6)	−0.168(1)	3.87(10)
C(22)	0.0148(7)	0.5884(7)	−0.238(1)	5.8(2)
C(23)	−0.1187(6)	0.6868(6)	−0.208(1)	5.2(2)
C(24)	0.1155(6)	0.8218(6)	−0.204(1)	6.0(2)

a) $B_{eq} = (8/3)\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2 +2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$.

Table 6. Selected Bond Lengths (Å) and Angles (deg) for **17b**

(a) Bond distances			
Si(8)–O(7)	1.644(5)	N(1)–C(5)	1.49(1)
O(6)–N(1)	1.275(8)	C(2)–C(3)	1.49(1)
O(7)–C(4)	1.432(9)	C(3)–C(4)	1.52(1)
N(1)–C(2)	1.28(1)	C(4)–C(5)	1.51(1)
(b) Bond angles			
Si(8)–O(7)–C(4)	128.3(5)	C(2)–C(3)–C(4)	103.1(7)
O(7)–C(4)–C(3)	109.1(7)	C(2)–N(1)–C(5)	110.7(7)
O(7)–C(4)–C(5)	107.4(7)	N(1)–C(2)–C(3)	112.3(8)
O(6)–N(1)–C(2)	128.4(9)	N(1)–C(5)–C(4)	104.2(7)
O(6)–N(1)–C(5)	120.7(9)	C(3)–C(4)–C(5)	102.7(7)

on request, free of charge, by quoting the publication citation and the deposition numbers CCDC 136016.

The complete $F_o - F_c$ data are deposited as Document No. 73007 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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