RADICAL CYCLIZATION IN HETEROCYCLE SYNTHESIS. 7.[1] SYNTHESIS OF CHIRAL 2-SUBSTITUTED 5-AMINO-4-PIPERIDINOLS *VIA* RADICAL CYCLIZATION

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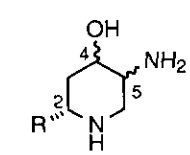
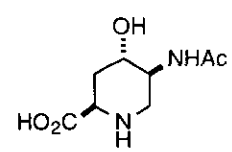
Abstract - Oxime ether connected by a tether to formyl group, which is available from natural amino acid, efficiently cyclizes *via* stannyl radical addition-cyclization or SmI_2-induced radical reaction to provide a new entry to asymmetric synthesis of 2-substituted 5-amino-4-piperidinols.

The preparation of cyclic compounds having an amino group and a hydroxyl group at the neighboring position on the ring has attracted considerable interest in recent years due to their variety of biological activities. Typical examples are balanol,[2] dysiherbaine,[3] pancratistatin,[4] and pseudodistomins.[5] Pseudodistomins A–C[5b] were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and shown to have *in vitro* antitumor activity against L1210 and L5178Y leukemia cells and inhibit calmodulin-activated brain phosphodiesterase. Pseudodistomins D–F[5c] were isolated from the Micronesian ascidian *Pseudodistoma megalarva* and shown to demonstrate potent inhibitory activity toward both DNA repair-competent and DNA repair-deficient strains of the yeast, *Saccharomyces cerevisiae*. The compound (**1**) synthesized from D-glucosamine has been reported[6] to be neuraminidase inhibitor. A common skeleton of these compounds is 2-substituted 5-amino-4-piperidinol. Although many synthetic methodologies of substituted piperidines have been developed, the efficient construction of 2-substituted 5-amino-4-piperidinol remains virtually unexplored. We have recently developed a new efficient carbon-carbon bond-forming reaction based on the radical addition-cyclization[7] of oxime ethers tethered to either a carbonyl[1,8] or alkene group[9] for the synthesis of highly functionalized cyclic compounds. We describe here the use of this sequence to construct chiral 2-substituted 5-amino-4-piperidinols which are regarded as useful synthetic precursors of biologically active natural products.



pseudodistomins

A 4α-H, 5α-H, R=
B 4α-H, 5α-H, R=
C 4β-H, 5β-H, R=
D 4β-H, 5α-H, R=
E 4β-H, 5β-H, R=
F 4α-H, 5α-H, R=



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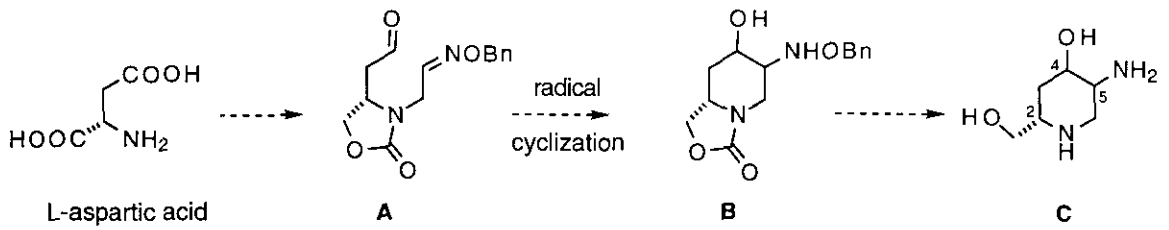
neuraminidase inhibitor

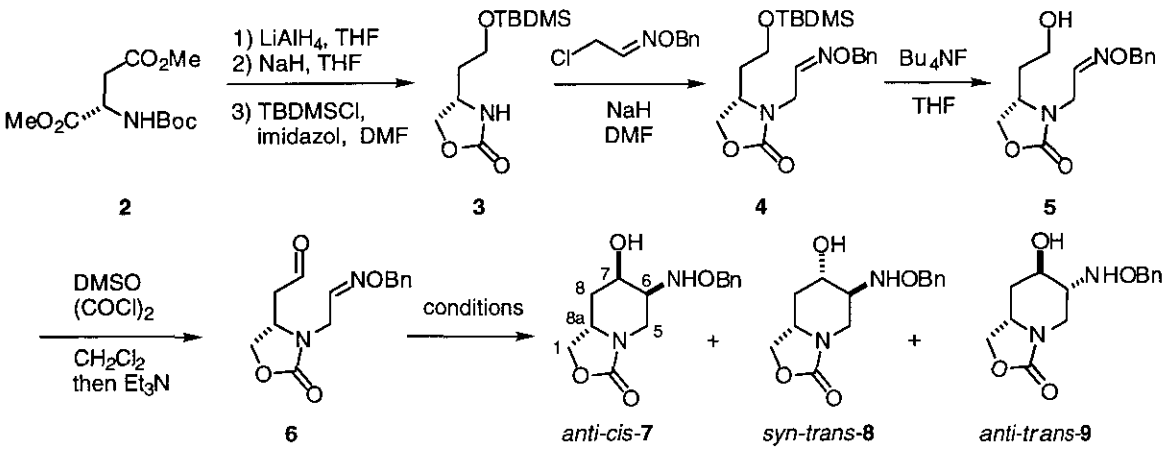
In continuation of our synthetic studies[2,8–10] of biologically active natural products employing the radical addition-cyclization as a key reaction, we designed a route to asymmetric construction of 2-substituted 5-amino-4-piperidinols as follows. Our synthetic route includes the radical addition-cyclization of aldehyde (**A**) connected with oxime ether, which is readily available from natural amino acid. The following cleavage of the oxazolidinone ring and removal of the protecting group in cyclized product (**B**) would give the target compounds (**C**) (Scheme 1).



L-aspartic acid **A** **B** **C**

Scheme 1

Preparation of the requisite substrate (**6**) for the radical reaction is shown in Scheme 2. Reduction of two ester moieties in *N*-Boc dimethyl L-asparatate (**2**)[11] with $LiAlH_4$ followed by treatment with sodium hydride gave the cyclized 4-(2-hydroxyethyl)oxazolidinone, which was then treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to afford the compound (**3**) in 59% yield from **2**. *N*-Alkylation of the oxazolidinone (**3**) with chloroacetaldehyde *O*-benzyloxime[2] afforded the oxime ether (**4**) in 84% yield which was then treated with tetrabutylammonium fluoride (TBAF) to give the alcohol (**5**) in 72% yield. Swern oxidation of the resulting alcohol (**5**) gave the unstable aldehyde (**6**) in favor of the *E*-oxime ether in 2 : 1 ratio. Bartlett[12] and we[2] have reported that the geometry of the oxime ether group does not influence the *trans/cis* selectivity of radical cyclization. Therefore, we investigated the radical addition-cyclization of a geometrical mixture of oxime ethers (**6**) without separation. A solution containing tributyltin hydride (2 equiv.) and AIBN (1 equiv.) in benzene was added dropwise to a solution of the oxime ether (**6**) in boiling benzene while stirring under nitrogen. The solution was then refluxed for a further 6 h to give a 2.3 : 2.1 : 1.0 mixture of three cyclized products, *anti-cis*-**7**, *syn-trans*-**8**, and *anti-trans*-**9** in 62% combined yield (Table 1, entry 1). Each isomer could be easily separated by medium pressure liquid chromatography (MPLC). Careful ^{1}H-NMR spectral analyses of **7**–**9** firmly established the stereostructures as shown. The *anti-cis*-product (**7**) bears a hydroxyl group in an axial orientation and a benzyloxyamino group in an equatorial orientation. The *syn-trans*-product (**8**) bears two substituents in the equatorial orientations, and the *anti-trans*-product (**9**) bears two substituents in axial orientations, respectively. The combined yield of three products obtained by the radical cyclization of **6** was modest, but the stereoselectivty was poor. However *trans*-selectivity (**8** + **9** : **7** = 3.1 : 2.3) was in accord with the previous result in the radical cyclization of simple substrate,[1] which had been explained by the electronic repulsion between the stannyloxy group and nitrogen and/or oxygen atom in the oxime ether group in the transition state.

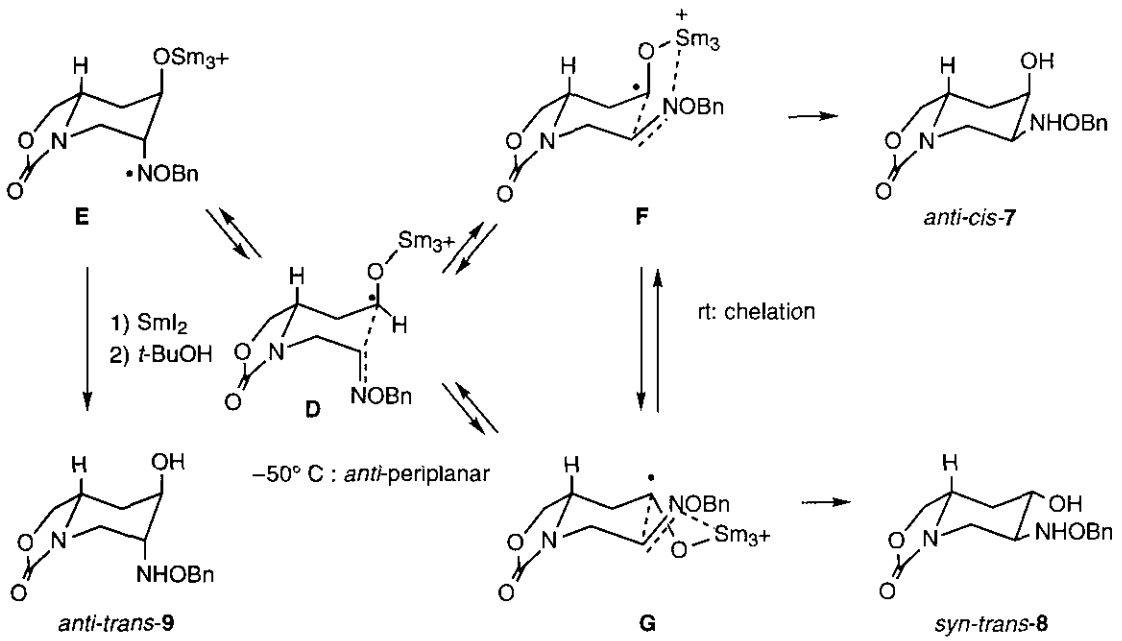


Scheme 2

Table 1. Radical Cyclization of **6**

entry	conditions	ratio **7** : **8** : **9**	combined yield (%)
1	Bu_3SnH, AIBN, C_6H_6, Δ	2.3 : 2.1 : 1.0	62
2	SmI_2, *t*-BuOH, THF, –50° C	1.6 : 1.0 : 2.3	47
3	SmI_2, *t*-BuOH, THF, rt	1.0 : 1.0 : trace	43
4	SmI_2, *t*-BuOH, THF, –50° C → rt	2.5 : 3.6 : 1.0	64
5	SmI_2, *t*-BuOH, HMPA, THF, –50° C	1.0 : 1.7 : 5.1	33
6	SmI_2, $(HOCH_2)_2$, THF, –50° C	1.2 : 1.0 : 1.0	61
7	SmI_2, THF, rt	12 : 1.0 : 3	5

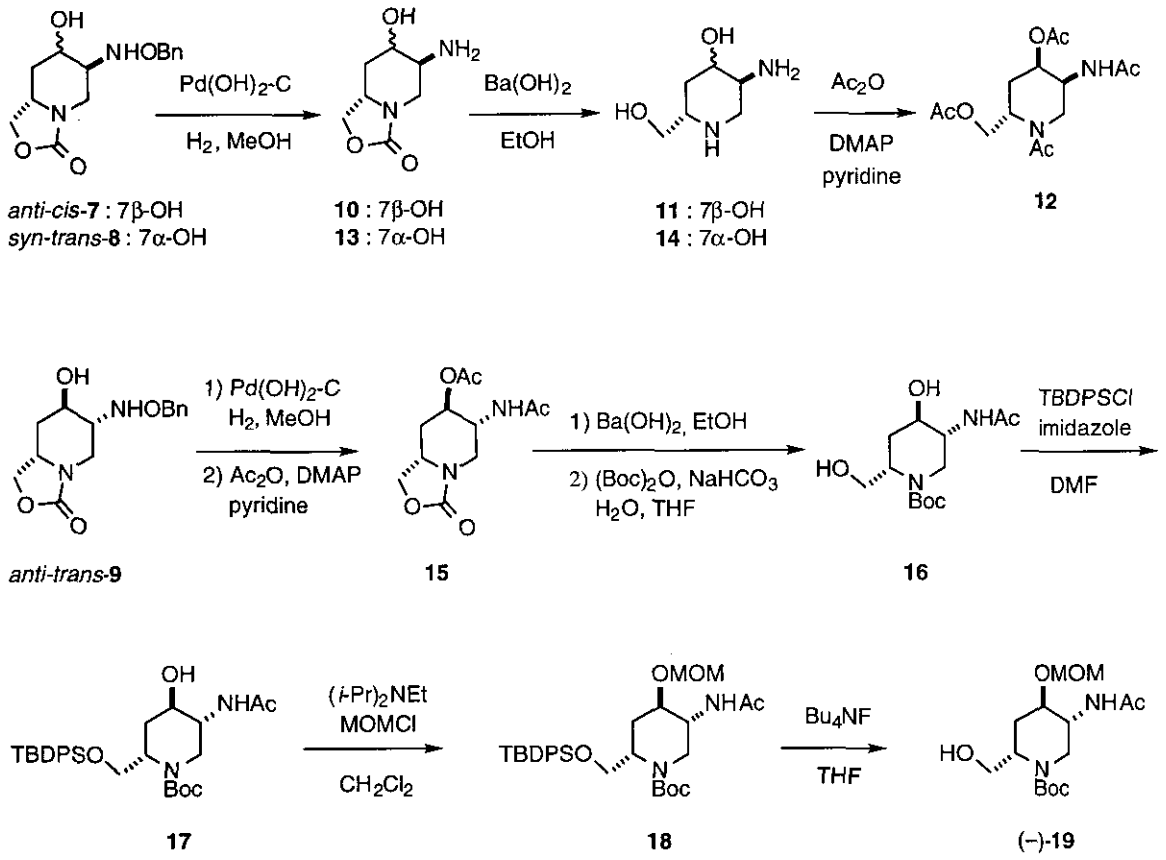
Our previous study[8b] on the radical cyclization of the oxime ether connected with the formyl group has established that the *trans*-selectivity was improved when samarium(II) diiodide (SmI_2) is used instead of tributyltin hydride. Therefore, SmI_2-induced radical reaction of the substrate (**6**) was examined under a variety of conditions. Results are shown in Table 1 (entries 2–7). Treatment of an *E*/*Z* mixture of **6** with commercially available 0.1M solution of SmI_2 in THF (3.0 equiv.) in the presence of *tert*-BuOH as a proton donor at –50° C for 2.5 h underwent smooth cyclization to give a 1.6 : 1.0 : 2.3 mixture of three cyclized products (**7**–**9**) in 47% combined yield in favor of *anti-trans*-product (**9**) (entry 2). Interestingly, this 6-*exo-trig* radical cyclization as well as 5-*exo-trig* radical cyclization[8b,13] took place smoothly even in the absence of HMPA, in contrast to the analogous 7-*exo-trig* radical cyclization in our previous work.[2] When the reaction was carried out at room temperature for 3.5 h (entry 3) or when the reaction mixture was stirred at room temperature for 15.5 h after reaction at –50° C for 7 h (entry 4), the yield of *anti-trans*-product (**9**) was significantly low. On the other hand, in the presence of HMPA, the SmI_2-induced radical cyclization took place with *anti-trans*-stereoselectivity, but the yield was not improved (entry 5). When ethylene glycol was used as a proton donor, the yield increased but stereoselectivity lowered (entry 6) and slow reaction was observed in the absence of proton donor (entry 7).



Scheme 3

These results suggest that the stereoselectivty is dependent on the reaction temperature. While SmI_2-induced radical cyclization has been extensively studied, the nature and magnitude of diastereoselection remain ambiguous.[14] We propose a plausible reaction pathway of SmI_2-induced radical cyclization as shown in Scheme 3. The reaction is initiated by single-electron reduction of the formyl group with SmI_2 and the resulting ketyl radical attacks the carbon of the oxime ether group in *anti*-periplanar manner to form the intermediate aminyl radical (**E**) through the transition state (**D**). The intermediate (**E**) would be reduced rapidly to an anion by a second equiv. of SmI_2 and then protonated by *tert*-BuOH to give **9**. At room temperature, the transition state (**D**) would be at equilibrium with other transition states (**F**) and (**G**) both of which have the chelation of Sm(III) to alcoholic oxygen and the oxime ether group. These transition states (**F**) and (**G**) may contribute to give **7** and **8**. Thus we infer that the *anti-trans*-product (**9**) is the kinetic product of the reaction. Further study will be required to disclose these reaction pathways.

Conversion of the cyclized products (**7**–**9**) to 2-substituted 5-amino-4-piperidinols was readily achieved as shown in Scheme 4. First, we investigated the conversion of the cyclized products (**7**) and (**8**) into the 5-amino-2-hydroxymethyl-4-piperidinols (**11**) and (**14**). Hydrogenolysis of the benzyloxyamino group in **7** and **8** in the presence of Pearlman's catalyst afforded the amino alcohols (**10**) and (**13**) in 89 and 85% yields, respectively. Cleavage of the oxazolidinone ring in **10** and **13** with $Ba(OH)_2$ gave the 5-amino-2-hydroxymethyl-4-piperidinols (**11**) and (**14**) in 40 and 87 % yields, respectively. Acetylation of *anti-cis*-**11** gave the tetraacetyl derivative (**12**), which was found to be identical with the authentic sample of (+)-**12** upon comparison of their spectral data,[15] including optical rotation {**12**; mp 167–172° C (MeOH-Et_2O), $[\alpha]_D$ +45° (c = 0.11, MeOH), lit.,[15] $[\alpha]_D$ +28° (c = 0.10, MeOH)}.



Scheme 4

Next, another isomer (**9**) was converted to the trisubstituted piperidine (**19**), an enantiomer of the synthetic intermediate of neuraminidase inhibitor,[6] which had been prepared from D-glucosamine. Hydrogenolysis of the benzyloxyamino group in **9** followed by acetylation gave the acetyl derivative (**15**) in 93% yield. Cleavage of the oxazolidinone ring in **15** with $Ba(OH)_2$ afforded the piperidine which was treated with di-*tert*-butyl dicarbonate ($(Boc)_2O$) to give the diol (**16**) in 79% yield. Selective protection of the primary hydroxyl group by silyl group and the secondary hydroxyl group by methoxymethyl (MOM) group of the diol (**16**) gave **18**. Desilylation of **18** with TBAF gave (−)-**19** in 97% yield, $[\alpha]_D$ −83°(c = 0.6, $CHCl_3$) {lit.,[6] $[\alpha]_D$ +76°($CHCl_3$) for (+)-**19**}. (−)-**19** exhibited superimposable ^{1}H-NMR spectrum with that of the authentic sample ((+)-**19**),[6] kindly provided by Professor Vasella. (+)-**19** had previously been transformed into neuraminidase inhibitor (**1**) in two steps including oxidation and deprotection.

In conclusion, the stannyl and SmI_2-induced radical addition-cyclization of oxime ether connected with formyl group, which is available from natural amino acid has provided a general method for the asymmetric synthesis of 2-substituted 5-amino-4-piperidinols which are regarded as useful synthetic precursors of pseudodistomins and neuraminidase inhibitor.

EXPERIMENTAL

^{1}H-NMR spectra were measured with Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz), and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform unless otherwise stated (with tetramethylsilane as the internal reference). IR spectra were measured with a Perkin Elmer 1600 FTIR machine for solutions in chloroform unless otherwise stated and MS were taken with Hitachi M-4100 instruments. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mps were determined with Kofler-type hot-stage apparatus and are uncorrected. Reactions were carried out under an N_2 atmosphere unless otherwise stated and extracts from the reaction mixture were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Thin layer chromatography (TLC) was performed on precoated Silica gel 60F-254 plates (0.25 mm thick, Merck) and preparative TLC (*p*-TLC) on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck), with UV detection at 254 and 300 nm. MPLC was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar grosse B column (310-25, Lichroprep Si60, Merck) as column adsorbent. Flash column chromatography (FCC) was performed on Silica gel 60 (230–400 mesh, Merck) as column adsorbent. Short column chromatography (SCC) was undertaken on a short glass filter using Silica gel 60 (230–400 mesh, Merck) under reduced pressure.

(*S*)-4-[2-[(1,1-Dimethylethyl)dimethylsilyloxy]ethyl]-2-oxazolidinone (3) A solution of the diester (**2**)[11] (18.2 g, 70 mmol) in THF (210 mL) was added dropwise to a suspension of $LiAlH_4$ (10.6 g, 280 mmol) in THF (300 mL) with stirring at 0° C. The mixture was stirred at rt for 2 h, then condensed, and ether was added to the residue. The excess $LiAlH_4$ was then decomposed by successive addition of H_2O. The organic phase was separated by decantation, dried and concentrated to give the crude diol which was used for the following reaction without further purification.

A suspension of NaH (2.5 g, 60% assay; 62 mmol) in THF (48 mL) was added dropwise to a solution of the above crude diol in THF (200 mL) with stirring at rt. The mixture was stirred at 60°C for 2.5 h, then cooled to rt, acidified with 10% HCl, and concentrated. The residue was diluted with MeOH and insoluble material was filtered off. The filtrate was concentrated to give the crude oxazolidinone[13] which was used for the following silylation without further purification.

A solution of the crude oxazolidinone, imidazole (11.5 g, 169 mmol), and TBDMSCl (12.7 g, 84.2 mmol) in DMF (157 mL) was stirred at rt for 22 h. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with aqueous K_2CO_3 (10%), dried, and concentrated. Purification of the residue by FCC (AcOEt-hexane = 1 : 1) afforded **3** (10.2 g, 59%) as a colorless oil. IR: 1755 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ: 0.00 (6H, s, Me×2), 0.83 (9H, s, *t*-Bu), 1.62–1.84 (2H, m, CH_2CH_2OSi), 3.67 (2H, t, J = 6.5 Hz, CH_2CH_2OSi), 3.94 (1H, br quint., J = 6.5 Hz, 4-H), 4.02 (1H, dd, J = 8, 6.5 Hz, 5-H), 4.44 (1H, t, J = 8 Hz, 5-H), 5.95 (1H, br s, NH). HRMS *m/z*: Calcd $C_{11}H_{24}NO_3Si$ [(M+H)$^+$] 246.1524. Found: 246.1541.

[(*S*)-(*E*/*Z*)]-4-[2-[(1,1-Dimethylethyl)dimethylsilyloxy]ethyl]-3-[2-(phenylmethoxyimino)ethyl]-2-oxazolidinone (4) A small portion of NaH (2.12 g, 60% assay; 53 mmol) was added to a solution of **3** (13.0 g, 53 mmol) in DMF (55 mL) with stirring at rt and then the solution was stirred at the same temperature for 40 min. Chloroacetaldehyde *O*-benzyloxime[2] (10.9 g, 60 mmol) was added to the above solution, and the mixture was stirred at rt for 5 h. The reaction mixture was diluted with AcOEt

and washed with a small amount of H_2O and aqueous K_2CO_3 (10%). The organic phase was dried and concentrated to give a residue which was purified by FCC (AcOEt-hexane = 3 : 7) to afford **4** (17.5 g, 84%) as colorless oil and a mixture of *E/Z*-oxime (*E* : *Z* = 5 : 2). IR: 1748 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 0.00 (6H, s, Me×2), 0.84 (9H, s, *t*-Bu), 1.57, 1.87 (each 1H, m, CH_2CH_2OSi), 3.49, 3.60 (each 1H, m, CH_2CH_2OSi), 3.64–4.18 (4H, m, 4-H, 5-H, CH_2CH=N), 4.34 (1H, t, *J* = 8.5 Hz, 5-H), 5.02 (10/7H, s, CH_2Ph (*E*)), 5.08 (4/7H, s, CH_2Ph (*Z*)), 6.70 (2/7H, t, *J* = 6.5 Hz, C*H*=N (*Z*)), 7.20–7.37 (40/7H, m, ArH, C*H*=N (*E*)). HRMS *m/z*: Calcd $C_{20}H_{32}N_2O_4Si$ (M^+) 392.2129. Found: 392.2144.

[(*S*)-(*E*)]-4-(2-Hydroxyethyl)-3-[2-(phenylmethoxyimino)ethyl]-2-oxazolidinone (**5**) A solution of **4** (*E* : *Z* = 5 : 2) (932 mg, 2.4 mmol) and TBAF (1 M in THF) (2.4 mL, 2.4 mmol) in THF (100 mL) was stirred at rt for 1.2 h. The reaction mixture was concentrated to give a residue which was purified by SCC (AcOEt) to afford the *E*-oxime (**5**) (478 mg, 72%) as colorless oil. IR: 3628–3250 (OH), 1748 (NCOO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.63, 1.92 (each 1H, m, CH_2CH_2OH), 3.55–3.66 (2H, m, CH_2CH_2OH), 3.81 (1H, m, 4-H), 3.82 (1H, dd, *J* = 16, 6.5 Hz, CH_2CH=N), 4.06 (1H, dd, *J* = 9, 7 Hz, 5-H), 4.19 (1H, dd, *J* = 16, 4.5 Hz, CH_2CH=N), 4.41 (1H, t, *J* = 9 Hz, 5-H), 5.07 (2H, s, CH_2Ph), 7.29–7.38 (5H, m, ArH), 7.39 (1H, dd, *J* = 6.5, 4.5 Hz, C*H*=N). HRMS *m/z*: Calcd $C_{14}H_{18}N_2O_4$ (M^+) 278.1265. Found: 278.1267.

[(*S*)-(*E/Z*)]-4-(2-Oxoethyl)-3-[2-(phenylmethoxyimino)ethyl]-2-oxazolidinone (**6**) A solution of DMSO (1.22 mL, 17.3 mmol) in CH_2Cl_2 (1.8 mL) was added dropwise to a solution of $COCl_2$ (0.73 mL, 7.9 mmol) in CH_2Cl_2 (1.8 mL) at –50° C and the solution was stirred for 30 min. Then a solution of **5** (1.0 g, 3.6 mmol) in CH_2Cl_2 (3.6 mL) was added dropwise to the above solution at –50° C. The mixture was stirred at –50° C for 50 min, then Et_3N (2.5 mL, 18.1 mmol) was added dropwise, and the whole was stirred at –50° C for 40 min and further at rt for 30 min. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with brine, dried, and concentrated to give a residue which was purified by MPLC (AcOEt-hexane = 4 : 1) to afford **6** (853 mg, 86%) as colorless oil and a mixture of *E/Z*-oxime (*E* : *Z* = 2 : 1). After being characterized by NMR spectra, unstable **6** was immediately subjected to the following reaction. IR: 1752 (NCOO), 1723 (CHO) cm^{-1}. ^{1}H-NMR (300 MHz) δ: 2.49 (2/3H, dd, *J* = 18.5, 9 Hz, CH_2CHO (*E*)), 2.58 (1/3H, dd, *J* = 18.5, 9 Hz, CH_2CHO (*Z*)), 2.93 (2/3H, dd, *J* = 18.5, 4 Hz, CH_2CHO (*E*)), 2.96 (1/3H, dd, *J* = 18.5, 4 Hz, CH_2CHO (*Z*)), 3.80–3.90 (2H, m, 4-H, 5-H), 4.03–4.17 (2H, m, CH_2CH=N), 4.56 (2/3H, t, *J* = 9 Hz, 5-H (*E*)), 4.58 (1/3H, t, *J* = 9 Hz, 5-H (*Z*)), 5.07 (4/3H, s, CH_2Ph (*E*)), 5.12 (2/3H, s, CH_2Ph (*Z*)), 6.76 (1/3H, t, *J* = 5 Hz, C*H*=N (*Z*)), 7.28–7.40 (17/3H, m, ArH, C*H*=N (*E*)), 9.52 (2/3H, br s, CHO (*E*)), 9.59 (1/3H, br s, CHO (*Z*)). HRMS *m/z*: Calcd $C_{14}H_{16}N_2O_4$ (M^+) 276.1109. Found: 276.1119.

Radical Cyclization of 6 Using Bu_3SnH A solution of Bu_3SnH (1.1 g, 3.7 mmol) and AIBN (302 mg, 1.8 mmol) in benzene (20 mL) was added dropwise (10 mL/h) to a boiling solution of **6** (508 mg, 1.8 mmol) in benzene (28 mL). The reaction mixture was heated at reflux for 6 h and then the solvent was evaporated. The resulting residue was diluted with acetonitrile and the acetonitrile phase was washed with hexane and concentrated. Purification of the residue by MPLC (AcOEt) afforded [6*S*-(6β,7β,8aβ)]-(–)-hexahydro-7-hydroxy-6-(phenylmethoxyamino)-3*H*-oxazolo[3,4-*a*]pyridin-3-one (**7**) (140 mg, 27%) as colorless needles, mp 89–92° C (AcOEt), [6*S*-(6β,7α,8aβ)]-(–)-hexahydro-7-hydroxy-6-(phenyl-

methoxyamino)-3*H*-oxazolo[3,4-*a*]pyridin-3-one (**8**) (123 mg, 24%) as colorless needles, mp 59–63° C (AcOEt-Et_2O), and [6*R*-(6α,7β,8aβ)]-(–)-hexahydro-7-hydroxy-6-(phenylmethoxyamino)-3*H*-oxazolo-[3,4-*a*]pyridin-3-one (**9**) (56 mg, 11%) as colorless needles, mp 90–94° C (AcOEt-Et_2O).

7; IR: 3620–3170 (OH, NH), 1743 (NCOO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.50 (1H, br t, *J* = 13 Hz, 8-Hax), 2.06 (1H, dt, *J* = 13, 4 Hz, 8-Heq), 2.44 (1H, br s, OH), 2.92 (1H, br t, *J* = 12.5 Hz, 5-Hax), 3.07 (1H, br ddt, *J* = 11.5, 5, 1 Hz, 6-H), 3.73 (1H, dd, *J* = 12.5, 5 Hz, 5-Heq), 3.90 (1H, dd, *J* = 8, 5 Hz, 1-H), 4.04 (1H, m, 8a-H), 4.16 (1H, br dt, *J* = 4, 2 Hz, 7-H), 4.39 (1H, t, *J* = 8 Hz, 1-H), 4.66, 4.70 (2H, ABq, *J* = 11.5 Hz, CH_2Ph), 5.53 (1H, br s, NH), 7.31–7.41 (5H, m, ArH). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.46; H, 6.18; N, 11.02. $[\alpha]_D$ –48° (*c* = 1.02, MeOH).

8; IR: 3640–3460 (OH, NH), 1751 (NCOO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.45 (1H, br q, *J* = 12, 8-Hax), 2.15 (1H, dt, *J* = 12, 4 Hz, 8-Heq), 2.72 (1H, br s, OH), 2.76 (1H, td, *J* = 11, 5 Hz, 6-H), 2.89 (1H, dd, *J* = 13, 11 Hz, 5-Hax), 3.68 (1H, m, 7-H), 3.74 (1H, m, 8a-H), 3.95 (1H, dd, *J* = 9, 5 Hz, 1-H), 4.08 (1H, dd, *J* = 13, 5 Hz, 5-Heq), 4.40 (1H, t, *J* = 9 Hz, 1-H), 4.68 (2H, s, CH_2Ph), 5.84 (1H, br s, NH), 7.31–7.39 (5H, m, ArH). HRMS *m/z*: Calcd $C_{14}H_{18}N_2O_4$ (M^+) 278.1265. Found: 278.1277. $[\alpha]_D$ –10° (*c* = 1.23, MeOH).

9; IR: 3620–3470 (OH, NH), 1749 (NCOO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.68 (1H, br dt, *J* = 13.5, 3.5 Hz, 8-Heq), 1.76 (1H, ddd, *J* = 13.5, 11.5, 2.5 Hz, 8-Hax), 2.09 (1H, br s, OH), 3.13 (1H, br s, 6-H), 3.38 (1H, dd, *J* = 14, 3 Hz, 5-Hax), 3.79 (1H, br d, *J* = 14 Hz, 5-Heq), 3.88 (1H, dd, *J* = 8.5, 5.5 Hz, 1-H), 4.07 (1H, m, 8a-H), 4.12 (1H, m, 7-H), 4.39 (1H, t, *J* = 8.5 Hz, 1-H), 4.66, 4.74 (2H, ABq, *J* = 12 Hz, CH_2Ph), 5.50 (1H, br s, NH), 7.28–7.36 (5H, m, ArH). HRMS *m/z*: Calcd $C_{14}H_{18}N_2O_4$ (M^+) 278.1265. Found: 278.1282. $[\alpha]_D$ –26° (*c* = 0.76, MeOH).

Radical Cyclization of 6 Using SmI_2 (a) Table 1, entries 2 and 6; SmI_2 (0.1 M in THF) (93 mL, 9.3 mmol) was added dropwise to a solution of **6** (853 mg, 3.1 mmol) and either *t*-BuOH (0.73 mL, 7.7 mmol) or $(HOCH_2)_2$ (0.41 mL, 7.7 mmol) in THF (155 mL) under an argon atmosphere at –50° C. The reaction mixture was stirred at the same temperature for 3.5 h. After the solvent was evaporated, the resulting residue was diluted with AcOEt and washed with brine. The organic phase was dried and concentrated. Purification of the residue by MPLC (AcOEt) afforded **7–9** as shown in Table 1. ^{1}H-NMR spectra of **7–9** were identical with those of **7–9** prepared by radical cyclization of **6** using Bu_3SnH.

(b) Table 1, entry 3; SmI_2 (0.1 M in THF) (40 mL, 4.0 mmol) was added to a solution of **6** (366 mg, 1.3 mmol) and *t*-BuOH (0.31 mL, 3.3 mmol) in THF (66 mL) under an argon atmosphere at rt. After being stirred at the same temperature for 3.5 h, SmI_2 (0.1 M in THF) (10 mL, 1.0 mmol) was added dropwise. After 1 h, the reaction mixture was treated as the procedure described above.

(c) Table 1, entry 4; SmI_2 (0.1 M in THF) (53 mL, 5.3 mmol) was added dropwise to a solution of **6** (490 mg, 1.8 mmol) and *t*-BuOH (0.42 mL, 4.4 mmol) in THF (89 mL) under an argon atmosphere at –50° C. The mixture was stirred at the same temperature for 7 h and then slowly allowed to reach rt. After being stirred at rt for 15.5 h, the reaction mixture was treated as the procedure described above.

(d) Table 1, entry 5; SmI_2 (0.1 M in THF) (17 mL, 1.7 mmol) was added dropwise to a solution of *t*-BuOH (0.14 mL, 1.5 mmol) and **6** (162 mg, 0.59 mmol) in HMPA (1.64 mL, 9.4 mmol) under an argon atmosphere at –50° C. After being stirred at the same temperature for 1.5 h, another SmI_2 (0.1 M in THF) (5 mL, 0.5 mmol) was added dropwise. After being stirred at –50° C for 25 min, the reaction mixture was

treated as the procedure described above.

(e) Table 1, entry 7; SmI_2 (0.1 M in THF) (12 mL, 1.2 mmol) was added to a solution of **6** (111 mg, 0.40 mmol) in THF (20 mL) under an argon atmosphere at rt. After being stirred at the same temperature for 1 h, another SmI_2 (0.1 M in THF) (4 mL, 0.4 mmol) was added dropwise. After 1 h, the reaction mixture was treated as the procedure described above.

Hydrogenolysis of the Benzyloxyamino Group in 7 and 8. Typical Procedure. A suspension of 20% $Pd(OH)_2$-C (20 mg) in MeOH (10 mL) was stirred under a hydrogen atmosphere at rt for 1 h. A solution of **7** (143 mg, 0.51 mmol) in MeOH (13 mL) was added to the above suspension. After being stirred under a hydrogen atmosphere at rt for 22 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. Purification of the residue by *p*-TLC (MeOH-CH_2Cl_2-28% NH_4OH = 1 : 9 : 0.08) afforded **10** (79 mg, 89%).

[6*S*-(6β,7β,8aβ)]-6-Aminohexahydro-7-hydroxy-3*H*-oxazolo[3,4-*a*]pyridin-3-one (10); colorless viscous oil. IR (film): 3670–3000 (OH, NH), 1732 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.58 (1H, ddd, *J* = 13.5, 11.5, 2 Hz, 8-Hax), 2.08 (1H, br dt, *J* = 13.5, 3 Hz, 8-Heq), 2.87 (1H, br d, *J* = 12 Hz, 6-H), 2.97 (1H, t, *J* = 12 Hz, 5-Hax), 3.67 (1H, dd, *J* = 12, 4 Hz, 5-Heq), 3.92 (1H, dd, *J* = 8, 5 Hz, 1-H), 3.97 (1H, br dt, *J* = 4, 2 Hz, 7-H), 4.07 (1H, m, 8a-H), 4.43 (1H, t, *J* = 8 Hz, 1-H). HRMS *m/z*: Calcd $C_7H_{12}N_2O_3$ (M^+) 172.0847. Found: 172.0853.

[6*S*-(6β,7α,8aβ)]-6-Aminohexahydro-7-hydroxy-3*H*-oxazolo[3,4-*a*]pyridin-3-one (13); colorless powder, yield, 85%. IR (nujol): 3700–3000 (OH, NH), 1732 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.45 (1H, q, *J* = 12 Hz, 8-Hax), 2.12 (1H, dt, *J* = 12, 4 Hz, 8-Heq), 2.57–2.69 (2H, m, 5-Hax, 6-H), 3.36 (1H, m, 7-H), 3.84 (1H, m, 8a-H), 3.92 (1H, m, 5-Heq), 3.98 (1H, dd, *J* = 8.5, 5 Hz, 1-H), 4.42 (1H, t, *J* = 8.5 Hz, 1-H). HRMS *m/z*: Calcd $C_7H_{12}N_2O_3$ (M^+) 172.0847. Found: 172.0856.

Cleavage of the Oxazolidinone Ring in 10 and 13. Typical Procedure. A mixture of **10** (79 mg, 0.46 mmol) and saturated aqueous $Ba(OH)_2$ (7.3 mL) in EtOH (37 mL) was heated at reflux for 9 h. The reaction mixture was concentrated and the residue was diluted with THF. The organic phase was separated by decantation and concentrated to give a residue which was purified by *p*-TLC (EtOH-28% NH_4OH = 5 : 1) to give **11** (27 mg, 40%).

[2*S*-(2α,4β,5β)]-(−)-5-Amino-4-hydroxy-2-piperidinemethanol (11); colorless viscous oil. IR (film): 3700–3000 (OH, NH) cm^{-1}. ^{1}H-NMR (500 MHz) δ (D_2O): 1.34 (1H, br td, *J* = 14, 3 Hz, 3-Hax), 1.71 (1H, br dt, *J* = 14, 3 Hz, 3-Heq), 2.57 (1H, t, *J* = 11 Hz, 6-Hax), 2.73 (1H, br ddd, *J* = 11, 4.5, 3 Hz, 5-H), 2.77 (1H, br dd, *J* = 11, 4.5 Hz, 6-Heq), 2.84 (1H, m, 2-H), 3.30 (1H, dd, *J* = 11, 7 Hz, C*H*$_2$OH), 3.44 (1H, dd, *J* = 11, 4.5 Hz, C*H*$_2$OH), 3.92 (1H, br q, *J* = 3 Hz, 4-H). HRMS (CI, isobutane) *m/z*: Calcd $C_6H_{14}N_2O_2$+H (QM^+) 147.1133. Found: 147.1150. $[\alpha]_D$ −16° (*c* = 1.17, H_2O).

[2*S*-(2α,4α,5β)]-(+)-5-Amino-4-hydroxy-2-piperidinemethanol (14); colorless powder, yield 87%. IR (nujol): 3360–3000 (OH, NH) cm^{-1}. ^{1}H-NMR (500 MHz) δ (D_2O): 0.99 (1H, br q, *J* = 12 Hz, 3-Hax), 1.80 (1H, ddd, *J* = 12, 5, 2.5 Hz, 3-Heq), 2.20 (1H, dd, *J* = 12, 11 Hz, 6-Hax), 2.42 (1H, ddd, *J* = 11, 9.5, 5 Hz, 5-H), 2.60 (1H, m, 2-H), 2.93 (1H, br dd, *J* = 12, 4.5 Hz, 6-Heq), 3.24 (1H, ddd, *J* = 12, 9.5, 5 Hz, 4-H), 3.32 (1H, dd, *J* = 11, 7 Hz, CH_2OH), 3.40 (1H, dd, *J* = 11, 4.5 Hz, CH_2OH). HRSIMS *m/z*: Calcd $C_6H_{14}N_2O_2$+H (QM^+) 147.1133. Found: 147.1139. $[\alpha]_D$ +38° (*c* = 1.13, H_2O).

[3*S*-(3β, 4β, 6α)]-(+)-*N*-[1-Acetyl-4-acetyloxy-6-(acetyloxymethyl)-3-piperidinyl]-acetamide (12) A solution of the piperidine (**11**) (25 mg, 0.17 mmol), Ac_2O (300 mg, 3 mmol), and dimethylaminopyridine (DMAP) (2 mg) in pyridine (1 mL) was stirred at rt for 12.5 h. The reaction mixture was diluted with EtOH and stirred at rt for 1 h for decomposition of the excess Ac_2O. The reaction mixture was then condensed to give a residue which was purified by *p*-TLC (MeOH-CH_2Cl_2 = 1 : 20) to give **12** (42 mg, 80%), as colorless crystals, mp 167–172°C (MeOH-Et_2O). The IR and ^{1}H-NMR spectra of **12** were found to be identical with those of an authentic specimen.[15] HRMS *m/z*: Calcd $C_{14}H_{22}N_2O_6$ (M^+) 314.1476. Found: 314.1486. $[\alpha]_D$ +45°(*c* = 0.11, MeOH) (lit.,[15] $[\alpha]_D$ +28°(*c* = 0.10, MeOH).

[6R-(6α, 7β, 8aβ)]-(–)-*N*-(7-Acetyloxyhexahydro-3-oxo-3*H*-oxazolo[3,4-*a*]pyridin-6-yl)acetamide (15) According to the general procedure, **9** (251 mg, 0.9 mmol) was treated with 20% $Pd(OH)_2$-C (115 mg) in MeOH (40 mL) under a hydrogen atmosphere to give a crude amine which was used for the following reaction without further purification. ^{1}H-NMR (300 MHz) δ: 1.76–1.93 (2H, m, 8-H_2), 2.98 (1H, br s, 7-H), 3.42–3.57 (2H, m, 5-Hax, 6-H), 3.88–3.98 (2H, m, 1-H, 5-Heq), 4.08 (1H, m, 8a-H), 4.45 (1H, t, *J* = 8.5 Hz, 1-H). According to the procedure described for the preparation of **12**, the crude product was acetylated with Ac_2O (947 mg, 9.3 mmol) and DMAP (6 mg) in pyridine (9.8 mL) to give **15** (214 mg, 93%) as colorless needles, mp 190–192° C (MeOH-Et_2O) after purification by FCC (MeOH-CH_2Cl_2 = 1 : 24). IR: 1740 (NCOO, COO), 1681 (NHCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.87 (1H, br ddd, *J* = 14, 11.5, 3 Hz, 8-Hax), 2.01, 2.10 (each 3H, s, Ac×2), 2.09 (1H, dt, *J* = 14, 3 Hz, 8-Heq), 3.46 (1H, dd, *J* = 14, 3.5 Hz, 5-Hax), 3.71 (1H, br d, *J* = 14 Hz, 5-Heq), 3.93–4.00 (2H, m, 1-H, 8a-H), 4.12 (1H, br dt, *J* = 7, 3 Hz, 6-H), 4.47 (1H, m, 1-H), 5.16 (1H, br q, *J* = 3 Hz, 7-H), 6.92 (1H, br d, *J* = 7 Hz, NH). Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N,10.93. Found: C, 51.46; H, 6.18; N, 11.02. $[\alpha]_D$ –63°(*c* = 1.29, MeOH).

1,1-Dimethylethyl [2*S*-(2α,4β,5α)]-5-Acetylamino-4-hydroxy-2-hydroxymethyl-1-piperidinecarboxylate (16) According to the general procedure, **15** (164 mg, 0.64 mmol) was treated with saturated aqueous $Ba(OH)_2$ (11 mL) in EtOH (47 mL) to give a crude residue which was used for the following reaction without further purification. ^{1}H-NMR (200 MHz) δ: 1.55–1.65 (2H, m, 3-H_2), 1.92, 1.98 (each 3H, s, Ac×2), 2.75 (1H, dd, *J* = 12.5, 4 Hz, 6-Hax), 3.00 (1H, m, 2-H), 3.15 (1H, dd, *J* = 12.5, 4 Hz, 6-Heq), 3.43–3.53 (2H, m, CH_2OH), 3.73 (1H, q, *J* = 4 Hz, 5-H), 3.85 (1H, q, *J* = 4 Hz, 4-H). A solution of $(Boc)_2O$ (140 mg, 0.64 mmol) in THF (51 mL) was added dropwise to a solution of the crude amine in saturated aqueous $NaHCO_3$ (4 mL) and THF (85 mL) and the whole was heated at reflux for 6 h. The mixture was concentrated to give a residue which was diluted with THF. The organic phase was separated by decantation and concentrated The residue was purified by FCC (MeOH-CH_2Cl_2 = 3 : 22) to give **16** as colorless oil (145 mg, 79%). IR: 3690-3430 (OH, NH), 1672 (NCOO, NHCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.46 (9H, s, *t*-Bu), 1.62 (1H, br td, *J* = 13, 6 Hz, 3-Hax), 2.02 (3H, s, Ac), 2.11 (1H, br dd, *J* = 13, 4 Hz, 3-Heq), 2.73 (1H, t, *J* = 13 Hz, 6-Hax), 3.58–3.68 (3H, m, 5-H, CH_2OH), 3.74 (1H, br td, *J* = 12, 4 Hz, 4-H), 4.15 (1H, br dd, *J* = 13, 4.5 Hz, 6-Heq), 4.34 (1H, br q, *J* = 6 Hz, 2-H), 6.85 (1H, br s, NH). HRMS *m/z*: Calcd $C_{13}H_{25}N_2O_5$ [$(M+H)^+$] 289.1762. Found: 289.1738.

1,1-Dimethylethyl [2*S*-(2α,4β,5α)]-5-Acetylamino-2-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-hydroxy-1-piperidinecarboxylate (17) According to the procedure described for the preparation of **3**, treatment of **16** (121 mg, 0.42 mmol), *t*-butyldiphenylsilyl chloride (TBDPSCl) (127 mg, 0.46 mmol) and imidazole (127 mg, 0.46 mmol) in DMF (0.7 mL) gave **17** (47 mg, 21%) as colorless oil after purification by SCC (AcOEt). IR: 1676 (NCOO, NHCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.05 (9H, s, *t*-BuSi), 1.43 (9H, s, *t*-BuO), 1.63 (1H, m, 3-Hax), 2.02 (3H, s, Ac), 2.21 (1H, br d, *J* = 12.5 Hz, 3-Heq), 2.56 (1H, br t, *J* = 11.5 Hz, 6-Hax), 3.60–3.69 (4H, m, 2-CH_2, 4-H, 5-H), 4.19 (1H, br d, *J* = 11.5 Hz, 6-Heq), 4.43 (1H, m, 2-H), 5.38 (1H, br s, NH), 7.37–7.46 (6H, m, ArH), 7.62–7.66 (4H, m, ArH). HRMS *m/z*: Calcd $C_{29}H_{43}N_2O_5Si$ [(M+H)$^+$] 527.2938. Found: 527.2947.

1,1-Dimethylethyl [2*S*-(2α,4β,5α)]-(−)-5-Acetylamino-2-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-(methoxymethoxy)-1-piperidinecarboxylate (18) A solution of **17** (34 mg, 0.065 mmol), MOMCl (15.6 mg, 0.19 mmol) and (*i*-Pr)$_2$NEt (0.11 mL, 0.65 mmol) in CH_2Cl_2 (0.6 mL) was heated at reflux for 10 h. Then another MOMCl (15.6 mg, 0.19 mmol) and (*i*-Pr)$_2$NEt (0.11 mL, 0.65 mmol) were added four times at 10 h intervals to the reaction mixture. After 50 h (total), the reaction mixture was diluted with aqueous AcOH (15%) and extracted with CH_2Cl_2. The organic phase was washed with brine, dried, and concentrated. Purification of the residue by SCC (AcOEt) gave **18** (27 mg, 73%) as colorless powder. IR: 1681 (NCOO, NHCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.06 (9H, s, *t*-BuSi), 1.44 (9H, s, *t*-Bu), 1.71 (1H, ddd, *J* = 13.5, 11, 6.5 Hz, 3-Hax), 1.97 (3H, s, Ac), 2.24 (1H, br d, *J* = 13.5 Hz, 3-Heq), 2.58 (1H, dd, *J* = 13, 11 Hz, 6-Hax), 3.38 (3H, s, OCH_3), 3.62–3.72 (4H, m, 6-CH_2, 4-H, 5-H), 4.44 (1H, br dd, *J* = 13, 4 Hz, 6-Heq), 4.45 (1H, m, 2-H), 4.59, 4.64 (2H, ABq, *J* = 7 Hz, OCH_2O), 5.65 (1H, br s, NH), 7.38–7.46 (6H, m, ArH), 7.64 (4H, m, ArH). HRMS (CI, isobutane) *m/z*: Calcd $C_{31}H_{46}N_2O_6Si$+H (QM^+) 571.3201. Found: 571.3208. $[\alpha]_D$ −42° (*c* = 1.25, MeOH).

1,1-Dimethylethyl [2*S*-(2α,4β,5α)]-(−)-5-Acetylamino-2-hydroxymethyl-4-methoxymethoxy-1-piperidinecarboxylate (19) A solution of **18** (37 mg, 0.065 mmol) and TBAF (1.0 M in THF) (0.065 mL, 0.065 mmol) in THF (1.8 mL) was stirred at rt for 2.3 h. The reaction mixture was concentrated to give a residue which was purified by SCC (MeOH-AcOEt = 1 : 49) to give **19** (21 mg, 97%), as colorless needless, mp 146–148°C (AcOEt). The IR and ^{1}H-NMR spectra of **19** were found to be identical with those of an authentic specimen.[6] IR: 3640–3170 (OH, NH), 1676 (NCOO, NHCO) cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.47 (9H, s, *t*-Bu), 1.72 (1H, m, 3-Hax), 1.99 (3H, s, Ac), 2.08 (1H, ddd, *J* = 13.5, 4, 2.5 Hz, 3-Heq), 2.38 (1H, br t, *J* = 5 Hz, OH), 2.79 (1H, dd, *J* = 13, 10 Hz, 6-Hax), 3.39 (3H, s, OCH_3), 3.60–3.78 (4H, m, CH_2OH, 4-H, 5-H), 4.35 (1H, br dd, *J* = 13, 4.5 Hz, 6-Heq), 4.38 (1H, m, 2-H), 4.62, 4.69 (2H, ABq, *J* = 7 Hz, OCH_2OCH_3), 5.90 (1H, br d, *J* = 5 Hz, NH). HRMS *m/z*: Calcd $C_{15}H_{29}N_2O_6$ [(M+H)$^+$] 333.2024. Found: 333.2034. $[\alpha]_D$ −83° (*c* = 0.6, $CHCl_3$) (lit.,[6] $[\alpha]_D$ +76° ($CHCl_3$), mp 138–140°C).

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